Pharmacologically Increasing Sleep Spindles Enhances Recognition for Negative and High-arousal Memories

Erik J. Kaestner[1], John T. Wixted[1], and Sara C. Mednick[2]

Abstract

■ Sleep affects declarative memory for emotional stimuli differently than it affects declarative memory for nonemotional stimuli. However, the interaction between specific sleep characteristics and emotional memory is not well understood. Recent studies on how sleep affects emotional memory have focused on rapid eye movement sleep (REM) but have not addressed non-REM sleep, particularly sleep spindles. This is despite the fact that sleep spindles are implicated in declarative memory as well as neural models of memory consolidation (e.g., hippocampal neural replay). Additionally, many studies examine a limited range of emotional stimuli and fail to disentangle differences in memory performance because of variance in valence and arousal. Here, we experimentally increase non-REM sleep features, sleep spindle density, and SWS, with pharmacological interventions using zolpidem (Ambien) and sodium oxybate (Xyrem) during daytime naps. We use a full spread of emotional stimuli to test all levels of valence and arousal. We find that increasing sleep spindle density increases memory discrimination (d_a) for highly arousing and negative stimuli without altering measures of bias (c_a). These results indicate a broader role for sleep in the processing of emotional stimuli with differing effects based on arousal and valence, and they raise the possibility that sleep spindles causally facilitate emotional memory consolidation. These findings are discussed in terms of the known use of hypnotics in individuals with emotional mood disorders. ■

INTRODUCTION

Compared with nonemotional stimuli, emotional stimuli are preferentially attended to and processed, increasing the probability of successful memory retrieval (Kensinger, 2009). Memory retention is also facilitated by a period of sleep between encoding and retrieval (Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011; Stickgold, 2005). Recent studies that examine the effect of sleep on emotional memory consolidation have demonstrated that sleep has a greater facilitative effect on declarative memory for emotional stimuli than nonemotional stimuli (Nishida, Pearsall, Buckner, & Walker, 2009; Wagner, Gais, & Born, 2001), increases retention of emotional components of scenes but not nonemotional components (Payne, Stickgold, Swanberg, & Kensinger, 2008), and alters the neural network underlying emotional memory retrieval relative to the network for nonemotional stimuli (Lewis, Cairney, Manning, & Critchley, 2011; Payne & Kensinger, 2011; Sterpenich et al., 2009). The aim of this article is to identify sleep features that may be causally related to the enhancement of emotional memories. More specifically, we use a pharmacological approach to experimentally alter specific sleep features in an effort to identify the mechanisms underlying emotional memory consolidation.

Emotional Memory

What are emotional memories, and how do they differ from nonemotional memories? Emotion is a motivational force promoting an organism's survival and is driven by two factors: valence and arousal. Valence can either be a pleasant appetitive/approach reaction (procreation, sustenance) or be an unpleasant aversive/withdrawal reaction (anxiousness, fearfulness). Arousal reflects how intensely (low, high) these two motivational systems are activated by stimuli (Lang, 2010; Lang & Bradley, 2010). Presumably because of finite attentional and processing resources, the brain focuses on and consolidates limited aspects of stimuli (Marois & Ivanoff, 2005). Because emotional information is linked to survival, it is both preferentially attended to and preferentially processed relative to nonemotional information. Some defining features of emotional memory include vividness, a focus on central emotional detail to the exclusion of nonemotional peripheral detail, and the much-replicated "emotional memory enhancement effect" (Kensinger & Schacter, 2011; Kensinger, Garoff-Eaton, & Schacter, 2007).

Most prior studies have focused on a narrow comparison of negative-valence, high-arousal stimuli with neutral-valence, low-arousal stimuli. Recently, several studies have expanded the range of emotional stimuli studied (Kaestner & Polich, 2011; Mickley-Steinmetz & Kensinger, 2009), which is the approach we also followed in the current study. By investigating both positive and negative stimuli

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controlled for arousal, we compared the memory-related effects of the full range of emotional stimuli—low- and high-arousal, negative, positive, and neutral—under different sleep conditions.

Several studies have raised concerns about potential biases when measuring memory performance with the basic recognition memory paradigm when using emotional stimuli (Grider & Malmberg, 2008; Dougal & Rotello, 2007) and have recommended the use of confidence ratings to allow for more precise measurement. We followed that recommendation and collected confidence ratings in our study (see Methods for a discussion of this issue).

Sleep and Memory

Sleeping between learning and retrieval can improve many aspects of memory, including association and integration of both procedural and declarative memories (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Fenn, Nusbaum, & Margoliash, 2003; Fischer, Hallschmid, Elsner, & Born, 2002). Sleep is thought to facilitate the consolidation of the initial memory trace, thereby increasing resistance to interference and promoting superior retrieval compared with the same period without sleep (Mednick et al., 2011; Walker, 2009). For declarative memories, consolidation is hypothesized to rely on hippocampal–cortical interactions associated with SWS and sleep spindles (Clemens et al., 2007; Gais & Born, 2004). SWS is characterized by slow oscillations (<1 Hz), which synchronize firing patterns in large neuronal populations (Dang-Vu et al., 2008). Sleep spindles are short (0.5–3 sec), medium oscillations (11–16 Hz) of excitatory thalamo-cortical activity that correlate with activity in the hippocampus (Peyrache, Battaglia, & Destexhe, 2011).

Studies of emotional memory have focused on rapid eye movement (REM) sleep. REM sleep is characterized by transient theta activity (4–7 Hz) restricted to the hippocampus and not observed cortically (Cantero et al., 2003). Emotional declarative memory may benefit from theta during REM sleep (Nishida et al., 2009). In a series of experiments disrupting early SWS-dominated sleep while leaving later REM-dominated sleep largely intact, memory for nonemotional stimuli was disrupted, but memory for negative emotional stimuli was unaffected (Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005; Wagner et al., 2001). Indeed, the superiority of negative emotional memories compared with nonemotional memories after sleep disruption was still present 4 years after the initial experiment (Wagner, Hallschmid, Rasch, & Born, 2006). In contrast, Baran and colleagues recently examined negative and neutral memories that varied in arousal and found a benefit of sleep for both emotional and nonemotional stimuli but no correlations of memory performance with REM sleep (Baran, Pace-Schott, Ericson, & Spencer, 2012).

Although sleep spindles are correlated with improved declarative memory (Schmidt et al., 2006; Clemens, Fabo, & Halasz, 2005; Schabus et al., 2004; Gais, Molle, Helms, & Born, 2002) and play a critical role in hippocampal–cortical communication during consolidation (Siapas & Wilson, 1998), previous studies have addressed non-REM (NREM) sleep stages but have not explicitly examined the association of sleep spindles with emotional memory. Importantly, a recent study has linked sleep spindles to emotion regulation in children. This study found positive correlations between Stage 2 sleep spindles and positive high ego-involvement coping strategies (Mikoteit et al., 2012). This leaves open the question of whether sleep spindle density contributes to the consolidation of emotional memory as well. This is one of the key issues we address in our experiment.

Sleep studies are usually correlational in nature, making causal inferences between observed changes in sleep and emotional memory difficult. This study did not use a correlational design but instead used hypnotics to pharmacologically manipulate sleep spindle density to investigate effects on emotional memory. Two drugs, zolpidem (ZOL; Ambien; Sanofi Aventis) and sodium oxybate (SO; Xyrem; Jazz Pharmaceuticals), were chosen to maximize differences in sleep features across naps. ZOL has been shown to enhance sleep spindle density (Feinberg, Maloney, & Campbell, 2000; Brunner, Dijk, Münch, & Borbély, 1991). Mednick and colleagues pharmacologically increased spindle density with ZOL during a 90-min nap, which led to superior declarative verbal memory, but not non-declarative memory, compared with control conditions (Mednick et al., 2013). ZOL is also associated with increased hippocampal sharp wave ripple complexes (Koniaris, Drimala, Sotiriou, & Papatheodoropoulos, 2011) and decreased and/or delayed REM (Feinberg et al., 2000; Brunner et al., 1991). SO is associated with robust increases in SWS but decreases in sleep spindle density (Walsh et al., 2010). We selected doses of ZOL (10 mg) and SO (2.5 g) based on a pilot dose-response study (Mednick et al., 2013). The nap took place at 9 a.m. to capitalize on circadian fluctuations, which allowed us to maximize differences in sleep stages between the two drug conditions and the placebo (PBO) condition. We expected to find that naps with SO would show increased SWS and decreased sleep spindle density relative to PBO, whereas naps with ZOL would show both increased SWS and increased sleep spindle density and decreased REM sleep compared with PBO. Regarding the interaction with sleep and memory, we hypothesized that increased Stage 2 spindles with ZOL would promote emotional memory consolidation, whereas the decreased Stage 2 spindles with SO would not facilitate emotional memory, compared with PBO.

METHODS

Participants

Thirty (15 women, 15 men) undergraduates served as participants between the ages of 18 and 39 years; all were

normal sleepers who habitually obtained approximately 8 hr of sleep each night, were free of neurological and psychiatric disorders, and gave informed consent to participate in the experiment after viewing several aversive and appetitive pictures. Two women declined to participate in the memory task after learning that they would be seeing aversive images, leading to the uneven participant split of 15 men and 13 women. The experiment was approved by the institutional review board of the University of California, San Diego.

Drugs

ZOL is a positive allosteric modulator of $GABA_A$ receptors with a short half-life (1.5–4.5 hr) and rapid onset (mean T_{max} = 1.6 hr; Farrant & Nusser, 2005; Drover, 2004). SO is a GABA agonist acting via $GABA_B$ receptors with a half-life of 30–60 min and reaches peak plasma level at 45–120 min. Although SO also binds to γ-hydroxybutarate receptors, this pharmacological property is not thought to contribute to the effects on sleep (Andriamampandry et al., 2007; Kaupmann et al., 2003).

General Procedure

In this within-subject, cross-over design, all participants completed three study days, one for each drug (PBO, SO, and ZOL). The order of the drugs was counterbalanced across participants. Each study day was separated by 5–10 days to allow for drug washout and a recovery from any sleep changes related to the nap and/or study drugs. For the full period of the study, participants wore an actigraph and completed daily sleep diaries to document sleep–wake schedules. These diaries documented participants' adherence to the agreed-upon sleep/wake schedule (corresponding as closely as possible to their habitual sleep/wake schedule) through the remainder of the study. For 48 hr before and including study days, participants were asked to refrain from alcohol, caffeine, and all stimulants because these three factors can affect sleep patterns and the ability to nap. Starting the prohibition 48 hr early also minimized the chance of active caffeine withdrawals during the study although moderate-to-heavy caffeine users (>200 mg/day) who are most likely to experience significant withdrawal symptoms were not enrolled.

Figure 1 shows the progression of the participants' day. After a night of sleep with polysomnography (PSG) monitoring, participants were awakened at 5 a.m. and given breakfast. Cognitive testing took place at 6 a.m. At 8:30 a.m., participants went back to their beds for an electrode check and nap. Drugs were administered immediately before lights out (2.5 g of SO, 10 mg of ZOL, PBO). This timing was chosen as the best method for establishing a uniform measure of sleep latency (SL). The nap took place at 9 a.m. The participants were fully in bed with PSG monitoring and drug administered to capitalize on circadian fluctuations in REM sleep (highest in the morning). This allowed us to maximize differences in sleep stages between the drug and PBO conditions. Morning naps with PBO should be relatively rich in REM. With ZOL, sleep spindles and SWS should be enhanced and REM should be diminished compared with PBO; whereas with SO, SWS should be enhanced and sleep spindles should be diminished compared with PBO. Participants were allowed to sleep for up to 2 hr in bed or until they achieved 90 min of sleep. Sleep was scored online to ensure that all participants had the same total sleep time (TST; Mednick, Nakayama, & Stickgold, 2003). Questionnaires administered after each nap measured mood. Participants were continuously monitored during the hours between the nap and the second test session (3 p.m.). They were allowed to watch TV, eat lunch, shower, read, and work on the laboratory computer. Subjective sleepiness was measured five times during the day (6 a.m., 7 a.m., 10:30 a.m., 3 p.m., and 4 p.m.) using the Karolinska Sleepiness Scale. Testing took place at 3 p.m. to allow for the drug to wash out completely before cognitive testing. Participants were sent home around 4 p.m.

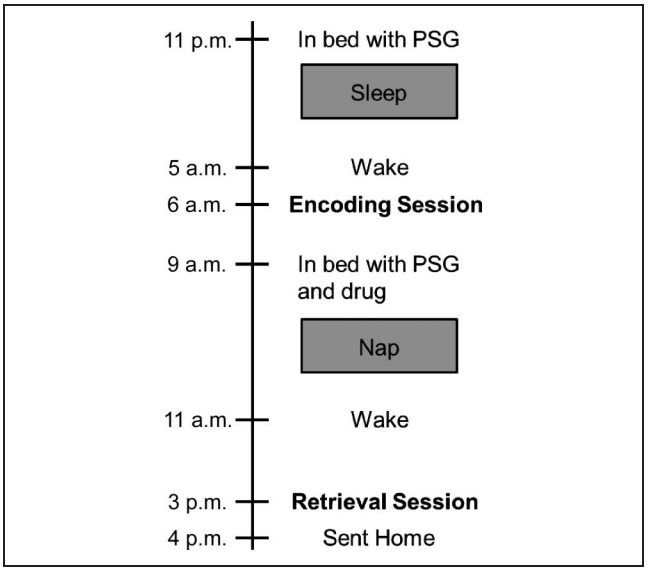

Figure 1. Experimental procedure.

PSG

PSG included standard EEG, EOG, and EMG measures for recording sleep. On the first experimental night, PSG recordings identified sleep apnea and periodic limb movements to exclude participants with these disorders. Sleep was visually scored in 30-sec epochs according to Rechtschaffen and Kales' sleep staging criteria (Rechtschaffen & Kales, 1968). The variables examined from these PSG data were minutes of Stage 1, Stage 2, SWS, and REM as well as TST, SL, wake-after-sleep onset (WASO), and nap sleep efficiency (SE). Sleep spindles were visually scored

for both C3 (left hemisphere) and C4 (right hemisphere), and sleep spindle densities for C3 and C4 were calculated as the number of spindles in Stage 2 divided by the minutes of Stage 2.

Stimuli

Figure 2 illustrates the distribution of the visual stimuli's ratings on the International Affective Picture System scale (1–9) for valence (*x* axis) and arousal (*y* axis). Selections were made such that 120 pictures were chosen for each of five stimulus sets: four emotional sets (negative and positive stimuli, each divided into high- and low-arousal stimuli) and one neutral-valence, low-arousal set, for an overall total of 600 stimuli. The 120 pictures per emotional set were split into three groups of 40, one for each of the three drug conditions. The three groups were counterbalanced across the drug conditions. These 40 pictures were then randomly split into 20 targets and 20 foils.

Recognition Memory Procedure

Emotional memory testing consisted of two phases: an encoding phase and a retrieval phase. Participants slept overnight in the laboratory and were awakened at 5 a.m. They underwent training on the encoding phase of the emotional memory task between 6 and 8 a.m. During the encoding phase, participants saw one of the three possible sequences, one sequence for each study day counterbalanced between participants. They viewed 100 target images (20 from each stimuli group) for 1000 msec each with an ITI of 1000 msec and were instructed to watch while discriminating whether the scene being viewed was indoors or outdoors to ensure attention to the stimuli. Participants were informed that there would be a memory test later.

After the morning training, the participants were taken to bed, the PSG was reconnected, and one of the three drugs was administered. The participants then took a nap beginning at 9 a.m. and were awakened at 11 a.m. (see Results for sleep characterization). The retrieval phase took place between 3 and 4 p.m.

During the retrieval phase, participants saw the same 100 target pictures randomly rearranged and intermixed with the 100 foil pictures. Each picture was displayed for 1000 msec followed by a response prompt asking whether the picture had been seen previously. This recognition decision was made using a standard 6-point confidence scale: "very certain old," "moderately certain old," "not very certain old," "not very certain new," "moderately certain new," "very certain new." There was no response deadline. Before taking the recognition test, participants were given a practice test involving unrelated stimuli to ensure that the instructions were understood. All stimuli were 20 × 15 cm, centrally displayed on a black background at a normal luminance level on a computer monitor.

Old/new recognition memory performance is often quantified using two standard measures based on signal-detection theory. One measure quantifies the ability to discriminate between relevant target and irrelevant foil

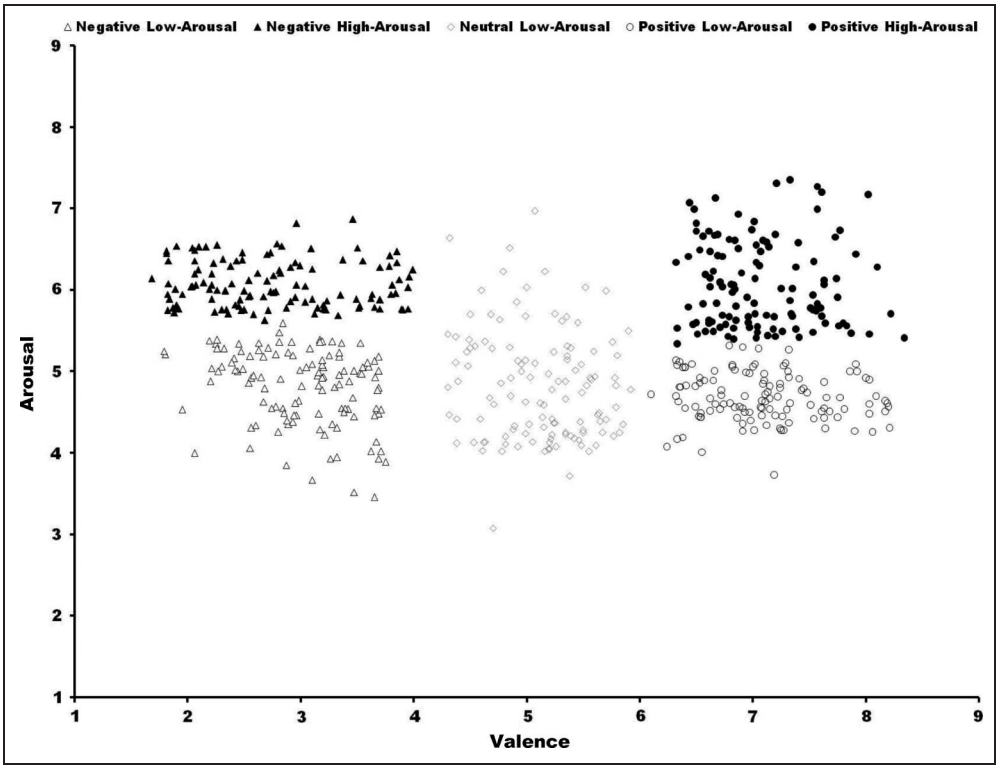

Figure 2. Scatterplot of valence and arousal ratings (scale of 1–9) for International Affective Picture System pictures used in this study. The four emotional groups are low- and high-arousal negative and low- and high-arousal positive, with an additional low-arousal neutral valence group.

stimuli (d'), and the other measure quantifies bias to say "old" or "new" (c). However, several studies have raised concerns about using these measures because they are based on an equal-variance signal-detection model (Grider & Malmberg, 2008; Dougal & Rotello, 2007). Much evidence suggests that recognition memory is better described by an unequal-variance signal-detection model (Wixted, 2007). In that case, when different stimulus groups elicit different response biases, d' may not successfully correct for these differences. Given that different emotional groupings typically do elicit different response biases (Kaestner & Polich, 2011; Dougal & Rotello, 2007), participants were asked to rate their confidence for each recognition decision, thereby allowing for the calculation of the more appropriate d_a and c_a performance measures and the inspection of the receiver operating characteristic (ROC) curve (see Grider & Malmberg, 2008, for equations used).

Analysis

All statistical tests were two-tailed, and the alpha level used was 0.05, unless otherwise noted. We used a repeated-measures ANOVA and a priori t tests to test differences in sleep and memory performance across conditions, and we used Pearson's r correlations to relate performance measures to spindle features (i.e., density, frequency, and amplitude). Nap questionnaires, administered after each nap, measured subjective nap experience, drug effects, and mood. For these variables, repeated-measure ANOVAs were used to test for differences across drug conditions. Variables for the experimental nap included sleep architecture (i.e., Stage 1; Stage 2; SWS; REM; TST; SL; SE; spindle densities of C3, C4, and combined). A one-way ANOVA (across the three drug conditions) was run on all the measured sleep effects to test for the main effects of drug on sleep. Any significant differences were then further investigated using a priori t tests of PBO versus SO and PBO versus ZOL.

Analysis of spindle features was conducted in BrainVision Analyzer 2.0, following Wamsley et al. (2012). Spindle amplitude and frequency were quantified based on analysis of 2-sec EEG epochs centered on the point at which each spindle was manually marked. The amplitude of a spindle was defined as the maximal voltage in this 2-sec window following 12- to 15-Hz band-pass filtering. The peak frequency of a spindle was defined as the frequency in the 11- to 16-Hz range showing maximal power spectral density (μV^2/Hz) following FFT decomposition. Spindles with a peak frequency below 13.5 Hz were classified as "slow" spindles, whereas spindles with a peak frequency above 13.5 Hz were classified as "fast." For each participant, we computed the average spindle density and amplitude, separately for fast and slow spindles (Wamsley et al., 2012; Schabus et al., 2007; De Gennaro & Ferrara, 2003).

All the behavioral dependent measures, "hit rate," "false alarm rate," d_a, and c_a, were analyzed the same way. First, differences between emotional stimuli groups were tested with a three-way ANOVA (3 Drug × 2 Valence × 2 Arousal). If drug interactions were found, a priori t tests for PBO versus SO and PBO versus ZOL were performed. Additionally, within-drug a priori t tests (i.e., high-arousal PBO vs. low-arousal PBO) were performed. The neutral stimuli group was analyzed with two two-way ANOVAs (3 Drugs × 3 Valence), one ANOVA comparing it with the two low-arousal emotional stimuli groups (matched based on arousal level) and one ANOVA comparing it with the two high-arousal emotional stimuli groups (classical "emotional vs. neutral" analysis). A priori t tests comparing neutral with negative and neutral with positive stimuli were used in the event when a significant effect of valence was found. Furthermore, partial η^2 values were calculated to ascertain measures of effect size for significant ANOVA outcomes. All non–a priori t tests were controlled for multiple comparisons by Bonferonni corrections when examining the interaction effects identified by the ANOVAs.

Four participants displayed inappropriate confidence estimate responding (i.e., they predominantly used the "very certain old" and "very certain new" responses). These participants' data were included in the calculations of hit rates and false alarms because their responses were adequate to ascertain these measures. But because it is impossible to calculate their d_a and c_a without a larger range of confidence ratings, they were excluded from analyses based on those two measures.

RESULTS

Sleep Effects

Table 1 contains the quantitative values for the measured sleep features. We began by examining how the drugs affected the common measures of sleep characteristics (namely, minutes of Stage 1, Stage 2, SWS, REM, and sleep spindle densities for C3 and C4 as well as TST, SL, WASO, and SE. As expected, there was a significant effect of Drug on SWS [$F(2, 54) = 9.31$, $p < .001$] with both SO [$t(27) = -2.85$, $p = .008$] and ZOL [$t(27) = -4.26$, $p < .001$] producing more minutes of SWS than PBO. There was also a trend of Drug on REM sleep [$F(2, 54) = 2.86$, $p = .052$] with REM being reduced in ZOL compared with PBO [$t(27) = 2.59$, $p = .015$] but not reduced in SO compared with PBO [$t(27) = 1.42$, $p = .16$]. Finally, Drug had a main effect on Stage 1 sleep [$F(2, 52) = 4.34$, $p = .017$]. SO had a lower number of Stage 1 minutes than PBO [$t(27) = 3.08$, $p = .004$], but no significant difference was found for ZOL versus PBO [$t(27) = 0.19$, $p = .84$]. No other sleep stages were different from PBO (all ps $> .46$).

We also investigated how these drugs affected sleep spindle density. Because sleep spindle density was measured in both the left (C3) and right (C4) hemispheres, we first performed a 3 × 2 ANOVA (3 Drugs × 2 Hemisphere) on

Table 1. Mean (Standard Deviation) of Sleep Features for the Three Drug Conditions

	PBO	*Sodium Oxybate*	*ZOL*	*One-way ANOVA*
TST (minutes)	91.5 (21.1)	91.1 (15.1)	92.8 (8.1)	$F(2, 52) = 0.08$
				$p = .91$
SL (minutes)	9.75 (8.3)	9.61 (5.8)	10.59 (7.3)	$F(2, 52) = 0.33$
				$p = .71$
SE	77.49 (20.2)	79.17 (14.6)	79.82 (11.3)	$F(2, 52) = 0.21$
				$p = .81$
WASO	18.36 (23.7)	14.74 (15.3)	13.84 (16.8)	$F(2, 52) = 0.56$
				$p = .56$
Stage 1 sleep (minutes)	8.51 (5.0)	5.82 (2.7)	8.29 (5.4)	$F(2, 52) = 4.34$
				$p = .02$
Stage 2 sleep (minutes)	43.83 (13.9)	40.50 (15.2)	38.88 (16.1)	$F(2, 52) = 0.77$
				$p = .46$
SWS (minutes)	8.66 (7.6)	18.47 (16.8)	23.14 (17.3)	$F(2, 52) = 9.28$
				$p < .001$
REM sleep (minutes)	30.51 (13.6)	26.28 (14.8)	22.48 (14.7)	$F(2, 52) = 2.86$
				$p = .052$
Spindle density	2.67 (1.58)	1.93 (1.24)	3.23 (1.38)	$F(2, 54) = 13.18$
				$p < .001$

The p-values are from the one-way ANOVA. Significant drug interaction effects were investigated using a priori t tests between drug (SO and ZOL) and PBO.

the sleep spindle data. This test revealed no Hemisphere interaction ($p = .67$), so we averaged the C3 and C4 spindle density data and found a significant difference for Drug [$F(2, 54) = 13.18, p < .001$]. ZOL increased sleep spindle density compared with PBO [$t(27) = 2.2, p = .038$], whereas SO decreased sleep spindle density compared with PBO [$t(27) = -3.4, p = .002$]. In summary, as hypothesized, SO increased SWS but decreased sleep spindle density and Stage 1 sleep compared with PBO, whereas ZOL increased SWS and sleep spindle density as well as a trend toward decreased REM sleep compared with PBO.

Next, we asked whether, in addition to changing spindle density, the drugs also affected spindle morphology relative to PBO. For morphology, we examined the frequency and amplitude of fast, slow, and combined sleep spindles (see Table 2 for quantitative values). First, we tested for hemispheric differences in a 3 × 2 ANOVA (3 Drug × 2 Hemisphere) performed for frequency and a 3 × 2 × 2 ANOVA (3 Drug × 2 Hemisphere × 2 Speed) performed for amplitude and density. There was no frequency Drug × Hemisphere interaction ($p = .20$) nor was there a Drug main effect ($p = .09$). In addition, there were no Amplitude × Hemisphere interactions (all ps > .18) nor were there any Speed interactions (all ps > .18). The lack of Hemisphere interactions allowed us to average the C3 and C4 spindle amplitude data. Although there were no drug interactions, ZOL had a small but significant decrease in sleep spindle amplitude compared with PBO [$F(2, 46) = 7.49, p = .001$].

In addition, we tested whether the drug interventions differentially affected fast and slow spindle densities. There were no Density × Hemisphere interactions (all ps > .24) or Spindle × Speed interactions (all ps > .24). ZOL produced a trend toward greater density than PBO for fast [$t(24) = -1.88, p = .07$] and slow [$t(24) = -1.81, p = .08$] spindles, whereas SO produced less density than PBO for fast [$t(24) = 2.76, p = .01$] and slow [$t(24) = 2.08, p = .04$] spindles. The lack of interactions in these additional analyses and similar relationships for fast and slow sleep spindle densities between drugs and PBO suggest that the drugs did not alter the quality of the sleep spindles beyond a small but significant decrease in spindle amplitude for ZOL compared with PBO.

Emotional Memory

Discriminability (d_a)

To determine if the drug interventions differentially affected emotional memory, we examined d_a interaction

Table 2. Mean (Standard Deviation) of Sleep Spindle Characteristics for the Three Drug Conditions

	PBO	*Sodium Oxybate*	*ZOL*	*One-way ANOVA*
Spindle frequency	13.53 (0.5)	13.44 (0.5)	13.42 (0.5)	$F(2, 52) = 2.41$
				$p = .09$
Fast spindle density	1.78 (1.4)	1.46 (1.2)	2.35 (1.5)	$F(2, 48) = 7.05$
				$p = .002$
Slow spindle density	0.98 (0.9)	0.77 (0.6)	1.55 (1.7)	$F(2, 48) = 4.64$
				$p = .01$
Fast spindle amplitude	16.03 (2.7)	16.7 (2.5)	15.46 (2.6)	$F(2, 46) = 4.93$
				$p = .01$
Slow spindle amplitude	16.79 (2.3)	17.12 (2.2)	15.9 (2.1)	$F(2, 52) = 8.17$
				$p < .001$

The *p*-values are from a one-way ANOVA. Significant drug interaction effects were investigated using a priori *t* tests between drug (SO and ZOL) and PBO.

terms between drug conditions and each stimulus type (i.e., negative and positive valence, and high and low arousal). Two interactions with the drug condition emerged: Drugs × Valence [$F(2, 46) = 3.4, p = .041$] and Drugs × Arousal [$F(2, 46) = 3.5, p = .036$]. These interactions were investigated by a priori *t* tests for d_a performance between SO and PBO, between ZOL and PBO, and also between valence/arousal stimulus type within each drug condition. For the valence interaction, d_a was greater for the negative stimuli in ZOL compared with PBO ($t = 3.05, p = .005$) but not for the negative stimuli in SO compared with PBO ($p > .24$). Positive stimuli did not show a difference between either drug and PBO (both ps $> .58$). Furthermore, negative stimuli d_a was greater than positive stimuli d_a during ZOL ($t = 2.7, p = .01$) but not during PBO or SO (both ps $> .15$; Figure 3). For the arousal interaction, ZOL produced increased d_a for high-arousal stimuli during ZOL compared with PBO ($t = 3.08, p = .005$) but not between SO compared with PBO ($p > .17$; Figure 4). Low-arousal stimuli did not show a difference between ZOL and PBO or between SO and PBO (both ps $> .42$). In summary, there were increases in memory for negative and high-arousal stimuli in ZOL compared with PBO that were not present in SO compared with PBO.

To investigate if sleep features correlated with emotional memory, we examined correlations between sleep spindle density and both negative d_a scores and high-arousal d_a scores (the stimulus classes that showed significant interactions in our primary analysis). The results showed that d_a was significantly positively correlated with sleep spindle density in SO for both negative ($p = .03$) and high-arousal ($p = .02$) emotional memory, but not in ZOL (both ps $> .39$) or PBO (both ps $> .42$). As a comparison, we ran correlations for positive and low-

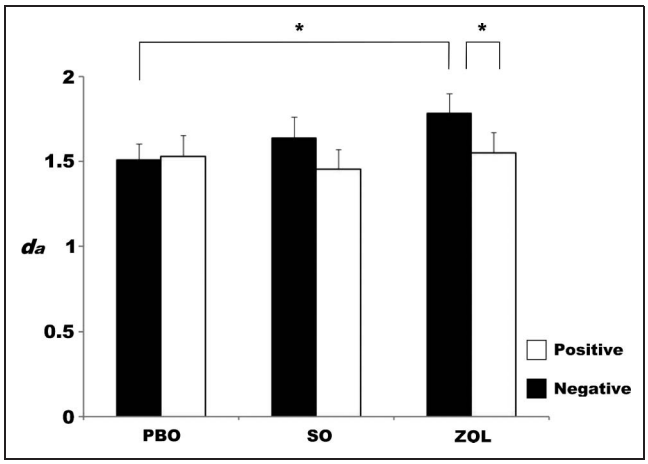

Figure 3. Behavioral d_a for negative and positive pictures for the PBO, SO, and ZOL drug conditions. *$p < .05$. Differences reflect a priori *t* tests between drug (SO and ZOL) and PBO and between negative and positive within-drug conditions.

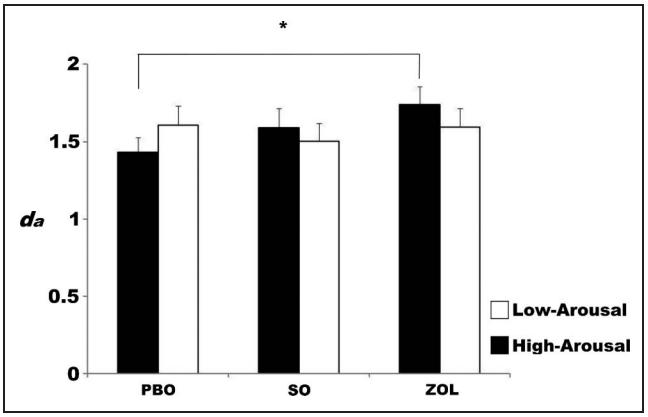

Figure 4. Behavioral d_a for low- and high-arousal pictures for the PBO, SO, and ZOL drug conditions. *$p < .05$. Differences reflect a priori *t* tests between drug (SO and ZOL) and PBO and between low- and high-arousal within-drug conditions.

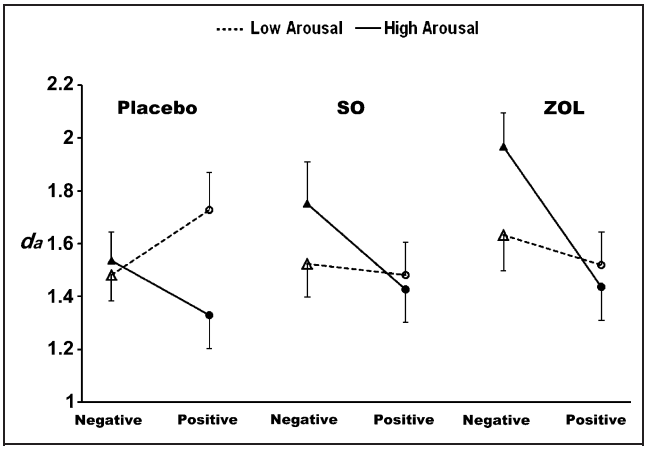

Figure 5. Behavioral d_a in terms of the four emotional groupings (negative and positive and low- and high-arousal) displayed for PBO, SO, and ZOL drug conditions (see Table 3 for ANOVAs).

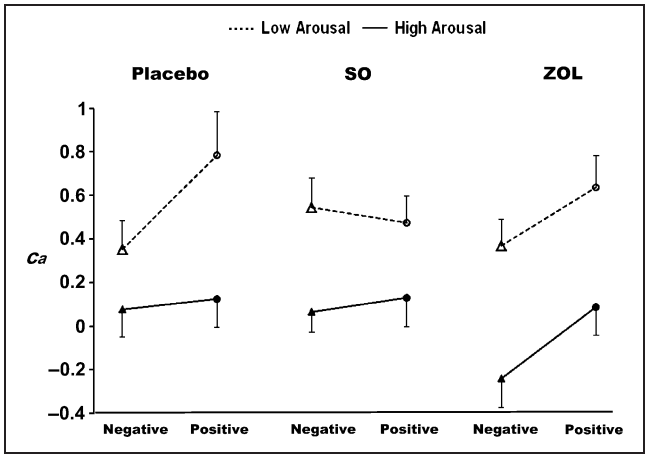

Figure 6. Behavioral c_a in terms of the four emotional groups (negative and positive, low- and high-arousal) displayed for PBO, SO, and ZOL drug conditions (see Table 3 for ANOVAs).

arousal d_a with sleep spindle density in the three drug conditions, but none of these correlations were significant (all ps $> .22$). We also examined correlations between minutes of each sleep stage (Stage 1, Stage 2, SWS, and REM) with these d_a scores. For the four sleep stages, we found three significant correlations. First, Stage 2 minutes during SO correlated positively with negative memory performance ($p = .021$) and also positively correlated with low-arousal memory ($p = .01$), related to prior findings of a correlation between Stage 2 and declarative memory (Van der Helm, Gujar, Nishida, & Walker, 2011). Low-arousal memory correlated negatively with REM sleep minutes ($p = .012$) during SO, which we will elaborate on in the Discussion. Correlations were also run between sleep spindle amplitude and d_a to investigate if the change in morphology was associated with memory effects, but no significant correlations were found (all ps $> .24$).

To characterize emotional memory components that were independent of sleep (i.e., significant effects not involving an interaction with drug condition), we investigated d_a effects identified in the ANOVA, collapsing across drug conditions. d_a was greater for negative high-arousal stimuli than for positive high-arousal stimuli, but no significant difference was observed between negative and positive low-arousal stimuli [Arousal × Valence; $F(2, 46) = 8.4$, $p = .008$].

Exploring the relationship between neutral stimuli and both high- and low-arousal emotional groups revealed that neutral stimuli demonstrated a higher d_a than the negative and positive low-arousal stimuli [$F(2, 46) = 7.1$, $p = .001$]. Neutral stimuli also elicited a greater d_a relative to positive high-arousal stimuli [$F(2, 46) = 13.1$, $p < .001$]. It is notable that neutral stimuli outperformed all emotional groups except negative high-arousal stimuli. The neutral stimuli did not show any drug interactions for their comparison with low-arousal and high-arousal stimuli.

Figure 5 illustrates the mean (+*SEM*) of d_a.

Table 3. Summaries of the Three-factor (3 Drug × 2 Valence × 2 Arousal) Repeated-Measures ANOVA Applied to the Four Behavioral Dependent Measures

	Hit Rate		*False Alarm Rate*			d_a		c_a	
	F	*Partial* η^2	*F*	*Partial* η^2		*F*	*Partial* η^2	*F*	*Partial* η^2
Drugs (2,54)	3.073^t	0.101^t	–	–	(2,46)	–	–	–	–
Valence (1,27)	8.461	0.232	–	–	(1,23)	–	–	4.603	0.166
Arousal (1,27)	14.018	0.341	45.402	.621	(1,23)	–	–	40.243	0.636
D × V (2,54)	–	–	–	–	(2,46)	3.409	0.129	–	–
D × A (2,54)	3.877	0.125	–	–	(2,46)	3.564	0.134	–	–
V × A (1,27)	5.495	0.167	6.975	.203	(1,23)	8.400	0.267	–	–
D × V × A (2,54)	–	–	–	–	(2,46)	–	–	–	–

All F values are $p < .05$; unless noted by a t, then $p < .06$. The partial η^2 indexes the proportion of variance account by each factor. Significant drug interaction effects were investigated using a priori t tests between drug (SO and ZOL) and PBO. D = drugs; V = valence; A = arousal.

Table 4. Summaries of the Two-factor (3 Valence × 3 Drug) Repeated-Measures ANOVA Applied to the Four Behavioral Dependent Measures

	Hit Rate		*False Alarm Rate*			d_a		C_a	
	F	*Partial* η^2	*F*	*Partial* η^2		*F*	*Partial* η^2	*F*	*Partial* η^2
Low Arousal × Neutral									
Valence (2,54)	9.944	.269	3.589	.117	(2,46)	7.169	.237	–	–
D × V (4,108)	–	–	–	–	(4,92)	–	–	–	–
High Arousal × Neutral									
Valence (2,54)	–	–	30.946	.534	(2,46)	13.127	.363	17.794	.438
D × V (4,108)	–	–	–	–	(4,92)	–	–	–	–

All *F* values are $p < .05$. The partial η^2 indexes the proportion of variance accounted by each factor. No drug effects were found, so they are not on the table.

Response Bias (c_a)

To determine if the drug interventions differentially affected response bias, we examined c_a interaction terms between drug conditions and each stimulus type (i.e., negative and positive valence and high and low arousal). No interactions were found (all ps $> .13$). Next, we examined whether alterations in response bias across the different stimulus groups could underlie the changes reported in memory. c_a was greater (more conservative) for positive stimuli relative to negative stimuli [$F(1, 23) = 4.6, p = .04$]. Low-arousal stimuli were associated with a greater c_a (more conservative) relative to high-arousal stimuli [$F(1, 23) = 40.2, p < .001$].

Neutral low-arousal stimuli did not differ from either emotional low-arousal stimuli in c_a, but neutral stimuli did have a greater c_a (more conservative) than positive and negative high-arousal stimuli [$F(2, 46) = 17.9, p < .001$). This is an interesting finding, demonstrating that measured bias is strongly affected by differences in arousal and less so by differences in valence.

Figure 6 illustrates the mean (+*SEM*) of c_a (response bias).

Hit Rates and False Alarm Rates

To provide a comparison with studies that rely on hits and false alarms for behavioral measures, we have included ANOVAs performed on these dependent measures in Tables 3 and 4. Additionally, Figure 7 displays the ROC curves for the data, a method for visualizing d_a and c_a based on hit rates and false alarms.

Mood

To assess the impact of drugs on mood and, thus, how the drugs might affect emotional memory, we measured mood after the administration of each drug. We found no significant differences for sadness [$F(2, 24) = 1.32, p > .27$], happiness [$F(2, 24) = 0.49, p > .61$], calmness [$F(2, 24) = 0.08, p > .91$], anxiousness [$F(2, 24) = 2.07, p > .13$], relaxedness [$F(2, 24) = 0.07, p > .92$], stress [$F(2, 24) = 0.16, p > .84$], or irritation [$F(2, 24) = 0.46, p > .63$].

DISCUSSION

We show that memory can be experimentally biased toward negative and highly arousing stimuli after a sleep period with pharmacologically elevated sleep spindles. Specifically, compared with PBO, naps with ZOL were associated with enhanced memory performance for both negative and high-arousal stimuli. By contrast, SO (a comparison hypnotic) did not affect memory for different classes of emotional stimuli. Why did ZOL (but not SO) have these effects? Both hypnotics elevated time spent in SWS sleep (and ZOL marginally decreased time spent in REM sleep), but they had opposite effects on sleep spindle density. Specifically, ZOL increased spindle density, whereas SO decreased spindle density. Thus, the enhanced memory performance for ZOL relative to PBO was more likely related to the increased spindle density than to changes in the duration of SWS or REM sleep. These results suggest that sleep spindles may be critical for the consolidation of negative and high-arousal memories.

Several caveats warrant consideration. First, small changes in spindle morphology, specifically a reduced spindle amplitude in the ZOL condition relative to PBO, were also found. However, spindle amplitude was not correlated with performance measures in the current study. This suggests that the amplitude differences may not have played an important role in the current findings. Second, the current study focused on Stage 2 sleep spindles, whereas sleep spindles in the rest of NREM sleep may also be important for emotional memory consolidation. Spindles in deeper stages of NREM sleep are optimally detected using frontal EEG sites (Cox, Hofman, &

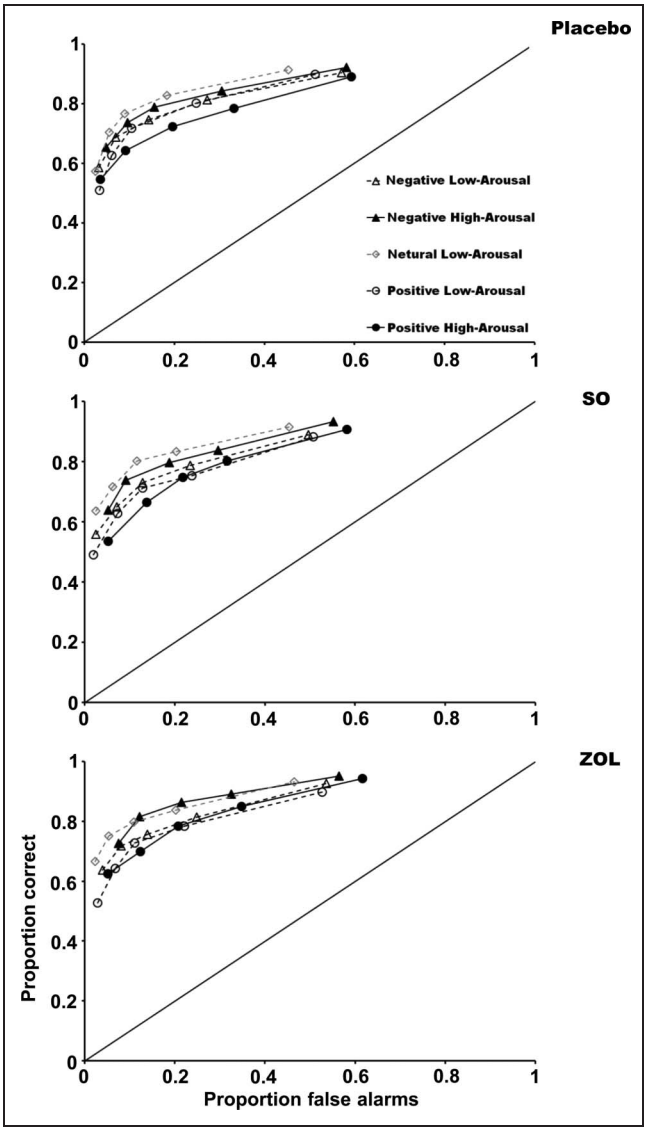

Figure 7. ROC graphs. The four emotional groups and the neutral group are displayed. Each point on the ROC represents the false alarm rate and hit rate at a particular confidence level, with points to the left representing "sure old" and each subsequent point to the right being cumulative for the less-certain confidence levels. The bolded line represents the "guessing line," from (0,0) to (1,1), with ROCs above and to the left of the line representing above-chance performance. The ROC curves closest to the top left have the higher d_a, (higher ability to distinguish between targets and foils), and operating points falling further to the right on a curve have lower c_a.

Talamini, 2012; Mölle, Bergmann, Marshall, & Born, 2011), and the current study employed electrodes at C3 and C4 positions. Thus, we limited our analyses to spindles from Stage 2 sleep. Third, spindle density was correlated with negative and high-arousal memory during SO but not PBO or ZOL. This discrepancy may be indicative of a ceiling effect in spindles in the PBO and ZOL conditions, whereas decreases in spindles in the SO condition produced greater range of spindles leading to a significant correlation with memory performance. An interesting test of this hypothesis would be to examine the relationship between emotional memory and spindles in populations that show decreased spindles such as in older adults (Pace-Schott & Spencer, 2011) and people with schizophrenia (Wamsley et al., 2012). In these populations, we hypothesize that stronger correlations would also be found.

It is possible that the drug effect on memory may have been mediated by a different mechanism than sleep spindles. For example, the memory benefits could have been because of changes in mood caused by ZOL (Hart, Ward, Haney, & Foltin, 2003; but see Dockhorn & Dockhorn, 1996). However, no differences were found in mood across conditions. In addition, TST and other measures of sleep were consistent across each drug manipulation, suggesting that these sleep features were not directly mediating the memory changes. Furthermore, all drug conditions contained sleep during offline consolidation. Thus, although it seems unlikely to us, it is possible that ZOL would have enhanced memory even if participants had remained awake. Finally, there was a decrease in Stage 1 sleep for SO but not for ZOL relative to PBO. Although Stage 1 sleep has been related to visual imagery after playing a video game (Stickgold, Malia, Maguire, Roddenberry, & O'Connor, 2000), we are unaware of further studies linking it to memory, and it did not correlate with measures of memory in this study. These considerations will be important in the future exploration of this topic.

Focusing on memory, using both a wide spread of emotional stimuli and sensitive recognition memory measures, our findings replicated prior emotional memory findings. Collapsing behavioral outcomes across all three drug conditions showed that negative stimuli had a more liberal c_a than positive stimuli and highly arousing stimuli had a more liberal c_a than low-arousal stimuli. However, there was a dissociation of high-arousal stimuli d_a, with negative high-arousal stimuli outperforming positive high-arousal stimuli. These findings relate to a presumed negativity bias (Carretié, Mercado, Tapia, & Hinojosa, 2001).

In the majority of emotional memory studies both including sleep and not, the emotional stimuli (typically high-arousal negative stimuli) outperform the neutral group on behavioral measures of memory (Kensinger, 2009). However, this is not true in every study (Dougal & Rotello, 2007; Sharot & Phelps, 2004; Ochsner, 2000). Here, although the neutral stimuli showed comparable outcomes to the negative high-arousal stimuli (the classical comparison), they showed greater memory performance than the other emotional groups.

Theoretical Implications

The behavioral differences between negative and positive and low- and high-arousal stimuli in this study highlight a growing literature regarding the neural separation of arousal and valence. Highly arousing stimuli increase

amygdala activity, modulating memory and attention through connections to the visual processing stream (Lane, Chua, & Dolan, 1999), hippocampus (Kensinger & Corkin, 2004), and medial prefrontal and orbitofronal cortex (Kringelbach, 2005; Dolan & Morris, 2000). But for low-arousal stimuli, the amygdala is not correlated with memory performance (Kensinger & Corkin, 2004). Positive stimuli show fMRI activity in the nucleus accumbens and medial pFC (Costa, Lang, Sabatinelli, Versace, & Bradley, 2010), whereas negative items activate the inferior frontal gyrus and the middle occipital gyrus (Mickley-Steinmetz, Addis, & Kensinger, 2010). Furthermore, data from Baran and colleagues suggest independent pathways for memory and emotional reactivity (i.e., arousal) and that sleep contributes to each process in different ways (Baran et al., 2012). In this study, we found several dissociations based on valence/arousal differences. For example, both negative and positive high-arousal stimuli exhibited a liberal bias associated with increased arousal. However, negative high-arousal stimuli had a superior d_a relative to positive high-arousal stimuli. This suggests different causes for the liberal high-arousal memory bias and for the memory benefit enjoyed by negative high-arousal stimuli. Taken together with our findings of a selective enhancement of memory for ZOL compared with PBO, these data suggest that sleep interacts with both the valence and arousal pathways when facilitating emotional memory consolidation. Continuing efforts to elucidate these neural and behavioral dissociations based on valence/arousal is critical to understand precisely how offline consolidation is affected by emotional stimuli.

With regards to sleep and emotional memory, past studies have focused on REM sleep. Studies reported that increases in emotional memory were correlated with prefrontal theta during REM sleep (Nishida et al., 2009) and that disrupting early night (SWS-rich) sleep but leaving late-night (REM-rich sleep) intact disrupted memory for nonemotional but not emotional stimuli (Wagner et al., 2001). Walker and van der Helm (Walker & Van der Helm, 2009) introduced a model suggesting a reciprocal relationship between the strengthening of declarative emotional memories and the weakening of the emotionally arousing aspects of the memory and suggest that this process occurs during REM sleep. Interestingly, Baran and colleagues (Baran et al., 2012) experimentally dissociated emotional memory and emotional arousal by examining negative and neutral memories that varied in arousal. In contrast with prior studies, they found an equal benefit of sleep for both emotional and nonemotional memories and no correlation between memory performance and arousal levels and that REM sleep correlated with emotional arousal rather than memory improvement. These results suggest that sleep's effect on emotional memory and emotional arousal may be independent. Similarly, the benefit of sleep did not differ between declarative memory for neutral and negative contexts (Lewis et al., 2011). In our study, the drug condition that showed enhanced emotional memory compared with PBO produced less REM sleep than PBO. Furthermore, REM did not correlate with memory for high-arousal or negative stimuli similar to the lack of correlation with memory measures in the Baran study. However, REM did correlate negatively with memory for low-arousal memory. Taken together, sleep spindles and REM sleep might contribute to the consolidation of emotional memory in different ways. Reconciling Walker's model and Baran's findings, we hypothesize that sleep may process emotional memories and emotional arousal independently through spindles and REM sleep, respectively. An interventional approach to determine the role of these specific sleep stages on emotional memory is recommended in future investigations.

Spindles have been suggested to be an important feature in the transfer of recent memories from the hippocampus to cortical long-term memory stores, that is, "neural replay." Findings in support of neural replay are based on rodent studies showing that the sequence of place cell activity measured during a learning episode tends to fire in a similar sequence during sleep (Ji & Wilson, 2007). Studies have shown the following: (1) Hippocampal replay during NREM sleep (Stage 2 and SWS) in rats is coordinated with firing patterns in the visual cortex (Ji & Wilson, 2007), (2) the hippocampus and cortex appear to communicate during sleep by means of hippocampal sharp waves or ripple (Buzsáki, 1989) during which place cells are reactivated (Diba & Buzsáki, 2007), and (3) these events are temporally correlated with sleep spindles in the medial pFC during NREM sleep (Siapas & Wilson, 1998). Although replay is the leading model for declarative memory consolidation, it has not been implicated in declarative emotional memories, to the best of our knowledge. The lack of research in this area is surprising given that consolidation of hippocampal-dependent, emotional memories does appear to rely on sleep (Hagewoud, Bultsma, Barf, Koolhaas, & Meerlo, 2011; Graves, Heller, Pack, & Abel, 2003).

Finally, we note that there may be broader implications of our finding that emotional memory for high-arousal and negative stimuli was enhanced after ZOL-rich sleep. These two characteristics, negativity and high arousal, predominate in anxiety disorders with a sleep-disruption component, such as posttraumatic stress disorder (PTSD; Germain, Buysse, & Nofzinger, 2008; Cukrowicz et al., 2006; Gillin, 1998; Ross, Ball, Sullivan, & Caroff, 1989). There is a high prevalence of insomnia in patients with PTSD (Wallace et al., 2011), which often leads to prescriptions for sleeping medication. Despite Veterans Affairs and Department of Defense clinical guidelines recommending against the routine use of benzodiazepines for PTSD, the adjusted prevalence of long-term use of benzodiazepines increased among men and women with PTSD between 2003 and 2010 (Hawkins, Malte, Imel, Saxon, & Kivlahan, 2012). In addition, the U.S. Air Force uses ZOL as one of the prescribed "no-go pills." Because

hypnotics and benzodiazepines produce similar effects on sleep (Mariotti & Ongini, 1983), our findings are relevant to these clinical practices. In light of the present results, it would be worthwhile to investigate whether the administration of benzodiazapine-like drugs may be increasing the retention of highly arousing and negative memories, which would have a countertherapeutic effect. Indeed, a week course of temazepam soon after trauma was not effective in preventing PTSD symptoms, even producing numerically worse outcomes (Mellman, Bustamante, David, & Fins, 2002). Further research on the relationship between hypnotics and emotional mood disorders would seem to be in order.

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