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How does sleep help regulate negative emotion?

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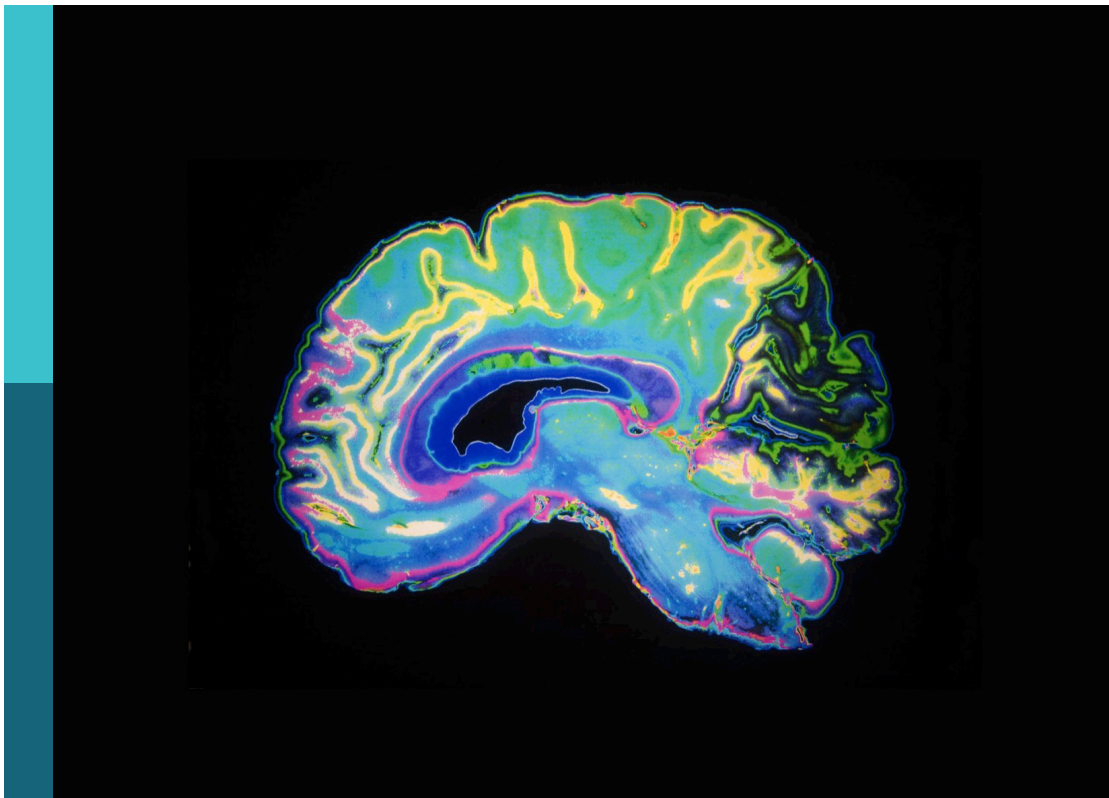

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How does sleep help regulate negative emotion?

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Editorial: How does sleep help regulate negative emotion?

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Editorial on the Research Topic
How does sleep help regulate negative emotion?

Introduction

In this volume, 15 scientific reports give a snapshot of some of the most exciting current research on how sleep helps regulate negative emotion. Articles illustrate state-of-the-art research paradigms from the cognitive, affective, and behavioral neurosciences, sleep medicine, biological psychiatry, and dream research.

Review and meta-analysis

This collection begins with a narrative review of sleep and emotional memory by Cunningham et al. and a meta-analysis of sleep and emotional reactivity by Lipinska et al.. Cunningham et al. focus on the timing of sleep manipulations and assessments in relation to memory encoding. They note that inconsistent findings in the literature may result when different memory processes occurring at different times following encoding confound one another. Both studies emphasize the limitations of empirical findings to date and advocate for increased sophistication, rigor and statistical power in sleep science. Specifically, they note that two tenets of conventional wisdom in sleep science—that sleep preferentially consolidates emotional memories while serving to moderate emotional reactivity—are generally unsupported or supported only under certain conditions.

Nonetheless, both reviews identify certain general findings. Cunningham et al. note that extreme sleep deprivation imposed at all stages of information processing negatively impacts memory, irrespective of whether or not memory holds emotional content (see also Davidson et al., 2021). Similarly, they report that total sleep deprivation (TSD) prior to encoding impairs memory of both emotional and neutral information equally, with the possible exception of aversive memories. Lipinska et al. report overall increases in subjective arousal ratings to negative stimuli following sleep whereas, following TSD, positive stimuli evoke more negative responses. Lipinska et al. also note the dearth of studies employing simple and affordable psychophysiological measures of arousal.

Sleep deprivation studies

Groeger et al. compared responses on the Positive and Negative Affect Scale (PANAS) after 40 h TSD following either a week of sleep-restriction (SR) or sleep-satiated laboratory sleep. They additionally examined changes in PANAS across the course of a forced desynchrony (FD) protocol. Interestingly, they showed larger effect sizes on positive vs. negative mood scales of the PANAS for all three of these sleep manipulations.

Kurinec et al. examined whether changes in electrodermal activity (EDA) during TSD compared to normal sleep correspond to changes in sleepiness, vigilant attention, and affect in a large sample of healthy adults. Skin conductance level (SCL) and rate of spontaneous skin conductance responses (NSSCR) were obtained over a 5-min rest interval. TSD produced expected changes in positive affect, sleepiness, and vigilance, while NSSCR but not SCL decreased following TSD. Neither parameter, however, correlated with any other measurements, suggesting that EDA does not adequately reflect experiences of arousal during either rested wakefulness or TSD.

Sundelin and Holding tracked state anxiety (Spielberger State anxiety index; STAI-S) across two large samples of healthy young adults, one of which underwent a full night's TSD while the other underwent two continuous days of sleep restricted to 4 h. In both, sleep loss resulted in an increase in state anxiety which correlated with trait anxiety (STAI-T). However, trait anxiety did not moderate the relationship between sleep loss and state anxiety suggesting that those with high levels of trait anxiety do not show a proportionately greater effect of sleep loss on state anxiety. These results notably conflict with findings from other published studies (Palmer and Alfano, 2020), highlighting a need for greater investigation of the potential impact of trait anxiety on emotional responses following sleep loss.

Thompson et al. examined interrelationships of inflammatory cytokines and stress hormones with cognition and mood across 24 h of TSD compared to baseline in healthy young adults. TSD resulted in an increase of inflammatory markers (CRP and IL-6) and suppressed the morning cortisol peak. In addition, they found TSD increased reaction time (RT) on some cognitive tasks (without impairing accuracy) and increased negative mood states (Profile of Mood States; POMS) and anxiety (STAI-S).

Targeted memory reactivation

Borghese et al. and Halonen et al. applied targeted memory reactivation (TMR), a cutting-edge experimental paradigm in sleep science (Schouten et al., 2016; Lewis and Bendor, 2019; Hu et al., 2020), to emotional memory. In TMR, specific sensory stimuli (e.g., odor, sounds) are associated with a learning session after which the associated stimulus and/or a control stimulus are presented during sleep. Memory performance is then compared, within- or between-subjects, after waking between sleep presentation of the learning-associated stimulus and its control and is often found superior following the associated stimulus (Hu et al., 2020). The stimuli are typically presented during slow wave sleep (SWS) during which the influential active systems consolidation model (Klinzing et al., 2019) suggests that coupling of specific EEG oscillations facilitate memory consolidation. However, the association of REM sleep with emotion processing has prompted these investigators [and a few others (Hutchison et al., 2021)] to examine the possible use of TMR during REM.

Halonen et al. used an embarrassment-induction procedure (Wassing et al., 2019) with replay of a sound stimulus or sham stimulus during REM or SWS. When tested for overnight habituation using skin-conductance response (SCR), they found no effect of TMR during either stage. However, greater proportion and fragmentation of REM was negatively associated with habituation and this effect was moderated by trait shame proneness.

Borghese et al. similarly used one week of acoustic TMR during REM sleep in persons with social anxiety disorder treated with two virtual reality exposure sessions involving public speaking. The encoding experience paired with replayed stimuli was the positive feedback given to participants after each exposure. Although TMR itself had no effect, having more REM sleep was associated with less anxiety (increased parasympathetic tone) when preparing for a subsequent exposure.

These results concur in finding no effect of TMR during REM (Hu et al., 2020). However, in one case, greater REM was associated with greater anxiety whereas in the other it was associated with less.

Applications to psychiatry

Blue light

In addition to the well-known circadian entrainment function of intrinsically photosensitive retinal ganglion cells, photostimulation of this pathway also affects mood, alertness and cognition (Chellappa et al., 2011; Lazzerini Ospri et al., 2017; Fernandez et al., 2018). Killgore, Vanuk et al. and Vanuk et al. examined the effects of morning blue light treatment compared to an amber light control given over 6-weeks in patients with post-traumatic stress disorder (PTSD). Blue light treatment lengthened sleep relative to the amber control whereas the amber light improved sleep efficiency (Killgore, Vanuk et al.). Structural MRI showed increased amygdala volume in the blue-light group that correlated with decreased nightmare severity. Vanuk et al. showed that the blue light treatment was superior in reducing participants' sleep complaints. Although

both treatments reduced the severity of PTSD symptoms, only in the blue light group did these improvements correlate with improved sleep. Additionally, the blue group better maintained extinction learning at 6 weeks compared to the amber group.

Suicidal ideation

Killgore, Grandner et al. report that the personality trait of extroversion is associated with elevated suicidal ideation in sleep deprived individuals and in those with insomnia. This was seen in both military service members in an extreme sleep deprivation protocol and among those with clinical levels of insomnia in a large community sample. Persons higher on the extroversion scale are more vulnerable to both the subjective and objective effects of sleep deprivation (Killgore et al., 2007). They hypothesize that this extroversion-associated risk may result from the synergistic effects of inattention and impulsivity, the former resulting from sleep deprivation and the latter being positively correlated with trait extroversion.

Similarly, Tavakoli et al. found that, in adolescents who had been hospitalized for a suicide attempt, performance on a test of inhibitory control negatively correlated with REM pressure (latency and percent) and sleep continuity. In contrast, an evoked response potential (ERP) index of inhibitory processing was positively correlated with SWS. The authors point out that this pattern mirrors the REM disinhibition and decreased SWS that is associated with adult depression.

Mindfulness

Mamede et al. used structural equation modeling (SEM) of data from a large online questionnaire study to examine interrelationships of sleep and trait mindfulness among other factors in explaining depressive and anxiety symptoms during the COVID-19 pandemic. They found significant mediation of the effects of mindfulness on overall mental health by the combined effects of rumination and insomnia symptoms.

Emotion regulation during dreaming

Barbeau et al. report evidence for an emotion regulatory function of dreams by comparing emotionality reported by the dreamer to emotionality rated by judges. They describe lesser emotionality in dream self-reports as a "positivity bias", quantified by subtracting the dreamers' mood ratings from judges' ratings. These authors found positivity bias to predict degree of positive mood reported upon waking.

In contrast, Sikka et al. provide evidence for a lack of an emotion regulatory effect of dreaming. Beginning with the common hypothesis that negative emotion in dreams functions to discharge or "work-through" negative emotion in wakefulness, these investigators tested whether, following nights containing negatively-toned dreams, individuals were less reactive to negatively-toned images and were better able to down-regulate negative responses *via* cognitive reappraisal. However, they found just the opposite: more negatively-toned dreams were associated with more negatively-toned post-sleep mood and affected neither the reactivity to negative images nor the ability to re-appraise. They postulate their findings support a continuity between dream and waking mood, as would be predicted by the "continuity hypothesis" (Schredl and Hofmann, 2003).

Conclusions

The mixed findings in this volume are instructive in illustrating how differences in experimental paradigms and measures can lead to quite different conclusions. Such differences aside, findings indicate that sleep is indeed an important component of emotion regulation, and that the specific mechanisms are fertile ground for future research.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Chellappa, S. L., Gordijn, M. C., and Cajochen, C. (2011). Can light make us bright? Effects of light on cognition and sleep. *Prog. Brain Res.* 190, 119–133. doi: 10.1016/B978-0-444-53817-8.00007-4

Davidson, P., Jonsson, P., Carlsson, I., and Pace-Schott, E. (2021). Does sleep selectively strengthen certain memories over others based on emotion and perceived future relevance? *Nat. Sci. Sleep* 13, 1257–1306. doi: 10.2147/NSS.S286701

Fernandez, D. C., Fogerson, P. M., Lazzerini Ospri, L., Thomsen, M. B., Layne, R. M., Severin, D., et al. (2018). Light affects mood and learning through distinct retina-brain pathways. *Cell* 175, 71–84e18. doi: 10.1016/j.cell.08.004

Hu, X., Cheng, L. Y., Chiu, M. H., and Paller, K. A. (2020). Promoting memory consolidation during sleep: a meta-analysis of targeted memory reactivation. *Psychol. Bull.* 146, 218–244. doi: 10.1037/bul0000223

Hutchison, I. C., Pezzoli, S., Tsimpanouli, M. E., Abdellahi, M. E. A., Pobric, G., Hulleman, J., et al. (2021). Targeted memory reactivation in REM but not SWS selectively reduces arousal responses. *Commun. Biol.* 4, 404. doi: 10.1038/s42003-021-01854-3

Killgore, W. D., Richards, J. M., Killgore, D. B., Kamimori, G. H., and Balkin, T. J. (2007). The trait of introversion-extraversion predicts vulnerability to sleep deprivation. *J. Sleep Res.* 16, 354–363. doi: 10.1111/j.1365-2007.00611.x

Klinzing, J. G., Niethard, N., and Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nat. Neurosci.* 22, 1598–1610.

Lazzerini Ospri, L., Prusky, G., and Hattar, S. (2017). Mood, the circadian system, and melanopsin retinal ganglion cells. *Annu. Rev. Neurosci.* 40, 539–556. doi: 10.1146/annurev-neuro-072116-031324

Lewis, P. A., and Bendor, D. (2019). How targeted memory reactivation promotes the selective strengthening of memories in sleep. *Curr. Biol.* (2019) 29, R906–R912. doi: 10.1016/j.cub.08.019

Palmer, C. A., and Alfano, C. A. (2020). Anxiety modifies the emotional effects of sleep loss. *Curr Opin Psychol.* 34: 100–104.

Schouten, D. I., Pereira, S. I., Tops, M., and Louzada, F. M. (2016). State of the art on targeted memory reactivation: sleep your way to enhanced cognition. *Sleep Med. Rev.* (2017) 32, 123–31. doi: 10.1016/j.smrv.04.002

Schredl, M., and Hofmann, F. (2003). Continuity between waking activities and dream activities. *Conscious Cogn.* 12, 298–308. doi: 10.1016/S1053-8100(02)00072-7

Wassing, R., Schalkwijk, F., Lakbila-Kamal, O., Ramautar, J. R., Stoffers, D., Mutsaerts, H., et al. (2019). Haunted by the past: old emotions remain salient in insomnia disorder. *Brain* 142, 1783–96. doi: 10.1093/brain/awz089

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BRIEF RESEARCH REPORT
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Self-Conscious Affect Is Modulated by Rapid Eye Movement Sleep but Not by Targeted Memory Reactivation–A Pilot Study

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The neurophysiological properties of rapid eye movement sleep (REMS) are believed to tune down stressor-related emotional responses. While prior experimental findings are controversial, evidence suggests that affective habituation is hindered if REMS is fragmented. To elucidate the topic, we evoked self-conscious negative affect in the participants ($N = 32$) by exposing them to their own out-of-tune singing in the evening. Affective response to the stressor was measured with skin conductance response and subjectively reported embarrassment. To address possible inter-individual variance toward the stressor, we measured the shame-proneness of participants with an established questionnaire. The stressor was paired with a sound cue to pilot a targeted memory reactivation (TMR) protocol during the subsequent night's sleep. The sample was divided into three conditions: control (no TMR), TMR during slow-wave sleep, and TMR during REMS. We found that pre- to post-sleep change in affective response was not influenced by TMR. However, REMS percentage was associated negatively with overnight skin conductance response habituation, especially in those individuals whose REMS was fragmented. Moreover, shame-proneness interacted with REM fragmentation such that the higher the shame-proneness, the more the affective habituation was dependent on non-fragmented REMS. In summary, the potential of REMS in affective processing may depend on the quality of REMS as well as on individual vulnerability toward the stressor type.

Keywords: targeted memory reactivation, REM sleep, REM fragmentation, shame, skin conductance response, embarrassment, affective habituation, slow-wave sleep

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INTRODUCTION

Understanding how sleep can promote offline emotional processing opens up new perspectives for the concept of emotion regulation. For example, evidence points to poorer downregulation of emotional distress overnight in individuals with insomnia (Wassing et al., 2019b). The neurochemical conditions and activity patterns specifically during rapid eye movement sleep (REMS) are suggested to depotentiate the affective strength of memories *via* repeated limbic circuit activations (Walker and Van Der Helm, 2009; Goldstein and Walker, 2014). However, experimental support is equivocal. While some evidence indicates that REMS attenuates the reactivity toward emotional stimuli (Gujar et al., 2011; Rosales-Lagarde et al., 2012; Wassing et al., 2019a), this

view is challenged by numerous reports showing REMS to be associated with elevated post-sleep electrodermal response (Pace-Schott et al., 2011; Gilson et al., 2015; Werner et al., 2015) and higher subjectively evaluated affect (Lara-Carrasco et al., 2009; Gilson et al., 2015; Werner et al., 2020).

The missing piece in this puzzle may be the quality of REMS. Disruptions of REMS can precede the onset of pathological conditions such as post-traumatic stress disorder (PTSD), where the emotional memories fail to dissipate during sleep (Pace-Schott et al., 2015). Additionally, the fragmentation of REMS is shown to disrupt the overnight processing of emotional distress (Wassing et al., 2016, 2019a), and it is also associated with more depressive symptoms and with a genetic propensity for depression (Pesonen et al., 2019). Conversely, a stronger overnight decrease in amygdala reactivity is observed with an increased duration of unperturbed REMS (Wassing et al., 2019a). However, disrupted slow-wave sleep (SWS) is also shown to impair mood (Finan et al., 2015), suggesting that emotional regulation is not limited to REMS.

An approach to directly modulate the content of sleep-driven processing is called targeted memory reactivation (TMR). Typically, in TMR, the processed material (unconditioned stimulus, UCS) is paired with a sensory stimulus such as an odor or a sound (conditioned stimulus, CS). During subsequent sleep, the person is exposed to the CS to reactivate the associated memory representation (Hu et al., 2020). While the potential of TMR during SWS on declarative memory improvement is acknowledged (Hu et al., 2020), attempts to enhance affective habituation with REMS-linked TMR are emerging. In a recent study, sound-cued TMR during REMS promoted the habituation of subjective arousal responses toward negative images (Hutchison et al., 2021). Another study focused on negative self-conscious emotion, having the participants listen to a recording of their own out-of-tune singing. The stressor was cued with an odor, and exposure to the odor during REMS attenuated the post-sleep amygdala reactivity of the participants toward the stressor (Wassing et al., 2019a).

In this study, we exposed the participants to self-conscious affect by having them listen to a playback of their own singing, a stimulus shown to cause shame and embarrassment (Wassing et al., 2019a). Piloting TMR, we paired the playback with a sound cue and examined how both physiological and subjective embarrassment were affected by TMR applied during REM or SWS. Additionally, we investigated how the proportion and fragmentation of both REMS and SWS are related to affective habituation. Finally, recognizing that the propensity for self-conscious affect may modulate autonomic responsivity (Hofmann et al., 2006), we also explored whether trait-like shame-proneness is associated with affective reactivity and its overnight habituation.

METHODS

Participants

Participants were recruited by word of mouth among the contacts of the research group and voluntary students from psychology courses. During the study, the participants were only in contact with a non-familiar experimenter. Exclusion criteria were any self-reported diagnosed sleep, mood, or anxiety disorder, the use of any medication that could affect sleep, acute sickness, and gold allergy (polysomnography electrodes were gold-plated). One participant was excluded due to generalized anxiety disorder, and another due to prevalent sleep disturbances caused by hypothyroidism medication. The analytical sample size was $N = 32$, randomized into SWS ($n = 11$), REM ($n = 10$), and control groups ($n = 11$). All participants were informed of the nature of the experiment in advance, and all gave written informed consent. The study was approved by the Ethics Committee of Helsinki University Central Hospital. All procedures followed were in accordance with the Declaration of Helsinki and its later amendments.

Study Flow and TMR Protocol

The participants arrived at the laboratory in the early evening. After the briefing, they sang a karaoke version of Abba's Dancing Queen without hearing their own voice through headphones, promoting out-of-tune singing. The singing was recorded, and the experimenter created a ∼1-min compilation of the recording without background music (UCS) using Audacity 2.3.2 software. The compilation consisted of three selected clips with 5-s silent intervals between clips. A 300 Hz sine wave sound, 250 ms (CS), was inserted in both silent intervals and at the beginning and the end of the compilation. Soon after this, the participants listened to the compilation (Playback 1), and the affective response was measured (refer to section Affective Response). The experimenter ensured that the participants had noticed the CS within the compilation. Polysomnography (PSG) was then attached, and before bedtime, Playback 2 took place. During sleep, TMR was applied for SWS and REM groups during their respective sleep stages. Aiming at the second and third sleep episode, the CS was played 12 times with 1.5-s intervals *via* a speaker in the bedroom (40 dB; reduced by 5 dB if arousal emerged), two times per sleep episode (i.e., four rounds, 78 s of cueing in total). After awakening and morning routines, Playback 3 was conducted. Refer to **Figure 1** for a process overview.

Affective Response

We assessed objective and subjective affective responses at Playbacks 1–3 (**Figure 1**). Objective response, i.e., skin conductance level (SCL), was measured from middle and ring fingers of the non-dominant hand using a galvanic skin sensor, connected to a Brain Products QuickAmp amplifier (Brain Products GmbH, Gilching, Germany). SCL was recorded at a 500 Hz sampling rate and analyzed using Matlab R2018a.

Baseline SCL was recorded from the participant sitting in a quiet room for 5 min and averaging over the period. Next, the participants listened to the UCS *via* headphones in the presence of the experimenter, and the SCL during the playback was measured and averaged. Skin conductance response (SCR) was the percentual difference between the baseline and playback SCLs. To represent an average electrodermal response of a person over the three playback occasions we calculated a mean over SCR_1, SCR_2, and SCR_3 (SCR_{Mean}).

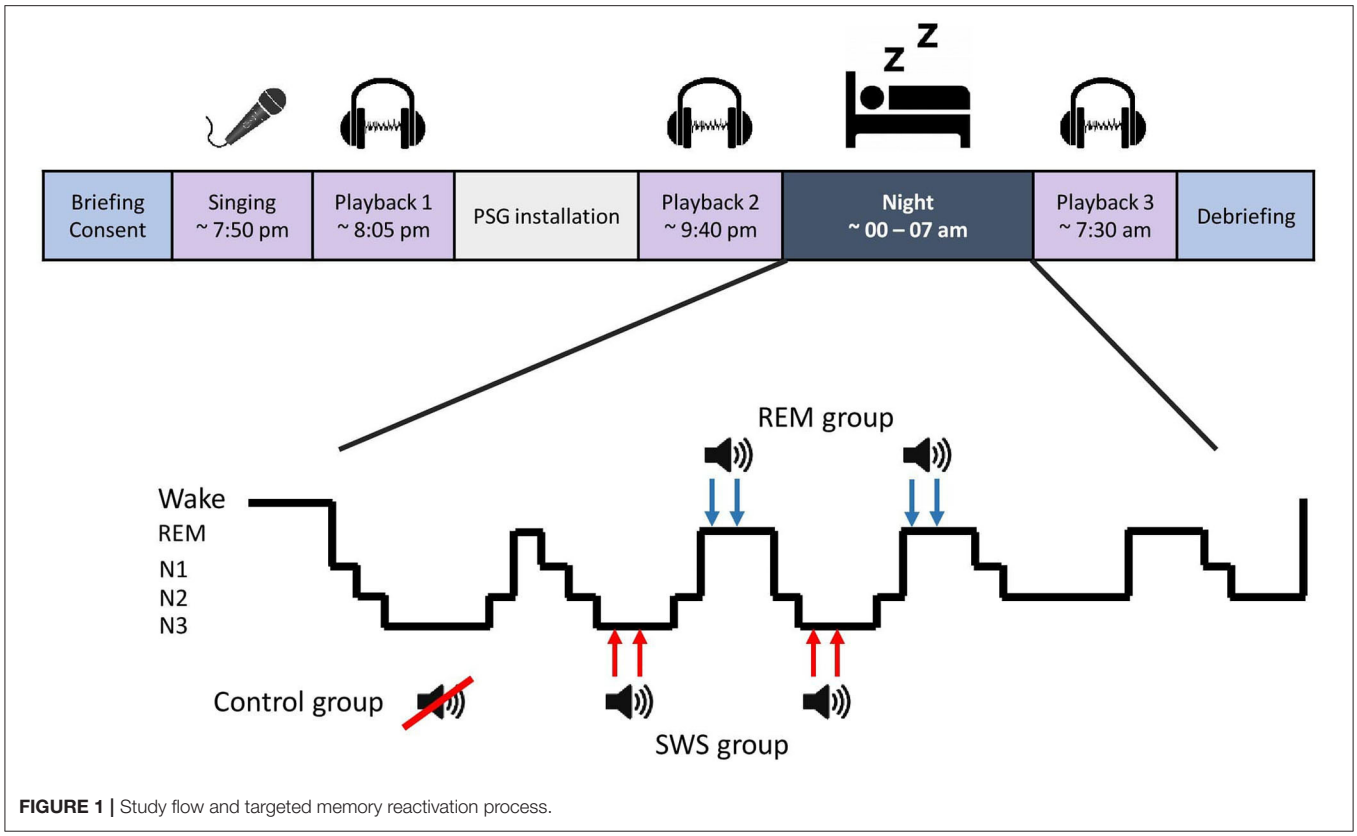

FIGURE 1 | Study flow and targeted memory reactivation process.

Subjective embarrassment (Emb) was verbally asked after each playback with questions: (1) "How ashamed did you feel during the playback?" and (2) "How stressful was it to listen to the playback?" on a scale from 0 to 4 (i.e., none to highly). The mean of these values denoted the Emb value. The mean of Emb_1, Emb_2, and Emb_3 (Emb_{Mean}) represented the average self-reported embarrassment of a person. Overnight affective habituation, i.e., response decrease, was calculated for objective and subjective responses as follows: $SCR_3 - SCR_2 = SCR_{Decr}$; and $Emb_3 - Emb_2 = Emb_{Decr}$.

Polysomnography and Sleep Fragmentation

All recordings were performed using either SOMNOscreen plus or SOMNOscreen HD (SOMNOmedics GmbH, Germany). Gold cup electrodes were attached at six electroencephalography (EEG) locations (frontal hemispheres: F3, F4; central: C3, C4; occipital: O1, O2), and mastoids (A1, A2). The electrooculogram (EOG) and the electromyogram (EMG) were measured using disposable adhesive electrodes (Ambu Neuroline 715, Ambu A/S, Denmark), two locations for EOG and three for EMG. An online reference Cz and a ground electrode in the forehead were used. The sampling rate was 256 Hz (the hardware filters for SOMNOscreen plus are 0.2–35 Hz). PSG data were scored manually using the DOMINO program (v2.7; SOMNOmedics GmbH, Germany) in 30-s epochs into N1, N2, N3, REM, and wake, according to AASM guidelines (AASM Manual for the Scoring of Sleep and Associated Events). Arousals were also marked. The proportions of each sleep stage were calculated by dividing the time spent in a certain stage by total sleep time (i.e., N1, N2, N3, and REM%).

Rapid eye movement fragmentation (REM_{Frag}) was defined as the time spent in either wake, N1, N2, or arousals during REMS episodes divided by REMS duration during the whole night. The first REM epoch denoted the start of a REM episode, and the episode was concluded with the start of at least 4 consecutive min of wake or non-REM. SWS episodes and fragmentation (SWS_{Frag}) were defined otherwise similarly, but SWS episodes ended at the start of a REM episode, or 4 min of consecutive wake, N1 or N2.

Questionnaires

To evaluate trait-like shame-proneness, the participants filled the Test of Self-Conscious Affect (TOSCA-3; Tangney et al., 2000). Shame-proneness comprised the sum of questions 1A, 2B, 3E, 4A, 5C, 6C, 7A, 8A, 9B, 10D, 11B, 12B, 13B, 14A, 15A, and 16C, i.e., $TOSCA\text{-}3_{Shame}$. We also assessed self-reported sleep characteristics (Pittsburgh Sleep Quality Index, PSQI; Buysse et al., 1989), depression symptoms (Beck Depression Inventory, BDI; Beck et al., 1996), and generalized anxiety symptoms (Generalized Anxiety Disorder 7, GAD-7; Williams, 2014).

The participants were screened for their experience in performing and singing by using two questions, scaling from 1 to 5 (none to very much): "Previous performing experience, e.g., speeches, presentations, acting, or singing?" and "Do you

TABLE 1 | Sample characteristics.

	SWS group ($n = 11$) Mean (SD)	REM group ($n = 10$) Mean (SD)	Control group ($n = 11$) Mean (SD)	p
Age (years)	28.5 (11.0)	28.5 (12.5)	25.2 (7.3)	0.70
Sleep duration (h:mm)	6:32 (1:14)	6:23 (0:58)	7:06 (0:45)	0.27
N1 (%)	7.5 (3.3)	11.1 (6.7)	8.5 (12.7)	0.62
N2 (%)	48.0 (5.6)	49.4 (6.2)	46.7 (9.7)	0.73
N3 (%)	23.2 (6.7)	21.9 (6.9)	23.3 (4.0)	0.85
REM (%)	21.3 (6.0)	17.7 (7.0)	21.5 (5.8)	0.31
REM fragmentation (%)	8.5 (6.6)	8.1 (5.0)	7.5 (6.2)	0.93
N3 fragmentation (%)	14.3 (9.0)	15.9 (10.1)	9.7 (7.2)	0.28
WASO (h:mm)	0:29 (0:39)	0:27 (0:28)	0:30 (0:29)	0.98
GAD-7	2.0 (1.8)	3.1 (2.7)	2.5 (2.2)	0.53
BDI	3.1 (3.1)	5.5 (5.2)	4.6 (4.5)	0.44
PSQI	7.6 (2.3)	7.3 (1.8)	7.4 (2.6)	0.94
TOSCA-3_{Shame}	42.3 (10.6)	49.1 (7.8)	41.5 (10.2)	0.16
Singing experience	2.4 (0.6)	2.9 (0.7)	2.5 (0.5)	0.20
SCR_{Mean} (%)	28.6 (11.0)	35.6 (13.1)	27.6 (19.3)	0.46
Emb_{Mean}	1.3 (1.0)	1.6 (0.8)	1.6 (1.1)	0.76

SWS, slow wave sleep; REM, rapid eye movement; N1–N3%, The percentage of sleep stages non-REM 1–3; REM%, the percentage of REM sleep; WASO, wake after sleep onset; GAD-7, sum score of Generalized Anxiety Disorder 7 questionnaire; BDI, sum score of Beck Depression Inventory questionnaire; PSQI, Pittsburgh Sleep Quality Index score; TOSCA-3_{Shame}, sum score of TOSCA-3 questionnaire's shame subscale; SCR_{Mean}, average electrodermal response over the three playback occasions ($n = 30$ due to excluded outliers); Emb_{Mean}, average self-reported embarrassment; SD, standard deviation; p, p-value of the difference between N3, REM, and control subgroups.

sing at leisure time or work?" The mean score was denoted as "singing experience."

Statistical Analyses

We used one-way ANOVA to test whether the TMR subgroups differed in age, sleep measures, questionnaire scores, singing experience, or affective habituation. The sex ratio between the subgroups was tested with chi-squared. To test for differences in subjective response between the playback occasions, we used repeated measures ANOVA. The difference between baseline and playback SCLs across Playbacks 1–3 was tested with mixed ANOVA, i.e., 3X2 design (three occasions; baseline and playback). We used linear regression to examine the associations between mean affective responses and the questionnaire scores and between overnight affective habituation and REM%, REM_{Frag}, SWS%, and $SWS_{Frag.}$ Two-way ANOVA was used to investigate how affective habituation was associated with the continuous-by-continuous interactions between REM% and REM_{Frag} or between SWS% and SWS_{Frag} as well as between TOSCA-3_{Shame} and REM%, REM_{Frag} SWS% or SWS_{Frag}.

In all analyses on overnight affective habituation, we ran a raw model without covariates, and a control model controlling for sex, age, singing experience, and time spent awake between Playbacks 2 and 3. Statistically significant raw model results were re-tested with the control model.

The nominal level of statistical significance was set at $p < 0.05$. In TMR piloting we focused on effect sizes, expecting large η^2 (>0.14), based on estimates from previous findings (Wassing et al., 2019a; Hutchison et al., 2021). Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Sample Characteristics

Table 1 presents the age, sleep measures, questionnaire scores, singing experience, and mean affective responses of the analytical sample ($N = 32$, 24 women). No significant differences were found between the N3, REM, and control subgroups (p-values ≥ 0.161). Sex ratio also did not differ between the subgroups ($p_{\chi 2} = 0.471$).

Preliminary Analyses

Due to technical issues, we lost the PSG data of one participant and morning SCR data of another, thus excluding these observations from the analyses on REMS parameters and overnight habituation. One participant's SCR_{Mean} exceeded the sample mean by 4.7 SDs, and another showed +3.8 SDs in SCR_{Decr}. We excluded these participants from the SCR analyses. Thus, analytical samples concerning SCR_{Mean} and Emb_{Mean} numbered 30 and 32, respectively. Tests regarding sleep parameters and SCR_{Mean}/Emb_{Mean} included 29/31 participants. TMR groups for SCR_{Decr}/Emb_{Decr} were as follows: N3 10/11; REM 8/10; and control 11/11. Non-normally distributed REM_{Frag} (Kolmogorov–Smirnov; $p = 0.006$) prompted us to deploy square root transformation, significant findings examined also with the transformed variable (sqrt-REM_{Frag}).

Emotional Response and Questionnaires

The time of the playback affected both SCR [Huynh–Feldt epsilon = 0.710, $F_{(1.42,54)} = 12.099$, $p < 0.001$; **Figure 2A**] and Emb [$F_{(2,62)} = 32.813$, $p < 0.001$] values (**Figure 2B**).

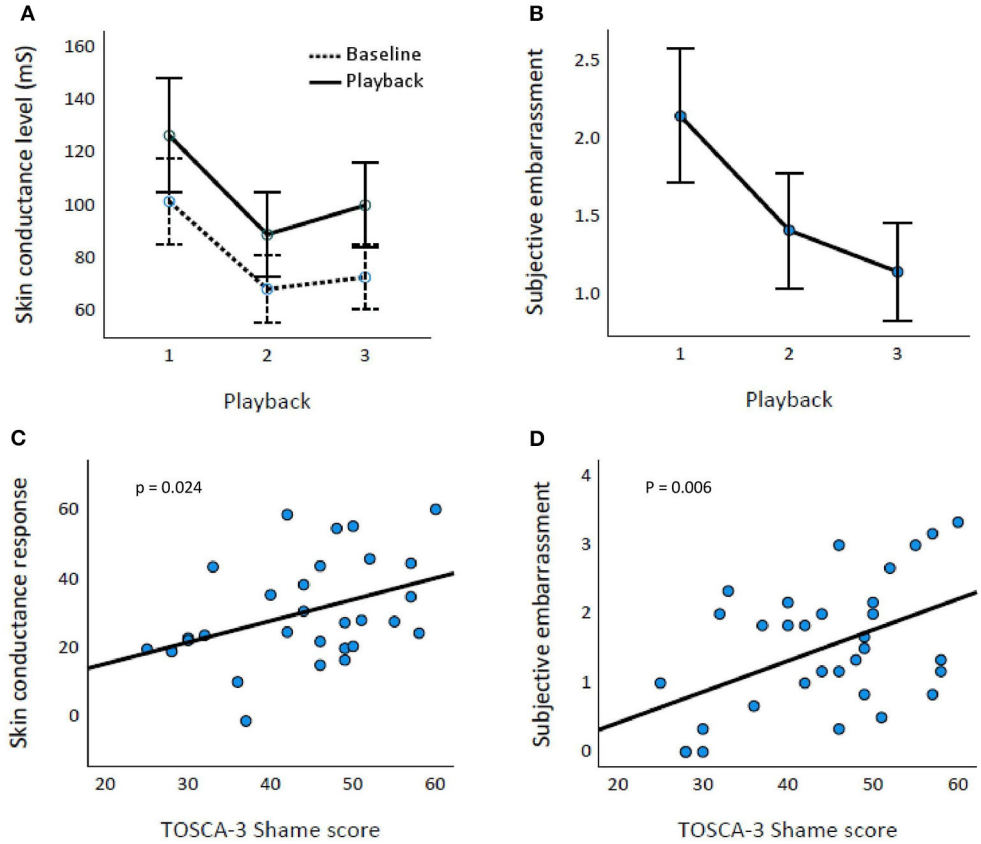

FIGURE 2 | Affective response and TOSCA-3_{Shame} scores. Baseline and playback skin conductance levels **(A)** and subjective embarrassment **(B)** across Playbacks 1–3. Error bars represent 95% CIs. TOSCA-3_{Shame} score is associated with both skin conductance response (percentual increase; $p = 0.024$) **(C)** and subjective embarrassment ($p = 0.006$) **(D)**.

The playback SCL differed significantly from the baseline SCL [$F_{(1,27)} = 65.734$, $p < 0.001$].

TOSCA-3_{Shame} was associated significantly with SCR_{Mean} [$t_{(1,28)} = 2.385$, $p = 0.024$] and Emb_{Mean} [$t_{(1,30)} = 2.950$, $p = 0.006$; **Figures 2C,D**, respectively]. BDI, GAD-7, or PSQI scores were not associated with SCR_{Mean} or Emb_{Mean} (p-values ≥ 0.075).

Targeted Memory Reactivation

Of the cues, 90% hit the intended sleep stage. The deviations concerned the SWS group, where some cues given at a stage later were scored as N2. While all participants were not cued four times due to short sleep, the mean amount of cueing did not differ between the SWS and REM groups (64 and 72 s, respectively; $p = 0.390$). TMR condition (SWS, REM, or control) was not associated with differences in SCR_{Decr} [$F_{(2,26)} = 0.012$, $p = 0.991$, $\eta^2 = 0.001$] or Emb_{Decr} [$F_{(2,28)} = 0.149$, $p = 0.862$, $\eta^2 = 0.010$].

REM, SWS, and Affective Habituation

The SCR_{Decr} was associated negatively with REM% [$t_{(1,26)} = -2.959$, $p = 0.00$] but not with REM_{Frag} [$t_{(1,26)} = 0.883$, $p = 0.386$]. REM% and REM_{Frag} interacted significantly on SCR_{Decr} [$F_{(6,21)} = 5.754$, $p = 0.025$; control model $p = 0.023$; sqrt-REM_{Frag} $p = 0.037$]. The scatterplots in **Figure 3A** show that higher REM% is associated with less habituated SCR if REMS is fragmented. Emb_{Decr} was not associated significantly with REM% or REM_{Frag} or with their interaction (p-values $\geq$ 0.372). SWS%, $SWS_{Frag,}$ or their interaction was not significantly associated with SCR_{Decr} or Emb_{Decr} (p-values ≥ 0.300).

Shame-Proneness, Sleep, and Affective Reactivity

With SCR_{Decr} as the dependent variable, the TOSCA-3_{Shame} score did not interact significantly with REM% [$F_{(3,24)} = 0.195$, $p = 0.663$]. However, "TOSCA-3_{Shame} X REM_{Frag}" was significant [$F_{(4,24)} = 5.083$, $p = 0.034$; control model $p = 0.041$; sqrt-REM_{Frag} $p = 0.047$]. **Figure 3B** illustrates that fragmented REMS associates with attenuated SCR when shame-proneness is low, the pattern being opposite for highly shame-prone individuals. Regarding Emb_{Decr}, TOSCA-3_{Shame} did not interact significantly with REM% or REM_{Frag} (p-values ≥ 0.292). Neither SWS% nor SWS_{Frag} interacted significantly with TOSCA-3_{Shame} on SCR_{Decr} or Emb_{Decr} (p-values > 0.436).

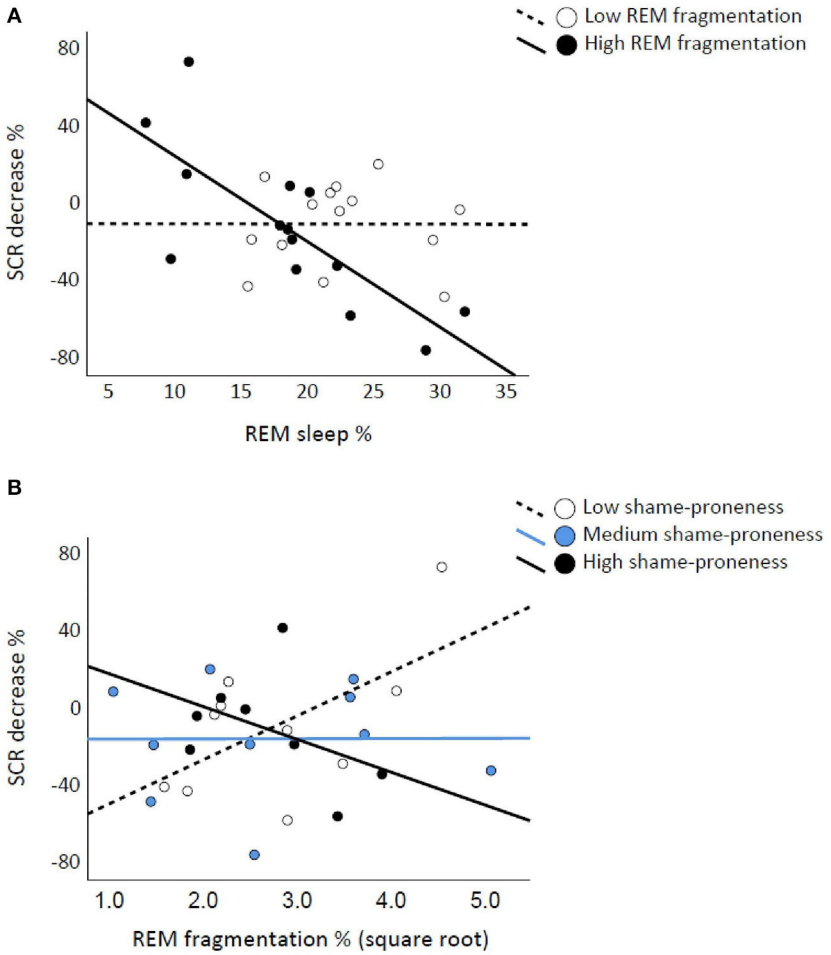

FIGURE 3 | Rapid eye movement (REM) fragmentation interacts with REM percentage and TOSCA-3_{Shame} on skin conductance response (SCR) decreases. REM percentage is associated with lower SCR decrease if REM sleep is fragmented, the continuous-by-continuous interaction illustrated with median split **(A)**. Low and High shame-prone individuals show opposite associations between REM fragmentation (square root transformed) and SCR decrease, illustrated with tertile division **(B)**.

DISCUSSION

In this study, we piloted whether TMR during REMS or SWS influenced pre- to post-sleep habituation of SCR or subjective embarrassment, but no effect was found. We found that a higher proportion of REMS was associated with reduced habituation to stress. However, this association was specifically observed when REMS was fragmented. Additionally, we found that shame-proneness moderated the association between fragmented REMS and overnight habituation.

According to theoretical and experimental work (Walker and Van Der Helm, 2009; Gujar et al., 2011; Rosales-Lagarde et al., 2012; Wassing et al., 2019a), REMS depotentiates the affective load of memories. However, several contrary results indicate that REMS conserves pre-sleep reactivity over a sleep period (Pace-Schott et al., 2011; Gilson et al., 2015; Werner et al., 2015, 2020), which is supported by the present study. We saw a negative association between REMS percentage and the overnight change of playback-induced SCR. Investigating the quality of REMS is necessary. Fragmentation reportedly modulates the influence of REMS on emotional processing (Wassing et al., 2019a). In our study, REM fragmentation as such did not associate with emotional habituation, but it interacted with REM percentage: higher REMS percentage associated with less overnight SCR habituation *via* non-continuous REMS. This pattern resembles a previous finding, where the habituation effect of REMS was lost in case of abundant interruptions (Wassing et al., 2019a). We did not find SWS to be associated with any habituation outcome. Experimentally disrupting these sleep stages yielded comparable results (Glosemeyer et al., 2020), supporting REMS as the primary sleep stage for affective processing.

What is adaptive emotional processing? Preserving affective load ensures readiness to respond rapidly under threat. However, allowing irrelevant non-threats to control nighttime recovery is equally disruptive. From this perspective, we assessed participants for their trait-like tendency to experience shame.

This trait was associated robustly with both physiological and subjective affective responses in our data (unlike other questionnaire scores), and it moderated the association between REM fragmentation and SCR habituation. Attenuated post-sleep SCR was observed in highly shame-prone individuals as a function of less REM fragmentation, the pattern being opposite in those with a low tendency to experience shame. This finding may reflect an adaptive nature of (consolidated) REMS, as it appears to preferably scale down the affect in those easily overridden by a shameful event. A completely effacing affective response is not adaptive either, perhaps reflected in preserved SCR in low-shame-prone individuals. Individual propensity should be considered in research deploying stressors that may be unequally experienced.

Notably, subjective response was not associated with either SCR or sleep parameters. Particularly, social stress may evoke uncorrelated objective and subjective responses (Mauss et al., 2004) relative to non-social stress (Reinhardt et al., 2012). Self-report is prone to cognitive appraisal and may dispel positive arousal more readily. We also observed subjective responses nearing a floor effect, several participants rating low embarrassment already in the pre-sleep assessment, compromising statistical resolution.

Piloting the TMR approach did not indicate differences in affective habituation. This diverges from a study where odor-bound TMR attenuated amygdala response toward a similar stressor (Wassing et al., 2019a). While an obvious difference from our study was their use of odors instead of sounds, TMR-enhanced affective habituation has also been shown using sounds (He et al., 2015; Hutchison et al., 2021). The properties of our TMR procedure probably underlie the negative results. First, the inter-cue interval was 1.5 s, confounding with the refractory period of a possible post-cue spindle during SWS and impairing processing (Antony et al., 2018). Second, the amount of cueing requires consideration. While repeated replays may reduce the excitability of concerned cortical networks (Lewis and Bendor, 2019), experimental evidence suggests that increasing the amount of cueing inflicts a stronger effect (He et al., 2015). Our less-intensive TMR was probably insufficient to cause observable effects.

Strengths and Limitations

In this study, we investigated the role of REMS as a modulator of emotional processing. We contributed to the emerging understanding that specifically fragmented REMS may underlie maintained stress response overnight. Moreover, considering the individual predisposition to experience self-conscious stress, we also show that this trait may modulate how REMS quality relates to the post-sleep response.

There are significant limitations to be considered. Mainly, the sample was small, decreasing statistical power and increasing the propensity for confounding factors. Observing a few participants resilient to the stress induction further highlights this limitation. While aiming at a statistically significant TMR effect likely requires a larger sample, the obtained effect sizes indicate that it would not have impacted the TMR outcome in our study. Along these lines, the TMR setting was possibly insufficiently intense to induce consequential differences in a neural replay, necessitating further undertakings to elucidate TMR's applicability in social stress. Regarding other findings, the significant results were correlational, precluding causal deductions. Measuring only one night disallows the examination of within-subject changes in relevant REMS parameters. Finally, we did not contrast the response to their own-singing-response with a response caused by hearing someone else's singing, partially disputing the response being related to the self-conscious affect. This is mitigated by the strong associations between the observed response and trait-like shame.

Conclusions

The potential of sleep in affective processing has gathered both interest and evidence in recent years. While we did not find TMR protocol to influence overnight habituation for self-conscious affect, we observed REMS and its fragmentation to be associated with post-sleep response intensity. Frequent interruptions in REMS can have adverse effects on emotional downscaling. Moreover, the need for this habituation, reflected by the trait of shame-proneness, may moderate how consolidated REMS scales the response.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors on request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Helsinki University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RH: conceptualization, methodology, writing—original draft preparation, formal analysis, investigation, and visualization. LK: conceptualization and review and editing. TM: technical preparation of skin conductance measurement and analysis. JK: set-up of karaoke recording and playback system. A-KP: conceptualization, review and editing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

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REFERENCES

Antony, J. W., Piloto, L., Wang, M., Pacheco, P., Norman, K., and Paller, K. (2018). Sleep spindle refractoriness segregates periods of memory reactivation. *Curr. Biol.* 28, 1736–1743.e1734. doi: 10.1016/j.cub.2018.04.020

Beck, A. T., Steer, R. A., and Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., and Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28, 193–213. doi: 10.1016/0165-1781(89)90047-4

Finan, P. H., Quartana, P. J., and Smith, M. T. (2015). The effects of sleep continuity disruption on positive mood and sleep architecture in healthy adults. *Sleep* 38, 1735–1742. doi: 10.5665/sleep.5154

Gilson, M., Deliens, G., Leproult, R., Bodart, A., Nonclercq, A., Ercek, R., et al. (2015). REM-enriched naps are associated with memory consolidation for sad stories and enhance mood-related reactivity. *Brain Sci.* 6:1. doi: 10.3390/brainsci6010001

Glosemeyer, R. W., Diekelmann, S., Cassel, W., Kesper, K., Koehler, U., Westermann, S., et al. (2020). Selective suppression of rapid eye movement sleep increases next-day negative affect and amygdala responses to social exclusion. *Sci. Rep.* 10:17325. doi: 10.1038/s41598-020-74169-8

Goldstein, A. N., and Walker, M. P. (2014). The role of sleep in emotional brain function. *Annu. Rev. Clin. Psychol.* 10, 679–708. doi: 10.1146/annurev-clinpsy-032813-153716

Gujar, N., Mcdonald, S. A., Nishida, M., and Walker, M. P. (2011). A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. *Cereb. Cortex* 21, 115–123. doi: 10.1093/cercor/bhq064

He, J., Sun, H.-Q., Li, S.-X., Zhang, W.-H., Shi, J., Ai, S.-Z., et al. (2015). Effect of conditioned stimulus exposure during slow wave sleep on fear memory extinction in humans. *Sleep* 38, 423–431. doi: 10.5665/sleep.4502

Hofmann, S. G., Moscovitch, D. A., and Kim, H.-J. (2006). Autonomic correlates of social anxiety and embarrassment in shy and non-shy individuals. *Int. J. Psychophysiol.* 61, 134–142. doi: 10.1016/j.ijpsycho.2005.09.003

Hu, X., Cheng, L. Y., Chiu, M. H., and Paller, K. A. (2020). Promoting memory consolidation during sleep: a meta-analysis of targeted memory reactivation. *Psychol. Bull.* 146, 218–244. doi: 10.1037/bul0000223

Hutchison, I. C., Pezzoli, S., Tsimpanouli, M.-E., Abdellahi, M. E. A., Pobric, G., Hulleman, J., et al. (2021). Targeted memory reactivation in REM but not SWS selectively reduces arousal responses. *Commun. Biol.* 4:404. doi: 10.1038/s42003-021-01854-3

Lara-Carrasco, J., Nielsen, T. A., Solomonova, E., Levrier, K., and Popova, A. (2009). Overnight emotional adaptation to negative stimuli is altered by REM sleep deprivation and is correlated with intervening dream emotions. *J. Sleep Res.* 18, 178–187. doi: 10.1111/j.1365-2869.2008.00709.x

Lewis, P. A., and Bendor, D. (2019). How targeted memory reactivation promotes the selective strengthening of memories in sleep. *Curr. Biol.* 29, R906–R912. doi: 10.1016/j.cub.2019.08.019

Mauss, I., Wilhelm, F., and Gross, J. (2004). Is there less to social anxiety than meets the eye? Emotion experience, expression, and bodily responding. *Cogn. Emot.* 18, 631–642. doi: 10.1080/02699930341000112

Pace-Schott, E. F., Germain, A., and Milad, M. R. (2015). Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. *Biol. Mood Anxiety Disord.* 5, 3–3. doi: 10.1186/s13587-015-0018-9

Pace-Schott, E. F., Shepherd, E., Spencer, R. M., Marcello, M., Tucker, M., Propper, R. E., et al. (2011). Napping promotes inter-session habituation to emotional stimuli. *Neurobiol. Learn Mem.* 95, 24–36. doi: 10.1016/j.nlm.2010.10.006

Pesonen, A. K., Gradisar, M., Kuula, L., Short, M., Merikanto, I., Tark, R., et al. (2019). REM sleep fragmentation associated with depressive symptoms and genetic risk for depression in a community-based sample of adolescents. *J. Affect. Disord.* 245, 757–763. doi: 10.1016/j.jad.2018.11.077

Reinhardt, T., Schmahl, C., Wüst, S., and Bohus, M. (2012). Salivary cortisol, heart rate, electrodermal activity and subjective stress responses to the Mannheim Multicomponent Stress Test (MMST). *Psychiatry Res.* 198, 106–111. doi: 10.1016/j.psychres.2011.12.009

Rosales-Lagarde, A., Armony, J. L., Del Río-Portilla, Y., Trejo-Martínez, D., Conde, R., and Corsi-Cabrera, M. (2012). Enhanced emotional reactivity after selective REM sleep deprivation in humans: an fMRI study. *Front. Behav. Neurosci.* 6:25. doi: 10.3389/fnbeh.2012.00025

Tangney, J. P., Dearing, R. L., Wagner, P. E., and Gramzow, R. (2000). (2000). *The Test of Self- Conscious Affect-3 (TOSCA-3).* Fairfax, VA: George Mason University.

Walker, M. P., and Van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135, 731–748. doi: 10.1037/a0016570

Wassing, R., Benjamins, J. S., Dekker, K., Moens, S., Spiegelhalder, K., Feige, B., et al. (2016). Slow dissolving of emotional distress contributes to hyperarousal. *Proc. Natl. Acad. Sci. U.S.A.*113, 2538–2543. doi: 10.1073/pnas.1522520113

Wassing, R., Lakbila-Kamal, O., Ramautar, J. R., Stoffers, D., Schalkwijk, F., and Van Someren, E. J. W. (2019a). Restless REM sleep impedes overnight amygdala adaptation. *Curr. Biol.* 29, 2351–2358.e2354. doi: 10.1016/j.cub.2019.06.034

Wassing, R., Schalkwijk, F., Lakbila-Kamal, O., Ramautar, J. R., Stoffers, D., Mutsaerts, H. J. M. M., et al. (2019b). Haunted by the past: old emotions remain salient in insomnia disorder. *Brain* 142, 1783–1796. doi: 10.1093/brain/awz089

Werner, G. G., Schabus, M., Blechert, J., Kolodyazhniy, V., and Wilhelm, F. H. (2015). Pre- to postsleep change in psychophysiological reactivity to emotional films: late-night REM sleep is associated with attenuated emotional processing. *Psychophysiology* 52, 813–825. doi: 10.1111/psyp.12404

Werner, G. G., Schabus, M., Blechert, J., and Wilhelm, F. H. (2020). Differential effects of REM sleep on emotional processing: initial evidence for increased short-term emotional responses and reduced long-term intrusive memories. *Behav. Sleep Med.* 19, 83–98. doi: 10.1080/15402002.2020.1713134

Williams, N. (2014). The GAD-7 questionnaire. *Occup. Med.* 64, 224–224. doi: 10.1093/occmed/kqt161

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Mindfulness as a Protective Factor Against Depression, Anxiety and Psychological Distress During the COVID-19 Pandemic: Emotion Regulation and Insomnia Symptoms as Mediators

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Objectives: Research has linked mindfulness to improved mental health, yet the mechanisms underlying this relationship are not well understood. This study explored the mediating role of emotion regulation strategies and sleep in the relationship between mindfulness and symptoms of depression, anxiety and psychological distress during the COVID-19 pandemic.

Methods: As detailed in this study's pre-registration (osf.io/k9qtw), a cross-sectional research design was used to investigate the impact of mindfulness on mental health and the mediating role of emotion regulation strategies (i.e., cognitive reappraisal, rumination and suppression) and insomnia. A total of 493 participants from the general population answered an online survey and were included in the final analysis. The online survey consisted of the short form of the Five-Facets Mindfulness Questionnaire (FFMQ-SF), the Impact of Event Scale-revised (IES-R), the Generalised Anxiety Disorder Scale (GAD-7), the Patient Health Questionnaire (PHQ-8), the Emotion Regulation Questionnaire (ERQ), the short form of the Rumination Response Scale (RSS-SF), and the Insomnia Severity Index (ISI).

Results: Structural equation modelling revealed that mindfulness was related to lower symptoms of depression, anxiety and psychological distress, both directly and indirectly. Mindfulness was negatively associated with rumination and insomnia. As hypothesised, models revealed that the associations between mindfulness and depression, anxiety and psychological distress were significantly mediated by its negative associations with rumination and insomnia. Our findings also demonstrated that rumination was related to increased insomnia symptoms, which in turn was associated with increased mental health problems, indicating a mediated mediation. Mindfulness was also positively associated with cognitive reappraisal and negatively associated with suppression, which were,

respectively, negatively and positively associated with depressive symptoms, and thus functioned as specific mediators of the association between mindfulness and depression.

Conclusion: Our findings suggest that rumination and insomnia operate transdiagnostically as interrelated mediators of the effects of mindfulness on mental health, whereas cognitive reappraisal and suppression function as specific mediators for depression. These insights emphasise the importance of targeting emotion regulation and sleep in mindfulness interventions for improving mental health. Limitations and implications for practice are discussed.

Keywords: mindfulness, depression, anxiety, emotion regulation, rumination, sleep, insomnia

INTRODUCTION

The global outbreak of the coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11th of 2020 (Mahase, 2020), leading to the implementation of social isolation measures throughout the world. Besides social isolation, most people have had to deal with other serious challenges, such as financial worries and health concerns. Consequently, research has reported alarming rates of anxiety (20–59%), depression (25–46%), and stress (34–70%) in the general population during the COVID-19 pandemic (Burke et al., 2020; Rodríguez-Rey et al., 2020; Vindegaard and Benros, 2020; Wang et al., 2020a; Varma et al., 2021). Such rates are considerably higher than 12 month prevalences for anxiety (10.6%) and depression (9.6%) reported in pre-pandemic epidemiological studies (Mojtabai et al., 2016; Remes et al., 2016). On the other hand, some studies demonstrated that certain individuals were less vulnerable to experiencing mental health problems during the pandemic (Killgore et al., 2020; Cunningham et al., 2021; Fields et al., 2021). It is well established that certain people are more vulnerable to mental health problems in highly stressful situations, whereas others seem incredibly resilient in the face of adversity. Therefore, besides monitoring individuals' mental health during the crisis, it is also crucial to identify modifiable risk and protective factors that can be targeted through cost-effective interventions to prevent mental health problems, both in times of adversity and in daily life. One of such factors is mindfulness, a state of nonjudgemental awareness of one's internal and external experiences in the present moment (Baer, 2003). Mindfulness has been identified as a buffer against the negative psychological effects of increased stress and as a general protective factor against mental health problems, which may thus have a particularly robust effect in times of adversity. However, in order to develop more effective mindfulness-based interventions (MBIs) and to understand who would benefit the most from them, it is also critical to investigate the cognitive and behavioural mechanisms underlying the associations between mindfulness and mental health. Additionally, the core constructs of mindfulness and how to measure them are not yet sufficiently understood.

Mindfulness as a Protective Factor Against Mental Health Problems

Over the last two decades, mindfulness has received increased attention for its positive influence on mental health and as a buffer against the negative psychological effects of highly stressful situations. Mindfulness meditation is the practice of cultivating states of mindfulness, wherein practitioners are taught to focus attention on the breath, bodily sensations and eventually on any object (i.e., thoughts, feelings, but also sounds and other sensory experiences) that appear in conscious awareness. Mindfulness has also been conceptualised as a disposition or trait, indicating one's tendency to evoke the state of mindfulness in daily life, outside of mindfulness meditation practice (Baer et al., 2006). Besides having been correlated with wellbeing, better interpersonal relations, less burnout and greater job and life satisfaction (Mesmer-magnus et al., 2017), trait mindfulness has been inversely associated with symptoms of depression, anxiety and stress (Soysa and Wilcomb, 2015).

Evidence has shown that MBIs can increase one's predisposition to be mindful in everyday life (i.e., mindfulness trait) by regularly cultivating state mindfulness through meditation (Gu et al., 2015), which mediated improvements in psychological symptoms. This finding opens new, potentially more promising, avenues for prevention and treatment of anxiety and mood disorders, as well as for the promotion of mental health in the general population. Recently, meta-analysis of MBIs has demonstrated that they were moderately effective at treating anxiety (Hedges's $g = 0.63$) and depressive symptoms (Hedges's $g = 0.59$; Hofmann et al., 2010), while another meta-analysis has found that the effects of mindfulness-based interventions for various psychiatric disorders were equivalent or superior to other evidence-based treatments (Goldberg et al., 2021).

Despite the bulk of evidence supporting the efficacy of MBIs and the increased interest in its therapeutic potentials, it is not yet well understood what elements of MBIs and what aspects of mindfulness are responsible for improvements in psychological health. To further improve the efficacy and delivery of MBIs, it is important to address the question of how these interventions are bringing about change. To that end, it is important to not only investigate which mechanisms underlie the link between trait mindfulness and mental health problems,

but also to examine which aspects of mindfulness are most strongly related to mental health and these key mechanisms. Such examination allows us to improve our understanding of which target constructs of mindfulness were critical in changing treatment outcomes in MBIs and to refine future interventions and measurement instruments accordingly.

Several different theories of mindfulness and corresponding measurement instruments have been outlined in the literature (for review see Sauer et al., 2013). Based on existing self-report measures of mindfulness, Baer et al. (2006) conducted a factor analysis which yielded five distinct but correlated facets of mindfulness: (1) *Observing*, defined as attending to internal and external experience; (2) *Describing*, defined in terms of labelling internal experience with language; (3) *Acting with awareness*, defined as attending to one's activities in the moment and as the opposite of acting on automatic pilot; (4) *Nonjudgement of inner experience*, defined in terms of adopting a nonevaluative stance towards thoughts and feelings; and (5) *Nonreactivity to inner experience*, defined as the tendency to allow thoughts and feelings to come and go, without getting caught up or carried away by them (Baer et al., 2008). Based on these findings, the five-facet mindfulness questionnaire (FFMQ) was created. Research has found that the facets *acting with awareness* and *nonjudgement* were stronger predictors of decreased anxiety and depression than other facets of mindfulness (Bohlmeijer et al., 2011; Veehof et al., 2011). Given that different facets of mindfulness may have unique influences on different psychopathologies, the use of broader multi-factorial measures of mindfulness may be essential to better understand how mindfulness facets can differentially protect against depression, anxiety and distress. Besides examining the facets of mindfulness and how to measure them, it is essential to investigate the key mechanisms underlying the link between mindfulness and mental health so that MBIs can be tailored accordingly to potentially increase their effectiveness.

Mindfulness and Emotion Regulation: Cognitive Reappraisal, Rumination, and Suppression

Recent research has suggested that one potential explanation for the protective effects of mindfulness on mental health is the implementation of more adaptive emotion regulation strategies instead of maladaptive ones. There is ample evidence demonstrating that emotion regulation problems are related with various psychopathologies, but particularly with higher risk of depression and anxiety (Aldao et al., 2010). For example, research has suggested that at least part of the positive effects of mindfulness may be explained by the greater use of adaptive cognitive reappraisal strategies, which has been linked to lower risk of anxiety and depression (Martin and Dahlen, 2005). Cognitive reappraisal involves reinterpreting the meaning of certain situations or stimuli so as to modify one's initial emotional responses (typically negative) to the experience. The tendency of mindful individuals to evoke nonevaluative awareness of experiences may not only be a form of reappraisal in itself, but such nonjudgemental awareness could also further facilitate the recognition and reinterpretation of negative thoughts and feelings (Desrosiers et al., 2013).

Mindfulness may also influence mental health by reducing the use of maladaptive emotion regulation strategies, such as rumination and suppression. Rumination is characterised by repetitive negative self-critical questioning of one's thoughts, emotions or circumstances, and, although it can occur as a normal part of human experience, it can be particularly dysfunctional when it is excessive and unmanageable (Treynor et al., 2003). Remarkably, trait mindfulness seems be negatively associated with rumination, possibly because the states of non-judgmental awareness and acceptance associated with mindfulness facilitate the recognition and regulation of negative cognitive patterns characteristic of rumination (Raes and Williams, 2010). Similarly, given the link between mindfulness and acceptance, mindfulness also has been thought to be negatively associated with expressive suppression, an emotion regulation strategy that involves the inhibition of behaviours associated with emotional responses (e.g., facial expressions) and is widely regarded as maladaptive. The use of both expressive suppression and rumination have been consistently linked to higher rates of anxiety and depression (Aldao et al., 2010).

Given that certain emotion regulation strategies may contribute uniquely or transdiagnostically to different psychopathologies, these emotion regulation strategies may partially explain the distinct and common mechanisms through which mindfulness influences risk of depression, anxiety and psychological distress. In support of this notion, a recent cross-sectional study found that the relationship between mindfulness and depression was mediated by its positive association with cognitive reappraisal and by its negative association with suppression and rumination. However, only reappraisal and rumination, but not suppression, mediated the effects of mindfulness on anxiety (Parmentier et al., 2019). Yet, another cross-sectional study found that rumination and reappraisal mediated the effects of mindfulness on depression, whereas its effect on anxiety was mediated by rumination and worry, but not by reappraisal (Desrosiers et al., 2013). Considering that the evidence comparing these mechanisms is still scarce, it is not clear whether rumination, suppression and reappraisal all mediate the effects of mindfulness on anxiety, depression and stress, or whether certain emotion regulation strategies act as distinct mediators for different psychopathologies.

Furthermore, emotion regulation strategies may also influence mental health indirectly through their effect on health behaviours. Difficulties in emotion regulation, characterised partially by maladaptive rumination and reduced use of adaptive strategies (e.g., cognitive reappraisal), may predisposes individuals to several behavioural problems, such as unhealthy eating, substance abuse and sleep problems (Aldao and Christensen, 2015; Pillai and Drake, 2015). Because emotions reflect tendencies of action and are closely related to physiological, motivational and decision-making processes (Desteno et al., 2013), the strategies used to regulate one's emotional responses can influence the probability of enacting certain behaviours (for review see Aldao and Christensen, 2015). Despite the impact of emotion regulation on health behaviour, few studies have investigated whether

the use of emotion regulation strategies (e.g., rumination) mediates the relationship between mindfulness and health behaviours, which may, in turn, partially explain the link between mindfulness and mental health.

Mindfulness and Sleep

Mindfulness has been positively associated with physical activity, healthy eating and negatively associated with sleep problems (e.g., insomnia) and alcohol use (Sala et al., 2019), all of which have been linked to mental health (Jané-Llopis and Matytsina, 2006; Lopresti et al., 2013; Khalid et al., 2017). Sleep, in particular, has been shown to be one of the strongest behavioural predictors of mental health (Wickham et al., 2020; Gilchrist et al., 2021), and ample evidence has demonstrated a mutually causal relationship between sleep and anxiety and depressive disorders (Alvaro et al., 2011). Given that sleep is highly susceptible to worry, stress and rumination (Pillai and Drake, 2015), mindfulness may be particularly beneficial for decreasing insomnia symptoms and improving sleep behaviour, since the nonjudgemental awareness characteristic of mindfulness has been shown to reduce stress and lessen engagement with worries and ruminative thoughts (Evans and Segerstrom, 2011; Petrocchi and Ottaviani, 2016; Lu et al., 2019). In line with this notion, previous studies have demonstrated that MBIs led to improvements in sleep quality, which were mediated by reductions in rumination (Greeson et al., 2018) and stress (Carlson and Garland, 2005). Additionally, a meta-analysis has found that MBIs were effective in reducing insomnia symptoms (Wang et al., 2020b). These findings indicate that mindfulness can reduce maladaptive emotion regulation (i.e., rumination) and buffer against stress, thereby reducing insomnia symptoms.

Given the well-established link between sleep and mental health, this interplay between improved emotion regulation and sleep may be an important mechanism through which mindfulness can prevent and treat mental health problems. Remarkably, researchers recently found that mindfulness buffered the impact of COVID-19-related stressors on sleep duration (Zheng et al., 2020). Considering that the disruption of routine and high levels of stress in times of adversity may be particularly detrimental to sleep behaviour (Hall et al., 2000; Arora and Grey, 2020) and has shown to increase insomnia symptom during the COVID-19 pandemic (Abdulah and Musa, 2020), sleep may be the most important behavioural mechanism underlying the effect of mindfulness on mental health during such times of crisis. However, no studies thus far have investigated whether this interplay between sleep and rumination mediates the relationship between mindfulness and mental health, which may be particularly relevant during highly stressful times such as the COVID-19 pandemic.

The Present Study

The COVID-19 pandemic and its repercussions have caused substantial increases in levels of depression, anxiety and psychological distress (Wang et al., 2019, 2020a; Rodríguez-Rey et al., 2020; Vindegaard and Benros, 2020; Varma et al., 2021). In Netherlands, two studies have observed increases in mental health symptoms in the general population during the COVID-19 lockdown that started on the 15th of March of 2020 (Pan et al., 2021; Vloo et al., 2021), whereas another study observed little change in rates of mental health problems of students (van Zyl et al., 2021). Certain protective factors, such as mindfulness and its facets, may reduce vulnerability to psychopathologies and partially explain the heterogeneity of findings regarding mental health outcomes during the pandemic. In face of this crisis, it is important to improve our understanding of the core facets of mindfulness with regards to mental health and the mechanisms underlying the relationship between mindfulness and mental health. To that end, this study firstly examined how mindfulness trait and its facets influence three mental health outcomes, namely, symptoms of depression, anxiety and COVID-19-related psychological distress. Secondly, this study examined whether emotion regulation strategies (i.e., cognitive reappraisal, rumination and suppression) and insomnia mediate the relationship between mindfulness and mental health during the COVID-19 pandemic, as well as whether these mediators operate transdiagnostically or specifically for depression, anxiety and COVID-19-related psychological distress. Finally, we investigated whether the relationship between mindfulness and insomnia was mediated by rumination. We hypothesised that mindfulness trait will be negatively associated with symptoms of mental health problems. We expect that more mindful individuals will use more adaptive (i.e., cognitive regulation) and less maladaptive (i.e., rumination and suppression) emotion regulation strategies, which in turn will be associated with less mental health problems and will mediate the relationship between mindfulness and the studied outcomes. Considering the vital role of sleep in mental health, we expected that mindfulness will be negatively associated with insomnia, which will mediate the negative relationship between mindfulness and the three studied mental health outcomes. Finally, in light of the evidence linking rumination to poor sleep, we hypothesised that rumination would mediate the negative relationship between mindfulness and insomnia.

MATERIALS AND METHODS

Participants and Procedure

From the 30th of May until the 20th of July of 2020, potential participants were invited to participate in a survey-study about the impact of the COVID-19 epidemic on mental health. Students from the Erasmus University of Rotterdam were initially recruited through online advertisements to participate in this study in exchange for study credits. Additionally, through social media posts, potential participants from the general population were also invited to participate, although no compensation was provided. At the end of the survey, participants were asked to share the survey with their social network and invite others who were interested in participating (i.e., snow-ball sampling). Participants were eligible to participate if they were at least 16 years old, spoke fluent English and provided informed consent for their participation. This study was approved by the Ethics Review

Committee of the Department of Psychology, Education and Child Studies, Erasmus University Rotterdam (application number 20-051).

Sample Size

We determined that a minimum sample size of 526 participants was needed for investigating the pre-specified model structure, based on an *a-priori* power calculation based on a small-medium effect size of 0.20, 0.90 estimated power and 0.05 probability level, performed through https://www.danielsoper.com/statcalc/calculator.aspx?id=89. As described in this study's pre-registration, considering the sensitive time frame of the study and that we expected to exclude 5–10% of survey respondents, we intended to stop data collection once we obtained 580 complete responses to the questionnaire, or by July 20th. Data collection was stopped at July 20th, and after exclusion of incomplete and invalid responses, data were collected from 493 participants.

Measures

Independent Variable

Five-Facets Mindfulness Questionnaire-Short Form

Mindfulness was assessed with the short form of the Five-Facets Mindfulness Questionnaire (FFMQ-SF; Bohlmeijer et al., 2011). The FFMQ-SF is a 24-item validated questionnaire that asks to rate the degree to which each statement is true for them, and items are rated on a 5-point Likert scale (from 1 for 'never or very rarely true' to 5 for 'very often or always true'). The FFMQ-SF has been found to have high internal reliability and measures five factors of mindfulness, namely, *observing* (alpha = 0.81), *describing* (alpha = 0.87), *acting with awareness* (alpha = 0.83), *nonjudging* (alpha = 0.83), and *nonreactivity* (alpha = 0.75; Bohlmeijer et al., 2011). Due to the conflicting findings in the literature regarding the factor structure of the FFMQ, particularly regarding the role of the *observing* facet (Bohlmeijer et al., 2011), we will investigate the factor structure of the FFMQ-SF before proceeding to the main analysis.

Outcome Measures

Impact of Event Scale-Revised

The psychological distress related to the COVID-19 pandemic was assessed with the Impact of Event Scale-revised (IES-R; Weiss and Marmar, 1997). The IES-R consists of 22 statements about feelings towards a specific event (i.e., COVID-19 pandemic), which are rated on a 5-point Likert scale indicating the extent to which participants relate to them (from 0 for 'not at all' to 4 for 'extremely'). The IES-R has a high test–retest reliability ranging from 0.89 to 0.94 and its validity has been demonstrated (Weiss and Marmar, 1997).

Patient Health Questionnaire

The Patient Health Questionnaire-8 (PHQ-8; Kroenke et al., 2009) was administered to measure clinical symptoms of depression. The PHQ-8 is an eight-item self-report scale in which participants are asked to rate how often; in the past 2 weeks, they have been bothered by several symptoms of depression. Items are rated on a 4-point scale, ranging from 0 for 'not at all' to 3 for 'nearly every day'. The PHQ-8 has good reliability (alpha = 0.88) and has been validated as a screening tool for depressive symptoms (Kroenke et al., 2009; Shin et al., 2019).

Generalised Anxiety Disorder Scale

The Generalised Anxiety Disorder Scale (GAD-7; Löwe et al., 2008) was used to assess symptoms of anxiety. The GAD-7 is a seven-item self-report scale in which participants are asked to rate how often, in the past 2 weeks, they have been bothered by the seven core symptoms of anxiety. Items are rated on a 4-point scale, ranging from 0 for 'not at all' to 3 for 'nearly every day'. The GAD-7 has been shown to have high internal consistency (alpha = 0.89) and its validity for screening of anxiety symptoms in the general population has been demonstrated (Löwe et al., 2008).

Mediators

Emotion Regulation Questionnaire: Cognitive Reappraisal and Suppression

To assess for the use of certain emotion regulation strategies, namely, cognitive reappraisal and suppression, the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) was administered. ERQ is a validated and widely used 10-item scale that is divided into two subscales: cognitive reappraisal (six items) and suppression (four items). Cognitive reappraisal subscale includes items such as 'I control my emotions by changing the way I think about the situation I'm in.' and the suppression subscale includes items such as, 'When I am feeling negative emotions, I make sure not to express them'. The ERQ items are rated on a 7-point Likert scale from 1 for 'strongly disagree' to 7 for 'strongly agree', with higher scores indicating increased use of that strategy.

Rumination Response Scale: Rumination

Rumination was assessed by administering the short form of the Rumination Response Scale (RRS-SF; Treynor et al., 2003). The RRS-SF consists of 10 items assessing ruminative tendencies, rated on a 4-point Likert scale indicating how frequent they experienced these ruminative tendencies (from 1 for 'almost never' to 4 for 'almost always'). The RRS-SF has been shown to have a high internal reliability (alpha = 0.85) and its validity has been demonstrated (Erdur-Baker and Bugay, 2010).

Insomnia Severity Index

Sleep problems and insomnia were evaluated with the Insomnia Severity Index (ISI; Bastien et al., 2001), which has been validated and shown to be a reliable self-report measure of perceived sleep difficulties (Bastien et al., 2001). The ISI is a brief seven-item screening measure that assesses as: (1) the severity of sleep-onset, (2) sleep maintenance, (3) early morning awakening problems, (4) satisfaction with current sleep pattern,

(5) interference with daily functioning, (6) noticeability of impairment attributed to the sleep problem and (7) level of distress caused by the sleep problem (Bastien et al., 2001). Each statement refers to the participant's experiences during the previous 2 weeks and is rated on a 5-point Likert scale (from 0 for 'not at all/none' to '4 for very much/severe'). The ISI has excellent internal consistency in both community (alpha = 0.90) and clinical samples (alpha = 0.91; Morin et al., 2011).

Covariates

Descriptive Statistics

Descriptive Statistics on Sociodemographic Characteristics Were Collected. Participants Were Asked about their Age, Gender, Relationship Status, Nationality, Country of Residency and their Highest Level of Education.

COVID-19-Related Experiences

We assessed potentially relevant COVID-19-related experiences including health status (presence of COVID-19 symptoms, belonging to risk group and confirmed diagnosis), health status of close relative or friends (know someone who was diagnosed, COVID-19 outcome), COVID-19-related financial worries and perceived risk of serious illness associated with COVID-19 infection. Participants were asked to answer in a Yes/No format to each of the three following single-item questions on COVID-19-related experiences: (a) 'Do you belong to an at-risk group for COVID-19 infection?', (b) 'Have you been officially diagnosed with COVID-19?', (c) 'Have any of your family or friends been seriously ill or passed away due to COVID-19?'. Participants were also asked to answer the following items on 5-point Likert scale (from 1 for 'Not at all' to 5 for 'Extremely'): (d) 'Do you worry about getting into financial difficulties due to the Corona crisis?'. (e) 'If someone you know did become infected with the Corona virus, to what extent are you concerned that they will be severely ill?'

Data Analysis

As described in the pre-registration of this study (Mamede et al., 2020), structural equation modelling was used to examine the role of emotion regulation strategies and insomnia on the relationship between mindfulness and mental health problems (symptoms of depression, anxiety and psychological distress). All analyses were performed using the *lavaan* package in R software. A two-step SEM procedure was used to analyse the mediating roles. First, the measurement model of the FFMQ-SF was examined. Subsequently, a path model was used to analyse the fit between the proposed theoretical models (See **Figures 1–3** of pre-registration), and the data in our sample. Analysis were conducted using the maximal likelihood estimation, and model fits will be evaluated using multiple indicators, including the chi-squared goodness-of-fit test, the root mean square error of approximation (RMSEA), standardised root mean square residual (SRMR) and the comparative fit index (CFI). We interpreted our findings by following the widely used cut-offs proposed by Hu and Bentler (1999). The RMSEA values of 0.08 or less indicate an acceptable fit, and values of 0.06 or less indicate a good fit. For the SRMR, a value of 0.08 or less indicates good fit. For the CFI, values of 0.90 or higher indicate acceptable fit, and values of 0.95 or higher indicate excellent fit. Furthermore, the Akaike's Information Criterion (AIC) and the Bayesian Information Criteria (BIC) will also be used to compare models, with lower AIC and BIC values indicating better model fit (West et al., 2012).

Factor Structure of FFMQ-SF

The factor structure of the FFMQ-SF will be assessed before investigating the mechanisms underlying the relationships between mindfulness and mental health outcomes. This is necessary because there has been conflicting findings in the literature about the factor structure of the FFMQ, particularly regarding the *observing* facet (Baer et al., 2006; Lilja et al., 2011; Abujaradeh et al., 2019). Since the short form of the FFMQ was used, item parcels would consist of only two or three items. After examining the covariance structure of the data, we opted to not use item parcelling in order to avoid the risk of mis-specifying our model (Little et al., 2009). Based on the original studies developing and validating the FFMQ (Baer et al., 2006, 2008), three different confirmatory factor analysis (CFAs) models were tested and compared for the FFMQ-SF. Firstly, we tested whether the FFMQ-SF measures a unidimensional construct of mindfulness by specifying a model in which all item load on a single factor, which is expected to fit the data poorly (Baer et al., 2006; Bohlmeijer et al., 2011). Subsequently, we examined two five-factor models, a hierarchical five-factor model, which assumes that the five facets are elements of an overall higher-order mindfulness construct and are allowed to correlate, and a non-hierarchical correlated five-factor model, which tests whether the FFMQ-SF scale measures five distinct but related facets of mindfulness. Both five-factor models demonstrated acceptable fit in studies evaluating the psychometric properties of the original FFMQ (Baer et al., 2006) and its short-form version (Bohlmeijer et al., 2011).

In accordance with evidence from the original validation studies of the FFMQ (Baer et al., 2006), a unidimensional single-factor model for the FFMQ-SF showed poor fit to the data, χ^2 ($df = 252$, $N = 536$) = 2627.495, CFI = 0.450, SRMR = 0.124, RMSEA (90% confidence interval [CI]) = 0.133 (0.128, 0.137). This finding suggests that the combination of all the items in the FFMQ-SF do not measure a unidimensional construct of mindfulness. In line with previous studies investigating the factor structure of the FFMQ (Baer et al., 2006) and its short-form version (Bohlmeijer et al., 2011), both five-factor models demonstrated an acceptable fit. The non-hierarchical five-factor model of the FFMQ, χ^2 ($df = 242$, $N = 493$) = 541.2, CFI = 0.926, SRMR = 0.065, RMSEA (90% [CI]) = 0.050 (0.044, 0.056), AIC = 29305.1, BIC = 29548.7, performed slightly better than the hierarchical five-factor model, χ^2 ($df = 247$, $N = 493$) = 567.44, CFI = 0.913, SRMR =0.070, RMSEA (90% [CI]) = 0.051 (0.046, 0.057), AIC = 29321.3, BIC = 29543.9. However, we found that while most FFMQ-SF facets correlated significantly with each

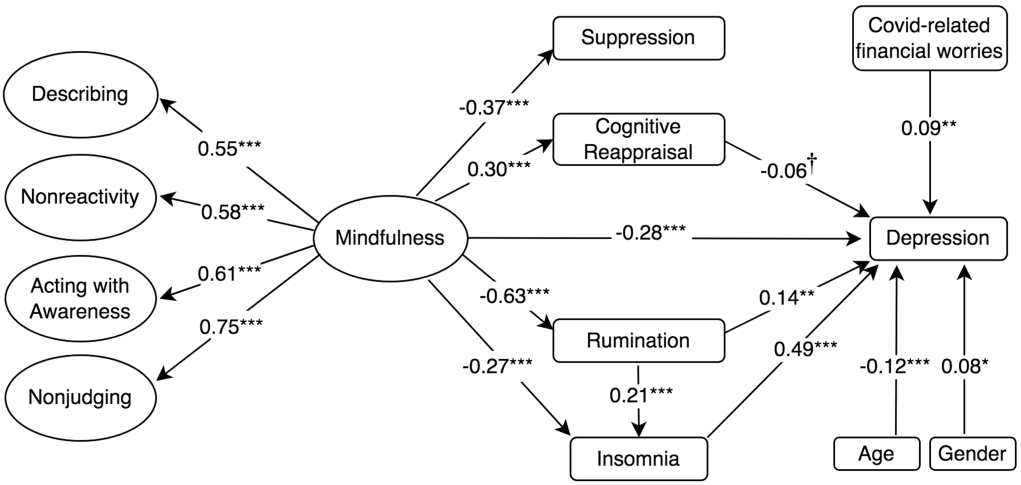

FIGURE 1 | Standardised mediation Model 1 of the effect of higher-order mindfulness on depression. Depression = PHQ-8, 8-item Patient Health Questionnaire; Rumination = RSS-SF, 10-item Rumination Response Scale-Short Form; Cognitive Reappraisal and Suppression = ERQ, 10-item Emotion Regulation Questionnaire; Insomnia = ISI, 7-item Insomnia Severity Index; and Mindfulness and facets = FFMQ-SF, 24-item Five-Facets Mindfulness Questionnaire-Short Form. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p \leq 0.001$.

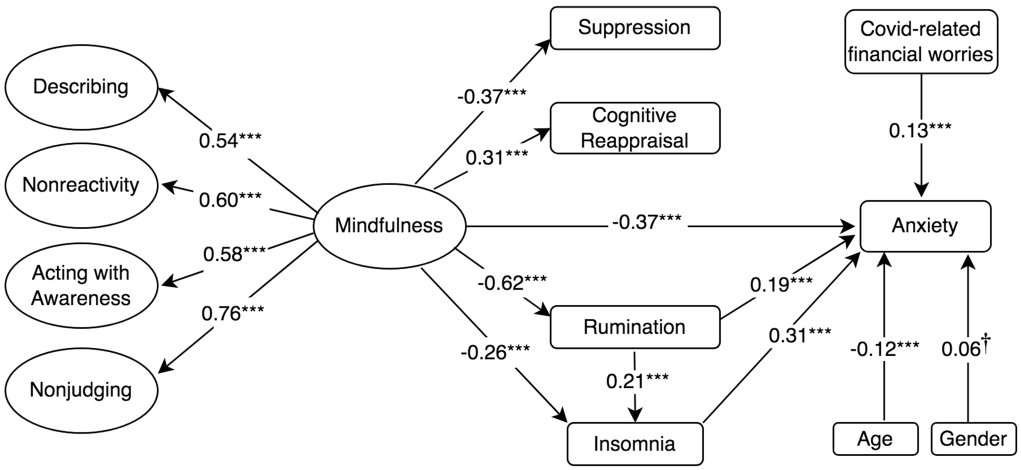

FIGURE 2 | Standardised mediation Model 2 of the effect of higher-order mindfulness on anxiety. Anxiety = GAD-7, a 7-item Generalised Anxiety Disorder; Rumination = RSS-SF, 10-item Rumination Response Scale-Short Form; Cognitive Reappraisal and Suppression = ERQ, 10-item Emotion Regulation Questionnaire; Insomnia = ISI, 7-item Insomnia Severity Index; and Mindfulness and facets = FFMQ-SF, 24-item Five-Facets Mindfulness Questionnaire-Short Form. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p \leq 0.001$.

other and loaded well into the higher construct of mindfulness, with r ranging from 0.32 to 0.75, the *observing* facet was not correlated with *nonreactivity* and *nonjudging* facets and only weakly correlated with the *describing* and *acting with awareness* facets. Additionally, the *observing* facet did not load well into the higher-order mindfulness facet (See **Supplementary Figures 7–12** and **Supplementary Table 3** in the additional material 1). Removing the *observing* facet significantly improved the fit of both models ($p \leq 0.001$), with the non-hierarchical four-factor model of the FFMQ-SF, χ^2 ($df = 164$, $N = 493$) = 407.1, CFI = 0.932, SRMR = 0.069, RMSEA (90% confidence interval [CI]) = 0.055 (0.048, 0.062), AIC = 24098.9, BIC = 24292.1, performing just marginally better than the hierarchical four-factor model, χ^2 ($df = 166$, $N = 493$) = 414.65, CFI = 0.930, SRMR = 0.071, RMSEA (90% confidence interval [CI]) = 0.055 (0.049, 0.062), AIC = 24102.5, BIC = 24287.3. Based on these findings and on the previous literature providing support for a four-factor model of mindfulness without the observing subscale (Abujaradeh et al., 2019), we fit our structural equation models testing mediation effects using two different four-factor structures of the FFMQ-SF as independent variables, namely, a hierarchical four-factor model and a non-hierarchical four-factor model of mindfulness.

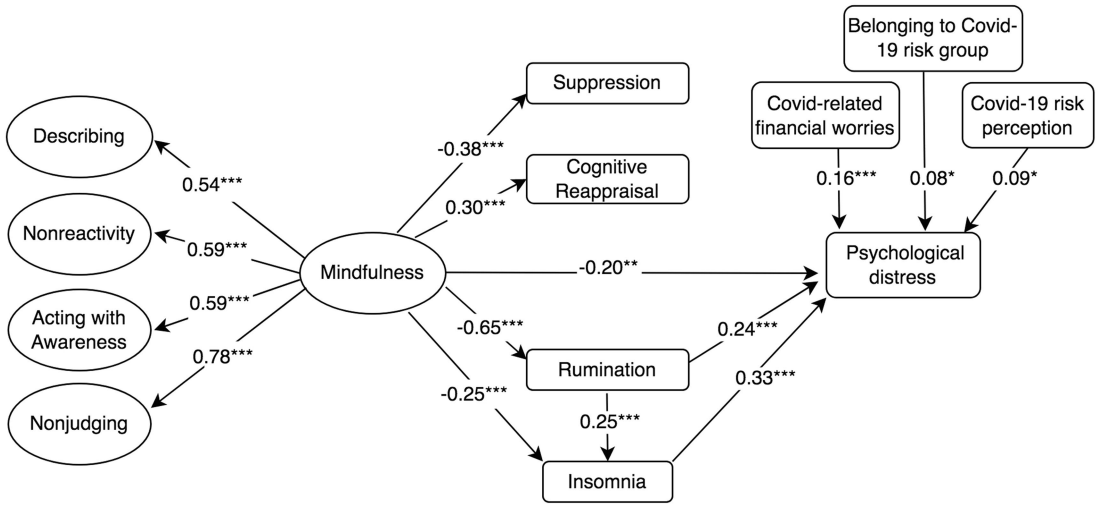

FIGURE 3 | Standardised mediation Model 3 of the effect of higher-order mindfulness on COVID-19-related psychological distress. Psychological impact of COVID-19 = IES-R, 22-item Impact of Event Scale-Revised; Rumination = RSS-SF, 10-item Rumination Response Scale-Short Form; Cognitive Reappraisal and Suppression = ERQ, 10-item Emotion Regulation Questionnaire; Insomnia = ISI, 7-item Insomnia Severity Index; and Mindfulness and facets = FFMQ-SF, 24-item Five-Facets Mindfulness Questionnaire-Short Form. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p \leq 0.001$.

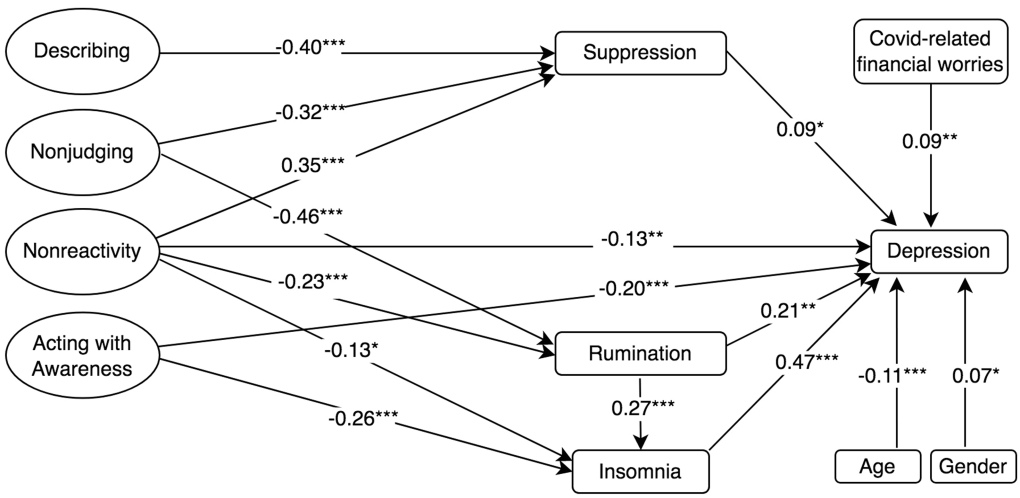

FIGURE 4 | Standardised mediation Model 4 of the effect of the five facets of mindfulness on depression. Depression = PHQ-8, 8-item Patient Health Questionnaire; Rumination = RSS-SF, 10-item Rumination Response Scale-Short Form; Cognitive Reappraisal and Suppression = ERQ, 10-item Emotion Regulation Questionnaire; Insomnia = ISI, 7-item Insomnia Severity Index; and Mindfulness and facets = FFMQ-SF, 24-item Five-Facets Mindfulness Questionnaire-Short Form. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p \leq 0.001$.

Structural Equation Modelling of Mindfulness Mechanisms

In this study, mindfulness was regarded as a latent variable, emotion regulation strategies and sleep problems were considered mediating variables, and symptoms of depression, anxiety and psychological distress were observed outcome variables in Models 1, 2, and 3, respectively. SEM was used to analyse the fit between the proposed theoretical model (See **Figures 2–4** of the pre-registration; Mamede et al., 2020) and the sample data. For each outcome variable, two models will be specified based on different factor structures of the FFMQ-SF, one utilising a higher-order construct of mindfulness as the independent variable (Models 1, 2, and 3) and another utilising the different facets of mindfulness as independent variables (Models 4, 5, and 6). As mentioned, a four-factor structure of the FFMQ (excluding the *observing* subscale) was used instead of the five-factor structured described in the pre-registration. Covariates that were not significantly ($p \leq 0.10$) associated with our outcome variables were excluded from the final models. The analysis of the present paper is described in detail in the pre-registration of this study (Mamede et al., 2020).

RESULTS

Descriptive Statistics

As described in the pre-registration, data screening involved the exclusion of responses with extremely short duration and incomplete responses, after which a total of 493 participants were included in the analysis. **Table 1** presents sample characteristics, and rates of participants exceeding cut-off for moderate depression, anxiety and insomnia, as well as for COVID-19-related psychological distress, financial worries and risk perception. Regarding nationality, 30.6% of participants were Dutch, 27.0% were German, 7.1% were Australian and 5.9% were British. At the time of data collection, 49.7% of participants resided in Netherlands and 24.2% in Germany. A considerable number of participants in this sample scored above the cut-off for moderate depression (28.8%), anxiety (23.2%), psychological distress (33.8%) and insomnia (19.5%). Additionally, 39.5% of participants indicated experiencing at least moderate COVID-19-related financial worries, and 85.7% of participants responded that they would be at least moderately concerned that they would become seriously ill if they became infected with COVID-19, while 12.2% indicated that they would be extremely concerned.

Structural Equation Modelling of Mindfulness Mechanisms

Higher-Order Mindfulness Model

The model assessing the proposed structural relationships between a higher-order construct of mindfulness, the mediators and depressive symptoms (Model 1 in **Figure 1**) demonstrated an acceptable fit to the data according to some indicators of fit (i.e., RMSEA and χ^2/df), but not others, χ^2 ($df = 338$, $N = 454$) = 1080.5, CFI = 0.835, SRMR = 0.098, RMSEA (90% confidence interval [CI]) = 0.070 (0.065, 0.074). In a similar fashion, Models 2 and 3 (**Figures 2, 3**) with anxiety and psychological distress as outcome variables, respectively, demonstrated acceptable fit to the data according to certain indicators, for example RMSEA, but not according to others, such as the CFI (See **Table 2** for comparison of fit indices between models).

The structural models were then used to test whether emotion regulation strategies and insomnia mediated the relationship between the higher-order construct of mindfulness and mental health outcome variables. Model 1 (**Figure 1**) showed that mindfulness had a negative direct effect on depression ($\beta = -0.28$, $p \leq 0.001$). Mindfulness was also found to have a negative direct effect on rumination ($\beta = -0.63$, $p \leq 0.001$) and insomnia ($\beta = -0.27$, $p \leq 0.001$). Rumination ($\beta = 0.14$, $p = 0.002$) and insomnia ($\beta = 0.49$, $p \leq 0.001$) were associated with depression. Rumination also had a positive direct effect on insomnia ($\beta = 0.21$, $p \leq 0.001$) and partially mediated the relationship between mindfulness and insomnia. In line with our Hypothesis, Model 1 revealed that the negative association between mindfulness and depression was mediated by its negative association with rumination and that the association between rumination and depression was in turn mediated by the positive association between rumination and insomnia, indicating a mediated mediation ($\beta = -0.06$, $p = 0.002$).

Model 1 also showed that while mindfulness had a positive effect on cognitive reappraisal ($\beta = 0.30$, $p \leq 0.001$) and a negative effect on suppression ($\beta = -0.37$, $p \leq 0.001$), neither cognitive reappraisal ($\beta = -0.06$, $p = 0.06$) or suppression ($\beta = 0.02$, $p = 0.57$) had a significant effect on depression ($p \leq 0.05$). Therefore, the indirect effects of mindfulness on depression *via* suppression ($\beta = -0.01$, $p = 0.57$) and cognitive reappraisal ($\beta = -0.02$, $p = 0.06$) were not significant, although the indirect effect *via* cognitive reappraisal was approaching significance ($p = 0.06$). Model 1 controlled for the negative association between depression and age, as well as for the positive association between female gender, COVID-19-related financial worries and depression. Model 1 accounted for 61.7% of the variance in depressive symptoms, as well as 39.1% in rumination scores, 9% in cognitive reappraisal, 13.8% in suppression, and 18.7% in insomnia.

Mindfulness also had a negative direct effect on anxiety ($\beta = -0.37$, $p \leq 0.001$; Model 2). Rumination ($\beta = 0.19$, $p \leq 0.001$) and insomnia ($\beta = 0.31$, $p \leq 0.001$) had a positive direct effect on anxiety. Model 2 (**Figure 2**) revealed similar pattern as model 4, wherein mindfulness had a negative indirect effect on anxiety through its negative associations with rumination and insomnia, in a mediated mediation ($\beta = -0.04$, $p = 0.003$). Models 2 found no indirect effect of mindfulness on anxiety through cognitive reappraisal or suppression. Regarding covariates, the model accounted for the negative association between anxiety and age, as well as for the positive association between female gender, COVID-19-related financial worries

TABLE 1 | Sample characteristics and rates of participants exceeding cut-off for moderate depression, anxiety and insomnia and for COVID-19-related psychological distress, financial worries and risk perception.

Participants (*n* = 493)	
Gender	*n* (%)
Male	152 (30.8%)
Female	334 (68.7%)
Education	*n* (%)
High-school degree or below	254 (51.5%)
Bachelor's degree	186 (37.7%)
Master's degree or higher	53 (10.7%)
Age (SD)	25.8 (10.5)
Country of residence	%
Netherlands	49.7%
Germany	24.2%
United Kingdom	4.07%
Others	22.04%
Depression (PHQ-8 score > 10) *n* (%)	141 (28.8%)
Anxiety (GAD-7 score > 10) *n* (%)	113 (23.2%)
Psychological distress (IES-R score > 33) *n* (%)	159 (33.8%)
Insomnia (ISI score > 15) *n* (%)	95 (19.5%)
Covid-related financial worried (>Moderate) *n* (%)	190 (39.5%)
Covid risk perception (>Moderate) *n* (%)	420 (85.7%)
PHQ-8 score (SD)	7.1 (5.3)
GAD-7 score (SD)	6.3 (4.8)
IES-R score (SD)	26.8 (21.9)
ISI score (SD)	8.55 (6.3)

TABLE 2 | Fit indices among the four-factor models tested.

	IV	DV	χ^2	*df*	χ^2/df	RMSEA	SRMR	CFI	BIC	AIC
Model 1	Higher order	Depression	1080.5	338	2.95	0.07	0.098	0.835	36000.5	35745.2
Model 2	Higher order	Anxiety	1065.6	338	2.92	0.069	0.097	0.824	35912.3	36167.9
Model 3	Higher order	Distress	1024.1	338	2.80	0.066	0.090	0.844	37888.6	38145.2
Model 4	Four facets	Depression	826.1	316	2.38	0.060	0.085	0.887	35534.9	35880.8
Model 5	Four facets	Anxiety	729.3	292	2.27	0.057	0.079	0.901	36243.1	36586.5
Model 6	Four facets	Distress	767.8	316	2.24	0.056	0.077	0.897	37676.3	38023.8

and anxiety. Model 2 accounted for 51.7% of the variance in anxiety symptoms.

Model 3 (**Figure 3**) showed that mindfulness had a negative direct effect on psychological distress ($\beta = -0.20$, $p = 0.006$; Model 3). Rumination ($\beta = 0.24$, $p \leq 0.001$) and insomnia ($\beta = 0.33$, $p \leq 0.001$) also had a positive effect on psychological distress. In the same fashion as models 1 and 2, model 3 revealed that mindfulness had a negative indirect effect on psychological distress through its negative association with rumination and insomnia, in a mediated mediation ($\beta = -0.05$, $p \leq 0.001$). Model 3 did not reveal any indirect effects of mindfulness on psychological distress through cognitive reappraisal or suppression. Model 3 controlled for positive associations between COVID-19-related psychological distress and COVID-19-related financial worries, risk perception and belonging to a COVID-19 risk group, and accounted for 41.8% of the variance in COVID-19-related psychological distress.

Four Facets of Mindfulness Model

The models assessing the proposed structural relationships between the four facets of mindfulness, the mediators and depressive symptoms (Model 4 in **Figure 4**) demonstrated a good fit according to two fit indices (i.e., RMSEA and χ^2/df), but not according to another (i.e., CFI), χ^2 ($df = 316$, $N = 493$) = 826.1, CFI = 0.887, SRMR = 0.085, RMSEA (90% [CI]) = 0.060 (0.055, 0.065). This pattern was similar for Models 5 and 6 that included, respectively, anxiety and psychological distress symptoms as outcome variables. Model 5 demonstrated a good model fit according to all indices and Model 6 demonstrated a good fit to the data according to three indices (i.e., RMSEA, SRMR and χ^2/df), but not according to another (i.e., CFI; See **Table 2**). Our findings indicated that, compared to the hierarchical four-factor model, the correlated four-factor model of mindfulness significantly improved the fit of the proposed theoretical models investigating the relationship between mindfulness and depression ($\chi^2_{diff} = 254.3$, $p \leq 0.001$), anxiety ($\chi^2_{diff} = 336.3$, $p \leq 0.001$) and psychological distress ($\chi^2_{diff} = 256.4$, $p \leq 0.001$). These structural models were used to test whether emotion regulation strategies (rumination, cognitive reappraisal and suppression) and sleep problems mediated the relationship between the facets of mindfulness and symptoms of depression (**Figure 4**), anxiety (**Figure 5**) and psychological distress (**Figure 6**).

Mindfulness facets *nonreactivity* and *acting with awareness* had a negative direct effect on depression (Model 4; **Figure 4**). *Nonjudging* and *nonreactivity* facets were negatively associated with rumination, whereas insomnia was negatively associated with *acting with awareness* and *nonreactivity*. Rumination ($\beta = 0.21$, $p \leq 0.001$) and insomnia ($\beta = 0.47$, $p \leq 0.001$) were positively associated with depression. Rumination had a positive direct effect on insomnia ($\beta = 0.27$, $p \leq 0.001$) and mediated the negative relationship between the *nonjudging* and *nonreactivity* facets and insomnia. Model 4 revealed that rumination mediated the negative association between *nonjudging*, *nonreactivity* and depression, as well as that the positive association between rumination and depression was, in turn, mediated by insomnia, indicating mediated mediation (**Figure 4**). Suppression was negatively associated with *describing* and *nonjudging* but was positively associated with *nonreactivity.* Suppression was positively associated with depression ($\beta = 0.09$, $p < 0.05$) and that suppression mediated the negative indirect effects of *describing* ($\beta = -0.03$, $p < 0.05$), *nonjudging* ($\beta = -0.03$, $p < 0.05$) and the positive indirect effect of *nonreactivity* ($\beta = 0.03$, $p < 0.05$) on depression. Cognitive reappraisal was positively associated with the *acting with awareness* ($\beta = 0.15$, $p < 0.01$), *nonreactivity* ($\beta = 0.45$, $p \leq 0.001$) and *describing* ($\beta = 0.24$, $p \leq 0.001$) facets, but negatively associated with *nonjudging* ($\beta = -0.3$, $p \leq 0.001$). However, cognitive reappraisal was not negatively associated with depression. Finally, Model 4 also controlled for the negative association between age and depression, as well as for the positive associations between depression, female gender and COVID-19-related financial worries. Model 4 accounted for 61.8% of the variance in depressive symptoms, as well as 37.8% in rumination scores, 28.8% in cognitive reappraisal, 33.6% in suppression and 21.4% in insomnia.

Model 5 demonstrated that the *nonreactivity* and *acting with awareness* facets also had a negative direct effect on anxiety. Regarding rumination and insomnia, Model 5 demonstrated a similar pattern as Model 4, wherein mindfulness facets *nonreactivity* and *nonjudging* had negative indirect effect on anxiety through rumination and insomnia, in a mediated mediation (See **Figure 5**). However, Model 5 did not reveal any effect of suppression or cognitive reappraisal on anxiety. Model 5 controlled for the positive and negative associations between anxiety and the covariates financial worries and age, respectively, and accounted for 52.5% of the variance in symptoms of anxiety.

Model 6 showed that only the *acting with awareness* facet had a negative direct effect on COVID-19-related psychological distress. Model 6 also showed that the *nonreactivity* and *nonjudging* facets had a negative indirect effect on psychological distress through rumination and insomnia, in a mediated mediation (See **Figure 6**). There

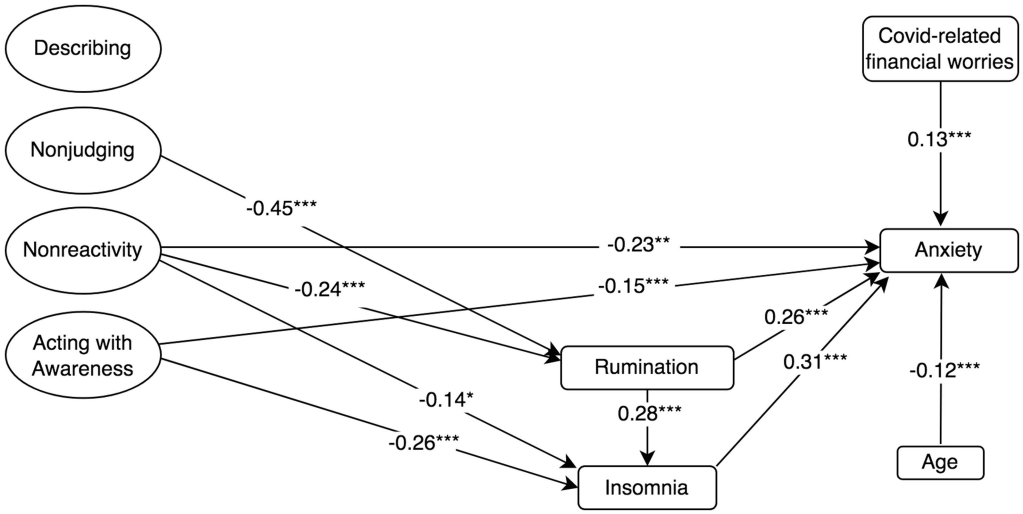

FIGURE 5 | Standardised mediation Model 5 of the effect of the five facets of mindfulness on anxiety. Anxiety = GAD-7, a 7-item Generalised Anxiety Disorder; Rumination = RSS-SF, 10-item Rumination Response Scale-Short Form; Cognitive Reappraisal and Suppression = ERQ, 10-item Emotion Regulation Questionnaire; Insomnia = ISI, 7-item Insomnia Severity Index; and Mindfulness and facets = FFMQ-SF, 24-item Five-Facets Mindfulness Questionnaire-Short Form. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p \leq 0.001$.

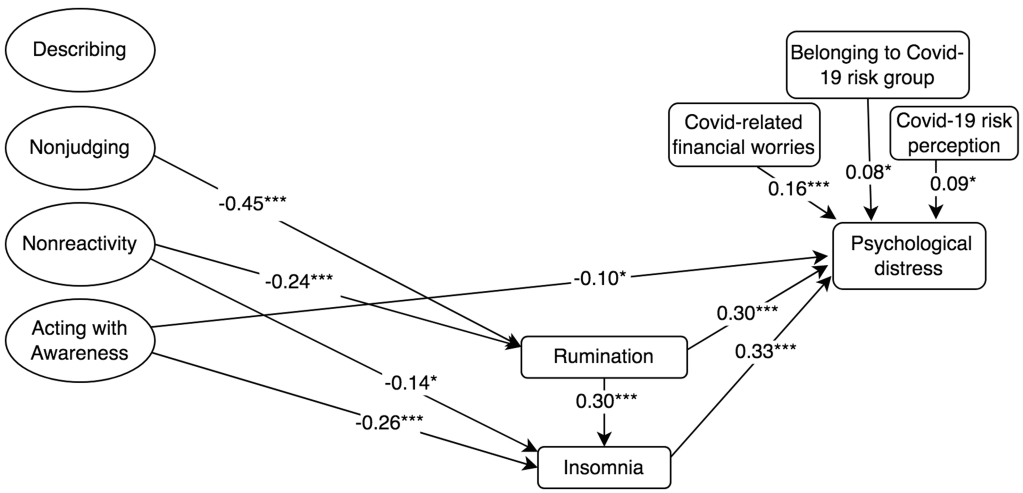

FIGURE 6 | Standardised mediation Model 6 of the effect of the five facets of mindfulness on COVID-19-related psychological distress. Psychological impact of COVID-19 = IES-R, 22-item Impact of Event Scale-Revised; Rumination = RSS-SF, 10-item Rumination Response Scale-Short Form; Cognitive Reappraisal and Suppression = ERQ, 10-item Emotion Regulation Questionnaire; Insomnia = ISI, 7-item Insomnia Severity Index; and Mindfulness and facets = FFMQ-SF, 24-item Five-Facets Mindfulness Questionnaire-Short Form. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p \leq 0.001$.

were no effects of suppression or cognitive reappraisal on psychological distress. The model controlled for the positive associations between psychological distress and the covariates COVID-19-related financial worries, risk perception and belonging to a COVID-19 risk group. Model 6 accounted for 41.6% of the variance COVID-19-related psychological distress.

Additional Analysis

The *observing* facet was removed from our models because it loaded poorly into the overall mindfulness facet and did not correlate with other facets of mindfulness. Nonetheless, given the conflicting findings in the literature regarding the observing facet, we also fit the standard mediation models using the hierarchical and non-hierarchical five-factor structure to examine the associations with the observing facet. The model fit indices and the standardised mediation models of the hierarchical and non-hierarchical five-factor models are presented in **Supplementary Table 4** in the additional material. Most notably, our findings revealed that the *observing* facet was positively associated with mental health problems and rumination, which was the opposite compared to other mindfulness facets.

DISCUSSION

The present study sheds light on the potential mechanisms through which mindfulness can influence mental health by demonstrating that certain emotion regulation strategies (i.e., rumination, cognitive reappraisal and suppression) and insomnia mediate the relationship between mindfulness and symptoms of depression, anxiety and psychological distress. Besides exploring the factor structure of the FFMQ-SF, this study investigated whether different facets of mindfulness and the mediators selected operate transdiagnostically or specifically for different psychopathologies. The present study demonstrated that, differently from cognitive reappraisal and suppression, rumination operated transdiagnostically as a mediator of the effects of mindfulness on symptoms of depression, anxiety and psychological distress during COVID-19. In line with our expectations, the relationships between higher trait mindfulness and mental health outcomes were also mediated by reductions in insomnia symptoms, which, in turn, were mediated by lower levels of rumination. This study also found support for a four-factor structure of the FFMQ-SF (i.e., excluding the *observing* facet) and demonstrated both specific and transdiagnostic effects of certain facets of mindfulness on symptoms of depression, anxiety and psychological distress.

MINDFULNESS AND MENTAL HEALTH: EMOTION REGULATION AND INSOMNIA

In our sample, higher-order mindfulness was directly and negatively associated with all mental health problems. Regarding mindfulness facets, *acting with awareness* and *nonreactivity* were directly linked to anxiety and depression, but only *acting with awareness* was directly related to psychological distress. As hypothesised, all of our models revealed that the association between mindfulness and mental health outcomes was significantly mediated by its negative association with rumination. This result is in line with previous studies demonstrating that rumination mediates the effects of mindfulness on mental health (Desrosiers et al., 2013; Parmentier et al., 2019) and indicates that rumination operates transdiagnostically as a mechanism of the protective effects of mindfulness on depression, anxiety and psychological distress.

Rumination is characterised by a pattern of repetitive negative thoughts about an emotional experience or situation. Theorists have suggested that the *nonjudging* and *acting with awareness* facets of mindfulness may be particularly protective against rumination, which could in turn explain how mindfulness may reduce symptoms of anxiety and depression (Brown et al., 2007; Nolen-Hoeksema et al., 2008). The *acting with awareness* involves consciously attending to moment-to-moment experience. It is plausible that higher levels of such facet may facilitate early recognition, control and disengagement from repetitive thinking patterns characteristics of rumination. *Nonjudging* involves facing one's internal experiences with an acceptant attitude rather than a judgemental one. Higher levels of *nonjudging* may lessen engagements with negative evaluative thoughts, as well as facilitate the acceptance of negative thoughts and feelings as transient experiences, which may reduce the initiation and perpetuation of rumination. Our findings partially support this notion, as our models 4, 5 and 6 revealed that the facets *nonjudging* and *nonreactivity* were negatively associated to rumination, which mediated the link between these facets and mental health outcomes, whereas *acting with awareness* was directly associated with mental health outcomes. In contrast with previous research (Petrocchi and Ottaviani, 2016; Iani et al., 2019), *nonreactivity* was also negatively associated with rumination in our models, which is plausible considering that nonreactivity and acceptance to certain moods could prevent the triggering of ruminative responses in face of negative moods or stimuli. Finally, our exploratory analysis revealed that the *observing* facet was positively associated with rumination, although it has been argued that this relationship may depend on the way in which individuals observe their experiences, which may depend on other mindfulness facets or on meditation experience (Desrosiers et al., 2014). Further research is needed to further examine the relationship between facets of mindfulness and rumination.

Our findings also confirmed our hypothesis that mindfulness was negatively associated with insomnia symptoms and that this relationship was mediated by rumination. Insomnia was directly associated with the *acting with awareness* and *nonreactivity* facets of mindfulness, as well as indirectly associated with *nonjudging* and *nonreactivity* through rumination. Several studies have shown that mindfulness has a positive influence on sleep (Rusch et al., 2019), but few studies have examined emotion regulation strategies (e.g., rumination) as possible mediators (Liu et al., 2018; Calvete and Joana, 2021). The evidence from these studies is consistent with our finding that mindfulness, particularly the *nonjudging, nonreactivity* and *acting with awareness* facets, seems to improve sleep and reduces insomnia symptoms either directly or indirectly by reducing rumination.

Furthermore, in our sample, insomnia mediated the associations between mindfulness and depression, anxiety and psychological distress, indicating that sleep may be a transdiagnostic working mechanism of the positive effects of mindfulness on mental health. Therefore, it seems that mindfulness not only affects mental health by reducing rumination, but also that these improvements in mood regulation translate to fewer insomnia symptoms, which in turn also positively influences mental health. These results are supported by both theory and empirical evidence, which suggests that emotion regulation, particularly rumination, plays an crucial role in sleep disturbances (Nolen-Hoeksema et al., 2008; Pillai and Drake, 2015) and that sleep, in turn, has a profound effect on mental health (Hall et al., 2000; Alvaro et al., 2011; Lopresti et al., 2013). Remarkably, while sleep is certainly affected by emotion regulation, evidence demonstrates that sleep can also influence emotional reactivity and the regulation of positive and negative emotions, suggesting a complex interplay between sleep and emotion regulation (Gruber and Cassoff, 2014). Research has found that sleep influences stress hormones and inflammation (Wright et al., 2015), which have been shown

to be involved in the development of depression (Iob et al., 2020), anxiety (Donovan et al., 2010) and psychological distress (Goldman-mellor et al., 2012). These pathways may partially explain how the complex interplay between sleep and emotion regulation, primarily rumination, operate transdiagnostically and contribute to different forms of psychopathology. Although further research is needed to explore the complex mechanisms linking sleep, emotion regulation and mental health, the present study demonstrates that mindfulness, particularly its *nonjudging*, *acting with awareness* and *nonreactivity* facets, seems to have a positive influence on mental health through reductions in rumination and insomnia symptoms. Future studies with experimental and longitudinal designs are needed to confirm our findings and further examine how increasing mindfulness and its facets can possibly prevent and treat mental health problems through improvements in emotion regulation and sleep behaviour. By using these insights, future research can develop more effective mindfulness interventions for mental health by, for instance, focusing on *nonjudging*, *nonreactivity* and *acting with awareness* facets of mindfulness, which seem to reduce sleep problems both directly and through reductions in rumination.

Our hypothesis on cognitive reappraisal and suppression as working mechanisms of mindfulness were only partially supported, as our findings indicated that cognitive reappraisal and suppression may mediate the effects of mindfulness on depression, but not on anxiety or psychological distress. Therefore, contrary to our expectations, cognitive reappraisal and suppression did not operate as transdiagnostic mediators of mindfulness, but rather specifically for depression. Cognitive reappraisal seemed to specifically mediate the influence of a higher-order mindfulness construct on depression, although this did not reach statistical significance. This result is in line with previous research demonstrating that cognitive reappraisal mediated the effects of mindfulness on depression, but not anxiety (Desrosiers et al., 2013), as well as with neuroimaging research indicating that dispositional mindfulness is associated with greater activation of brain regions responsible for emotion regulation during a reappraisal task (Modinos and Ormel, 2010). However, our finding is somewhat incongruent with one previous study which showed that cognitive reappraisal mediated the effects of mindfulness on both anxiety and depression (Parmentier et al., 2019). Therefore, further research is needed to examine whether cognitive reappraisal mediates the effects of mindfulness on anxiety. Additionally, our models revealed that suppression did not mediate the influence of higher-order mindfulness on depression, but it was a significant mediator of the effect of certain facets of mindfulness on depression, namely, the *describing*, *nonjudging* and *nonreactivity* facets. These findings are congruent with a previous studies examining the working mechanisms of mindfulness, which found that suppression significantly mediated the effects of mindfulness on depression, but not on anxiety (Parmentier et al., 2019). However, our results differ in that suppression did not significantly mediate the effects of higher-order mindfulness on depression, but rather mediated the effects of the *describing*, *nonjudging* and *nonreactivity* facets. It is important to note that, in line with previous literature (Zhang et al., 2019), we found that *nonreactivity* had a positive association with suppression, whereas *describing* and *nonjudging* had a negative association, which might be the explanation why suppression did not mediate the effect of higher-order mindfulness on depression in Model 1. Although further studies are needed to confirm our findings, future intervention studies can use these insights to target mindfulness facets that are most closely linked to poor emotion regulation, thereby more effectively reducing suppression and rumination. Together with the evidence from previous studies (Desrosiers et al., 2013; Parmentier et al., 2019), our findings suggest that while rumination and sleep operate as common mediating mechanisms of the effects of mindfulness on depression, anxiety and psychological distress, cognitive reappraisal and suppression appear to operate specifically on depression.

MEASURING MINDFULNESS: PSYCHOMETRIC PROPERTIES OF THE FFMQ-SF

In addition to investigating the working mechanisms of mindfulness, this study explored the psychometric properties of the FFMQ-SF. The confirmatory factor analysis provided the most support for both the hierarchical four-factor model and the non-hierarchical four-factor models of the FFMQ-SF, without the *observing* facet. This finding is in line with the original study investigating the psychometric properties of the FFMQ (Baer et al., 2006), as well as with subsequent studies investigating the validity of the Swedish (Lilja et al., 2011) and short-form English (Abujaradeh et al., 2019) versions of the questionnaire, which demonstrated that the *observing* facet was not a significant part of self-reported mindfulness in populations with limited meditation experience. Remarkably, while most facets of mindfulness were negatively associated with mental health outcomes in our sample, particularly the *acting with awareness*, *nonjudging* and *nonreactivity*, the *observing* facet was consistently positively associated with mental health problems, either directly or indirectly through its positive association with rumination. This is in line with findings from previous studies exploring the relationship between mindfulness facets, rumination and depression in adolescents (Royuela-Colomer and Calvete, 2016), which also found that *acting with awareness* and *nonreactivity* had a positive impact on mental health, whereas the observing facet had the opposite effect. Thus, while our findings provide support for the adaptive role of several facets of mindfulness, such as *acting with awareness* and *nonreactivity*, it seems that the observing facet may play a maladaptive role in the general population.

There are several possible explanations for the inconsistent functioning of the *observing* facet. One study found that *observing* was correlated with psychological adjustment in meditators, but not in nonmeditating samples (Baer et al., 2008). Baer et al. (2008) suggested that while the *observing* facet may capture maladaptive forms of attention in

nonmeditators, a higher score on *observing* in meditators may simply reflect a greater tendency to attend to a range of internal and external stimuli, rather than attending selectively to threatening or unpleasant ones. Recent studies have also suggested that the *observing* facet in the FFMQ lacks items assessing awareness of emotion and that this may explain the unexpected relationships found between the *observing* facet, psychological symptoms and other mindfulness facets (Rudkin et al., 2018). For example, this may explain differences between meditators and nonmeditators, since meditation trains the nonevaluative and accepting observation of all stimuli, including emotions, thoughts and external stimuli, the *observing* facet may in fact capture the awareness of emotions for meditators, but not for nonmeditators.

LIMITATIONS AND IMPLICATIONS

The current study should be interpreted in light of certain limitations. Firstly, the cross-sectional design limits the interpretation of causality between variables of interest in our models. Future research should conduct experimental or longitudinal studies involving mindfulness interventions to further examine the behavioural and cognitive mechanisms explored in our mediation analysis. Moreover, the collection of the data was based exclusively on self-report measures. To improve the validity of our findings and to further explore the mechanisms linking mindfulness to mental health, future studies could implement additional measurements methods, such as neuroimaging measures and objective assessments of sleep duration and quality. Considering that this study relied on data from an international sample consisting largely of university students, future research is also needed to examine generalisability of our findings to other populations (e.g., low-income older adults). Finally, we did not assess for meditation experiences, which would have allowed us to explore possible differences between meditators and non-mediators.

Despite these constraints, several strengths and implications of the current study should be mentioned. This study showed that rates of depression, anxiety, psychological distress and insomnia were considerably higher during the initial period of the pandemic (May–June 2022) than prevalence rates reported in pre-pandemic studies with international (Ohayon, 2002; Varma et al., 2021) and Dutch samples (De Graaf et al., 2012; Ormel et al., 2015). Additionally, a large proportion of participants reported moderate-to-extreme COVID-19-related financial worries and risk perception. Although some research has observed resilience to mental health problems during the pandemic in certain groups (e.g., older adults; Fields et al., 2021), we observed elevated rates of mental health problems in this study's international sample consisting mainly of young adults residing in Netherlands and Germany. These findings reinforce the importance of investigating, as we did, whether and how mindfulness could partially explain the heterogeneity in risk for psychopathology during the COVID-19 pandemic.

Our findings contributed to the existing evidence (Desrosiers et al., 2013; Freudenthaler et al., 2017; Parmentier et al., 2019) supporting the role of emotion regulation strategies as mediators of the effects of mindfulness on mental health. This study also added to the literature (Gruber and Cassoff, 2014; Pillai and Drake, 2015) by investigating whether and how the interplay between maladaptive emotion regulation (i.e., rumination) and insomnia mediates the relationship between mindfulness and mental health in a large sample. Our findings indicated that both rumination and sleep operate transdiagnostically as working mechanisms of mindfulness, and our models revealed that the *acting with awareness*, *nonjudging* and *nonreactivity* facets of mindfulness were most strongly related to decreases in rumination and insomnia symptoms. Future MBIs could more effectively improve mental health by targeting mindfulness facets that are more strongly associated with reductions in rumination (i.e., *nonjudging* and *nonreactivity*) and insomnia (i.e., *acting with awareness*). This study also emphasises the benefit of targeting mindfulness interventions for individuals with poor emotion regulation and sleep. Nonetheless, given the strong associations between mindfulness, mental health and improved emotion regulation and sleep, our results also highlight the potential usefulness of offering MBIs to the general population, particularly in times of crisis, such as the COVID-19 pandemic. Given that mindfulness buffers stress, the effects of mindfulness on mental health observed in this study may have been particularly robust due to the study being conducted during a highly stressful period. However, similar findings have been observed in pre-pandemic studies (Desrosiers et al., 2013; Parmentier et al., 2019). Even though levels of stress and rumination observed in pre-pandemic studies could be expected to be lower, they were nonetheless relevant for mental health. Therefore, we argue that the effects of mindfulness on emotion regulation, sleep and mental health observed in the present study are also likely applicable to normal circumstances.

Moreover, our findings indicated that cognitive reappraisal and suppression were relevant mediators of the effects of mindfulness on depression, but not for anxiety or psychological distress. Although further research is warranted to confirm these findings, especially given the conflicting findings in the literature regarding, for example, the role of cognitive reappraisal in anxiety (Desrosiers et al., 2013; Parmentier et al., 2019), these results indicate that certain emotion regulation strategies like cognitive reappraisal may be particularly relevant for depressive symptoms, rather than operate transdiagnostically for various psychopathologies. Finally, in an exploratory fashion, this study also examined the psychometric properties of the FFMQ-SF and found the greatest support for a four-factor model without the *observing* facet, which is in line with previous literature. Future studies should continue to measure the elements of mindfulness separately in order to investigate how meditation practice may affect them differently, as well as to explore how the facets may relate differently with other variables of interest. These insights may shed light on the specific processes that

are influenced by meditation and their role in promoting mental health, which could guide the tailoring of future MBIs to improve their effectiveness.

CONCLUSION

Findings of our structural equation models suggest that mindfulness and its facets impact mental health both directly and indirectly through emotion regulation strategies and insomnia. *Acting with awareness*, *nonreactivity* and *nonjudging* seemed to be the mindfulness facets that exerted the strongest positive influence on mental health, emotion regulation and insomnia symptoms. Rumination and sleep seem to be interconnected mediating mechanisms of the effects of mindfulness on symptoms of depression, anxiety and psychological distress, operating transdiagnostically, whereas cognitive reappraisal and suppression functioned specifically as mechanisms for depression and had less robust effects. These findings emphasise the need of disentangling the unique components of mindfulness, emotion regulation and their potential interactions with health behaviours to more clearly understand the mechanisms through which mindfulness can influence symptoms of depression, anxiety and psychological distress. Such insights can facilitate the development of more effective mindfulness interventions for mental health by, for instance, guiding the tailoring and/or targeting of mindfulness interventions for individuals with poor emotion regulation or sleep. Moreover, our findings emphasise the potential benefits of offering mindfulness interventions to the general population in order to prevent and treat mental health problems, particularly in times of crisis such as during the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethics Review Committee of the Department of Psychology, Education and Child Studies, Erasmus University Rotterdam (application number 20-051). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM took the lead in the conception and design for the study. AM was responsible for collecting, analysing and interpreting the data, as well as for drafting the manuscript under the supervision and with feedback from IM, GN, and SD. IM, GN, and SD critically revised the manuscript, provided feedback, and contributed to writing the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.820959/full#supplementary-material

REFERENCES

Abdulah, D. M., and Musa, D. H. (2020). Insomnia and stress of physicians during COVID-19 outbreak. *leep Med.: X* 2:100017. doi: 10.1016/j.sleepx.2020.100017

Abujaradeh, H., Colaianne, B. A., Roeser, R. W., Tsukayama, E., and Galla, B. M. (2019). Evaluating a short-form five facet mindfulness questionnaire in adolescents: evidence for a four-factor structure and invariance by time, age, and gender. *Int. J. Behav. Dev.* 44, 20–30. doi: 10.1177/0165025419873039

Aldao, A., and Christensen, K. (2015). Linking the expanded process model of emotion regulation to psychopathology by focusing on behavioral outcomes of regulation. *Psychol. Inq.* 26, 27–36. doi: 10.1080/1047840X.2015.962399

Aldao, A., Nolen-hoeksema, S., and Schweizer, S. (2010). Clinical psychology review emotion-regulation strategies across psychopathology: a meta-analytic review. *Clin. Psychol. Rev.* 30, 217–237. doi: 10.1016/j.cpr.2009.11.004

Alvaro, P. K., Honors, B. P., Roberts, R. M., Hons, B. A., Clinical, M., Harris, J. K., et al. (2011). A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* 36, 1059–1068. doi: 10.5665/sleep.2810

Arora, T., and Grey, I. (2020). Health behaviour changes during COVID-19 and the potential consequences: a mini-review. *J. Health Psychol.* 25, 1155–1163. doi: 10.1177/1359105320937053

Baer, R. A. (2003). Mindfulness training as a clinical intervention: a conceptual and empirical review. *Clin. Psychol. Sci. Pract.* 10, 125–143. doi: 10.1093/clipsy/bpg015

Baer, R. A., Smith, G. T., Hopkins, J., and Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment* 13, 27–45. doi: 10.1177/1073191105283504

Baer, R. A., Smith, G. T., Lykins, E., Button, D., Sauer, S., Duggan, D., et al. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment* 15, 329–342. doi: 10.1177/1073191107313003

Bastien, Â. H., Vallie, A., and Morin, C. M. (2001). Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med.* 2, 297–307. doi: 10.1016/S1389-9457(00)00065-4

Bohlmeijer, E., Klooster, P. M., Fledderus, M., Veehof, M., and Baer, R. (2011). Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. *Assessment* 18, 308–320. doi: 10.1177/1073191111408231

Brown, K. W., Ryan, R. M., Creswell, J. D., Warren, K., Ryan, R. M., Mindfulness, J. D. C., et al. (2007). Mindfulness: theoretical foundations and evidence for its salutary effects mindfulness: theoretical foundations and evidence for its salutary effects. *Int. J. Adv. Psychol. Theory* 18, 211–237. doi: 10.1080/10478400701598298

Burke, T., Berry, A., Taylor, L. K., Stafford, O., Murphy, E., Shevlin, M., et al. (2020). Increased psychological distress during COVID-19 and quarantine in Ireland: a national survey. *J. Clin. Med.* 9, 1–15. doi: 10.3390/jcm9113481

Calvete, E., and Joana, G. (2021). The role of dispositional mindfulness profiles as predictors of sleep problems through rumination in adolescents over time. *Personal. Individ. Differ.* 180:110966. doi: 10.1016/j.paid.2021.110966

Carlson, L. E., and Garland, S. N. (2005). Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. *Int. J. Behav. Med.* 12, 278–285. doi: 10.1207/s15327558ijbm1204_9

Cunningham, T. J., Fields, E. C., Garcia, S. M., and Kensinger, E. A. (2021). The relation between age and experienced stress, worry, affect, and depression during the spring 2020 phase of the COVID-19 pandemic in the United States. *Emotion* 21, 1660–1670. doi: 10.1037/emo0000982

De Graaf, R., Ten Have, M., Van Gool, C., and Van Dorsselaer, S. (2012). Prevalence of mental disorders and trends from 1996 to 2009. results from the Netherlands mental health survey and incidence study-2. *Soc. Psychiatry Psychiatr. Epidemiol.* 47, 203–213. doi: 10.1007/s00127-010-0334-8

Desrosiers, A., Vine, V., Curtiss, J., and Klemanski, D. H. (2014). Observing nonreactively: a conditional process model linking mindfulness facets, cognitive emotion regulation strategies, and depression and anxiety symptoms. *J. Affect. Disord.* 165, 31–37. doi: 10.1016/j.jad.2014.04.024

Desrosiers, A., Vine, V., Klemanski, D. H., and Nolen-Hoeksema, S. (2013). Mindfulness and emotion regulation in depression and anxiety: common and distinct mechanisms of action. *Depress. Anxiety* 30, 654–661. doi: 10.1002/da.22124

Desteno, D., Gross, J. J., and Kubzansky, L. (2013). Affective science and health: the importance of emotion and emotion. *Regulation* 32, 474–486. doi: 10.1037/a0030259

Donovan, A. O., Hughes, B. M., Slavich, G. M., Lynch, L., Cronin, M., Farrelly, C. O., et al. (2010). Brain, behavior, and immunity clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion – biology relationships. *Brain Behav. Immun.* 24, 1074–1077. doi: 10.1016/j.bbi.2010.03.003

Erdur-Baker, Ö., and Bugay, A. Ö. (2010). The short version of ruminative response scale: reliability, validity and its relation to psychological symptoms. *Procedia Soc. Behav. Sci.* 5, 2178–2181. doi: 10.1016/j.sbspro.2010.07.433

Evans, D. R., and Segerstrom, S. C. (2011). Why do mindful people worry less? *Cogn. Ther. Res.* 35, 505–510. doi: 10.1007/s10608-010-9340-0

Fields, E. C., Kensinger, E. A., Garcia, S. M., Ford, J. H., and Cunningham, T. J. (2021). With age comes well-being: older age associated with lower stress, negative affect, and depression throughout the COVID-19 pandemic. *Aging Ment. Health* 1–9, 1–9. doi: 10.1080/13607863.2021.2010183

Freudenthaler, L., Turba, J. D., and Tran, U. S. (2017). Emotion regulation mediates the associations of mindfulness on symptoms of depression and anxiety in the general population. *Mindfulness* 8, 1339–1344. doi: 10.1007/s12671-017-0709-y

Gilchrist, J. D., Battista, K., Patte, K. A., Faulkner, G., Carson, V., and Leatherdale, S. T. (2021). Effects of reallocating physical activity, sedentary behaviors, and sleep on mental health in adolescents. *Ment. Health Phys. Act.* 20:100380. doi: 10.1016/j.mhpa.2020.100380

Goldberg, S. B., Riordan, K. M., Sun, S., and Davidson, R. J. (2021). The empirical status of mindfulness-based interventions: a systematic review of 44 meta-analyses of randomized controlled trials. *Perspect. Psychol. Sci.* 17, 108–130. doi: 10.1177/1745691620968771

Goldman-mellor, S., Hamer, M., and Steptoe, A. (2012). Early-life stress and recurrent psychological distress over the lifecourse predict divergent cortisol reactivity patterns in adulthood. *Psychoneuroendocrinology* 37, 1755–1768. doi: 10.1016/j.psyneuen.2012.03.010

Greeson, J. M., Zarrin, H., Smoski, M. J., Brantley, J. G., Lynch, T. R., Webber, D. M., et al. (2018). Mindfulness meditation targets transdiagnostic symptoms implicated in stress-related disorders: understanding relationships between changes in mindfulness, sleep quality, and physical symptoms. *Evid. Based Complement. Alternat. Med.* 2018:4505191. doi: 10.1155/2018/4505191

Gross, J. J., and John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J. Pers. Soc. Psychol.* 85, 348–362. doi: 10.1037/0022-3514.85.2.348

Gruber, R., and Cassoff, J. (2014). The interplay between sleep and emotion regulation: conceptual framework empirical evidence and future directions. *Curr. Psychiatry Rep.* 16:500. doi: 10.1007/s11920-014-0500-x

Gu, J., Strauss, C., Bond, R., and Cavanagh, K. (2015). How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clin. Psychol. Rev.* 37, 1–12. doi: 10.1016/j.cpr.2015.01.006

Hall, M., Buysse, D. J., Nowell, P. D., Nofzinger, E. A., Houck, P., Reynolds, C. F., et al. (2000). Symptoms of stress and depression as correlates of sleep in primary insomnia. *Psychosom. Med.* 62, 227–230. doi: 10.1097/00006842-200003000-00014

Hofmann, S. G., Sawyer, A. T., Witt, A. A., and Oh, D. (2010). The effect of Mindfulness-based therapy on anxiety and depression: a meta-analytic review. *J. Consult. Clin. Psychol.* 78, 169–183. doi: 10.1037/a0018555

Hu, L.-t, and Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct. Equ. Modeling* 6, 1–55. doi: 10.1080/10705519909540118

Iani, L., Lauriola, M., Chiesa, A., and Cafaro, V. (2019). Associations between mindfulness and emotion regulation: the key role of describing and nonreactivity. *Mindfulness* 10, 366–375. doi: 10.1007/s12671-018-0981-5

Iob, E., Kirschbaum, C., and Steptoe, A. (2020). Persistent depressive symptoms, HPA-axis hyperactivity, and inflammation: the role of cognitive-affective and somatic symptoms. *Mol. Psychiatry* 25, 1130–1140. doi: 10.1038/s41380-019-0501-6

Jané-Llopis, E., and Matytsina, I. (2006). Mental health and alcohol, drugs and tobacco: a review of the comorbidity between mental disorders and the use of alcohol, tobacco and illicit drugs. *Drug Alcohol Rev.* 25, 515–536. doi: 10.1080/09595230600944461

Khalid, S., Williams, C. M., and Reynolds, S. A. (2017). Is there an association between diet and depression in children and adolescents? A systematic review. *Br. J. Nutr.* 116, 2097–2108. doi: 10.1017/S0007114516004359

Killgore, W. D. S., Taylor, E. C., Cloonan, S. A., and Dailey, N. S. (2020). Psychological resilience during the COVID-19 lockdown. *Psychiatry Res.* 291, 113216. doi: 10.1016/j.psychres.2020.113216

Kroenke, K., Strine, T. W., Spitzer, R. L., Williams, J. B. W., Berry, J. T., and Mokdad, A. H. (2009). The PHQ-8 as a measure of current depression in the general population. *J. Affect. Disord.* 114, 163–173. doi: 10.1016/j.jad.2008.06.026

Lilja, J. L., Frodi-lundgren, A., Hanse, J. J., Lundh, L., Sköld, C., Hansen, E., et al. (2011). Five facets mindfulness questionnaire — reliability and factor structure: a swedish version. *Cogn. Behav. Ther.* 40, 291–303. doi: 10.1080/16506073.2011.580367

Little, T. D., Cunningham, W. A., Shahar, G., Widaman, K. F., Little, T. D., Cunningham, W. A., et al. (2009). To parcel or not to parcel: exploring the question, weighing the merits. *Struct. Equ. Model.* 9, 151–173. doi: 10.1207/S15328007SEM0902

Liu, Q., Zhou, Z., Yang, X., Kong, F., and Sun, X. (2018). Personality and individual differences mindfulness and sleep quality in adolescents: analysis of rumination as a mediator and self-control as a moderator. *Personal. Individ. Differ.* 122, 171–176. doi: 10.1016/j.paid.2017.10.031

Lopresti, A. L., Hood, S. D., and Drummond, P. D. (2013). A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. *J. Affect. Disord.* 148, 12–27. doi: 10.1016/j.jad.2013.01.014

Löwe, B., Decker, O., Müller, S., Brähler, E., Herzog, W., Herzberg, P. Y., et al. (2008). Validation and standardization of the generalized anxi disorder screener (GAD-7) in the general population. *Med. Care* 46, 266–274. doi: 10.1097/MLR.0b013e318160d093

Lu, J., Mumba, M. N., Lynch, S., Li, C., Hua, C., and Allen, R. S. (2019). Nursing students' trait mindfulness and psychological stress: a correlation and mediation analysis. *Nurse Educ. Today* 75, 41–46. doi: 10.1016/j.nedt.2018.12.011

Mahase, E. (2020). Covid-19: WHO Declares Pandemic because of "Alarming Levels" of Spread, Severity, and Inaction. *BMJ* 68:m1036. doi: 10.1136/bmj.m1036

Mamede, A., Noordzij, G., Merkelbach, I., and Denktas, S. (2020). The relationship between mindfulness and mental health during the COVID-19 pandemic: exploring sleep and emotional regulation as potential mechanisms of action. doi: 10.17605/OSF.IO/K9QTW

Martin, R. C., and Dahlen, E. R. (2005). Cognitive emotion regulation in the prediction of depression, anxiety, stress, and anger. *Pers. Individ. Differ.* 39, 1249–1260. doi: 10.1016/j.paid.2005.06.004

Mesmer-magnus, J., Manapragada, A., Viswesvaran, C., and Allen, J. W. (2017). Trait mindfulness at work: a meta-analysis of the personal and professional correlates of trait mindfulness. *Hum. Perform.* 30, 79–98. doi: 10.1080/08959285.2017.1307842

Modinos, G., and Ormel, J. (2010). Individual differences in dispositional mindfulness and brain activity involved in reappraisal of emotion. *Soc. Cogn. Affect. Neurosci.* 5, 369–377. doi: 10.1093/scan/nsq006

Mojtabai, R., Olfson, M., and Han, B. (2016). National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics* 138:e20161878. doi: 10.1542/peds.2016-1878

Morin, C. M., Belleville, G., Bélanger, L., and Ivers, H. (2011). The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 34, 601–608. doi: 10.1093/sleep/34.5.601

Nolen-Hoeksema, S., Wisco, B. E., and Lyubomirsky, S. (2008). Rethinking rumination. *Perspect. Psychol. Sci.* 3, 400–424. doi: 10.1111/j.1745-6924.2008.00088.x

Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med. Rev.* 6, 97–111. doi: 10.1053/smrv.2002.0186

Ormel, J., Raven, D., Van Oort, F., Hartman, C. A., Reijneveld, S. A., Veenstra, R., et al. (2015). Mental health in Dutch adolescents: a TRAILS report on prevalence, severity, age of onset, continuity and co-morbidity of DSM disorders. *Psychol. Med.* 45, 345–360. doi: 10.1017/S0033291714001469

Pan, K. Y., Kok, A. A. L., Eikelenboom, M., Horsfall, M., Jörg, F., Luteijn, R. A., et al. (2021). The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: a longitudinal study of three Dutch case-control cohorts. *Lancet Psychiatry* 8, 121–129. doi: 10.1016/S2215-0366(20)30491-0

Parmentier, F. B. R., García-toro, M., and García-campayo, J. (2019). Mindfulness and symptoms of depression and anxiety in the general population: the mediating roles of worry, rumination, reappraisal and suppression. *Front. Psychol.* 10:506. doi: 10.3389/fpsyg.2019.00506

Petrocchi, N., and Ottaviani, C. (2016). Mindfulness facets distinctively predict depressive symptoms after two years: the mediating role of rumination. *Personal. Individ. Differ.* 93, 92–96. doi: 10.1016/j.paid.2015.08.017

Pillai, V., and Drake, C. L. (2015). "Sleep and repetitive thought: the role of rumination and worry in sleep disturbance," in *Sleep and Affect: Assessment, Theory, and Clinical Implications*. eds. K. A. Babson and M. T. Feldner (San Diego: Elsevier Academic Press), 201–225.

Raes, F., and Williams, J. M. G. (2010). The relationship between mindfulness and uncontrollability of ruminative thinking. *Mindfulness* 1, 199–203. doi: 10.1007/s12671-010-0021-6

Remes, O., Brayne, C., van der Linde, R., and Lafortune, L. (2016). A systematic review of reviews on the prevalence of anxiety disorders in adult populations. *Brain Behav.* 6, e00497. doi: 10.1002/brb3.497

Rodríguez-Rey, R., Garrido-Hernansaiz, H., and Collado, S. (2020). Psychological impact of COVID-19 in Spain: early data report. *Psychol. Trauma* 12, 550–552. doi: 10.1037/tra0000943

Royuela-Colomer, E., and Calvete, E. (2016). Mindfulness facets and depression in adolescents: rumination as a mediator. *Mindfulness* 7, 1092–1102. doi: 10.1007/s12671-016-0547-3

Rudkin, E., Medvedev, O. N., and Siegert, R. J. (2018). The five-facet mindfulness questionnaire: why the observing subscale does not predict psychological symptoms. *Mindfulness* 9, 230–242. doi: 10.1007/s12671-017-0766-2

Rusch, H. L., Rosario, M., Levison, L., Olivera, A., Livingston, W. S., Wu, T., et al. (2019). The effect of mindfulness meditation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. *Ann. N. Y. Acad. Sci.* 1445, 5–16. doi: 10.1111/nyas.13996

Sala, M., Rochefort, C., Lui, P. P., and Baldwin, A. S. (2019). Trait mindfulness and health behaviours: a meta-analysis. *Health Psychol. Rev.* 14, 345–393. doi: 10.1080/17437199.2019.1650290

Sauer, S., Walach, H., Schmidt, S., Hinterberger, T., Lynch, S., Büssing, A., et al. (2013). Assessment of mindfulness: review on state of the art. *Mindfulness* 4, 3–17. doi: 10.1007/s12671-012-0122-5

Shin, C., Lee, S., Han, K., Yoon, H., and Han, C. (2019). Comparison of the usefulness of the PHQ-8 and PHQ-9 for screening for major depressive disorder: analysis of psychiatric outpatient data. *Psychiatry Investig.* 16, 300–305. doi: 10.30773/pi.2019.02.01

Soysa, C. K., and Wilcomb, C. J. (2015). Mindfulness, self-compassion, self-efficacy, and gender as predictors of depression, anxiety, stress, and well-being. *Mindfulness* 6, 217–226. doi: 10.1007/s12671-013-0247-1

Treynor, W., Gonzalez, R., and Nolen-Hoeksema, S. (2003). Rumination reconsidered: a psychometric analysis. *Cogn. Ther. Res.* 27, 247–259. doi: 10.1023/A:1023910315561

van Zyl, L. E., Rothmann, S., and Zondervan-Zwijnenburg, M. A. J. (2021). Longitudinal trajectories of study characteristics and mental health before and during the COVID-19 lockdown. *Front. Psychol.* 12:633533. doi: 10.3389/fpsyg.2021.633533

Varma, P., Junge, M., Meaklim, H., and Jackson, M. L. (2021). Younger people are more vulnerable to stress, anxiety and depression during COVID-19 pandemic: a global cross-sectional survey. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 109, 110236–110238. doi: 10.1016/j.pnpbp.2020.110236

Veehof, M. M., Klooster, P. M., Taal, E., Westerhof, G. J., and Bohlmeijer, E. T. (2011). Psychometric properties of the Dutch five facet Mindfulness questionnaire (FFMQ) in patients with fibromyalgia. *Clin. Rheumatol.* 30, 1045–1054. doi: 10.1007/s10067-011-1690-9

Vindegaard, N., and Benros, M. E. (2020). COVID-19 pandemic and mental health consequences: systematic review of the current evidence. *Brain Behav. Immun.* 89, 531–542. doi: 10.1016/j.bbi.2020.05.048

Vloo, A., Alessie, R. J. M., Mierau, J. O., Boezen, M. H., Mierau, J. O., Franke, L., et al. (2021). Gender differences in the mental health impact of the COVID-19 lockdown: longitudinal evidence from the Netherlands. *SSM - Popul. Health.* 15:100878. doi: 10.1016/j.ssmph.2021.100878

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S., et al. (2019). Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int. J. Environ. Res. Public Health* 17:1729. doi: 10.3390/ijerph17051729

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Mcintyre, R. S., et al. (2020a). A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. *Brain Behav. Immun.* 87, 40–48. doi: 10.1016/j.bbi.2020.04.028

Wang, Y. Y., Wang, F., Zheng, W., Zhang, L., Ng, C. H., Ungvari, G. S., et al. (2020b). Mindfulness-based interventions for insomnia: a meta-analysis of randomized controlled trials. *Behav. Sleep Med.* 18, 1–9. doi: 10.1080/15402002.2018.1518228

Weiss, D. S., and Marmar, C. R. (1997). "The impact of event scale revised," in *Assessing Psychological Trauma and PTSD*. eds. J. P. Wilson and T. M. Keane (New York: Guilford Press).

West, S. G., Taylor, A. B., and Wu, W. (2012). "Model fit and model selection in structural equation modeling," in *Handbook of Structural Equation Modeling*. ed. R. H. Hoyle (The Guilford Press), 209–231.

Wickham, S., Amarasekara, N. A., Bartonicek, A., and Conner, T. S. (2020). The big three health behaviors and mental health and well-being among young adults: a cross-sectional investigation of sleep, exercise, and diet. *Front. Psychol.* 11:579205. doi: 10.3389/fpsyg.2020.579205

Wright, K. P., Drake, A. L., Frey, D. J., Fleshner, M., Desouza, C. A., Gronfier, C., et al. (2015). Brain, behavior, and immunity influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. *Brain Behav. Immun.* 47, 24–34. doi: 10.1016/j.bbi.2015.01.004

Zhang, J., Deng, X., Huang, L., Zeng, H., Wang, L., and Wen, P. (2019). Personality and individual differences profile of trait mindfulness and its association with emotional regulation for early adolescents. *Personal. Individ. Differ.* 147, 12–17. doi: 10.1016/j.paid.2019.04.008

Zheng, M. X., Theodore Charles, M., Jingzian, Y., Yizhen, L., Noriko, T., and Jayanth, N. (2020). Stay mindful and carry on: mindfulness neutralizes

Covid-19 stressors on work engagement *via* sleep duration. *Front. Psychol.* 11:610156. doi: 10.3389/fpsyg.2020.610156

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Targeted Memory Reactivation During REM Sleep in Patients With Social Anxiety Disorder

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Background: Social anxiety disorder (SAD) is characterized by a significant amount of fear when confronted to social situations. Exposure therapy, which is based on fear extinction, does not often lead to full remission. Here, based on evidence showing that rapid eye movement (REM) sleep promotes the consolidation of extinction memory, we used targeted memory reactivation (TMR) during REM sleep to enhance extinction learning in SAD.

Methods: Forty-eight subjects with SAD were randomly assigned to two groups: control or TMR group. All patients had two successive exposure therapy sessions in a virtual reality (VR) environment, where they were asked to give a public talk in front of a virtual jury. At the end of each session, and only in the TMR group ($N = 24$), a sound was paired to the positive feedback phase of therapy (i.e., approval of their performance), which represented the memory to be strengthened during REM sleep. All participants slept at home with a wearable headband device which automatically identified sleep stages and administered the sound during REM sleep. Participants' anxiety level was assessed using measures of parasympathetic (root mean square of successive differences between normal heartbeats, RMSSD) and sympathetic (non-specific skin conductance responses, ns-SCRs) activity, and subjective measures (Subjective Units of Distress Scale, SUDS), during the preparation phase of their talks before (T1) and after (T2) one full-night's sleep and after 1 week at home (T3). Participants also filled in a dream diary.

Results: We observed an effect of time on subjective measures of anxiety (SUDS). We did not find any difference in the anxiety levels of the two groups after 1 week of TMR at home. Importantly, the longer the total duration of REM sleep and the more stimulations the TMR group had at home, the less anxious (increased RMSSD) these participants were. Finally, fear in dreams correlated positively with ns-SCRs and SUDS at T3 in the TMR group.

Conclusion: TMR during REM sleep did not significantly modulate the beneficial effect of therapy on subjective anxiety. Yet, our results support that REM sleep can contribute to extinction processes and substantiate strong links between emotions in dreams and waking stress levels in these patients.

Keywords: sleep, REM sleep, dreaming, social anxiety, targeted memory reactivation, exposure therapy

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INTRODUCTION

Social anxiety disorder (SAD) is characterized by an exaggerated and persistent amount of fear when confronted with social situations (1), which can lead individuals with SAD to either avoid such situations or endure them with significant discomfort (1, 2). It is a chronic disorder with a lifetime prevalence rate of 13% and an early onset in adolescence (3, 4). Studies looking into the mechanisms underlying anxiety disorders converge to suggest that these disorders are characterized by dysfunctional fear extinction (5).

Fear conditioning is a form of associative learning between a neutral stimulus (conditioned stimulus CS) and an innately aversive stimulus (unconditioned stimulus US), after repeated pairings of the CS and the US. After fear conditioning, presentation of the CS alone triggers an emotional response (conditioned response, CR) (6, 7). Fear extinction learning (or inhibitory learning) is a process during which the conditioned fear response decreases or is inhibited when there is a repeated presentation of the CS in the absence of the US. Existing data support that extinction induces the learning of a new association "CS-noUS," in which the CS no longer predicts the US (5, 8). Inhibitory learning is central to extinction and deficit in this process could contribute to the development of anxiety disorders (6, 9).

Exposure therapy is a treatment based on extinction learning mechanisms and involves the gradual and repeated exposure to the feared stimuli in the absence of the negative outcome (5). It is a popular and efficient treatment of SAD and other anxiety disorders such as generalized anxiety disorder (GAD) and specific phobias (10). However, while there is a consensus in the field of psychotherapy regarding the efficiency of exposure therapy to treat SAD, patients are reluctant to seek treatment, as they can be hesitant to engage in social interactions. The use of virtual reality (VR) allows a better control of exposure conditions and the ability to stop or take breaks if the patient is overwhelmed (11). A meta-analysis conducted by Carl et al. (12) indicated that virtual exposure and *in vivo* exposure showed similar efficacy in the treatment of anxiety disorders (including SAD), both leading to reduction of anxiety symptoms. However, exposure is not a foolproof solution to treat anxiety disorders, as its efficacy is not always significant in the long run. Many patients experience a return of fear at the end of the exposure therapy, with rates up to 62% (5). Therefore, there is an emerging need to find ways to enhance the therapeutic outcome of this therapy.

In order to enhance extinction learning, before, during or after exposure therapy, several methods have been used, such as administration of cortisol (13) or stimulation of medial prefrontal cortex (mPFC) with repetitive transcranial magnetic stimulation (14). A simple positive reinforcement or feedback (e.g., positive compliments) regarding the patient's performance, which represents extinction-related violation of expectancy (5), was also found to reduce social anxiety (15), and is an integral part of self-focused exposure therapy (16). Other protocols have used periods of sleep (naps or full night's sleep) to reinforce the consolidation of extinction learning after exposure therapy for anxiety disorders, such as spider phobia (17, 18). A preliminary study recently demonstrated that naps after exposure therapy for SAD lowered sympathetic responses (as measured by skin conductance response and cortisol levels) during anticipation of a social challenge at a trend level (19). In their conclusion, these authors suggested that the lack of significance could potentially be due to the fact that post-exposure sleep was not long enough for the participants to experience rapid eye movement (REM) sleep, and that REM sleep could play an important role in the consolidation of extinction learning.

Indeed, accumulating evidence shows that REM sleep may represent a permissive condition for the processing of extinction memory. Healthy participants who had REM sleep after extinction learning exhibited greater extinction recall, accompanied by stronger activation of the ventromedial prefrontal cortex (vmPFC) in response to the extinguished stimulus (20, 21). Moreover, a greater retention of extinction learning was associated with REM percent in an intervening overnight sleep (22), while a subsequent study elegantly demonstrated that REM sleep (but not slow wave sleep-SWS or wakefulness) causes successful consolidation of extinction memory (23). Other studies also showed that REM sleep helps to decrease the experienced arousal or affective tonus associated with emotional events, thus leading to higher familiarity and habituation to emotionally negative stimuli (emotional depotentiation) (24, 25). Recent neuroimaging data also indicated that negative emotions in dreams, and specifically fear, may contribute to (or reflect) emotional regulation processes during sleep and yield better adapted responses to aversive stimuli during waking life (26).

Importantly, most of the previous studies have been restricted to analyzing the effects of a single night of sleep [or using a split-night design (23)] on fear conditioning and extinction. A recent study (27), showed that baseline REM sleep duration measured over several days (mean, 7.88 days; range, 5–13 days) can predict subsequent reduced fear-related activity in the amygdala, hippocampus, and vmPFC, supporting the enhancing role of this sleep stage not only in extinction, but in reducing fear conditioning too. This effect was present but weaker when markers of fear acquisition were related to a single night of measurement. Such studies (27, 28) stress the importance of assessing REM sleep over several nights to better predict the future level of conditioning (i.e., there is a trait-level rather than state-level effect of sleep on fear conditioning and emotional reactivity).

Memory reactivation during sleep can be induced or intensified with targeted memory reactivation (TMR). This method consists in associating a sensory cue with a learning experience, and subsequently presenting this cue to increase the likelihood that the memory of this experience is reactivated. Thus, presenting the cue during sleep will trigger a neuronal replay of the associated memory, which will strengthen memory consolidation (29). Rasch et al. (30) showed that presenting during sleep an odor, which was previously associated with a learning phase (location of objects), improved the retention of the learned information, as shown by a superior memory performance when tested post-sleep. Such a reactivation during sleep can take place when using odor cues, but also auditory

cues (31, 32). Studies have demonstrated that such cued memory reactivation can improve the consolidation of declarative and procedural memories to levels up to 35% as compared to wakefulness (31, 33, 34). While the benefits of applying TMR during non-REM (NREM) sleep have been established across many studies, results are more inconsistent when cueing occurs during REM sleep, due probably to the predominance of nap studies (containing no or only short periods of REM sleep) (34). TMR during REM sleep enhanced memory (35, 36), including associative emotional memory and generalization (37) [contrary to SWS; Ashton, Cairney (38)], while it increased positive valence of negative stimuli (39, 40) and reduced emotional arousal (41). Therefore, using TMR during REM sleep could be an efficient method to enhance extinction memory consolidation and improve inhibition learning, which is lacking in individuals presenting anxiety disorders.

Lastly, a dominant theory suggests that memories are initially encoded into a fast-learning store (i.e., the hippocampus) and are gradually transformed into a long-term storage (i.e., the cortex) during consolidation (42, 43). In order to avoid the return of fear after extinction (44) and to permanently consolidate the formation of the new (i.e., initially labile) safety memory during sleep, TMR during REM sleep may have to be repeated over several successive nights (at least 1 week), the time needed to make the extinction memory hippocampus-independent (45).

The main goal of this study was to investigate whether TMR during REM sleep over several consecutive nights may enhance exposure therapy in SAD. Even though REM sleep and dreaming appear to have an important role in extinction learning and emotional depotentiation, to our knowledge, no study to date used TMR during REM sleep in the context of treating anxiety disorders. In our study, participants with SAD took part in virtual reality exposure sessions during which they were asked to perform public presentations. Anxiety levels were assessed at different time points with subjective and physiological measures. Specifically, the anticipatory phase of their performance, being particularly stressful (46–48), was chosen as a critical period for stress measurement. Following the public presentations in VR, participants received positive feedback of their performance (16), which served as an extinction period of the therapy. Indeed, as there are no negative consequences such as negative judgment from the jury following the feared situation, this period represents a CS-noUS association reminiscent of extinction learning (5). During this period, participants in the experimental group (TMR group) were exposed to an auditory cue, while those in the control group were not. In the frame of the TMR technique, this allows for an association between the sound and the extinction memory. During eight nights following the first virtual exposure session, participants from both groups received the auditory cue selectively during REM sleep at home.

The primary hypothesis of this study was that (a) participants in the TMR group will show reduced intensity of social anxiety compared to participants in the control group, based on subjective reports and physiological measures, after eight nights of stimulations during REM sleep. Secondary hypotheses included the following: (b) the aforementioned effect could be already observable after one night of sound presentation during REM sleep; (c) participants in the TMR group will experience generalization of extinction compared to participants in the control group, after eight nights of sound presentation during REM sleep; and (d) the number of stimulations in the TMR group and/or REM sleep duration will have a beneficial effect on stress, respectively due to increased TMR-related events and the proposed role of REM sleep in extinction learning and emotional depotentiation. Considering recent evidence on the links between dreams and emotional processing in wakefulness (26), we also hypothesized that: (e) fear in dreams should positively correlate with reduced stress in wakefulness.

METHODS

Participants

Participants were recruited through flyers and advertisements on social media. Inclusion criteria were: being aged between 16 and 40 years old, having SAD according to the Diagnostic and Statistical Manual of Mental Disorder, 5th edition (49), not being under treatment for social anxiety, and not presenting other mental disorders or sleep disorders. Patients with symptoms of obstructive sleep apnea syndrome, restless legs syndrome, insomnia disorder, or under anxiolytics, antipsychotic or antidepressant medication were excluded. Initially, 51 participants were recruited. Three of them were not included in the final analyses because they withdrew from the study. The final sample of participants was composed of 48 participants (32 females and 16 males) with SAD, as assessed by an interview with a certified psychologist. Participants gave their written consent to take part in this study and received a participant fee. The study was approved by the Ethical Committee of the Canton of Geneva, Switzerland ("*Commission Cantonale d'Ethique de la Recherche sur l'être humain*").

Procedure

Forty-eight SAD patients were randomly assigned into two groups (TMR group and control group, **Figure 1**). This randomization took place on Day 1 (T1). Patients of the TMR group received a neutral auditory stimulus [i.e., a 1-second piano chord (C69)], which was associated with the positive feedback phase of exposure therapy. The aim was to consolidate this new associative memory during REM sleep through TMR. Therefore, two positive feedback phases took place on T1: T1a and T1b. The only purpose of the T1b timepoint was to further reinforce the association between the sound and the positive feedback period before the first experimental night, and it was therefore not used in the statistical analyses. After this session, all participants had a full night of polysomnography (PSG). During sleep, patients of both groups received the sound during REM sleep with a wireless sleep headband. On Day 2, the participants underwent another VR session of exposure therapy (T2). Then, they spent 1 week at home with the headband device administrating the sound during REM sleep. On day 9, participants came for one last VR session of exposure therapy (T3). Social anxiety for a public talk was measured during the preparation of the talk at six different time points: before (T1a) and after (T1b) the first session of VR exposure therapy, after one night of sleep with

TMR (T2), and after 1 week of TMR at home (T3). In order to test for generalization of extinction, we tested anxiety for another context (being approached by virtual characters) at time points T0 and T4. Throughout all phases of the VR sessions (baseline, preparation, presentation, and positive feedback) (see Section 'Structure of Each VR Exposure Session' for details), anxiety was measured at the subjective level (Subjective Units of Distress Scale) and physiological level, including heart rate variability and electrodermal activity.

Materials

VR Environment

Participants were immersed in a virtual environment, with an Oculus Rift Headset (Meta Quest, Irvine, California, United States). The virtual environment was designed on Unity 3D (Unity Software Inc., San Francisco, United States) by the Virtual Reality and Robotics facility of the Human Neuroscience Platform, Fondation Campus Biotech Geneva. The virtual environment consisted of a theater stage and an audience space. On the stage, there was a microphone stand in front of which the participant made his/her presentations. From the stage, the participants could see the audience space, where there was a table (with a timer on it), two virtual jury members (one male and one female) and a virtual audience of about 20 members. Electrodes for the recording of electrodermal activity and electrocardiogram signals were placed on the participant before he/she entered the booth, where the VR sessions took place. The participant could communicate and hear the instructions from the experimenter through the headphones and microphone included in the VR headset.

Structure of Each VR Exposure Session

All the VR sessions of the main task (T1a, T1b, T2, and T3) in this experiment have the same structure (see **Supplementary Material 1** for detailed description). They started with a 3-min baseline phase during which participants had to stay seated, relaxed and get used to the environment (baseline phase). The goal of this phase was to allow any distress the participant might feel to dissipate. After this phase, they were allowed 5 min to mentally prepare a short speech on a given topic (preparation phase), which they would present afterwards for 5 min in a virtual theater room with a two-person jury and a public in the background (presentation phase). At the end of their performance, a virtual feedback was given to them: first, a standard positive feedback from the virtual audience and jury (0.5 min), and then the experimenter gave an individualized positive feedback (3 min). During this phase (positive feedback phase), a sound was administered every 10 s in the TMR group, while no such sound was administered in the control group.

Sleep Headband Dreem®

The Dreem® headband is a wireless sleep headband designed by the company Dreem (Dreem SAS, Paris, https://dreem.com/). It is composed of fabric and foam and can be adjusted with an elastic band behind the head. The device records and analyses physiological data: (1) brain activity *via* EEG dry electrodes (derivations: FpZ-O1, FpZ-O2, FpZ-F7, F8-F7, F7-O1, F8-O2, FpZ-F8; 250 Hz with a 0.4–35 Hz bandpass filter), (2) movements, (3) sleep position, and (4) heart rate. The EEG electrodes are placed at the front and back of the device. Sound can be delivered *via* bone-conduction transducers integrated in the headband. The headband monitors sleep and can detect different sleep stages through a reliable algorithm (50). In our experiment, whenever REM sleep was detected for more than 5 min, the sound was delivered to the participants every 10 s. These auditory stimulations were interrupted whenever a new sleep stage was detected (after which they restarted after 5 min of REM), after detection of a movement (90 s of interruption), after detection of an alpha wave (45 s of interruption), after detection of a blink (10 s of interruption), and after bad quality signal (4 s of interruption). The headband was connected to a smartphone application, which provided a summary on sleep quality, and allowed each participant to choose the volume of the sound. Remote access to the raw sleep data and stimulations per night was possible, with daily controls ensuring patient compliance to the protocol.

Questionnaires

As part of the recruitment, participants filled several online questionnaires used to verify inclusion criteria: general socio-demographic and medical questionnaires, the Liebowitz Social Anxiety Scale (LSAS) (51), the Pittsburgh Sleep Quality Index (PSQI) (52), the Beck Anxiety Inventory (BAI) (53), the Beck Depression Inventory II (BDI II) (54), and the Insomnia Severity Index (ISI) (55). During initial assessment, a certified psychologist used the Mini-International Neuropsychiatric Interview (MINI) module on social anxiety disorder (56), a short structured diagnostic interview instrument, based on the DSM-5 criteria.

The LSAS was administered to assess the presence and degree of social anxiety, while the MINI was used in order to establish a SAD diagnosis according to DSM-5. The PSQI and ISI were administered in order to detect and exclude participants with sleeping issues, as the latter could interfere with the study. Finally, we also used the BAI and BDI-II to detect anxious and depressive symptoms, respectively. The internal consistency rates of these questionnaires, as assessed in this study, were calculated with Cronbach's alpha and are considered good/excellent for LSAS ($\alpha = 0.81$), BAI ($\alpha = 0.94$), BDI-II ($\alpha = 0.82$), and acceptable for PSQI ($\alpha = 0.71$) and ISI ($\alpha = 0.77$).

Dream Diary, Sleep Agenda, Psychomotor Vigilance Task

During 2 weeks (starting from 1 week before the first VR session and finishing at the end of the protocol), participants filled out a dream diary and a sleep agenda. The dream diary was filled in every morning upon awakening [see also (26)]. Upon awakening, participants were asked to report whether they had a dream with or without recall or no dream at all, during the immediately preceding night. Whenever they reported having a dream with recall, they were asked to answer additional categorical questions related to the length, clarity, perceptual features, and emotionality of the dream (i.e., whether they

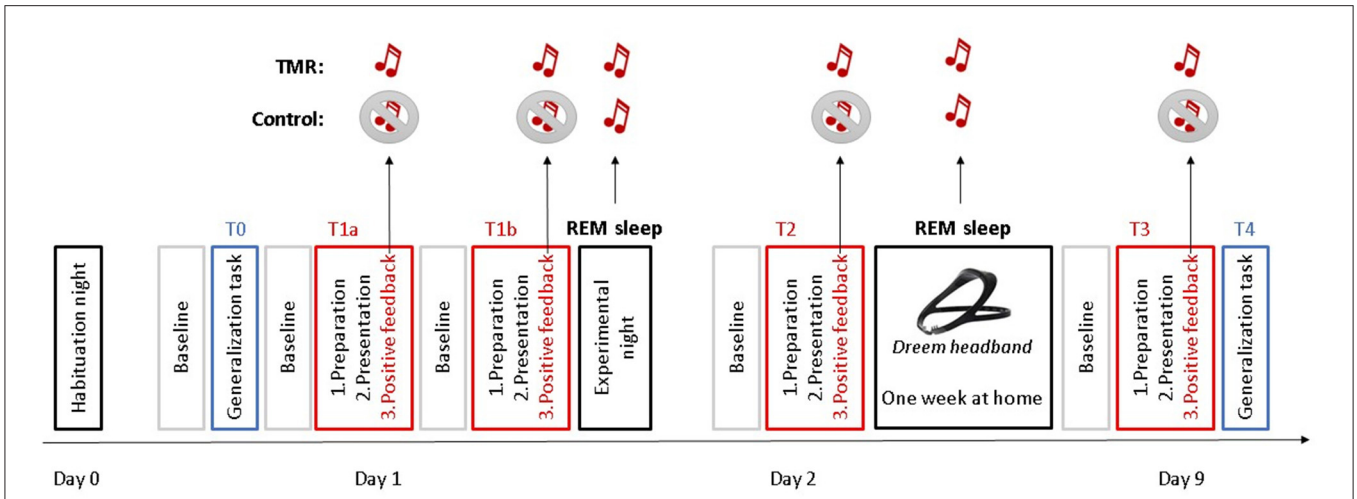

FIGURE 1 | Study design. Participants underwent a habituation night on Day 0. The following day (Day 1), they had one VR session of generalization task (T0) and two VR sessions of self-focused exposure therapy (T1a and T1b), before the experimental night. On Day 2, participants underwent another VR session of exposure therapy (T2). Then, they spent 1 week at home with a headband sleep device. On day 9, participants came for one last VR session of exposure therapy (T3) and one VR session of generalization task (T4). During the positive feedback phases of the VR, a sound was administered to the TMR group, while no sound was administered to the control group. Both groups were administered the sound during their REM sleep at the experimental night and during the nights at home with a sleep headband.

experienced fear, anger, frustration, sadness, embarrassment, confusion, disgust, and joy). Specifically regarding the emotions, participants had to choose whether they were feeling a particular emotion in a dichotomous way, by stating if this emotion was present or not in their dreams. Finally, they were asked to freely describe the dreams they had experienced during their sleep. In the present study, we focused on the closed-ended questions about the emotions experienced in the dream.

Before each VR session, participants also performed a psychomotor vigilance task (PVT), which is a sustained-attention, reaction-timed task (57). Lasting for 5 min, this task consisted in pressing on a computer key as fast as possible, as soon as a millisecond timer appeared on the screen after the disappearance of a fixation cross. This allowed us to ensure that the participants in the two groups did not differ in their general vigilance state during the VR sessions. Additionally, after the two nights at the lab, and after 1 week of sleeping at home, participants filled out post-sleep the St. Mary's Hospital questionnaire (58) to evaluate the quality of their sleep.

Measurements

Measures of Anxiety

During the VR tasks, we assessed stress levels with two physiological measures: heart rate variability (HRV) (59–61) and electrodermal activity (EDA) (62, 63), which provide estimates of parasympathetic and sympathetic nervous system activity, respectively. We have also used a subjective measure of anxiety, the Subjective Units of Distress Scale (SUDS) (64).

HRV was measured using three ECG electrodes (including one ground) placed below the rib (left), under the clavicle (right) and on the hip (right) for the ground. For our study, we were interested in the root mean square of successive differences between normal heartbeats (RMSSD, in ms) for each VR session phase. The RMSSD is used to estimate the vagally mediated changes in heart rate variability (HRV) (65) and presents the advantage of closely representing parasympathetic activity (66), and being relatively free of respiratory influences compared to other variables calculated from HRV (67). Lower levels of RMSSD have been associated with higher anxiety in several anxiety disorders, including SAD (66, 68).

EDA is a term used to define autonomic changes in the electrical properties of the skin and is used as an objective index of emotional stress (62). It was measured with disposable adhesive sensors on the distal phalanges of the index and middle finger of the non-dominant hand of participants. EDA was analyzed to obtain skin conductance responses (SCRs). For our study, we were interested in the non-specific SCRs (ns-SCRs), which are spontaneous, phasic increases in EDA that are not associated with any specific stimuli (62). An increased frequency of ns-SCRs is considered a biomarker of high arousal in situations of stress, emotional reactivity and anticipatory anxiety (46, 62, 69).

The adapted Subjective Units of Distress Scale, SUDS (64, 70) was used during the Virtual Reality (VR) sessions to measure the intensity of distress of people suffering from social anxiety. It consists in a single question scale, in which the subject rates on a scale from 0 to 10 the level of distress that they were feeling at a specific moment. The SUDS was given after each positive feedback and preparation phase, after T0, as well as before the preparations T2 and T3.

Both ns-SCRs and RMSSD were recorded using the Biopac MP160 System (Biopac Systems Inc., Goleta, CA, 2013), and the software AcqKnowledge v.5.0. Details of data analysis of ns-SCRs and RMSSD are provided in **Supplementary Material 2**. The internal consistency rates of these measures in this study were

calculated with Cronbach's alpha and are considered excellent for RMSSD ($\alpha = 0.92$) and good for SUDS ($\alpha = 0.88$) and ns-SCRs ($\alpha = 0.84$).

In this study, the primary psychophysiological outcome measure was the RMSSD, during the preparation phase of exposure therapy (67). The primary subjective measure of distress was the SUDS collected immediately after the end of the preparation phase and before the oral presentation in the VR environment. The secondary outcome measure was the ns-SCRs (46) during the preparation phase of exposure therapy. The anticipatory phase of social performance (e.g., preparation of public speaking) was chosen as the main phase to study social anxiety, as it has been shown to be particularly stressful (71). We have originally selected the RMSSD as the primary physiological measure, while ns-SCRs as the secondary outcome measure, as it has been shown that heart rate measures may be more sensitive in measuring social anxiety than electrodermal activity (66, 68, 72).

Other exploratory variables included the change of fear in dreams (average of fear during the 2nd week with stimulations minus the 1st week without stimulations) (see also Section 'Emotional Dream Content').

Polysomnography

To assess the sleep structure of the participants we recorded polysomnography (PSG) for two nights at the sleep laboratory (one habituation night without auditory stimulations, one experimental night with auditory stimulations). There were six electrodes (F3, F4, C3, C4, O1, and O2) placed on the head using the 10–20 system. We also put two electrodes to measure the eye movements (EOG1 and EOG2) and three electrodes to measure muscle tone (EMG1, EMG2, and EMG3). We placed the references on the mastoids and the ground was placed on the cheekbone. We also placed two electrodes to measure the heart rate (ECG). The setup and sleep scoring were done according to the AASM manual guidelines (73).

Sample Size Consideration

Based on a previous study (74) on the difference of SAD vs. control group for HRV with an effect size of $d = 0.77$, 44 patients (22 per arm) would be required to have an 80% chance of detecting this difference between patients with TMR vs. those in the control group. Besides, based on a study (37) on the effect of associated vs. non-associated sound during REM sleep on associative memory with a large effect size ($g = 1.01$), this sample size would be sufficient for the aforementioned detection.

Statistical Analysis

Levels of Anxiety

These analyses were done on 46 participants (two participants from the initial sample were excluded due to unusable data). Data were entered into a multilevel regression model, with either RMSSD levels or SUDS scores, as dependent variables, and time and group as (interacting) independent variables. The latter represented the fixed effects of the multilevel model, while random effects were represented by a random intercept for subjects [Y $\sim$ group*time + (1|ID)]. The random intercept accounted for correlation between repeated measures, by assuming baseline differences between subjects in the average DV. A multilevel regression was chosen for these data, due to its ability to handle (a) missing data in the time variable, (b) time-varying covariates, and (c) continuous within-subject covariates. Once the model was fitted, we performed a Type II ANOVA breakdown of fixed effects using *F*-tests, starting with the interaction test of Time $\times$ Group, followed by main effects tests for Time and Group separately. Multiple testing correction for eventual follow-up pairwise comparisons was done using the Bonferroni method. As there were 3 time points (T1a, T2, and T3), a threshold of 0.0167 (= 0.05/3) for determining significance was used. Degrees of freedom for all *F*- and *t*-tests were adjusted for the random effects structure using Satterthwaite's method (75) yielding fractional degrees of freedom. Multilevel analyses were conducted with the R statistical language, version 1.2.5019 (RStudio Team, Boston, MA, 2019), using the packages "lme4" for model estimation (76) and "lmerTest" for inferential tests (77). The secondary psychophysiological outcome measure, i.e., ns-SCRs, underwent the same analysis structure.

Sleep Variables

Data on several sleep variables (e.g., duration of sleep stages, total sleep time, number of auditory stimulations, and volume of sound) were delivered directly from the automatic algorithm of the Dreem headband (50) or were collected after manual scoring of the two PSGs. A correlational analysis was done between the absolute REM duration on average during 1 week at home and the stress variables (RMSSD, SUDS, and ns-SCRs) at T3 for the two groups separately. The same analysis was done with the number of auditory stimulations on average during 1 week. Before the correlations were performed, a normality test was done on the different variables that were used, to use the appropriate test.

We would like to note that we applied a purely marginal (i.e., without adjusting for covariates), model-free analysis of the relation between REM sleep and stress variables after several days of stimulation (T3). The correlations for the other sleep stages and at T2 were conducted only after the hypothesis-driven ones i.e., the relation between REM sleep and stress variables at T3 had been performed, and only for reasons of completeness and transparency.

Emotional Dream Content

Among all emotions reported in the dreams (see Section Materials), we focused on fear (see Introduction section), which was assessed as follows. We first assessed the presence of fear in dreams by checking whether the participants had reported having the emotion of fear in their dream or not. We then calculated the proportion of dreams containing fear in the week without the stimulations and during the week with stimulations. More specifically, we took the number of nights where this emotion was reported as being present divided by the number of nights where participants reported that they had a dream with recall. This gave us a proportion of this emotion for each participant, with one value for the week before stimulations and one value for the week with stimulations.

TABLE 1 | Means, standard deviations, and comparison between the control and TMR group, of the age and the initial scores at the Liebowitz Social Anxiety Scale (LSAS), the Pittsburgh Sleep Quality Index (PSQI), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI II), the Insomnia Severity Index (ISI), and the psychomotor vigilance task (PVT) preceding the first VR session.

	TMR group ($N = 24$)	Control group ($N = 24$)	t (df)	p
Age	24.7 ± 5.78	24.12 ± 3.97	0.4 (40, 74)	0.68
Liebowitz	101.08 ± 12.1	100.29 ± 11.95	0.22 (45, 99)	0.82
PSQI	3.20 ± 1.28	3.08 ± 1.24	0.34 (45, 96)	0.73
BDI	7 ± 6.06	6.62 ± 5.41	0.22 (45, 43)	0.82
BAI	26.5 ± 14.85	21.16 ± 13.83	1.28 (45, 76)	0.2
ISI	3.83 ± 2.42	3.12 ± 2.32	1.03 (45, 92)	0.3
PVT	269.62 ± 36.03	263.83 ± 22.79	0.66 (38, 87)	0.5

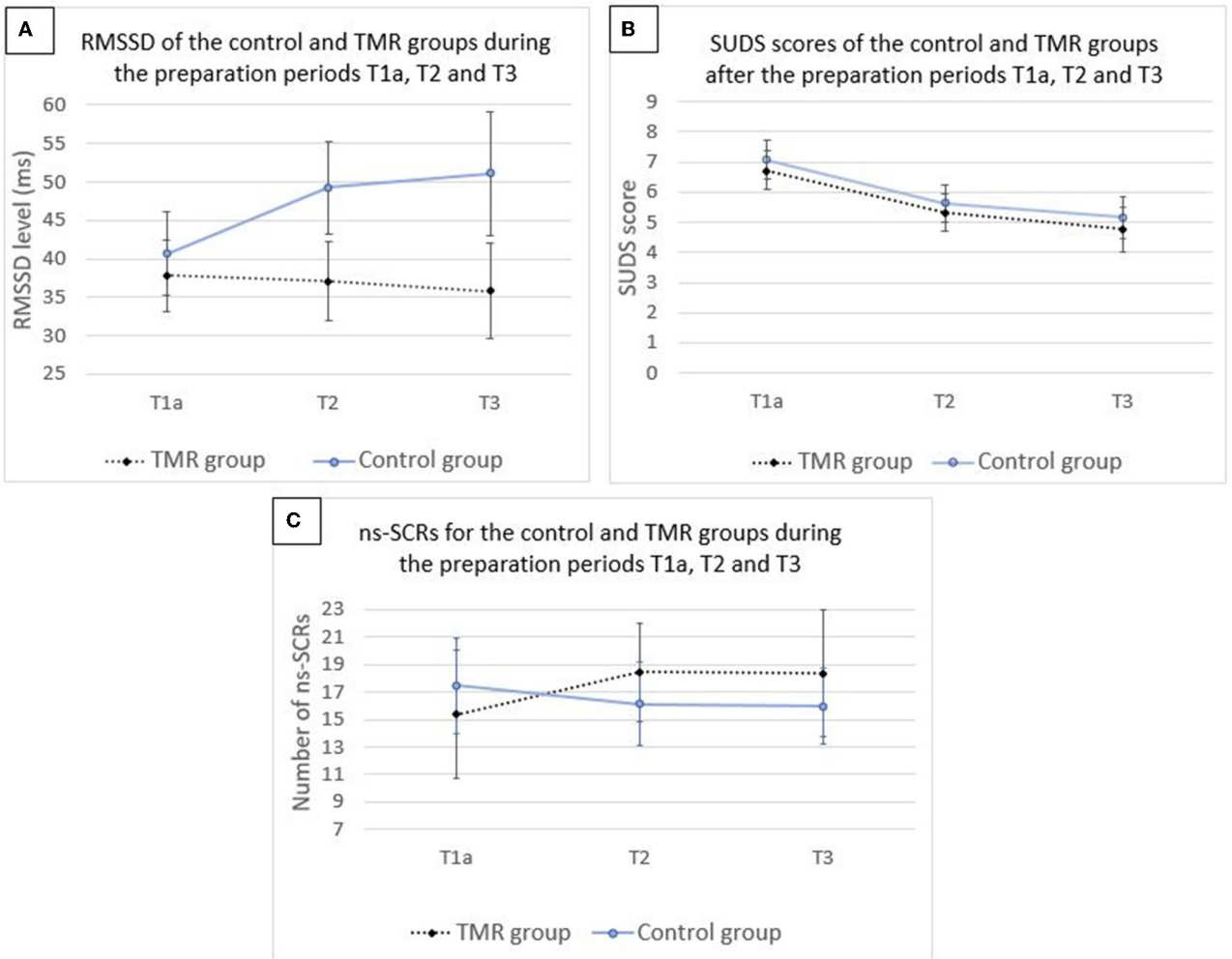

FIGURE 2 | Mean values for the level of RMSSD **(A)**, score of SUDS **(B)**, and number of ns-SCRs **(C)** for the control and TMR groups during the preparation periods T1a, T2, and T3. $N = 46$. Error bars represent 95% CI.

A correlational analysis was done between the change of fear in dreams (average of fear during the 2nd week with stimulations minus the 1st week without stimulations) and the primary outcome measures (RMSSD, SUDS) and secondary outcome measure (ns-SCRs) at T3 for the two groups separately.

RESULTS

Recruitment took place from July 2020 to June 2021. **Supplementary Figure 1** provides a flow diagram of study participants.

TABLE 2 | Means and standard deviations of the TMR and control groups on RMSSD (ms) levels, SUDS score, and ns-SCRs (number of events) during the T1a, T2, and T3 preparation periods.

		TMR group *N* = 22	Control group *N* = 24
T1a	RMSSD	37.79 (15.93)	40.69 (18.54)
	SUDS	6.73 (2.19)	7.08 (2.16)
	ns-SCRs	16.15 (16.03)	17.44 (12.11)
T2	RMSSD	37.14 (17.96)	49.26 (20.76)
	SUDS	5.32 (2.19)	5.625 (2.14)
	ns-SCRs	18.42 (12.25)	16.12 (10.55)
T3	RMSSD	35.83 (21.30)	51.11 (27.69)
	SUDS	4.77 (2.59)	5.16 (2.43)
	ns-SCRs	18.35 (15.93)	15.95 (9.67)

N = 46.

Baseline Characteristics

There were no differences between the two groups in age, social anxiety (assessed by the LSAS), sleep quality (assessed by the PSQI), anxiety (assessed by the BAI-II), depression (assessed by the BDI-II), severity of insomnia (assessed by the ISI), and vigilance at T1 (assessed by PVT), as indicated in **Table 1**.

Detailed results on the comparison between stress levels of the preparation, baseline and feedback phases of the VR sessions are reported in **Supplementary Material 3**, while comparison of several sleep measures across time and groups are reported in **Supplementary Table 1**.

Effects of TMR on Social Anxiety (T1a, T2, and T3)

RMSSD

No significant group × time interaction was shown [$F_{(2,76.848)} = 0.7393$, $p = 0.481$], nor a main effect of time [$F_{(2,76.799)} = 1.0190$, $p = 0.366$]. Results showed a significant main effect of group [$F_{(1,41.035)} = 4.1536$, $p = 0.048$].

SUDS

Analysis on SUDS scores showed no significant group × time interaction [$F_{(2,88)} = 0.0142$, $p = 0.986$] and no main effect of group [$F_{(1,44)} = 0.3382$, $p = 0.564$]. There was a significant main effect of time [$F_{(2,88)} = 30.0611$, $p < 0.001$].

ns-SCRs

No significant group × time interaction was shown [$F_{(2,71.174)} = 0.3229$, $p = 0.725$], neither a main effect of group [$F_{(1,40.772)} = 0.1041$, $p = 0.749$] nor a main effect of time [$F_{(2,71.120)} = 0.0691$, $p = 0.933$].

The results are illustrated in **Figure 2** and the means and standard deviations per group are reported in **Table 2**. Fixed effects estimates are reported in the **Supplementary Table 2**.

TABLE 3 | Means and standard deviations of the TMR and control groups on the ns-SCRs (number of events) and RMSSD (ms) levels during the generalization task periods (T0 and T4).

		TMR group *N* = 22	Control group *N* = 24
T0	RMSSD	33.09 (13.47)	35.24 (14.13)
	ns-SCRs	12.28 (9.59)	13.57 (7.44)
T4	RMSSD	30.71 (17.11)	33.42 (11.78)
	ns-SCRs	8.61 (6.64)	8.75 (5.75)

N = 46.

Effect of Long-Term TMR on Generalization of Anxiety (T0 and T4)

RMSSD

Regarding RMSSD levels, results showed no group × time interaction [$F_{(1,37.405)} = 0.0005$, $p = 0.982$], no main effect of group [$F_{(1,39.291)} = 0.5326$, $p = 0.469$] and no main effect of time [$F_{(1,37.405)} = 0.7808$, $p = 0.382$].

ns-SCRs

Analysis revealed no significant group × time interaction [$F_{(1,34.555)} = 0.0846$, $p = 0.773$], and no main effect of group [$F_{(1,35.903)} = 0.2140$, $p = 0.646$]. A main effect of time was found [$F_{(1,34.416)} = 6.5407$, $p = 0.015$].

The results are illustrated in **Supplementary Figure 2** and the means and standard deviations per group are reported in **Table 3**. Fixed effects estimates are reported in **Supplementary Table 3**.

Association Between REM, TMR, and Stress Levels

RMSSD

RMSSD levels in T3 correlated with REM duration in the TMR group ($p = 0.047$, tau = 0.307; **Figure 3A**). The control group did not present this effect ($p = 0.916$, tau = −0.019). We used a Kendall correlation as the distribution of RMSSD was not normal ($p = 0.001$). After transformation of tau values to Pearson *r*-values (78), a Fisher *r*-to-*z* transformation test showed that the coefficients were significantly different ($p = 0.046$, $z = 1.68$). The correlation between REM sleep percentage and RMSSD in T3 was also significant for the TMR group ($p = 0.024$, tau = 0.347), but not for the control group ($p = 0.834$, tau = −0.035), with the two coefficients being significantly different ($p = 0.026$, $z = 1.93$).

A similar effect was observed for the correlation between the number of auditory stimulations and RMSSD in T3 (**Figure 3B**). The TMR group showed a significant effect ($p = 0.019$, tau = 0.359), but not the control group ($p = 0.248$, tau = −0.177). After transformation of tau values to Pearson *r*-values (78), a Fisher *r*-to-*z* transformation test showed that the coefficients were significantly different ($p = 0.003$, $z = 2.77$).

This significant positive correlation between REM sleep duration/ auditory stimulations and RMSSD was not present after one night of stimulations (T2) and no significant correlation was found between the stress variables in T2 or T3 and the other sleep stages (N1, N2, and N3).

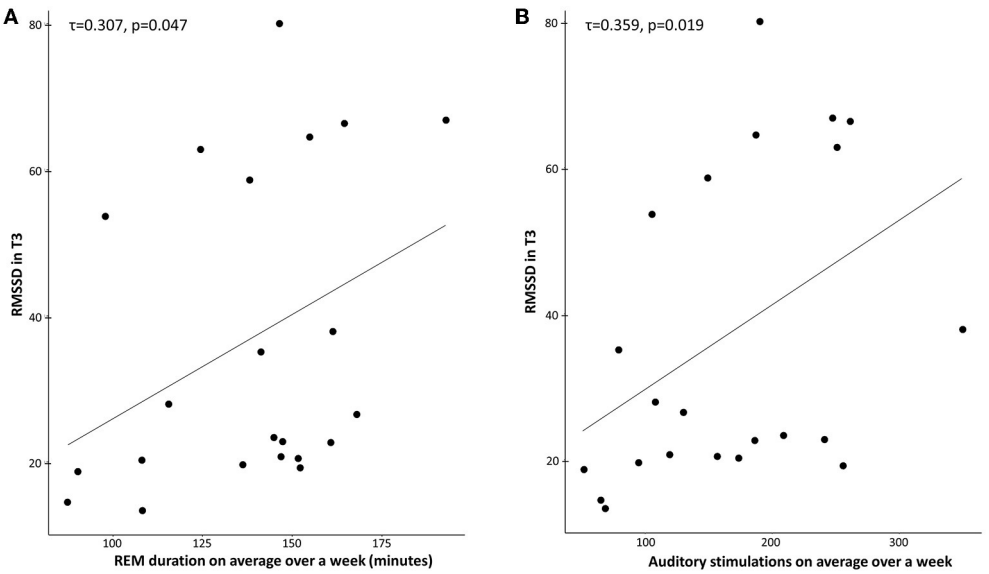

FIGURE 3 | (A) Correlation between REM duration (minutes) and RMSSD in T3 for the TMR Group. Across participants, RMSSD scores were positively correlated with the mean REM duration over 1 week in the TMR group ($\tau = 0.307$, $p = 0.047$). **(B)** Correlation between the number of stimulations on average over a week and RMSSD in T3 for the TMR group. Across participants, RMSSD scores were positively correlated with the mean number of stimulations in the TMR group ($\tau = 0.359$, $p = 0.019$). Each dot indicates a participant.

When removing three potential outliers (all in the control group), the number of stimulations and RMSSD in T3 were still not correlated for this group (p-value = 0.2879, tau = −0.2371), neither did REM duration with RMSSD (p-value = 0.188, tau = −0.2987).

There was a positive correlation between the number of auditory stimulations (STIMs) and the duration of REM sleep over a week in the TMR group [$r = 0.6458$, $t_{(DF)} = 22$, $p < 0.001$]. We therefore tested whether the effect of STIMs on stress levels (RMSSD) at T3 was mediated by REM sleep. This was achieved with a bootstrap mediation test using 10000 approximate simulations ["mediate" function in R (79)]. The analysis revealed no significant direct effect of stimulations ($p = 0.17$) nor a significant mediated effect of stimulations through REM sleep ($p = 0.54$), but a significant total effect of stimulations ($p = 0.015$; **Supplementary Table 4**). These results indicate that REM sleep does not mediate the STIMs-RMSSD association.

SUDS

The correlation between REM duration and SUDS in T3 did not show any significant results for the TMR group ($p = 0.295$, $r = 0.222$) and the control group ($p = 0.368$, $r = -0.191$).

No significant results were found for the correlation between the number of auditory stimulations and SUDS in T3, in the TMR group ($p = 0.522$, $r = 0.137$) and the control group ($p = 0.941$, $r = 0.015$).

ns-SCR

The correlation between REM duration and ns-SCR in T3 did not show any significant results for the TMR group ($p = 0.103$, $r = 0.396$) and the control group ($p = 0.546$, $r = -0.162$).

Concerning the correlation of the number of auditory stimulations and ns-SCR in T3, no significant results were found in the TMR group ($p = 0.39$, $r = 0.215$) or the control group ($p = 0.441$, $r = -0.207$).

Link Between Fear in Dreams and Stress in Wakefulness

No significant effect was found for the correlation between the change of fear in dreams (average of fear during the 2nd week with stimulations minus the 1st week without stimulations) and RMSSD in T3 for the TMR group ($p = 0.1912$, tau = −0.242) or the control group ($p = 0.791$, tau = −0.044).

A significance is shown for the correlation between the change of fear and SUDS for the TMR group ($p = 0.0046$, $r = 0.6513$; **Figure 4A**), but not for the control group ($p = 0.759$, $r = -0.0712$). A Fisher r-to-z transformation test showed that the coefficients were significantly different ($p = 0.009$, $z = -2.382$).

A similar significant correlation between the change of fear in dreams and ns-SRCs was found for the TMR group ($p = 0.0155$, $r = 0.6308$; **Figure 4B**), but not for the control group ($p = 0.7995$, $r = -0.0747$). A Fisher r-to-z transformation test showed that the coefficients were significantly different ($p = 0.011$, $z = -2.294$).

DISCUSSION

The primary hypothesis of this study was to test if adding TMR during REM sleep in addition to standard exposure therapy would be more effective than exposure therapy alone in reducing anxiety in individuals suffering from SAD. TMR consisted in associating a sound with an isolated extinction period (i.e., the positive feedback of exposure therapy), and reactivating this memory by presenting the same sound during REM sleep. We

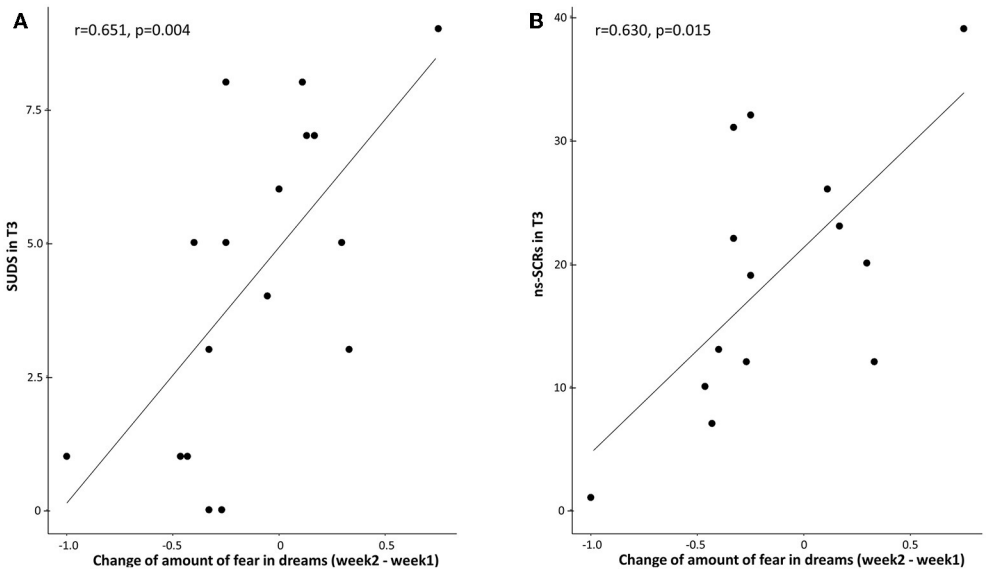

FIGURE 4 | (A) Correlation between the change of fear in dreams (average of fear during the 2nd week with stimulations minus the 1st week without stimulations) and SUDS in T3 for the TMR group. Across participants, SUDS scores were positively correlated with the change of fear in the TMR group ($r = 0.6513$, $p = 0.0046$). **(B)** Correlation between the change of fear in dreams (average of fear during the 2nd week with stimulations minus the 1st week without stimulations) and ns-SCRs in T3 for the TMR group. Across participants, ns-SCRs scores were positively correlated with the change of fear in the TMR group ($r = 0.6308$, $p = 0.0155$). Each dot indicates a participant.

did not observe lower anxiety levels in the TMR group, compared to the control group, during the preparation period preceding a speech after 8 days of auditory stimulation during REM, for any of our measures. However, we found that subjective anxiety was reduced across the experiment for both groups, indicating the efficiency of a small number of exposure therapy sessions in reducing social anxiety. In accordance with the depotentiation theory of REM sleep, secondary analyses also indicated that the number of auditory stimulations during REM sleep and REM sleep duration were positively correlated with RMSSD in the TMR group. A positive correlation between increased presence of fear in dreams and SUDS/ns-SCRs was also observed in the TMR group, reflecting a possible link between emotional content in dreams and waking stress levels in these patients. Such a result supports the idea that psychotherapeutic approaches targeting emotional dream content [e.g., reducing nightmare frequency and distress with Imagery Rehearsal Therapy (IRT)] (80), could be used to alleviate daytime depressive and anxiety symptoms too.

Effect of Time

Among the three measures of anxiety, the SUDS was the only one to show an effect of time, indicating higher anxiety during the first preparation period (T1a) compared to the third (T2) and last (T3) ones in both groups. By contrast, the physiological measures did not show any modulation by time, probably because the small number of exposure therapy sessions in this protocol did not allow for such an improvement. The effect of time on subjective anxiety is in line with studies showing that exposure is efficient in reducing symptoms of anxiety disorders even without any other manipulation (10, 16, 81). However, strictly speaking, the lack of a control group without exposure therapy in the design of the current study cannot rule out that the significant reduction of subjective anxiety was not related to other factors (e.g., patient expectations; see limitations section below).

Challenges to Isolate a Safety Memory

TMR during REM sleep in our experiment did not enhance the beneficial effect of exposure therapy on anxiety-related distress (SUDS). An explanation for these results could be that the sound in our experiment was not sufficiently associated with a safety memory (i.e., positive feedback). Indeed, when comparing anxiety levels of the preparation and feedback periods, physiological measures generally indicated similar levels between the two periods (**Supplementary Material 3**). Furthermore, anxiety levels were higher during feedbacks compared to the baseline periods, further demonstrating that the participants were still in a state of physiological stress during the feedback periods (**Supplementary Material 3**). Moreover, as patients with SAD show altered processing of feedback compared to healthy controls (82–84), positive feedback might not have been sufficient to change their expectations of a negative outcome.

Previous studies have associated a sound to aversive stimuli and presented this sound (conditioned stimulus, CS) during NREM sleep. This TMR procedure led to either a reduction in fear responses (85, 86) or increase of fear responses (87, 88). Protocol differences, such as reinforcement contingencies,

relevance of the aversive stimuli or frequency of cueing during sleep, could explain such discrepancies (89). While these studies implicated memory reactivation during NREM sleep, and not REM sleep, these findings bring attention to the necessity to test multiple new experimental protocols in order to identify the mechanisms allowing sleep cueing to enhance extinction and those leading to opposite results. To this date, we do not know if consolidation of a positive memory during REM sleep would be more advantageous (90) than consolidation and subsequent depotentiation of a negative one (25).

Effect of REM Sleep and TMR on Stress

We here found a positive correlation between REM duration over 1 week and RMSSD in T3 in the TMR group. Although pertaining to a secondary analysis and limited by its correlational nature, this result in a clinical population (i.e., SAD patients) supports the idea that REM sleep is beneficial for reducing some physiological manifestations of stress levels during wakefulness, in line with enhanced extinction (20, 22, 23) and emotional depotentiation (25, 40). Importantly, this correlation was not found for other sleep stages, in accordance with previous research (23–25, 39, 40). Indeed, results on the possible effects of N2 sleep and/or SWS on extinction learning are inconsistent. Some results show that N2 sleep is beneficial to reduce self-reported fear for spider phobia (17), while others show that N2/SWS (with or without TMR) does not enhance exposure therapy for spider phobia (91) or for SAD (19). As previously mentioned, TMR during SWS can also either enhance extinction (85, 86) or strengthen a fear memory (87, 88, 92). Thus, REM sleep would not strengthen the emotional tone of memories (93–96), but might instead consolidate negative memories while attenuating their emotional tone (24, 25, 39, 40, 97). REM sleep and dreaming (26, 98) might offer a permissive condition for the remodeling of negative experienced events.

The aforementioned links between REM sleep duration and RMSSD over eight nights are in line with previous findings that REM sleep measures averaged over several nights (trait-level effect of REM sleep) have a protective role in fear conditioning and suggest that REM deficiencies may predate the development of anxiety disorders and post-traumatic stress disorder (PTSD) (27, 99). Therefore, these results further substantiate previous evidence that REM sleep is a determinant factor in the modulation of anxiety and affective disorders (100), and that its structure and functional role should be protected in order to promote mental health (101).

Previous studies have explored the emotional role of REM sleep mainly in healthy participants. Our study suggests that REM sleep could benefit anxious patients but only after a TMR manipulation. Indeed, a positive effect of REM sleep on stress reduction was only seen in the TMR group of our study, where the sound has been associated with a previous waking emotional event. This observation may be related to the additional beneficial effects of (a) post-learning REM sleep on extinction, as REM sleep enhances such a function especially after a pre-sleep extinction training (23, 102), and (b) the further emotional depotentiation with TMR during REM sleep (39, 41). Notably, the aforementioned beneficial effects of TMR during REM sleep did not appear after one single night, but only after 1 week of stimulation at home. Therefore, apart from the trait-level effect of REM sleep mentioned above (27), repeated TMR stimulation over successive nights might be needed to permanently consolidate the formation of a new (i.e., initially labile) safety memory during sleep [e.g., make it hippocampus-independent (45)].

Association Between Fear in Dreams and Anxiety in SAD Patients

The frequency of fear experienced in dreams correlated with the primary clinical outcome measure (SUDS) and the secondary psychophysiological outcome measure (ns-SCRs) in the TMR group (but not in the control group). The more these participants experienced fear in their dreams, the more they were stressed in T3, as measured with ns-SCRs and SUDS. In a previous study (26), we demonstrated that increased fear in dreams benefits reduced stress when healthy participants are exposed to fearful stimuli during wakefulness, and which was in accordance with an extinction function of dreaming in healthy participants (103). The results of the present study suggest that this fear extinction function of dreams (26, 103) might be deficient in clinical populations, such as anxious people here. For example, although healthy participants experiencing fearful dreams have higher mPFC activity in fearful situations in wakefulness (26), nightmare patients demonstrate a decreased mPFC activity during the viewing of negative pictures (104). We speculate that a similar failure of the fear extinction function of dreams can explain our result in patients with SAD, who also demonstrate a decreased mPFC activity and increased amygdala activity during social stressors (105). Whether there is a causal relationship between anxiety disorders and such a deficient extinction function of dreaming in these patients should be tested in future studies.

A strong link between dream emotions and daytime stress levels supports the idea that psychotherapeutic approaches aiming at modulating distressful emotions in dreams could also have an impact in daytime depressive and anxiety symptoms. For example, IRT is a cognitive-behavioral technique, where the nightmare sufferer changes the negative story line, toward a more positive ending, and rehearses the rewritten dream scenario during the day, which ultimately helps to reduce nightmares during sleep (106). This technique can be learned in one session (107) and practiced for 5–10 min per day while awake. It has been shown that IRT in PTSD patients can improve not only nightmare frequency and intensity, but daytime symptoms too (e.g., flashbacks, depressive symptoms, and dissociation) (80). The beneficial "halo" effect of IRT on daytime symptoms (and not only nightmares), may be related to its mechanism of action, which seems to implicate extinction learning (108). Our results support the idea that psychotherapeutic methods targeting negative emotions in dreams could be used to alleviate anxiety symptoms.

Limitations

Apart from the challenges to isolate a safety memory (see Section Effect of Time), there are some other limitations in this study. First, all three measures of anxiety did not

always concur (see **Supplementary Table 5**). On the one hand, a dissociation between physiological and subjective measures of anxiety is very common (19, 109) and seems to reflect a different response of the autonomic nervous system and of subjective (conscious) experience to perceived stress (19, 110). A dissociation between heart rate and skin conductance reactions is also found in SAD (72). On the other hand, this dissociation may be related to the use of a VR setting for the measurement of stress during exposure therapy. While such a setting allows for realistic and controlled exposure to feared stimuli, it may have reduced the participants' immersion in the feared situation (63, 111). Comparing subjective assessments with different physiological measurements is needed to have more insight on the implication of different systems in stress responses (112). Another limitation, linked to the assessment of anxiety, relates to the physiological measures (RMSSD, ns-SCRs). While in our study we use RMSSD and ns-SCRs to assess anxiety levels, the fact that these measures can be modulated by other factors should not be overlooked. Indeed, RMSSD and ns-SCRs reflect some physiological manifestations of stress, but have also been linked to depression, worry, and measures of inflammation or cognitive functions involving the prefrontal cortex (113, 114).

Moreover, it is possible that a reduction of sleep quantity may have accounted for the negative results of our study. Indeed, total sleep time (TST) and N2 sleep were decreased during the week at home compared to the habituation night (see **Supplementary Material 4**, **Supplementary Table 1**). Moreover, TMR participants were almost significantly ($p = 0.08$) less vigilant compared to those of the control group, as measured by the PVT before the last VR session at T3 (see **Supplementary Table 1**), while HRV is sensitive to sleep deprivation (115). This means that, even though REM sleep and auditory stimulations had a positive effect on stress within this group, sleep conditions may be a more important determinant for the participant's wellbeing and stress levels (although the relationship between stress and sleep is bidirectional) (116). Indeed, TMR seems to lose its positive effect when sleep is compromised (117), while sufficient sleep predicts treatment outcome of exposure therapy in patients with SAD (118, 119). Our results hence suggest that the strengthening of a safety memory during REM sleep with TMR can be helpful to reduce stress only when controlling for sleep disruption, in line with previous research (117). Indeed, in a recent paper (101), the authors stated that the beneficial effects of REM sleep on extinction are not noticeable if sleep is disturbed.

Finally, this experiment lacks a SAD group without any stimulation or a SAD group without exposure therapy or a SAD group with exposure therapy but no positive feedback. Therefore, although we know that exposure therapy promotes extinction (5) and that REM sleep enhances extinction in healthy participants after an extinction task compared to wakefulness or NREM sleep (22, 23), we cannot safely conclude from our study that TMR during REM sleep or a positive feedback period of exposure therapy would add an extra benefit in extinction processes. Indeed, previous studies indicate the presence of a ceiling effect of the highly effective exposure therapy or of REM sleep alone in extinction processes (22, 91). Moreover, to control for any unspecific effect of the sound played during the positive feedback phase of the exposure therapy (e.g., S1, in the TMR group), future studies may use a different sound (e.g., S2) played during the feedback phase in the control group, while the same sound (S1) would be played during sleep of both groups. This sound (S2) in the control group would need to be similar in terms of valence and intensity to the sound (S1) in the TMR group, but sufficiently different to minimize generalization between the two sounds in the control group. With such a design, the two groups would be similar in the total auditory stimuli they receive during both wakefulness and sleep and potential confounds of playing a sound only in the TMR group in wakefulness would be avoided.

As a technical note, in the present study, we applied TMR during REM sleep, irrespective of REM tonic or phasic states. Yet, for the purpose of extinction consolidation, TMR should ideally be performed during phasic REM sleep, as phasic P-waves seem important for the retention of fear extinction memory occurring after the acquisition of fear extinction learning (102). Therefore, future technical development of TMR applied during REM may aim at achieving selective stimulations during phasic REM.

Future Perspectives

To the best of our knowledge, this is the first TMR study exploring the links between REM sleep, extinction and anxiety in a clinical population. Although this study does not allow to ascertain a positive effect of TMR on SAD, TMR remains an efficient tool for the reprocessing of emotional memories (37, 39), and further research with TMR could be the key to develop efficient therapies for SAD or other emotional disorders implicating deficient extinction learning (90). TMR application during sleep may avoid certain disadvantages of traditional exposure therapies during wakefulness, such as worsening mood and anxiety during the recall of painful experiences. By deploying and popularizing easy-to-use devices at home in order to enhance the consolidation of safety memories, these therapies could reach a big part of the general population and lead to new approaches for promoting emotional wellbeing.

Future studies should better characterize the nature of the link between anxiety disorders and the deficient extinction function of dreaming, and they could also test whether psychotherapeutic methods targeting distressful dreams, such as IRT, can be helpful for treating anxiety disorders as well.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Canton of Geneva, Switzerland (Commission Cantonale d'Ethique de la Recherche sur l'être humain). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS and LP designed the experiments. FB, PH, FG, CP, and LP conducted the experiments and analyzed the data. FB, PH, FG, CP, SD, SS, and LP wrote the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.904704/full#supplementary-material

REFERENCES

1. Leichsenring F, Leweke F. Social Anxiety Disorder. *New Engl J Med.* (2017) 376:2255–64. doi: 10.1056/NEJMcp1614701
2. Stein MB, Stein DJ. Social Anxiety Disorder. *Lancet.* (2008) 371:1115–25. doi: 10.1016/S0140-6736(08)60488-2
3. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci.* (2015) 17:327–35. doi: 10.31887/DCNS.2015.17.3/bbandelow
4. Morrison AS, Heimberg RG. Social anxiety and social anxiety disorder. *Annu Rev Clin Psycho.* (2013) 9:249–74. doi: 10.1146/annurev-clinpsy-050212-185631
5. Craske MG, Hermans D, Vervliet B. State-of-the-art and future directions for extinction as a translational model for fear and anxiety. *Philos Trans R Soc Lond B Biol Sci.* (2018) 25:373. doi: 10.1098/rstb.2017.0025
6. Graham BM, Milad MR. The study of fear extinction: implications for anxiety disorders. *Am J Psychiatry.* (2011) 168:1255–65. doi: 10.1176/appi.ajp.2011.11040557
7. Neumann DL, Waters AM. The use of an unpleasant sound as an unconditional stimulus in a human aversive Pavlovian conditioning procedure. *Biol Psychol.* (2006) 73:175–85. doi: 10.1016/j.biopsycho.2006.03.004
8. Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biol Psychiatry.* (2002) 52:976–86. doi: 10.1016/S0006-3223(02)01546-9
9. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: an inhibitory learning approach. *Behav Res Ther.* (2014) 58:10–23. doi: 10.1016/j.brat.2014.04.006
10. Kaczkurkin AN, Foa EB. Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. *Dialogues Clin Neuro.* (2015) 17:337–46. doi: 10.31887/DCNS.2015.17.3/akaczkurkin
11. Bouchard S, Dumoulin S, Robillard G, Guitard T, Klinger E, Forget H, et al. Virtual reality compared with *in vivo* exposure in the treatment of social anxiety disorder: a three-arm randomised controlled trial. *Br J Psychiatry.* (2017) 210:276–83. doi: 10.1192/bjp.bp.116.184234
12. Carl E, Stein AT, Levihn-Coon A, Pogue JR, Rothbaum B, Emmelkamp P, et al. Virtual reality exposure therapy for anxiety and related disorders: a meta-analysis of randomized controlled trials. *J Anxiety Disord.* (2019) 61:27–36. doi: 10.1016/j.janxdis.2018.08.003
13. Soravia LM, Heinrichs M, Winzeler L, Fisler M, Schmitt W, Horn H, et al. Glucocorticoids enhance *in vivo* exposure-based therapy of spider phobia. *Depress Anxiety.* (2014) 31:429–35. doi: 10.1002/da.22219
14. Raij T, Nummenmaa A, Marin MF, Porter D, Furtak S, Setsompop K, et al. Prefrontal cortex stimulation enhances fear extinction memory in humans. *Biol Psychiatry.* (2018) 84:129–37. doi: 10.1016/j.biopsych.2017.10.022
15. Hartanto D, Kampmann IL, Morina N, Emmelkamp PG, Neerincx MA, Brinkman WP. Controlling social stress in virtual reality environments. *PLoS ONE.* (2014) 9:e92804. doi: 10.1371/journal.pone.0092804
16. Borgeat F, Stankovic M, Khazaal Y, Rouget BW, Baumann MC, Riquier F, et al. Does the form or the amount of exposure make a difference in the cognitive-behavioral therapy treatment of social phobia? *J Nerv Ment Dis.* (2009) 197:507–13. doi: 10.1097/NMD.0b013e3181aacc08
17. Kleim B, Wilhelm FH, Temp L, Margraf J, Wiederhold BK, Rasch B. Sleep enhances exposure therapy. *Psychol Med.* (2014) 44:1511–9. doi: 10.1017/S0033291713001748
18. Pace-Schott EF, Verga PW, Bennett TS, Spencer RM. Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. *J Psychiatr Res.* (2012) 46:1036–44. doi: 10.1016/j.jpsychires.2012.04.015
19. Pace-Schott EF, Bottary RM, Kim SY, Rosencrans PL, Vijayakumar S, Orr SP, et al. Effects of post-exposure naps on exposure therapy for social anxiety. *Psychiatry Res.* (2018) 270:523–30. doi: 10.1016/j.psychres.2018.10.015
20. Spoormaker VI, Schroter MS, Andrade KC, Dresler M, Kiem SA, Goya-Maldonado R, et al. Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. *Hum Brain Mapp.* (2012) 33:2362–76. doi: 10.1002/hbm.21369
21. Spoormaker VI, Sturm A, Andrade KC, Schroter MS, Goya-Maldonado R, Holsboer F, et al. The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. *J Psychiatr Res.* (2010) 44:1121–8. doi: 10.1016/j.jpsychires.2010.04.017
22. Pace-Schott EF, Tracy LE, Rubin Z, Mollica AG, Ellenbogen JM, Bianchi MT, et al. Interactions of time of day and sleep with between-session habituation and extinction memory in young adult males. *Exp Brain Res.* (2014) 232:1443–58. doi: 10.1007/s00221-014-3829-9
23. Menz MM, Rihm JS, Buchel C. Rem sleep is causal to successful consolidation of dangerous and safety stimuli and reduces return of fear after extinction. *J Neurosci.* (2016) 36:2148–60. . doi: 10.1523/JNEUROSCI.3083-15.2016
24. Gujar N, McDonald SA, Nishida M, Walker MP. A role for rem sleep in recalibrating the sensitivity of the human brain to specific emotions. *Cereb Cortex.* (2011) 21:115–23. doi: 10.1093/cercor/bhq064
25. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. Rem sleep depotentiates amygdala activity to previous emotional experiences. *Curr Biol.* (2011) 21:2029–32. doi: 10.1016/j.cub.2011.10.052
26. Sterpenich V, Perogamvros L, Tononi G, Schwartz S. Fear in dreams and in wakefulness: evidence for day/night affective homeostasis. *Hum Brain Mapp.* (2020) 41:840–50. doi: 10.1002/hbm.24843
27. Lerner I, Lupkin SM, Sinha N, Tsai A, Gluck MA. Baseline levels of rapid eye movement sleep may protect against excessive activity in fear-related neural circuitry. *J Neurosci.* (2017) 37:11233–44. doi: 10.1523/JNEUROSCI.0578-17.2017
28. Lerner I, Lupkin SM, Corter JE, Peters SE, Cannella LA, Gluck MA. The influence of sleep on emotional and cognitive processing is primarily

trait- (but not state-) dependent. *Neurobiol Learn Mem.* (2016) 134:275–86. doi: 10.1016/j.nlm.2016.07.032
29. Oudiette D, Paller KA. Upgrading the sleeping brain with targeted memory reactivation. *Trends Cogn Sci.* (2013) 17:142–9. doi: 10.1016/j.tics.2013.01.006
30. Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science.* (2007) 315:1426–9. doi: 10.1126/science.1138581
31. Diekelmann S. Sleep for cognitive enhancement. *Front Syst Neurosci.* (2014) 8:46. doi: 10.3389/fnsys.2014.00046
32. Rudoy JD, Voss JL, Westerberg CE, Paller KA. Strengthening individual memories by reactivating them during sleep. *Science.* (2009) 326:1079. doi: 10.1126/science.1179013
33. Klinzing JG, Diekelmann S. Cued memory reactivation: a tool to manipulate memory consolidation during sleep. In: Drinhenberg HC, editor, *Handbook of Behavioral Neuroscience*. London: Elsevier (2019). p. 471–88. doi: 10.1016/B978-0-12-813743-7.00031-1
34. Schouten DI, Pereira SI, Tops M, Louzada FM. State of the art on targeted memory reactivation: sleep your way to enhanced cognition. *Sleep Med Rev.* (2017) 32:123–31. doi: 10.1016/j.smrv.2016.04.002
35. Guerrien A, Dujardin K, Mandai O, Sockeel P, Leconte P. Enhancement of memory by auditory stimulation during postlearning rem sleep in humans. *Physiol Behav.* (1989) 45:947–50. doi: 10.1016/0031-9384(89)90219-9
36. Smith C, Weeden K. Post training rems coincident auditory stimulation enhances memory in humans. *Psychiatr J Univ Ott.* (1990) 15:85–90.
37. Sterpenich V, Schmidt C, Albouy G, Matarazzo L, Vanhaudenhuyse A, Boveroux P, et al. Memory reactivation during rapid eye movement sleep promotes its generalization and integration in cortical stores. *Sleep.* (2014) 37:1061–75. doi: 10.5665/sleep.3762
38. Ashton JE, Cairney SA, Gaskell MG. No effect of targeted memory reactivation during slow-wave sleep on emotional recognition memory. *J Sleep Res.* (2018) 27:129–37. doi: 10.1111/jsr.12542
39. Rihm JS, Rasch B. Replay of conditioned stimuli during late rem and stage N2 sleep influences affective tone rather than emotional memory strength. *Neurobiol Learn Mem.* (2015) 122:142–51. doi: 10.1016/j.nlm.2015.04.008
40. Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull.* (2009) 135:731–48. doi: 10.1037/a0016570
41. Hutchison IC, Pezzoli S, Tsimpanouli ME, Abdellahi MEA, Pobric G, Hulleman J, et al. Targeted memory reactivation in rem but not Sws selectively reduces arousal responses. *Commun Biol.* (2021) 4:404. doi: 10.1038/s42003-021-01854-3
42. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci.* (2010) 11:114–26. doi: 10.1038/nrn2762
43. Rasch B, Born J. About sleep's role in memory. *Physiol Rev.* (2013) 93:681–766. doi: 10.1152/physrev.00032.2012
44. Maren S, Chang CH. Recent fear is resistant to extinction. *Proc Natl Acad Sci USA.* (2006) 103:18020–5. doi: 10.1073/pnas.0608398103
45. Frankland PW, Bontempi B. The organization of recent and remote memories. *Nat Rev Neurosci.* (2005) 6:119–30. doi: 10.1038/nrn1607
46. Carrillo E, Moya-Albiol L, Gonzalez-Bono E, Salvador A, Ricarte J, Gomez-Amor J. Gender differences in cardiovascular and electrodermal responses to public speaking task: the role of anxiety and mood states. *Int J Psychophysiol.* (2001) 42:253–64. doi: 10.1016/S0167-8760(01)00147-7
47. Gonzalez-Bono E, Moya-Albiol L, Salvador A, Carrillo E, Ricarte J, Gomez-Amor J. Anticipatory autonomic response to a public speaking task in women: the role of trait anxiety. *Biol Psychol.* (2002) 60:37–49. doi: 10.1016/S0301-0511(02)00008-X
48. Tardy CH, Allen MT. Moderators of cardiovascular reactivity to speech: discourse production and group variations in blood pressure and pulse rate. *Int J Psychophysiol.* (1998) 29:247–54. doi: 10.1016/S0167-8760(98)00003-8
49. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing (2013). doi: 10.1176/appi.books.9780890425596
50. Arnal PJ, Thorey V, Debellemaniere E, Ballard ME, Bou Hernandez A, Guillot A, et al. The dreem headband compared to polysomnography for electroencephalographic signal acquisition and sleep staging. *Sleep.* (2020) 43:zsaa097. doi: 10.1093/sleep/zsaa097
51. Liebowitz MR. Social phobia. *Mod Probl Pharmacopsychiatry.* (1987) 22:141–73. doi: 10.1159/000414022
52. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
53. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol.* (1988) 56:893–7. doi: 10.1037/0022-006X.56.6.893
54. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-Ii*. San Antonio, TX: Psychological Corporation (1996). doi: 10.1037/t00742-000
55. Morin CM, Belleville G, Belanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep.* (2011) 34:601–8. doi: 10.1093/sleep/34.5.601
56. Sheehan DV. *Mini Neuropsychiatric International Interview 7.0 (Mini 7.0)*. Jacksonville, FL: Medical Outcomes Systems, Jacksonville (2015).
57. Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (Pvt) to sleep loss. *Sleep.* (2011) 34:581–91. doi: 10.1093/sleep/34.5.581
58. Ellis BW, Johns MW, Lancaster R, Raptopoulos P, Angelopoulos N, Priest RG. The St. Mary's hospital sleep questionnaire: a study of reliability. *Sleep.* (1981) 4:93–7. doi: 10.1093/sleep/4.1.93
59. Alvares GA, Quintana DS, Kemp AH, Van Zwieten A, Balleine BW, Hickie IB, et al. Reduced heart rate variability in social anxiety disorder: associations with gender and symptom severity. *PLoS ONE.* (2013) 8:e70468. doi: 10.1371/journal.pone.0070468
60. Pulopulos MM, Vanderhasselt MA, De Raedt R. Association between changes in heart rate variability during the anticipation of a stressful situation and the stress-induced cortisol response. *Psychoneuroendocrinology.* (2018) 94:63–71. doi: 10.1016/j.psyneuen.2018.05.004
61. Wendt J, Neubert J, Koenig J, Thayer JF, Hamm AO. Resting heart rate variability is associated with inhibition of conditioned fear. *Psychophysiology.* (2015) 52:1161–6. doi: 10.1111/psyp.12456
62. Boucsein W, Fowles DC, Grimnes S, Ben-Shakhar G, Roth WT, Dawson ME, et al. Publication recommendations for electrodermal measurements. *Psychophysiology.* (2012) 49:1017–34. doi: 10.1111/j.1469-8986.2012.01384.x
63. Wilhelm FH, Pfaltz MC, Gross JJ, Mauss IB, Kim SI, Wiederhold BK. Mechanisms of virtual reality exposure therapy: the role of the behavioral activation and behavioral inhibition systems. *Appl Psychophysiol Biofeedback.* (2005) 30:271–84. doi: 10.1007/s10484-005-6383-1
64. Wolpe J. *The Practice of Behavior Therapy*. 4th ed New York: Pergamon Press (1990).
65. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health.* (2017) 5:258. doi: 10.3389/fpubh.2017.00258
66. Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front Psychiatry.* (2014) 5:80. doi: 10.3389/fpsyt.2014.00080
67. Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research - recommendations for experiment planning, data analysis, and data reporting. *Front Psychol.* (2017) 8:213. doi: 10.3389/fpsyg.2017.00213
68. Madison A, Vasey M, Emery CF, Kiecolt-Glaser JK. Social anxiety symptoms, heart rate variability, and vocal emotion recognition in women: evidence for parasympathetically-mediated positivity bias. *Anxiety Stress Coping.* (2021) 34:243–57. doi: 10.1080/10615806.2020.1839733
69. Petrescu L, Petrescu C, Mitrut O, Moise G, Moldoveanu A, Moldoveanu F, et al. Integrating biosignals measurement in virtual reality environments for anxiety detection. *Sensors.* (2020) 20:47088. doi: 10.3390/s20247088
70. Wolpe J. *The Practice of Behavior Therapy*. New York, NY: Pergamon Press (1969).
71. Cornwell BR, Johnson L, Berardi L, Grillon C. Anticipation of public speaking in virtual reality reveals a relationship between trait social anxiety and startle reactivity. *Biol Psychiat.* (2006) 59:664–6. doi: 10.1016/j.biopsych.2005.09.015

72. Iffland B, Sansen LM, Catani C, Neuner F. Rapid heartbeat, but dry palms: reactions of heart rate and skin conductance levels to social rejection. *Front Psychol.* (2014) 5:956. doi: 10.3389/fpsyg.2014.00956
73. Berry RB, Brooks R, Gamaldo CE, Hardling S, Marcus C, Vaughn B. *The Aasm Manual for the Scoring of Sleep and Associated Events. Rules, Terminology and Technical Specifications*. Darien, IL: American Academy of Sleep Medicine (2012).
74. Gaebler M, Daniels JK, Lamke JP, Fydrich T, Walter H. Heart rate variability and its neural correlates during emotional face processing in social anxiety disorder. *Biol Psychol.* (2013) 94:319–30. doi: 10.1016/j.biopsycho.2013.06.009
75. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*: Hoboken, NJ: Wiley-Interscience (2004).
76. Bates D, Mächler M, Bolker B, Walker SC. Fitting linear mixed-effects models using Lme4. *J Stat Softw.* (2015) 67:1–48. doi: 10.18637/jss.v067.i01
77. Kuznetsova A, Brockhoff PB, Christensen RHB. Lmertest package: tests in linear mixed effects models. *J Stat Softw.* (2017) 82:1–26. doi: 10.18637/jss.v082.i13
78. Walker DA. Converting Kendall's tau for correlational or meta-analytic analyses. *J Mod Appl Stat Methods.* (2003) 2:525–30. doi: 10.22237/jmasm/1067646360
79. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *J Stat Softw.* (2014) 59:1–38. doi: 10.18637/jss.v059.i05
80. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder - a randomized controlled trial. *J Am Med Assoc.* (2001) 286:537–45. doi: 10.1001/jama.286.5.537
81. Klinger E, Bouchard S, Legeron P, Roy S, Lauer F, Chemin I, et al. Virtual reality therapy versus cognitive behavior therapy for social phobia: a preliminary controlled study. *Cyberpsychol Behav.* (2005) 8:76–88. doi: 10.1089/cpb.2005.8.76
82. Glazier BL, Alden LE. Social anxiety disorder and memory for positive feedback. *J Abnorm Psychol.* (2019) 128:228–33. doi: 10.1037/abn0000407
83. Koban L, Schneider R, Ashar YK, Andrews-Hanna JR, Landy L, Moscovitch DA, et al. Social anxiety is characterized by biased learning about performance and the self. *Emotion.* (2017) 17:1144–55. doi: 10.1037/emo0000296
84. Voegler R, Peterburs J, Bellebaum C, Straube T. Modulation of feedback processing by social context in social anxiety disorder (sad)-an event-related potentials (Erps) study. *Sci Rep.* (2019) 9:4795. doi: 10.1038/s41598-019-41268-0
85. Hauner KK, Howard JD, Zelano C, Gottfried JA. Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nat Neurosci.* (2013) 16:1553–5. doi: 10.1038/nn.3527
86. He J, Sun HQ, Li SX, Zhang WH, Shi J, Ai SZ, et al. Effect of conditioned stimulus exposure during slow wave sleep on fear memory extinction in humans. *Sleep.* (2015) 38:423–31. doi: 10.5665/sleep.4502
87. Barnes DC, Wilson DA. Slow-wave sleep-imposed replay modulates both strength and precision of memory. *J Neurosci.* (2014) 34:5134–42. doi: 10.1523/JNEUROSCI.5274-13.2014
88. Rolls A, Makam M, Kroeger D, Colas D, de Lecea L, Heller HC. Sleep to forget: interference of fear memories during sleep. *Mol Psychiatry.* (2013) 18:1166–70. doi: 10.1038/mp.2013.121
89. Diekelmann S, Born J. Cueing fear memory during sleep–to extinguish or to enhance fear? *Sleep.* (2015) 38:337–9. doi: 10.5665/sleep.4484
90. Schwartz S, Clerget A, Perogamvros L. Combined treatment of nightmares with targeted memory reactivation and imagery rehearsal therapy: a randomized controlled trial. *medRxiv.* (2022). doi: 10.1101/2022.02.17.22270256
91. Rihm JS, Sollberger SB, Soravia LM, Rasch B. Re-presentation of olfactory exposure therapy success cues during non-rapid eye movement sleep did not increase therapy outcome but increased sleep spindles. *Front Hum Neurosci.* (2016) 10:340. doi: 10.3389/fnhum.2016.00340
92. Ai SZ, Dai XJ. Causal role of rapid-eye-movement sleep on successful memory consolidation of fear extinction. *J Thorac Dis.* (2018) 10:1214–6. doi: 10.21037/jtd.2018.01.163
93. Baran B, Pace-Schott EF, Ericson C, Spencer RMC. Processing of emotional reactivity and emotional memory over sleep. *J Neurosci.* (2012) 32:1035–42. doi: 10.1523/JNEUROSCI.2532-11.2012
94. Jones BJ, Spencer RMG. Sleep preserves subjective and sympathetic emotional response of memories. *Neurobiol Learn Mem.* (2019) 166:107096. doi: 10.1016/j.nlm.2019.107096
95. Wagner U, Fischer S, Born J. Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. *Psychosom Med.* (2002) 64:627–34. doi: 10.1097/00006842-200207000-00013
96. Werner GG, Schabus M, Blechert J, Kolodyazhniy V, Wilhelm FH. Pre- to postsleep change in psychophysiological reactivity to emotional films: late-night rem sleep is associated with attenuated emotional processing. *Psychophysiology.* (2015) 52:813–25. doi: 10.1111/psyp.12404
97. Cunningham TJ, Crowell CR, Alger SE, Kensinger EA, Villano MA, Mattingly SM, et al. Psychophysiological arousal at encoding leads to reduced reactivity but enhanced emotional memory following sleep. *Neurobiol Learn Mem.* (2014) 114:155–64. doi: 10.1016/j.nlm.2014.06.002
98. Vallat R, Chatard B, Blagrove M, Ruby P. Characteristics of the memory sources of dreams: a new version of the content-matching paradigm to take mundane and remote memories into account. *PLoS ONE.* (2017) 12:185262. doi: 10.1371/journal.pone.0185262
99. Pace-Schott EF, Germain A, Milad MR. Sleep and rem sleep disturbance in the pathophysiology of Ptsd: the role of extinction memory. *Biol Mood Anxiety Disord.* (2015) 5:3. doi: 10.1186/s13587-015-0018-9
100. Wassing R, Lakbila-Kamal O, Ramautar JR, Stoffers D, Schalkwijk F, Van Someren EJW. Restless rem sleep impedes overnight amygdala adaptation. *Curr Biol.* (2019) 29:2351–8 e4. doi: 10.1016/j.cub.2019.06.034
101. Davidson P, Pace-Schott E. The role of sleep in fear learning and memory. *Curr Opin Psychol.* (2020) 34:32–6. doi: 10.1016/j.copsyc.2019.08.016
102. Datta S, O'Malley MW. Fear extinction memory consolidation requires potentiation of pontine-wave activity during rem sleep. *J Neurosci.* (2013) 33:4561–9. doi: 10.1523/JNEUROSCI.5525-12.2013
103. Nielsen T, Levin R. Nightmares: a new neurocognitive model. *Sleep Med Rev.* (2007) 11:295–310. doi: 10.1016/j.smrv.2007.03.004
104. Marquis L, Blanchette-Carriere C, Carr M, Julien S, Paquette T, Nielsen T. Decreased activity in medial prefrontal cortex and anterior cingulate cortex in idiopathic nightmare sufferers during wakefulness. *Sleep.* (2016) 39:A226–7.
105. Marazziti D, Abelli M, Baroni S, Carpita B, Ramacciotti CE, Dell'Osso L. Neurobiological correlates of social anxiety disorder: an update. *Cns Spectrums.* (2015) 20:100–11. doi: 10.1017/S109285291400008X
106. Krakow B, Zadra A. Imagery rehearsal therapy: principles and practice. *Sleep Med Clin.* (2010) 5:289–98. doi: 10.1016/j.jsmc.2010.01.004
107. Germain A, Nielsen T. Impact of imagery rehearsal treatment on distressing dreams, psychological distress, and sleep parameters in nightmare patients. *Behav Sleep Med.* (2003) 1:140–54. doi: 10.1207/S15402010BSM0103_2
108. Rousseau A, Belleville G. The mechanisms of action underlying the efficacy of psychological nightmare treatments: a systematic review and thematic analysis of discussed hypotheses. *Sleep Med Rev.* (2018) 39:122–33. doi: 10.1016/j.smrv.2017.08.004
109. Campbell J, Ehlert U. Acute psychosocial stress: does the emotional stress response correspond with physiological responses? *Psychoneuroendocrinology.* (2012) 37:1111–34. doi: 10.1016/j.psyneuen.2011.12.010
110. Grillon C. D-cycloserine facilitation of fear extinction and exposure-based therapy might rely on lower-level, automatic mechanisms. *Biol Psychiatry.* (2009) 66:636–41. doi: 10.1016/j.biopsych.2009.04.017
111. Kritikos J, Tzannetos G, Zoitaki C, Poulopoulou S, Koutsouris PD. Anxiety detection from electrodermal activity sensor with movement interaction during virtual reality simulation. In: *International IEEE/EMBS Conference on Neural Engineering, NER*; *March 2019*. San Francisco, CA. (2019). p. 1–6.
112. Kerous B, Bartecek R, Roman R, Sojka P, Becev O, Liarokapis F. Examination of electrodermal and cardio-vascular reactivity in virtual reality through a combined stress induction protocol. *J Amb Intel Hum Comp.* (2020) 11:6033–42. doi: 10.1007/s12652-020-01858-7

113. McCraty R, Shaffer F. Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Glob Adv Health Med.* (2015) 4:46–61. doi: 10.7453/gahmj.2014.073
114. Kim AY, Jang EH, Choi KW, Jeon HJ, Byun S, Sim JY, et al. Skin conductance responses in major depressive disorder (Mdd) under mental arithmetic stress. *PLoS ONE.* (2019) 14:e0213140. doi: 10.1371/journal.pone.0213140
115. Bourdillon N, Jeanneret F, Nilchian M, Albertoni P, Ha P, Millet GP. Sleep deprivation deteriorates heart rate variability and photoplethysmography. *Front Neurosci.* (2021) 15:642548. doi: 10.3389/fnins.2021.642548
116. Lo Martire V, Caruso D, Palagini L, Zoccoli G, Bastianini S. Stress & sleep: a relationship lasting a lifetime. *Neurosci Biobehav R.* (2020) 117:65–77. doi: 10.1016/j.neubiorev.2019.08.024
117. Göldi M, Rasch B. Effects of targeted memory reactivation during sleep at home depend on sleep disturbances and habituation. *Npj Sci Learn.* (2019) 4:2. doi: 10.1038/s41539-019-0044-2
118. Kushnir J, Marom S, Mazar M, Sadeh A, Hermesh H. The link between social anxiety disorder, treatment outcome, and sleep difficulties among patients receiving cognitive behavioral group therapy. *Sleep Med.* (2014) 15:515–21. doi: 10.1016/j.sleep.2014.01.012
119. Zalta AK, Dowd S, Rosenfield D, Smits JAJ, Otto MW, Simon NM, et al. Sleep quality predicts treatment outcome in Cbt for social anxiety disorder. *Depress Anxiety.* (2013) 30:1114–20. doi: 10.1002/da.22170

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BRIEF RESEARCH REPORT
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Trait Anxiety Does Not Predict the Anxiogenic Response to Sleep Deprivation

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Sleep deprivation has in several studies been found to increase anxiety. However, the extent to which this anxiogenic effect depends on one's underlying trait anxiety has not previously been determined. Using two separate sleep-loss experiments, the current research investigated whether trait anxiety (STAI-T) moderates the increase in state anxiety (STAI-S) following one night of total sleep loss (study 1, $N = 182$, age 25.3 ± 6.5, 103 women) and two nights of partial sleep restriction (study 2, $N = 67$, age 26.5 ± 7.4, 38 women). Both studies showed the expected anxiogenic effect of sleep loss, and a clear relationship between trait anxiety and state anxiety. However, the anxiogenic effect of sleep loss was not moderated by trait anxiety, as there was an equal impact regardless of trait anxiety level. These findings indicate that, although sleep loss is related to general anxiety as well as anxiety disorders, for a non-clinical sample the anxiogenic effect of short-term sleep loss is not affected by baseline levels of anxiety.

Keywords: anxiety, STAI, sleep loss, individual differences, sleep restriction

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INTRODUCTION

Sleep is intertwined with daily anxiety, with higher levels of anxiety acting both as a predictor of sleep quality and a consequence of sleep loss (Alvaro et al., 2013; Horváth et al., 2016; Pires et al., 2016). Several studies have focused on the anxiogenic effect of sleep deprivation, suggesting that hypoactivity in the medial prefrontal cortex is a potential mechanism (Ben Simon et al., 2020a) and that gray matter volume may determine vulnerability differently for men and women (Goldstein-Piekarski et al., 2018), indicating that there are individual differences in this anxiogenic effect. Indeed, although the relationship between sleep and anxiety does not seem to depend on the impact of mood (Ben Simon et al., 2020a), the emotional responses to sleep loss of anxious individuals may be amplified compared to those with less trait anxiety (Goldstein et al., 2013; Alfano et al., 2020). This suggests that trait anxiety may predict vulnerability to the anxiogenic effects of sleep deprivation as well, but surprisingly little attention has been devoted to the relationship between trait anxiety and the effects of sleep loss in healthy subjects (Palmer and Alfano, 2020).

In order to understand who is vulnerable or resilient to the anxiogenic effects of sleep loss, more research is needed regarding underlying predictive factors. For example, there are large individual differences in how people respond to sleep deprivation in the cognitive domains (Tkachenko and Dinges, 2018), and these may in part be predicted by trait-level, domain-specific, cognitive abilities (Brieva et al., 2021; Floros et al., 2021). If the same is true for affective domains, those low in trait anxiety may have a smaller anxiogenic effect of sleep deprivation than those high in trait anxiety. For example, in adolescents with generalized anxiety disorder (GAD), natural variations in sleep duration has been shown as a predictor of morning anxiety, whereas for healthy controls it has not (Mullin et al., 2017). Specifically, for the adolescents with GAD, shorter sleep duration was associated with more morning anxiety the following day. However, as disturbed sleep is strongly comorbid with anxiety disorders it is difficult to disentangle cause and effect from observational studies of clinical samples. In other words, it is yet unknown whether there is a moderating effect of subclinical variations in trait anxiety on the anxiogenic effect of experimentally induced sleep loss. The aim of this brief report is thus to elucidate whether interindividual, subclinical variation in trait anxiety predicts the impact of sleep deprivation (study 1) and sleep restriction (study 2) on state anxiety.

METHODS

Study 1

Participants

One hundred and eighty-two healthy participants were randomly assigned to one of two conditions: one night of total sleep deprivation (TSD; N = 91, average age 25.4 ± 6.21, range 18–45 years; 52 women) or normal 8h-sleep (NS; N = 91, average age 25.3 ± 6.82, range 17–45 years; 51 women). Exclusion criteria during the initial screening included physical or mental health problems, sleep disturbances, a subjective sleep need outside of 7–9 h, shift work in the previous 3 weeks, and addiction to coffee or other drugs (see Holding et al., 2019 for a complete list of exclusion criteria). Participants provided written informed consent and were compensated for their time. The study was approved by the Regional Ethical Review Board in Stockholm (2014/1766-21).

Procedure

Prior to being informed of their condition, participants filled out the trait version of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983; Julian, 2011). This assesses "How you generally feel" with statements such as "I feel safe" and "I am a stable person." The response options range from "1-almost never" to "4-almost always." Participants were then instructed to sleep 8–9 h per night (between 22:00 and 08:00) in their home for three nights, with sleep times assessed using actigraphy (Sadeh, 2011) and sleep diaries. After the third night, they were informed of their sleep condition and were either instructed to spend one more night according to this schedule (NS group) and come into the lab at 10:00 the following day (the test day), or arrive at the lab at 22:00 that evening and stay awake until the following day (TSD group). Participants in the sleep-deprivation condition were monitored throughout the night, and not allowed to engage in any strenuous activities. Around 10:30 on the test day (∼26.5 h awake for the TSD group, ∼2.5 h awake for the NS group) they filled out the state version of STAI. This version assesses "How you feel at this moment" with statements such as "I feel safe" and "I feel nervous." Response options range from "1-not at all" to "4-very much so."

Analyses

State-Trait Anxiety Inventory was scored according to the standard instructions, adding up the responses to all items while reverse-scoring anxiety-absent items. This results in a value between 20 and 80 for each scale. All STAI scores were then converted to z-scores, and Bayesian linear modeling was used to test the main effects and interaction of TSD and trait anxiety on state anxiety. The Bayesian models provide a point effect estimate and a probability distribution of plausible alternative values (posterior distribution). To determine uncertainty around our point estimate, we use the 95% Credible Interval (95% CI; 2.5 and 97.5% quantiles of the posterior). The 95% credible interval is analogous to the 95% confidence interval though with greater precision (Gray et al., 2015).

A key benefit of taking a Bayesian approach is the ability to assess the relative strength of evidence for different hypotheses. Therefore, we can state (unlike in classical frequentist analysis which can only be used to reject the null hypothesis and never support it) whether the data supports the alternative hypothesis, the null hypothesis, or doesn't provide enough information to support either. In other words, we can make clearer conclusions about situations in which no effect is present. In our case, we compare models with and without a coefficient of interest to calculate Bayes factors (BF_{10}). A rule of thumb for interpreting these is that a BF_{10} greater than 3 suggests that there is evidence for the alternative hypothesis (i.e., that the coefficient improves the model prediction), a BF_{10} of less than 0.33 provides evidence of the null hypothesis (i.e., that the coefficients does not improve the model prediction), and a BF_{10} between these values suggests that there is not enough data to support either hypothesis (Dienes, 2014).

Data and analysis code can be found at https://osf.io/tcdne/. STAI values (both state and trait) over 3 SD from the mean were excluded. The data of three participants (all from the normal-sleep condition) were excluded for this reason. One further participant (from the normal-sleep condition) was excluded due to not completing the state STAI and another participant (from the sleep-deprivation condition) was excluded due to not completing the trait STAI.

The analysis was run using in R (version 4.1.0; R Core Team, 2021) with RStudio (version 1.4.1106; RStudio Team, 2021). To run the main analysis we used the brms (version 2.16.1; Bürkner, 2017) package using 8 chains and 40,000 iterations (20,000 warm-up). Priors were set on the coefficients with mean 0 and SD 1. All other parameters used the default non-informative regularizing priors of the brms package. To calculate the relative evidence of adding coefficients of interest

(compared to a simpler model without this coefficient, i.e., the null hypothesis), we computed Bayes factors (BF_{10}) using the BayestestR package (version 0.10.0; Makowski et al., 2019). For data preprocessing we used the following packages: dplyr, readxl, sjplot, tidyr, and readr (Wickham and Bryan, 2019; Wickham and Hester, 2020; Lüdecke, 2021; Wickham, 2021; Wickham et al., 2021).

Study 2

Participants

Sixty-seven healthy participants (average age 26.5 ± 7.4, range 18–46 years; 38 women) took part in a within-subject protocol with two conditions: normal sleep and sleep restriction. Exclusion criteria included poor physical or mental health, sleep disturbances, a sleep need outside of 7–9 h, shift work during the previous 3 weeks, and an addiction to coffee or other drugs. Participants provided written informed consent and were compensated for their time. The study was approved by the Regional Ethical Review Board in Stockholm (2010/1506-31).

Procedure

Participants came to the lab on two occasions, with sleep conditions in a randomized counterbalanced order and a washout period of minimum 1 week between the two. They arrived at the lab in the afternoon (14:30 ± 1 h). The arrival time could vary between 13:00 and 16:00, but was always the same within participant. Upon arrival, they spent 30 min sitting down in a light-controlled room and filling out questionnaires. In the normal-sleep condition (two consecutive nights of 8 h of sleep) they filled out both the state and trait versions of STAI, and in the sleep-restriction condition (two consecutive nights of no more than 4 h of sleep) they filled out only the state version. In order to ensure adherence to the study protocol, participants wore actigraphs during all four nights, filled out sleep diaries, and sent a text message to the experimenter upon bedtime and waking.

Analyses

Hypotheses and analyses for study 2 were preregistered prior to looking at the data. All STAI scores were converted to *z*-scores, and Bayesian mixed-effect modeling was used to test the main effects and interaction of TSD and trait anxiety on state anxiety. Preregistration, data, and analysis code can be found at https://osf.io/ysa42 and https://osf.io/tcdne/.

As planned in the preregistration, STAI values (both state and trait) over 3 SD from the mean were excluded. Since the study was a repeated-measures cross-over design, it was possible for individuals to be excluded for a single session only. Two participants' data were excluded in the sleep-restriction session for this reason, and thus their data is only represented in the normal-sleep session. A further participant did not complete the state STAI for the sleep-restriction session, and thus their data was only included in the normal-sleep session.

The statistical analysis was essentially identical to study 1. The only difference is that due to the repeated-measures design, we included random intercepts for participant ID to account for clustering of variance within these units.

RESULTS

See **Table 1** for average sleep times and anxiety scores between groups and conditions. See **Supplementary Table 1** for average sleep and wake times.

In both studies, sleep loss led to a clear increase in state anxiety, and trait anxiety predicted higher state anxiety for all groups and conditions (**Table 2**). However, there was no apparent moderating effect of trait anxiety on the anxiogenic effect of sleep loss (**Table 2** and **Figure 1**). The Bayes factor of the interaction coefficients suggests that the data is approximately 4.6–6.8 times more likely to be generated under a model without a moderating effect of trait anxiety on the effect of sleep loss.

State anxiety when well rested and when sleep restricted were correlated (study 2; estimate = 0.46, 95% CI [0.23, 0.70], BF_{10} = 110.51 compared to intercept only model), and trait anxiety in a univariate model reliably predicted state anxiety (study 1: estimate = 0.46, 95% CI [0.32, 0.60], BF_{10} compared to intercept-only model = 42700000; study 2: estimate = 0.52, 95% CI [0.38, 0.66], BF_{10} compared to intercept-only model = 171000000).

As preregistered robustness checks, we ran the analysis in two further ways. Firstly, we compared participants in both studies who rated higher or lower than 1 SD from the mean trait anxiety score (see **Supplementary Figure 1** and **Supplementary Table 2**). We also conducted the primary analyses without excluding any participants (i.e., not excluding outliers, see **Supplementary Figure 2**

TABLE 1 | Descriptive statistics.

	Condition	Sleep duration	State anxiety		Trait anxiety	
		Mean ± SD	Mean ± SD	Range	Mean ± SD	Range
Study 1	Normal sleep	471 ± 54	31.17 ± 7.11	20–54	37.51 ± 8.09	22–57
	Sleep deprivation	0 ± 0	35.22 ± 7.38	21–56	35.37 ± 7.10	22–57
Study 2	Normal sleep	466 ± 36	30.91 ± 7.58	20–55	34.01 ± 7.33	20–53
	Sleep restriction	245 ± 24	35.65 ± 7.01	23–55		20–53

Study 1 is between participants, study 2 is within participants. Sleep duration is in minutes, based on actigraphy data. For study 1, it represents the last night before filling out the questionnaires; for study 2 it represents an average across the two nights before filling out the questionnaires. Data is missing for five participants in study 1 and for three participants in study 2 (see section "Methods" for more information).

TABLE 2 | Full models predicting state anxiety for studies 1 and 2.

	State anxiety (*z*-score)		
Predictors	**Estimates**	**CI (95%)**	**BF_{10}**
Study 1			
Intercept	−0.34	−0.51, −0.17	
Sleep deprivation	0.64	0.40, 0.88	94.39
Trait anxiety (*z*-score)	0.54	0.36, 0.71	8540000000
Sleep deprivation × trait anxiety (*z*-score)	−0.06	−0.32, 0.20	0.148
Study 2			
Intercept	−0.32	−0.49, −0.16	
Sleep restriction	0.59	0.36, 0.81	3890
Trait anxiety (*z*-score)	0.59	0.42, 0.76	637000000
Sleep restriction × trait anxiety (*z*-score)	−0.13	−0.36, 0.10	0.219

Study 1: observations = 177. R^2 Bayes = 0.31. Study 2: random effects: ICC = 0.10. Observations = 133. Marginal R^2 = 0.426. Conditional R^2 = 0.492. BF_{10}, Bayes factor for the alternative hypothesis, i.e., the model with the predictor added compared to the model without that predictor (i.e., the model with sleep restriction was compared to the intercept-only model, the model with trait anxiety was compared to the model with only sleep restriction, and the model with sleep restriction × trait anxiety was compared to the model with trait anxiety and sleep restriction).

and **Supplementary Table 3**). The results of these supplementary analyses follow the same pattern as the primary results presented.

As a non-preregistered robustness check, we also ran the analysis including participant gender as a covariate. The results follow the same pattern as the primary results presented (see **Supplementary Table 4**).

DISCUSSION

In the modern 24-society, sleep loss is prevalent (Webb and Agnew, 1975; Knutson et al., 2010; Shochat, 2012; Blom et al., 2020; but see Marshall and Lallukka, 2018 for discussion). Rates of anxiety are also high (Wiegner et al., 2015; Bosman et al., 2019), which studies have shown can have roots in lack of sleep (see Ben Simon et al., 2020b for review). We aimed to understand more about this relationship, by assessing whether the effect of sleep loss on anxiety was stronger in individuals who generally were already reporting high levels of anxiety.

In both studies, we found a clear influence of sleep loss on self-reported state anxiety. Sleep loss led to an increase in anxiety in the range of 0.60–0.65 SD, indicating a medium-to-large effect size (Sawilowsky, 2009). However, any potential moderation by trait anxiety of the impact of insufficient sleep on state anxiety was negligible. Bayes factors from both studies suggest that the data is much more likely if sleep loss has an approximately equal impact on state anxiety, irrespective of trait anxiety level. Additionally, this pattern was robust to two alternative methods of analyzing the data. These results provide important evidence regarding individual differences in the anxiogenic effects of sleep loss; although sleep loss causes an increase in state anxiety across levels of trait anxiety, the effect appears to be no different for those with high or low levels of trait anxiety.

The bidirectionality of sleep and anxiety has not been taken into account in this study. For example, it is possible that higher levels of anxiety following sleep loss is related to more subsequent rumination, in turn resulting in more troubled sleep (e.g., Gordon et al., 2019). This could amplify the effect for those high in trait anxiety across time, laying the foundation for the strong correlational relationship found between the two (e.g., Ben Simon et al., 2020a). Indeed, sleep disturbances in childhood are predictive of anxiety disorders in adulthood, even when controlling for internalizing problems and socioeconomic

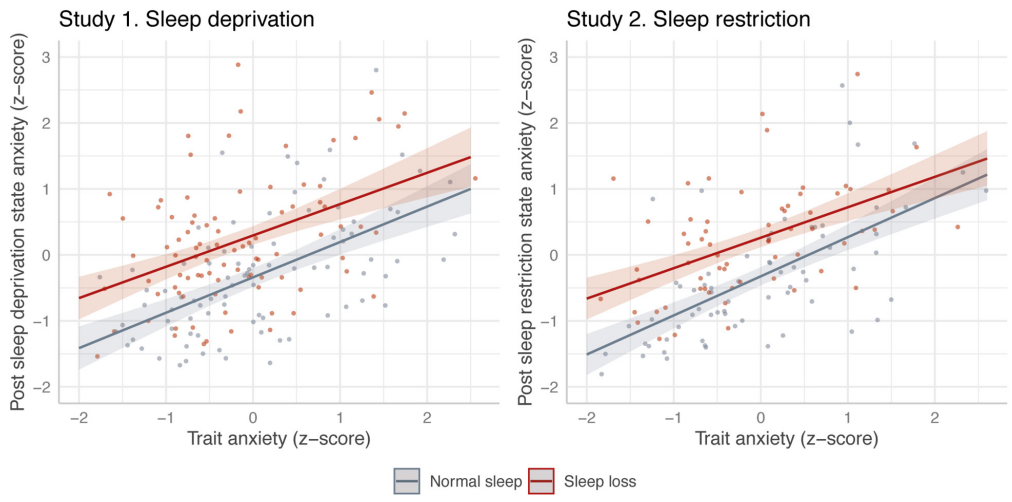

FIGURE 1 | Association between trait anxiety and state anxiety reported before (gray) and after (red) sleep loss. The left-hand graph represents the results from study 1, using between-subjects sleep deprivation. The right-hand graph represents the results from study 2, using within-subjects sleep restriction. Model predictions are based on the models in **Table 2**. Solid line represents estimated association, with 95% credible intervals. Dots represent raw data points (jittered).

status (Gregory et al., 2005). For those who are more vulnerable, i.e., have higher trait anxiety, the increase in state anxiety due to sleep loss may thus be more detrimental even though it is not objectively larger. A potential limitation here is the use of a self-report measure of anxiety, which may be affected differently than more objective measures (see, e.g., Egloff and Schmukle, 2004).

Although higher trait anxiety seems to modify the emotional effects of sleep loss (Alfano et al., 2020; Palmer and Alfano, 2020), our results indicate that this is not due to differences in the anxiogenic effect of sleep loss. Rather, the resulting high levels of state anxiety for those higher in trait anxiety may be the explaining factor. It is possible that there is an inflection point at which one's levels of anxiety relate to stronger emotional reactions to one's environment.

The results of the two studies do not appear to be due to ceiling effects in state anxiety for those with high trait anxiety. The range of state anxiety was similar between the two groups (study 1) and two conditions (study 2), with no participant getting the maximum possible score in either. Although our exclusion of individuals with state anxiety over 3 SD above the mean may have inadvertently induced such a ceiling effect, especially in those with high trait anxiety, our supplementary analysis where we do not use this exclusion criteria (**Supplementary Figure 2** and **Supplementary Table 3**) suggests that this did not affect the conclusions. Normative values for STAI-S in Sweden (where both studies were conducted) have been estimated at 33.2 ± 9.6, although this was based on a rather small sample (Forsberg and Björvell, 1993). Other reported normative values, in larger, non-Swedish samples were around 33–35.5 (SD ranging from 7.3 to 8.6) for STAI-S and 33–36 (SD ranging from 7.8 to 8.9) for STAI-T (Knight et al., 1983; Crawford et al., 2011). The participants in this study thus seem to represent a fairly normal population in terms of anxiety levels. Although those scoring high in trait anxiety (e.g., above 40 or 53) may be at a higher risk of developing an anxiety disorder (e.g., Dennis et al., 2013; Zingano et al., 2019), this was a subclinical sample and it is likely that individuals with clinical levels of anxiety respond differently to sleep loss, as indicated by previous research (e.g., Mullin et al., 2017).

In conclusion, variations in trait anxiety does not predict the anxiogenic effect of short-term sleep loss in a non-clinical sample. The findings of this study bring us closer to elucidating risk factors and protective mechanisms regarding the negative effects of sleep loss.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/tcdne/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethical Review Board in Stockholm. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS and BH conceptualized and designed the study. TS organized the data collections and wrote the first draft on the manuscript. BH performed the statistical analyses. Both authors wrote sections of and revised the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2022.880641/full#supplementary-material

REFERENCES

Alfano, C. A., Bower, J. L., Harvey, A. G., Beidel, D. C., Sharp, C., and Palmer, C. A. (2020). Sleep restriction alters children's positive emotional responses, but effects are moderated by anxiety. *J. Child Psychol. Psychiatry* 61, 1150–1159. doi: 10.1111/jcpp.13287

Alvaro, P. K., Roberts, R. M., and Harris, J. K. (2013). A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* 36, 1059–1068. doi: 10.5665/sleep.2810

Ben Simon, E., Rossi, A., Harvey, A. G., and Walker, M. P. (2020a). Overanxious and underslept. *Nat. Hum. Behav.* 4, 100–110. doi: 10.1038/s41562-019-0754-8

Ben Simon, E., Vallat, R., Barnes, C. M., and Walker, M. P. (2020b). Sleep loss and the socio-emotional brain. *Trends Cogn. Sci.* 24, 435–450. doi: 10.1016/j.tics.2020.02.003

Blom, V., Kallings, L. V., Ekblom, B., Wallin, P., Andersson, G., Hemmingsson, E., et al. (2020). Self-reported general health, overall and work-related stress, loneliness, and sleeping problems in 335,625 swedish adults from 2000 to 2016. *Int. J. Environ. Res. Public Health* 17:511. doi: 10.3390/ijerph17020511

Bosman, R. C., Ten Have, M., de Graaf, R., Muntingh, A. D., van Balkom, A. J., and Batelaan, N. M. (2019). Prevalence and course of subthreshold anxiety disorder in the general population: a three-year follow-up study. *J. Affect. Disord.* 247, 105–113. doi: 10.1016/j.jad.2019.01.018

Brieva, T. E., Casale, C. E., Yamazaki, E. M., Antler, C. A., and Goel, N. (2021). Cognitive throughput and working memory raw scores consistently

differentiate resilient and vulnerable groups to sleep loss. *Sleep* 44:zsab197. doi: 10.1093/sleep/zsab197

Bürkner, P.-C. (2017). brms: an R package for bayesian multilevel models using stan. *J. Stat. Softw.* 80, 1–28.

Crawford, J., Cayley, C., Lovibond, P. F., Wilson, P. H., and Hartley, C. (2011). Percentile norms and accompanying interval estimates from an australian general adult population sample for self-report mood scales (BAI, BDI, CRSD, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS, and SRAS). *Aust. Psychol.* 46, 3–14. doi: 10.1111/j.1742-9544.2010.00003.x

Dennis, C.-L., Coghlan, M., and Vigod, S. (2013). Can we identify mothers at-risk for postpartum anxiety in the immediate postpartum period using the State-Trait Anxiety Inventory? *J. Affect. Disord.* 150, 1217–1220. doi: 10.1016/j.jad.2013.05.049

Dienes, Z. (2014). Using bayes to get the most out of non-significant results. *Front. Psychol.* 5:781. doi: 10.3389/fpsyg.2014.00781

Egloff, B., and Schmukle, S. C. (2004). Gender differences in implicit and explicit anxiety measures. *Pers. Individ. Differ.* 36, 1807–1815. doi: 10.1016/j.paid.2003.07.002

Floros, O., Axelsson, J., Almeida, R., Tigerström, L., Lekander, M., Sundelin, T., et al. (2021). Vulnerability in executive functions to sleep deprivation is predicted by subclinical attention-deficit/hyperactivity disorder symptoms. *Biol. Psychiatry. Cogn. Neurosci. Neuroimaging* 6, 290–298. doi: 10.1016/j.bpsc.2020.09.019

Forsberg, C., and Björvell, H. (1993). Swedish population norms for the GHRI, HI and STAI-state. *Qual. Life Res.* 2, 349–356. doi: 10.1007/BF00449430

Goldstein, A. N., Greer, S. M., Saletin, J. M., Harvey, A. G., Nitschke, J. B., and Walker, M. P. (2013). Tired and apprehensive: anxiety amplifies the impact of sleep loss on aversive brain anticipation. *J. Neurosci.* 33, 10607–10615. doi: 10.1523/JNEUROSCI.5578-12.2013

Goldstein-Piekarski, A. N., Greer, S. M., Saletin, J. M., Harvey, A. G., Williams, L. M., and Walker, M. P. (2018). Sex, sleep deprivation, and the anxious brain. *J. Cogn. Neurosci.* 30, 565–578. doi: 10.1162/jocn_a_01225

Gordon, A. M., Del Rosario, K., Flores, A. J., Mendes, W. B., and Prather, A. A. (2019). Bidirectional links between social rejection and sleep. *Psychosom. Med.* 81, 739–748. doi: 10.1097/PSY.0000000000000669

Gray, K., Hampton, B., Silveti-Falls, T., McConnell, A., and Bausell, C. (2015). Comparison of bayesian credible intervals to frequentist confidence intervals. *J. Mod. Appl. Stat. Methods* 14, 43–52. doi: 10.22237/jmasm/1430453220

Gregory, A. M., Caspi, A., Eley, T. C., Moffitt, T. E., O'Connor, T. G., and Poulton, R. (2005). Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *J. Abnorm. Child Psychol.* 33, 157–163. doi: 10.1007/s10802-005-1824-0

Holding, B. C., Sundelin, T., Lekander, M., and Axelsson, J. (2019). Sleep deprivation and its effects on communication during individual and collaborative tasks. *Sci. Rep.* 9:3131. doi: 10.1038/s41598-019-39271-6

Horváth, A., Montana, X., Lanquart, J.-P., Hubain, P., Szûcs, A., Linkowski, P., et al. (2016). Effects of state and trait anxiety on sleep structure: a polysomnographic study in 1083 subjects. *Psychiatry Res.* 244, 279–283. doi: 10.1016/j.psychres.2016.03.001

Julian, L. J. (2011). Measures of anxiety: state-trait anxiety inventory (STAI), beck anxiety inventory (BAI), and hospital anxiety and depression scale-anxiety (HADS-A). *Arthritis Care Res.* 63, S467–S472. doi: 10.1002/acr.20561

Knight, R. G., Waal-Manning, H. J., and Spears, G. F. (1983). Some norms and reliability data for the state-trait anxiety inventory and the zung self-rating depression scale. *Br. J. Clin. Psychol.* 22, 245–249. doi: 10.1111/j.2044-8260.1983.tb00610.x

Knutson, K. L., Van Cauter, E., Rathouz, P. J., DeLeire, T., and Lauderdale, D. S. (2010). Trends in the prevalence of short sleepers in the USA: 1975–2006. *Sleep* 33, 37–45. doi: 10.1093/sleep/33.1.37

Lüdecke, D. (2021). *sjPlot: Data Visualization for Statistics in Social Science_. R package version 2.8.8*. Available online at: https://CRAN.R-project.org/package=sjPlot (accessed May 25, 2021).

Makowski, D., Ben-Shachar, M. S., and Lüdecke, D. (2019). bayestestR: describing effects and their uncertainty, existence and significance within the bayesian framework. *J. Open Source Softw.* 4:1541. doi: 10.21105/joss.01541

Marshall, N. S., and Lallukka, T. (2018). Sleep pirates–are we really living through a sleep deprivation epidemic and what's stealing our sleep? *Eur. J. Public Health* 28, 394–395. doi: 10.1093/eurpub/cky016

Mullin, B. C., Pyle, L., Haraden, D., Riederer, J., Brim, N., Kaplan, D., et al. (2017). A preliminary multimethod comparison of sleep among adolescents with and without generalized anxiety disorder. *J. Clin. Child Adolesc. Psychol.* 46, 198–210. doi: 10.1080/15374416.2016.1220312

Palmer, C. A., and Alfano, C. A. (2020). Anxiety modifies the emotional effects of sleep loss. *Curr. Opin. Psychol.* 34, 100–104. doi: 10.1016/j.copsyc.2019.12.001

Pires, G. N., Bezerra, A. G., Tufik, S., and Andersen, M. L. (2016). Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med.* 24, 109–118. doi: 10.1016/j.sleep.2016.07.019

R Core Team (2021). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

RStudio Team (2021). *RStudio: Integrated Development Environment for R. RStudio, PBC*. Available online at: http://www.rstudio.com/ (accessed February 22, 2021).

Sadeh, A. (2011). The role and validity of actigraphy in sleep medicine: an update. *Sleep Med. Rev.* 15, 259–267.

Sawilowsky, S. S. (2009). New effect size rules of thumb. *J. Mod. Appl. Stat. Methods* 8, 597–599. doi: 10.22237/jmasm/1257035100

Shochat, T. (2012). Impact of lifestyle and technology developments on sleep. *Nat. Sci. Sleep* 4, 19–31. doi: 10.2147/NSS.S18891

Spielberger, C. D., Gorsuch, R. L., Lushene, R., and Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Tkachenko, O., and Dinges, D. F. (2018). Interindividual variability in neurobehavioral response to sleep loss: a comprehensive review. *Neurosci. Biobehav. Rev.* 89, 29–48. doi: 10.1016/j.neubiorev.2018.03.017

Webb, W. B., and Agnew, H. W. (1975). Are we chronically sleep deprived? *Bull. Psychon. Soc.* 6, 47–48. doi: 10.3758/BF03333140

Wickham, H. (2021). *Tidyr: Tidy Messy Data. R package version 1.1.3*. Available online at: https://CRAN.R-project.org/package=tidyr (accessed March 3, 2021).

Wickham, H., and Bryan, J. (2019). *Readxl: Read Excel Files. R package version 1.3.1*. Available online at: https://CRAN.R-project.org/package=readxl (accessed May 5, 2021).

Wickham, H., and Hester, J. (2020). *Readr: Read Rectangular Text Data. R package version 1.4.0*. Available online at: https://CRAN.R-project.org/package=readr (accessed February 22, 2021).

Wickham, H., François, R., Henry, L., and Müller, K. (2021). *Dplyr: A grammar of data manipulation. R package version 1.0.6*. Available online at: https://CRAN.R-project.org/package=dplyr (accessed May 5, 2021).

Wiegner, L., Hange, D., Björkelund, C., and Ahlborg, G. (2015). Prevalence of perceived stress and associations to symptoms of exhaustion, depression and anxiety in a working age population seeking primary care—An observational study. *BMC Fam. Pract.* 16:38. doi: 10.1186/s12875-015-0252-7

Zingano, B., de, L., Guarnieri, R., Diaz, A. P., Schwarzbold, M. L., Wolf, P., et al. (2019). Hospital anxiety and depression scale-anxiety subscale (HADS-A) and the state-trait anxiety inventory (STAI) accuracy for anxiety disorders detection in drug-resistant mesial temporal lobe epilepsy patients. *J. Affect. Disord.* 246, 452–457. doi: 10.1016/j.jad.2018.12.072

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Electrodermal Activity Is Sensitive to Sleep Deprivation but Does Not Moderate the Effect of Total Sleep Deprivation on Affect

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Emotion is characterized by dimensions of affective valence and arousal, either or both of which may be altered by sleep loss, thereby contributing to impaired regulatory functioning. Controlled laboratory studies of total sleep deprivation (TSD) generally show alterations in physiological arousal and affective state, but the relationship of affect and emotion with physiological arousal during TSD has not been well characterized. Established methods for examining physiological arousal include electrodermal activity (EDA) measures such as non-specific skin conductance responses (NSSCR) and skin conductance level (SCL). These measures are robust physiological markers of sympathetic arousal and have been linked to changes in experienced emotion. To explore the link between physiological arousal and affect during sleep deprivation, we investigated individuals' EDA under TSD and its relationship to self-reported affect. We also investigated the relationship of EDA to two other measures known to be particularly sensitive to the arousal-decreasing effects of TSD, i.e., self-reported sleepiness and performance on a vigilant attention task. Data were drawn from three previously published laboratory experiments where participants were randomly assigned to either well-rested control (WRC) or 38 h of TSD. In this data set, comprising one of the largest samples ever used in an investigation of TSD and EDA (N = 193 with 74 WRC and 119 TSD), we found the expected impairing effects of TSD on self-reported affect and sleepiness and on vigilant attention. Furthermore, we found that NSSCR, but not SCL, were sensitive to TSD, with significant systematic inter-individual differences. Across individuals, the change in frequency of NSSCR during TSD was not predictive of the effect of TSD on affect, sleepiness, or vigilant attention, nor was it related to these outcomes during the rested baseline. Our findings indicate that while physiological

arousal, as measured by EDA, may be useful for assessing TSD-related changes in non-specific arousal at the group level, it is not associated with individuals' self-reported affect at rest nor their change in affect during TSD. This suggests that an essential aspect of the relationship between physiological arousal and self-reported affect is not well captured by EDA as measured by NSSCR.

Keywords: electrodermal lability, physiological arousal, affect, vigilant attention, sleepiness, mood, experienced emotion

INTRODUCTION

Multiple sources of evidence demonstrate that insufficient sleep alters the experience of emotion. Sleep loss has been found to decrease positive mood (Pilcher and Huffcutt, 1996; Dinges et al., 1997) and increase negative mood states (Scott et al., 2006; Kahn-Greene et al., 2007), and has been linked to difficulties in regulating emotion (Lustig et al., 2021; Lustig, 2021; Stenson et al., 2021). The experience of emotion is characterized by affective valence (positive/negative) and by the level of arousal (how intensely an affective state is experienced; Russell, 1980; Posner et al., 2005). Even though arousal is an essential component of emotion, studies of how emotional experience is influenced by sleep loss have generally been limited to self-report measures of arousal, with changes in arousal examined separately from emotion. As subjective measures are subject to cognitive biases (Podsakoff et al., 2003), to better understand the impact of sleep deprivation on emotion, there is a need to measure changes in emotion-related arousal due to sleep loss in a more direct and objective way. Such an objective measure of arousal during sleep loss would also be useful for monitoring personnel alertness in fields where individuals are remotely located and experience extended wake periods.

It is well-established that sleep deprivation decreases arousal, as the build-up of homeostatic sleep drive with time awake increases the pressure for sleep (modulated by circadian rhythm; Borbély et al., 2016). Individuals show increased sleepiness and fatigue on subjective and objective measures when sleep deprived (Daan et al., 1984; Oken et al., 2006; Åkerstedt et al., 2014) but across individuals, the increases in subjective sleepiness are distinct from those in objective measures (Van Dongen et al., 2004a; Franzen et al., 2008). Despite purportedly assessing the same construct, subjective and objective measures related to arousal often show a negative correlation (Danker-Hopfe et al., 2001) or no reliable association (Seidel et al., 1984)—a dissociation that extends to conditions of sleep deprivation (Leproult et al., 2003; Van Dongen et al., 2004a). A reasonable conclusion from these results is that subjective measures of arousal are unlikely to serve as adequate substitutes for more direct measures of physiological arousal and are correspondingly inadequate to assist in explaining objective changes in the experience of emotion due to sleep deprivation.

An objective measure that may be more useful for assessing an individual's physiological arousal and changes in mood during sleep deprivation is electrodermal activity (EDA). EDA provides a well-established method for assessing physiological arousal by measuring changes in current passed through two points of contact across the skin (Dawson et al., 2017). Unlike other measures of physiological arousal (e.g., EEG, heart rate, pupillary response) which are subject to a variety of influences by both sympathetic and parasympathetic activity, the activity of the sweat glands that determine electrical conductance across the skin is directly driven by the sympathetic nervous system. Thus, EDA provides a relatively unadulterated measure of sympathetic arousal. As sleep deprivation is thought to increase sympathetic tone and decrease parasympathetic tone (McEwen, 2006), using EDA as opposed to other measures of physiological arousal avoids the potential that these two nervous systems will exert confounding influences.

There are several indices drawn from EDA data with different functional properties. For changes in arousal in response to continuous situations such as sleep deprivation, the most useful electrodermal measures are skin conductance level (SCL) and non-specific skin conductance responses (NSSCR). SCL represents the tonic level of skin conductance, and NSSCR are skin conductance responses that occur without a specific eliciting stimulus (Dawson et al., 2017). Increases in either SCL or the frequency of NSSCR reflect increases in sympathetic activation, usually due to changes in task situation (e.g., anticipating or beginning performance). Notably, research has found that these measures of EDA may also be linked to experienced emotion, as individuals show increased SCL and NSSCR during emotion regulation (Gross and Levenson, 1993; Gross, 1998; Egloff et al., 2006; Duijndam et al., 2020) and following procedures to induce emotion over extended periods (Kreibig et al., 2007). More importantly, SCL and frequency of NSSCR have been found to be associated with changes in subjective arousal in rested individuals rating their emotional reactions to emotional pictures or films, such that SCL and NSSCR increase as emotional arousal ratings increase (Gomez et al., 2016; Duijndam et al., 2020; Rattel et al., 2020; Sato et al., 2020). Even without emotional stimuli, individuals report increased ratings of negative emotion during periods preceded by NSSCR compared to control periods with no preceding NSSCR, suggesting that NSSCR may be linked to more transient experiences of emotion (Nikula, 1991). Additionally, SCL and frequency of NSSCR are decreased in individuals with depression, which is characterized by long-term decreased mood (Iacono et al., 1984; Schwerdtfeger and Rosenkaimer, 2011). Therefore, these measures of EDA may be well-suited for assessing changes in physiological arousal as a component of experienced affect during sleep deprivation.

In addition to capturing physiological responses during exposure to more long-term stimuli or situations (as opposed to discrete stimuli or situations), SCL and NSSCR are also believed

to exhibit systematic inter-individual differences (Crider, 1993; Crider et al., 2004; Vaidyanathan et al., 2014). Individual measures of tonic EDA vary widely; according to Dawson et al. (2017), individual SCL typically ranges from 2 to 20 microsiemens (μS), and individual frequency of NSSCR ranges from 1 to 3 per min. Further, these tonic measures are influenced by factors such as age, with older adults showing lower values than younger adults (Surwillo and Quilter, 1965; Barontini et al., 1997); sex, with females generally showing higher levels than males (Kopacz and Smith, 1971; Ketterer and Smith, 1977) and female tonic EDA differing by stage of the menstrual cycle (Gómez-Amor et al., 1990; Goldstein et al., 2005); and ethnicity, with Black Americans showing lower tonic EDA than non-Black Americans (Juniper and Dykman, 1967; Korol et al., 1975; Kredlow et al., 2017). Based on the frequency with which they show NSSCR (or alternatively, based on how quickly individuals habituate and show decreased skin conductance responses to a given stimulus), individuals can be classified as either electrodermally labile or stable. Individuals who are labile show more NSSCR (or slow habituation), whereas stable individuals show fewer NSSCR (or fast habituation; Dawson et al., 2017). Individuals also sometimes show differences in emotional reactivity based on their electrodermal lability classification, such that labiles experience greater affective reactions than stables (Choi et al., 2012, 2015). Electrodermal lability measured by NSSCR or habituation is thought to reflect a single latent phenotype that is influenced by specific genetic and environmental factors (Crider et al., 2004). Electrodermal lability measures have been found to show high test-retest reliability (NSSCR $r = 0.76$, Schell et al., 2002; NSSCR $r = 0.70$, Crider et al., 2004) and are stable across time points (NSSCR ICC = 0.77, Bari, 2019). Research on twins has found that around 50% of the variance in electrodermal lability is heritable (Isen et al., 2012; Vaidyanathan et al., 2014). If there are systematic interindividual differences in electrodermal lability or tonic EDA more generally during sleep deprivation, it would suggest that some individuals are more vulnerable to sleep deprivation-related changes in EDA than others, and as such, should also show corresponding changes in self-reported affect. Further, the presence of systematic inter-individual differences would make the findings at the group level less reliable, as they could mask these individual-level effects.

Interest in whether electrodermal lability reflects systematic interindividual differences arose from work demonstrating that individuals differ by lability classification on certain cognitive tasks. For instance, individuals classified as electrodermally labile have been found to show better performance on vigilant attention tasks (Crider and Adgenbraun, 1975; Sostek, 1978; Munro et al., 1987) and simple response time (RT) tasks (Vossel, 1988; Wilson and Graham, 1989) than individuals classified as electrodermally stable. These same vigilant attention and simple RT tasks are also closely associated with changes in arousal during sleep deprivation (Ratcliff and Van Dongen, 2011), showing large sleep deprivation effects (Lim and Dinges, 2010) with substantial interindividual differences (Van Dongen et al., 2004a). Thus, in addition to affecting experienced emotion, sleep deprivation effects on EDA and physiological arousal more broadly may also affect other measures closely linked to changes in arousal, like vigilant attention.

The relationship between electrodermal lability or EDA measures and sleep deprivation has been previously investigated, but older studies used a variety of methodologies and sometimes employed extremely small sample sizes, yielding mixed findings (see Horne, 1978). However, recent work has produced more reliable results. For example, studies found that, as time awake increases, skin resistance level (the inverse of SCL) increases (Miró et al., 2002) and the frequency of NSSCR decreases (Posada-Quintero et al., 2017, 2018), although the change in NSSCR may be limited to electrodermal labiles (Michael et al., 2012). At least one study examined the relationship between EDA during sleep deprivation and emotion (Liu et al., 2015), but the inclusion of a crossed stressor condition in the absence of a no-stress control makes it difficult to determine whether changes in physiological arousal during sleep deprivation alone influenced experienced emotional states. Other studies showed that measures of EDA are associated with self-reported arousal and cognitive performance during sleep loss. Skin resistance level was observed to be positively correlated with both subjective sleepiness and performance on a simple RT task (Miró et al., 2002), and NSSCR were found to be negatively correlated with lapses on the psychomotor vigilance test (PVT; Dinges and Powell, 1985), the gold standard for assessing behavioral alertness during sleep deprivation (Posada-Quintero et al., 2018). These relationships may be moderated by lability, as electrodermal labiles have been found to show higher subjective sleepiness during total sleep deprivation than stables (Michael et al., 2012). These more recent studies still rely on relatively small samples (ranging from 10 to 40), but more critically for the present purposes, they do not make any direct connection between changes in electrodermal lability or EDA under sleep deprivation and changes in mood or affective state.

To clarify the relationship between physiological arousal and emotional states during sleep deprivation, we gathered data from three in-laboratory sleep deprivation protocols on which we have previously published (e.g., Whitney et al., 2017; Honn et al., 2019; Lawrence-Sidebottom et al., 2020; Kurinec et al., 2021; Stenson et al., 2021). With these data, which formed one of the largest samples used in an investigation of total sleep deprivation (TSD) and EDA, we investigated the relationship between EDA, as measured by NSSCR frequency and SCL, to experienced emotion, operationalized as self-reported affect, under TSD. Specifically, we investigated how TSD influences NSSCR and SCL, whether EDA shows systematic interindividual differences during sleep deprivation, and whether a change in EDA due to TSD is related to change in affect. Based on previous research, we expected that TSD would lead to decreases in tonic EDA and that vulnerability to these TSD-related changes would be a stable interindividual difference. Additionally, because less labile individuals have been found to show less emotional reactivity, we expected that the size of the decrease in affect during sleep deprivation would be positively associated with the level of decrease in EDA during TSD. Secondarily, we explored how changes in NSSCR frequency and SCL are associated with changes in other measures closely related to arousal, namely

self-reported arousal, and vigilant attention, during TSD. Given that interindividual differences in lability have been linked to interindividual differences in sleepiness and vigilant attention, we anticipated that the level of decrease in these measures during TSD would be positively associated with the size of the observed decrease in EDA.

MATERIALS AND METHODS

Participants

Participants (N = 193, 51.8% female, 83.9% White, 93.3% right-handed) were drawn from three in-laboratory protocols (N_1 = 62, 53.2% female, 90.3% White, 95.2% right-handed; N_2 = 54, 46.3% female, 87.0% White, 96.3% right-handed; N_3 = 77, 54.5% female, 76.6% White, 89.6% right-handed). These protocols were selected as they all included EDA measurements, contained relatively large samples, and used the same duration of TSD. Participants' ages ranged from 21 to 40 years (M = 26.8, SD = 4.8). All participants were screened to be physically and psychologically healthy and were free of drugs (except oral contraceptives); were not currently receiving medical treatment or pregnant; did not have any sleep or circadian disorders; had not traveled across time zones within 1 month or engaged in shift work within 3 months; and had normal or corrected to normal vision and hearing. During the week prior and during the study, participants refrained from caffeine, tobacco, drug, and alcohol use, as verified by a urine screening and breathalyzer. Participants were asked to maintain their habitual sleep schedule during the week prior to the study and to refrain from napping. Adherence to sleep schedule was verified by sleep diary, called-in sleep and wake times, and wrist-worn actigraphy.

Participants were randomly assigned to either a total sleep deprivation (TSD; n = 119) or a well-rested control (WRC; n = 74) condition. In the first protocol, the probability to be assigned to either condition was 0.50 (34 TSD, 28 WRC). In the latter two protocols, the probability to be assigned to the TSD condition was set to 0.67 as part of other investigations unrelated to the present study (Protocol 2: 36 TSD, 18 WRC; Protocol 3: 49 TSD, 28 WRC).

The procedures involved in the three protocols were approved by the Washington State University Institutional Review Board. Participants gave written informed consent to the procedures before beginning the studies, and they were compensated for their time.

Procedure

The in-laboratory protocols took place under controlled conditions in the Sleep and Performance Research Center at Washington State University Health Sciences Spokane. Ambient temperature (21 ± 1°C) and light levels during scheduled wakefulness (<100 lux) were fixed. For all three protocols, participants were in the laboratory for 4 days (three nights). Participants entered the laboratory in the late afternoon on day 1, and all participants had a 10-h (22:00–08:00) baseline sleep opportunity. On the evening of day 2, participants were informed of their condition assignments. Those in the TSD condition were kept awake for 38 h, whereas those in the WRC condition had another 10-h sleep opportunity. On day 3, all participants had a 10-h (recovery) sleep opportunity before leaving the laboratory on day 4. Up to four individuals participated at the same time, and participants were assigned to separate rooms for sleep and performance testing. Meals were provided every 4 h during scheduled wakefulness. When participants were not scheduled to sleep or not performing testing or having meals, they were allowed to engage in non-vigorous activities, such as watching innocuous movies or reading. Vigorous activities, such as exercise, were prohibited. Laptops, tablets, cell phones, live television, live radio, or other means of interacting outside the laboratory environment were not permitted, and visitors were not allowed. Participants' behavior was monitored continuously by trained research assistants to ensure compliance.

EDA data were collected from each protocol only before the start of morning and afternoon cognitive testing sessions on days 2 and 3. In the first protocol, morning testing started at 10:00, and afternoon testing started at 14:00. In the second protocol, morning testing started at 09:30, and afternoon testing started at 15:00. Finally, in the third protocol, morning testing started at 09:45, and afternoon testing started at 14:30 on day 2 and at 14:00 on day 3. Because of differences in the task batteries specific to each protocol, the protocols combined in this study started SCL measurement at slightly different times, which is the reason for the modest variability in SCL start times.

Self-reported affect, self-reported sleepiness, and vigilant attention were assessed every 2–4 h during scheduled wakefulness. Only morning and afternoon test bouts closest to the EDA recordings and shared across all three protocols, at 09:00 and 13:00 on days 2 and 3, were included in analyses to minimize circadian confounds in comparisons with EDA data.

Materials

Electrodermal Activity (EDA)

EDA measures of interest were mean SCL and NSSCR frequency. EDA was based on continuous sampling of SCL at 50 Hz during a 5-min interval at rest, when participants were not engaged in any tasks, prior to the beginning of the aforementioned morning and afternoon cognitive test sessions on days 2 and 3. EDA measurements from Protocols 1 and 2 were recorded with a Psychlab SC5 24-bit system (Contact Precision Instruments, Cambridge, MA), and data from Protocol 3 were recorded with a BIOPAC recording system (BIOPAC Systems, Inc., Goleta, CA). Disposable self-adhesive electrodes filled with isotonic gel for consistent ohmic contact were attached to the anterior surface of the non-dominant hand on the intermediate phalange of the index and middle fingers. Electrodes, which were the same size across protocols, were attached to the recording system through leads with pinch connectors, and real-time SCL was observed to ensure the electrodes were connected correctly and that SCL greater than zero was produced. Once the electrodes were attached, participants were instructed to keep their hands still, relax, and to avoid excessive movement while preparing for the forthcoming experimental test battery. Each participant's SCL was plotted and visually inspected before conducting any further analyses.

Mean SCL was computed across the 5-min sampling interval. NSSCR were calculated in each successive 10-s bin of the 5-min sampling interval. SCL at the beginning of each 10-s bin served as a reference measure, which was subtracted from the peak SCL during the remaining 10 s. All SCL values above 0.10 μS were analyzed; more than 99.7% of all samples were included. An obtained SCL amplitude $\geq$ 0.05 μS above reference was recorded as an NSSCR for that bin. Less than 2% of all SCL samples were below 0.50 μS, although two participants' SCL were consistently below 0.50 μS. However, as omitting these data points did not materially affect the subsequent analyses, we chose to keep the widest range of SCL values for this study and did not exclude the two participants. Any peak SCL of greater than 3 μS was considered to be an artifact of movement and was excluded. Such events were rare, i.e., <1% of all samples. The frequency of NSSCR was assessed as the number of bins flagged as having an NSSCR, with a maximum possible frequency of 30 across the 5-min sampling interval. We observed the vast majority of NSSCR in the range from 5 to 15 during the 5-min sampling interval, which is consistent with the typically reported range of 1–3 NSSCR per minute (Dawson et al., 2017).

Positive and Negative Affect Schedule (PANAS)

The PANAS (Watson et al., 1988) is a self-report questionnaire that assesses an individual's mood state at the present moment. The PANAS consists of two 10-item subscales designed to measure positive and negative affect. On each subscale, participants indicate the degree to which positive emotions (e.g., inspired) or negative emotions (e.g., distressed) describe their current emotional state using a 5-point Likert-type scale (1 = Very slightly to 5 = Extremely). The PANAS provides total scores for each subscale, ranging from 10 to 50, such that higher scores indicate greater positive or negative affect. Valence and arousal are deliberately intertwined on this instrument (Watson and Tellegen, 1985). The PANAS shows good internal consistency and construct validity (Watson et al., 1988; Crawford and Henry, 2004) and has been previously used to assess changes in self-reported mood during TSD (Franzen et al., 2008; Riedy et al., 2013; Stenson et al., 2021).

Karolinska Sleepiness Scale (KSS)

The KSS (Åkerstedt and Gillberg, 1990) is a self-report scale for assessing subjective sleepiness. On this measure, participants indicate their current level of sleepiness using a 9-point Likert-type scale (1 = Very alert; 9 = Very sleepy, great effort to keep awake, fighting sleep). The KSS has high sensitivity to sleep loss (Kaida et al., 2006; Åkerstedt et al., 2014).

Psychomotor Vigilance Test (PVT)

The PVT (Dinges and Powell, 1985) is a 10-min serial RT task that assesses an individual's ability to sustain vigilant attention. On this task, participants respond as quickly as possible (*via* button press) to a visual stimulus that appears on the screen at random intervals of 2–10 s. Vigilant attention was quantified by the log signal-to-noise ratio (LSNR), which is the log-transformed ratio of the power of the relevant information (signal) to the power of the irrelevant information (noise) in the RT distribution (Chavali et al., 2017). Performance on the PVT is highly sensitive to sleep loss (Van Dongen et al., 2003; Lim and Dinges, 2008).

Statistical Analyses

Individuals were included in analyses if they had available morning or afternoon NSSCR or SCL data for both days. There were 152 participants with both morning and afternoon data, 19 with only morning data, and 22 with only afternoon data; all had SCR data on both measurement days. In these data there were a total of 15 instances distributed over n = 9 participants (all from the TSD condition) with NSSCR values of zero (2.25% of all cases); however, these participants also had non-zero SCL for these instances, indicating that the electrodes were recording. Removing these zero NSSCR cases from analyses did not fundamentally change the results; therefore, these participants were retained in the analyses below. Using their sampling data from day 2 (baseline day), participants were then classified separately for the morning and afternoon sampling intervals as electrodermally labile or stable (Morning: labile = 86, stabile = 85; Afternoon: labile = 80, stable = 82) based on median split (Morning Median = 0.31; Afternoon Median = 0.25). A median split was used in accordance with how electrodermal lability has been traditionally defined in the literature (e.g., Sostek, 1978; Munro et al., 1987; Vossel, 1988; Wilson and Graham, 1989; Michael et al., 2012).

To assess whether TSD influenced affect, sleepiness, vigilant attention, and EDA outcomes, we ran separate mixed-effects ANCOVAs on PANAS positive and negative affect, KSS sleepiness ratings, PVT LSNR, NSSCR frequency, and SCL. All models included fixed effects of condition (WRC, TSD), day (baseline, intervention day), time of day (morning, afternoon), and their interactions, and a random effect over participants on the intercept; protocol (1, 2, or 3) and participant sex (male, female) were included as covariates. To explore whether lability classification moderated the effect of TSD on EDA, we conducted equivalent analyses on the frequency of NSSCR and SCL with additional fixed effects of lability classification (stable, labile) and its interactions with the condition, day, and time of day. Although EDA data are often not normally distributed (Society for Psychophysiological Research Ad Hoc Committee on Electrodermal Measures, 2012), the data presented here were not skewed enough to warrant transforming the data (absolute skew was less than 1 for NSSCR and less than 2 for SCL). Partial eta squared (η_p^2) values for effect size were calculated for significant effects. All pairwise comparisons in follow-up to significant interactions were Bonferroni-adjusted.

To determine if our dependent variables showed systematic interindividual differences across days including TSD, we performed a variance components analysis (Van Dongen et al., 2004b) and assessed the intraclass correlation coefficient (ICC) based on the mixed-effects ANCOVA model specified above (without lability classification as a covariate). The ICC, calculated as the ratio of the between-subjects variance to the between- and within-subjects variance, quantified the extent to which variability in the observations was explained by systematic interindividual differences. ICC values range from 0 to 1, representing the stability of the interindividual

differences from no systematic interindividual differences to perfectly stable interindividual differences. Standard errors and 95% confidence intervals were calculated using bootstrapping (1,000 simulations). To put the magnitude of interindividual differences in perspective, we calculated the absolute value of the ratio of the between-subjects standard deviation (square root of between-subjects variance) to the mean change from the baseline to the intervention day in the TSD condition.

To examine if a change in NSSCR frequency or SCL was related to the effect of TSD on affect, sleepiness, or vigilant attention, we calculated change scores from the baseline day to the TSD intervention day for all variables of interest, for the morning and afternoon times separately. We then ran separate mixed-effects ANCOVAs on the change scores for positive affect, negative affect, sleepiness, and LSNR as a dependent variable, using only data from the TSD participants. The models had a fixed effect for time of day (morning, afternoon) with a random effect over participants on the intercept. Change in EDA measure, protocol (1, 2, 3), and participant sex (male, female) were included as covariates. To determine whether a change in EDA was significantly related to the TSD effect, each model was compared to a reduced model without the change in EDA covariate using the variance ratio test, and the partial correlation (r_{partial}) between EDA and the dependent variable was assessed. To supplement our findings, we conducted follow-up variance ratio tests using similar mixed-effects ANCOVA models using data from the baseline day only in both the WRC and TSD conditions to determine whether EDA accounted for significant variance in our dependent variables at baseline.

RESULTS

Descriptive statistics for the dependent variables are presented by condition, day, and time of day in **Table 1**.

Effects of Total Sleep Deprivation

Figure 1 shows the effect of TSD on positive and negative affect, as well as sleepiness and PVT performance. **Table 2** displays the results of the corresponding statistical analyses, where the condition by day interaction is of particular interest. In agreement with earlier findings (Franzen et al., 2008; Talbot et al., 2010; Riedy et al., 2013), TSD decreased positive affect and increased negative affect ($p < 0.001$), although the impact on negative affect was very small. Also, as expected, TSD increased subjective sleepiness and degraded vigilant attention performance on the PVT ($p < 0.001$). The impact of TSD was somewhat greater in the morning of the intervention day than in the afternoon, in accordance with the known effect of circadian rhythmicity during TSD (Skeiky et al., 2021). Sex was a significant covariate for negative affect, with males exhibiting greater negative affect than females. The stability of interindividual differences in affect, sleepiness, and vigilant attention performance ranged from 0.34 to 0.75, as shown in **Table 3**. The interindividual differences were smaller than the magnitude of the group-mean TSD effect for positive affect, sleepiness, and vigilant attention, and nearly twice as large as the group-mean TSD effect for negative affect. For negative affect, therefore, systematic interindividual differences were the dominant source of variability in this data set.

Figure 2 shows the effects of TSD on NSSCR frequency and SCL, and **Table 4** displays the results of the corresponding statistics. The condition by day interaction is again of particular interest. In line with previous work (Posada-Quintero et al., 2017, 2018), TSD decreased the frequency of NSSCR ($p = 0.003$), although the effect was small. Unexpectedly, TSD did not have a significant effect on SCL ($p = 0.273$). Both the frequency of NSSCR and SCL were influenced by time of day, such that participants' frequency of NSSCR and SCL were higher in the morning than in the afternoon. Retaining only the frequency of NSSCR for further analyses, we evaluated whether lability moderated the effect of TSD on this measure of EDA. As shown in **Table 5**, adding lability classification to our analysis did not change the pattern of results, nor did lability significantly moderate the TSD effect. There were stable, systematic interindividual differences in the frequency of NSSCR; see **Table 3**. The magnitude of these interindividual differences was considerably larger than the group-mean TSD effect, indicating that interindividual differences were the dominant source of variability in our NSSCR data.

NSSCR as a Predictor of TSD Effects

Focusing attention on the TSD condition only, we analyzed the change from the baseline day to the intervention day in each of the outcome variables of interest (affect, sleepiness, vigilant attention, and NSSCR) and investigated whether the change in frequency of NSSCR predicted the change in any of the other variables. As is evident from **Figure 3**, we found that the change in frequency of NSSCR was not a significant predictor for the change in any of the other outcome variables (positive affect: $F_{(1,83)} = 1.27$, $p = 0.263$; negative affect: $F_{(1,83)} = 1.01$, $p = 0.317$; subjective sleepiness: $F_{(1,83)} = 1.20$, $p = 0.277$; and LSNR: $F_{(1,83)} = 1.01$, $p = 0.317$). Thus, EDA as measured by the frequency of NSSCR, although by itself sensitive to TSD, did not predict the TSD-related change in self-reported affect, nor did it predict the change in our other measures reflecting arousal, subjective sleepiness, and vigilant attention. This contrasted with relationships among the non-EDA variables; we found that TSD-induced change in positive affect was a significant predictor for sleepiness ($F_{(1,83)} = 10.31$, $p = 0.002$, $r_{\text{partial}} = -0.31$) and vigilant attention ($F_{(1,83)} = 5.03$, $p = 0.028$, $r_{\text{partial}} = 0.19$), such that decreases in positive affect were associated with increased sleepiness and decreased vigilant attention. These analyses were repeated after removing data points with zero NSSCR to confirm the robustness of the findings[1].

To determine whether the lack of relationship between NSSCR and the other variables during TSD was foreshadowed by a lack of relationship at baseline, we examined whether frequency

[1]Removing the zero NSSCR cases from analyses did not fundamentally change the results found, with the effect of TSD on NSSCR still being present, $F_{(1,454)} = 6.98$, $p = 0.009$, and still no effect of TSD on SCL, $F_{(1,454)} = 0.93$, $p = 0.334$. Further, the subsequent analyses of how change in NSSCR influenced TSD effects on affect, sleepiness, and vigilant attention also showed the same pattern: positive affect, $F_{(1,77)} = 1.07$, $p = 0.304$; negative affect, $F_{(1,77)} = 1.00$, $p = 0.321$; subjective sleepiness $F_{(1,77)} = 1.35$, $p = 0.249$; and LSNR, $F_{(1,77)} = 1.11$, $p = 0.295$.

TABLE 1 | Descriptive statistics for all dependent variables by condition, day, and time of day.

Condition	Dependent variable	Time of day	Day 2			Day 3		
			Mean	SD	Range	Mean	SD	Range
WRC	Positive affect	Morning	26.62	7.62	11.00–47.00	24.29	8.11	10.00–47.00
		Afternoon	24.16	7.81	11.00–45.00	23.02	8.12	10.00–43.00
	Negative affect	Morning	11.05	2.01	10.00–22.00	10.86	1.60	10.00–17.00
		Afternoon	11.20	2.03	10.00–21.00	10.98	1.64	10.00–19.00
	Sleepiness	Morning	3.06	1.43	0.00–6.00	2.94	1.30	0.00–8.00
		Afternoon	3.08	1.03	1.00–6.00	2.97	0.73	1.00–5.00
	LSNR	Morning	14.46	1.53	11.15–17.92	13.92	1.59	9.95–19.47
		Afternoon	13.76	1.52	10.47–17.18	13.82	1.41	10.73–16.36
	Frequency of NSSCR	Morning	0.31	0.10	0.08–0.50	0.30	0.11	0.07–0.47
		Afternoon	0.28	0.11	0.02–0.48	0.28	0.12	0.03–0.53
	SCL	Morning	3.94	1.86	0.79–8.89	3.63	1.94	1.05–8.61
		Afternoon	3.50	2.06	0.53–10.14	3.35	1.81	0.81–10.68
TSD	Positive affect	Morning	27.47	8.65	11.00–50.00	16.71	6.79	10.00–43.00
		Afternoon	26.21	8.39	10.00–50.00	19.88	7.89	10.00–44.00
	Negative affect	Morning	11.10	1.86	10.00–21.00	11.99	2.90	10.00–26.00
		Afternoon	11.08	1.65	10.00–18.00	11.62	2.40	10.00–24.00
	Sleepiness	Morning	2.94	1.39	0.00–7.00	6.08	1.88	0.00–9.00
		Afternoon	2.72	1.11	0.00–6.00	5.46	1.97	0.00–9.00
	LSNR	Morning	14.55	1.38	11.47–19.75	11.38	2.37	5.31–17.83
		Afternoon	13.76	1.30	10.94–16.83	11.87	2.14	6.30–17.57
	Frequency of NSSCR	Morning	0.28	0.12	0.00–0.48	0.22	0.13	0.00–0.45
		Afternoon	0.24	0.11	0.00–0.50	0.22	0.12	0.00–0.47
	SCL	Morning	4.02	2.56	0.52–15.52	3.41	2.26	0.39–12.70
		Afternoon	3.51	2.04	0.34–9.81	3.26	1.94	0.29–8.92

of NSSCR predicted WRC and TSD participants' baseline affect, sleepiness, and vigilant attention. Contrary to expectation, we found that frequency of NSSCR was not a significant predictor at baseline on any of our outcome variables (positive affect: $F_{(1,138)} = 0.82$, $p = 0.366$; negative affect: $F_{(1,138)} = 2.08$, $p = 0.152$; subjective sleepiness: $F_{(1,138)} = 1.27$, $p = 0.261$; and LSNR: $F_{(1,138)} = 1.32$, $p = 0.253$).

DISCUSSION

In our investigation of EDA and its relationship to changes in the emotional state during sleep loss, we found that TSD led to the expected decrease in positive affect, a small increase in negative affect, an increase in sleepiness, and the degradation of vigilant attention performance. Of the two EDA variables investigated, only the frequency of NSSCR (but not SCL) showed an effect of TSD, and this effect was not moderated by lability classification. Positive and negative affect, subjective sleepiness, and vigilant attention performance, as well as NSSCR, all displayed relatively stable, systematic individual differences, even during TSD. Importantly, though we observed the expected effects of TSD on affect, sleepiness, vigilant attention, and NSSCR, we found no evidence that TSD-induced changes in physiological arousal as measured by the frequency of NSSCR predicted the TSD effects on the other variables. Overall, these findings indicate that although EDA may be useful for assessing TSD-related changes in non-specific arousal at the group level, it does not appear to predict TSD-induced changes in self-reported affect, nor subjective sleepiness or vigilant attention, at the level of individuals. This suggests that there is an essential aspect of the relationship between physiological arousal and self-reported affect that is not well captured by EDA as measured by NSSCR.

Confidence in the findings of this study is bolstered by several factors. First, we used a large sample of participants. Compared to previous studies of sleep deprivation and EDA, which generally have around 10–30 participants undergo sleep deprivation, our sample had over 100 in the TSD condition alone. This large sample minimizes the chances that a single individual could have greatly influenced our results—a particularly important factor considering the significant interindividual differences we observed across all our measures. Second, we had extensive screening measures in place, and the data were collected under strict laboratory control. Participants in the laboratory were monitored during their entire stay and were not allowed to

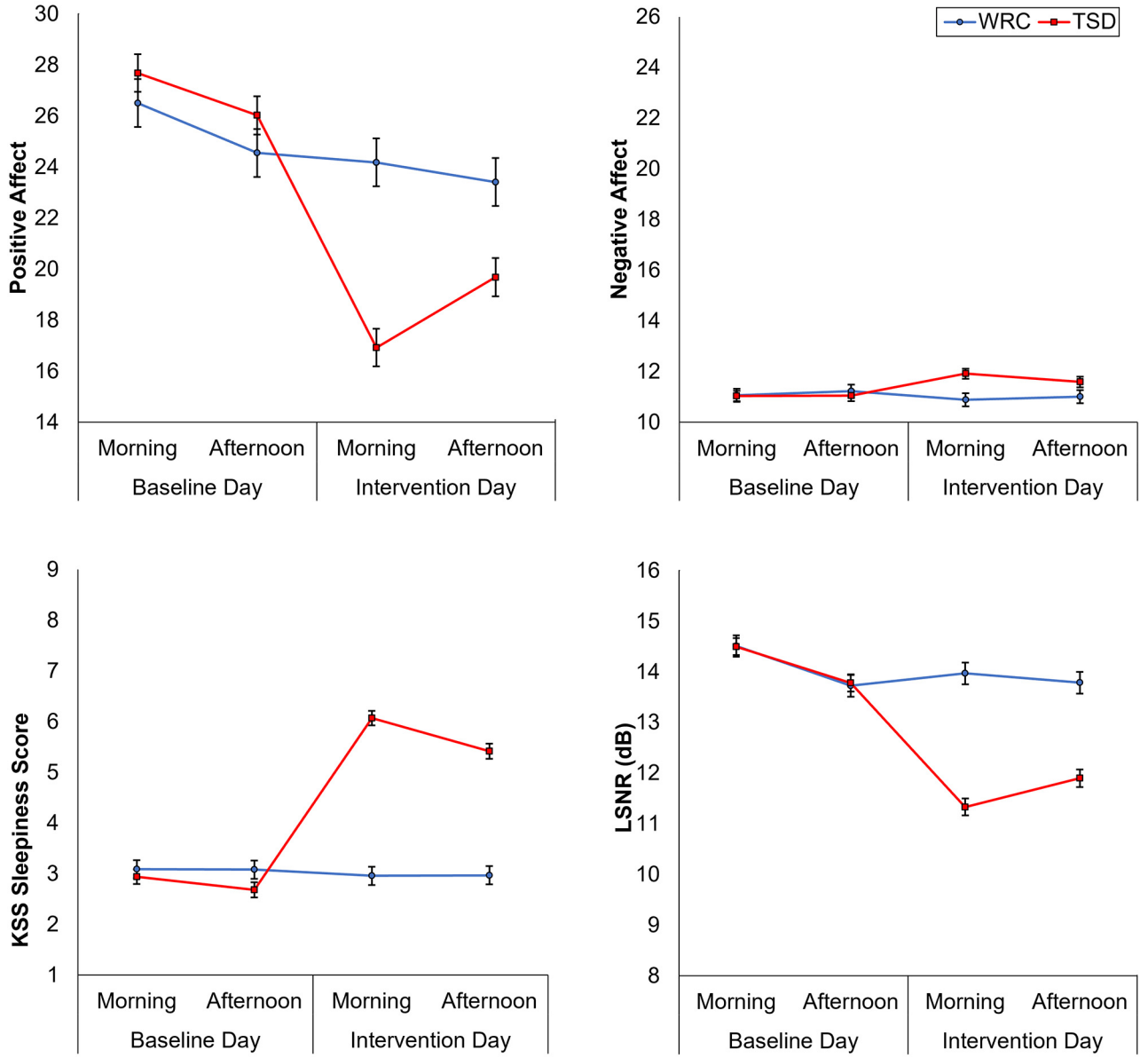

FIGURE 1 | Changes in positive and negative affect (top row), subjective sleepiness, and vigilant attention performance (bottom row), from the baseline day (morning and afternoon) to the intervention day (morning and afternoon). Error bars represent ±1 standard error of the mean.

engage in behaviors that may distort the findings (e.g., making phone calls or drinking caffeine). Third, unlike most recent studies of EDA and sleep deprivation (cf. Liu et al., 2015), this study also included a well-rested control, which allowed us to account for how time spent in the laboratory alone affected our measures. Fourth, using data from the same morning and afternoon time points on both days allowed us to account for circadian rhythm in our comparisons. Finally, unlike most previous studies of EDA and TSD, we accounted for interindividual differences, which we found to be systematic and substantial in nature. This allowed us to go beyond the group-level effects of TSD in our analyses and revealed the dissociation between EDA and other measures at the level of individuals.

Despite these strengths, our findings are limited by the fact that we included only data from two time points per day. Other studies of EDA during sleep deprivation generally collect measures of interest, such as EDA, affect, sleepiness, or PVT performance, across the circadian cycle (see Miró et al., 2002; Michael et al., 2012; Posada-Quintero et al., 2018), as do studies of interindividual differences (e.g., Van Dongen et al., 2004a,b; Lundholm et al., 2021). Because this study retrospectively analyzed previously collected data, we were only able to gather SCL and NSSCR data during time periods immediately preceding when SCR recording had taken place, which were limited to periods intended to study task-specific performance at two designated time intervals during the daytime hours. In a related

TABLE 2 | Mixed-effects ANOVAs for positive and negative affect, subjective sleepiness, and PVT LSNR.

Dependent variable	Effect	*F*	df	*p*	η_p^2
Positive affect	Condition	3.87	1,467	0.050	
	Day	**267.47**	**1,467**	**<0.001**	**0.36**
	Time of day	1.46	1,467	0.228	
	Condition × Day	**117.62**	**1,467**	**<0.001**	**0.20**
	Condition × Time of day	**8.01**	**1,467**	**0.005**	**0.02**
	Day × Time of day	**19.90**	**1,467**	**<0.001**	**0.04**
	Condition × Day × Time of day	**6.66**	**1,467**	**0.010**	**0.01**
	Protocol	0.09	2,467	0.917	
	Sex	2.70	1,467	0.101	
Negative affect	Condition	2.14	1,467	0.144	
	Day	**4.02**	**1,467**	**0.046**	**0.01**
	Time of day	0.01	1,467	0.943	
	Condition × Day	**12.85**	**1,467**	**<0.001**	**0.03**
	Condition × Time of day	1.27	1,467	0.261	
	Day × Time of day	0.55	1,467	0.457	
	Condition × Day × Time of day	0.37	1,467	0.542	
	Protocol	**3.25**	**2,467**	**0.040**	**0.01**
	Sex	**4.22**	**1,467**	**0.041**	**0.01**
Sleepiness ratings	**Condition**	**60.40**	1,467	**<0.001**	**0.12**
	Day	**219.71**	1,467	**<0.001**	**0.32**
	Time of day	**5.16**	**1,467**	**0.024**	**0.01**
	Condition × Day	**257.47**	1, 467	**<0.001**	**0.36**
	Condition × Time of day	**5.33**	**1,467**	**0.021**	**0.01**
	Day × Time of day	1.02	1,467	0.313	
	Condition × Day × Time of day	1.17	1,467	0.280	
	Protocol	0.07	2,467	0.933	
	Sex	2.39	1,467	0.123	
LSNR	**Condition**	**30.69**	**1,467**	**<0.001**	**0.06**
	Day	**180.07**	**1,467**	**<0.001**	**0.28**
	Time of day	**6.63**	**1,467**	**0.010**	**0.01**
	Condition × Day	**122.93**	**1,467**	**<0.001**	**0.21**
	Condition × Time of day	3.57	1,467	0.060	
	Day × Time of day	**20.98**	**1,467**	**<0.001**	**0.04**
	Condition × Day × Time of day	2.74	1,467	0.098	
	Protocol	0.45	2,467	0.636	
	Sex	0.44	1,467	0.509	

Note. Bold indicates $p < 0.05$.

TABLE 3 | Intraclass correlation coefficient analyses.

	VAR_{bs} (SE)	VAR_{ws} (SE)	ICC [95% CI]	Between-subjects SD as a Proportion of the TSD effect
Positive affect	45.89 (5.35)	15.61 (1.00)	0.75 [0.69, 0.79]	0.79
Negative affect	1.77 (0.27)	2.58 (0.17)	0.41 [0.33, 0.49]	1.86
Sleepiness ratings	0.73 (0.12)	1.43 (0.09)	0.34 [0.25, 0.43]	0.29
LSNR	1.33 (0.20)	1.68 (0.11)	0.44 [0.37, 0.53]	0.46
Frequency of NSSCR	0.008 (0.001)	0.006 (0.0004)	0.57 [0.49, 0.64]	2.23

Note. VAR_{bs}, between-subjects variance; VAR_{ws}, within-subjects variance; ICC, intraclass correlation coefficient; SE, standard error; CI, confidence interval.

vein, our use of retrospective data constrained what measures we could use to investigate affect, as only PANAS data were available across all three protocols. Although the PANAS is commonly used in sleep deprivation studies (Franzen et al., 2008; Riedy et al., 2013; Stenson et al., 2021), it does not allow affect to be decomposed by both arousal and valence, which may have limited our ability to detect a relationship between EDA and affect during TSD. Finally, although the three protocols we used here had similar procedures, they were run in different years. Changes to procedures, staff, and the demographic makeup of the local population may have all contributed to differences we observed between protocols and, although controlled for in statistical analyses, may have added noise to our data.

Despite the limitations, we replicated the well-reported group-level effects of TSD on positive and negative affect, on subjective sleepiness, and on vigilant attention performance. Further, we replicated the group-level effect of TSD on the frequency of NSSCR, such that the frequency of NSSCR diminished when individuals were sleep deprived (Michael et al., 2012; Posada-Quintero et al., 2017, 2018). At the individual level, we replicated the finding that individuals vary in their vulnerability to sleep deprivation. Positive and negative

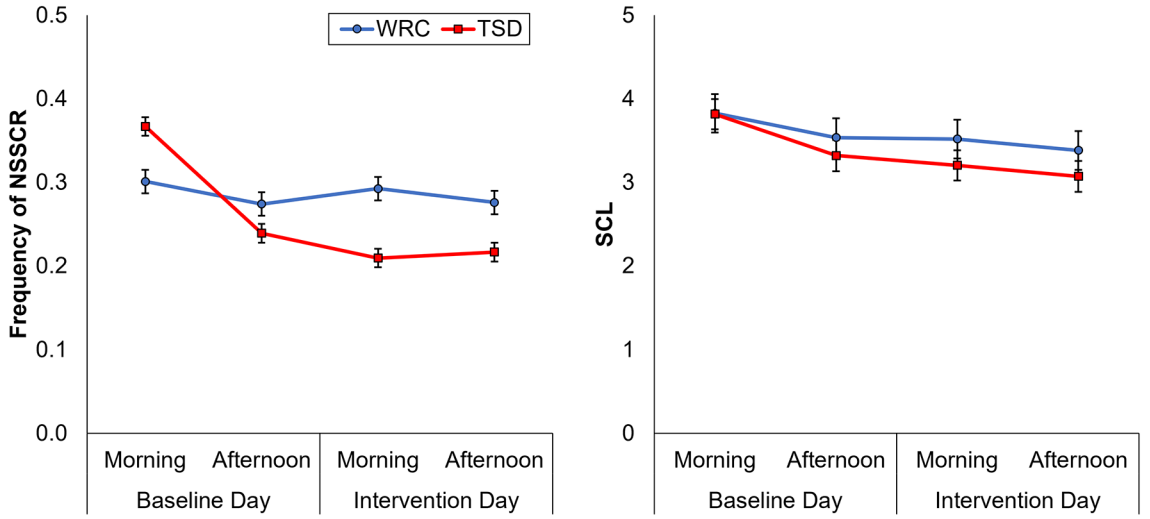

FIGURE 2 | Changes in frequency of non-specific skin conductance responses (NSSCR; left) and skin conductance level (SCL; right), from the baseline day (morning and afternoon) to the intervention day (morning and afternoon). In each panel, downward corresponds to less physiological arousal; error bars represent ±1 standard error of the mean.

TABLE 4 | Mixed-effects ANOVAs for frequency of NSSCR and SCL.

Dependent variable	Effect	*F*	df	*p*	η_p^2
NSSCR	**Condition**	**13.54**	**1,467**	**<0.001**	**0.03**
	Day	**12.93**	**1,467**	**<0.001**	**0.03**
	Time of day	**6.32**	**1,467**	**0.012**	**0.01**
	Condition × Day	**9.27**	**1,467**	**0.003**	**0.02**
	Condition × Time of day	0.80	1,467	0.371	
	Day × Time of day	3.51	1,467	0.062	
	Condition × Day × Time of day	1.04	1,467	0.308	
	Protocol	**4.87**	**2,467**	**0.008**	**0.02**
	Sex	1.38	1,467	0.241	
SCL	Condition	0.74	1,467	0.389	
	Day	**13.11**	**1,467**	**<0.001**	**0.03**
	Time of day	**7.32**	**1,467**	**0.007**	**0.02**
	Condition × Day	1.21	1,467	0.273	
	Condition × Time of day	0.27	1,467	0.605	
	Day × Time of day	2.03	1,467	0.155	
	Condition × Day × Time of day	0.33	1,467	0.568	
	Protocol	**26.08**	**2,467**	**<0.001**	**0.10**
	Sex	2.91	1,467	0.089	

Note. Bold indicates $p < 0.05$.

affect, subjective sleepiness, and vigilant attention performance exhibited systematic interindividual differences under sleep deprivation. The stability of these differences ranged from rather low (for sleepiness ratings) to moderate (for negative affect and LSNR) to rather high (for positive affect), with ICC values that were lower than found previously when nighttime measurements were also included in analyses (Van Dongen et al., 2004a). Furthermore, we expanded upon previous work reporting interindividual differences in EDA (Crider, 1993; Crider et al., 2004). Although previous investigations of the stability of the frequency of NSSCR were done using twin studies or using healthy rested adults (Isen et al., 2012; Vaidyanathan et al., 2014; Bari, 2019), to our knowledge this is the first study to document interindividual differences in the frequency of NSSCR under sleep deprivation. We found that these interindividual differences are moderately stable and considerably greater than the group-mean effect of one night of TSD on NSSCR.

In contrast to previous work, at the group level, we did not find a significant effect of TSD on SCL. In one study the skin resistance level, which is the inverse of SCL, was found to increase with time spent awake (Miró et al., 2002), but other work showed that SCL is less sensitive to sleep loss than NSSCR, a higher frequency measure of EDA (Posada-Quintero et al., 2017, 2018). Studies of TSD and EDA that observed a TSD effect on SCL also collected data during nighttime wakefulness, when the effect of TSD is amplified by circadian rhythm. We

TABLE 5 | Mixed-effects ANOVA for frequency of NSSCR with lability classification.

Effect	*F*	df	*p*	η_p^2
Condition	**13.24**	**1,459**	**<0.001**	**0.03**
Day	**13.60**	**1,459**	**<0.001**	**0.03**
Time of Day	**6.23**	**1,459**	**0.013**	**0.01**
Condition × Day	**13.69**	**1,459**	**<0.001**	**0.03**
Condition × Time of day	0.12	1,459	0.725	
Day × Time of day	3.59	1,459	0.059	
Condition × Day × Time of day	1.20	1,459	0.274	
Lability	**265.53**	**1,459**	**<0.001**	**0.37**
Lability × condition	<0.01	1,459	0.945	
Lability × Day	**17.45**	**1,459**	**<0.001**	**0.04**
Lability × Time of day	2.18	1,459	0.140	
Lability × Condition × Day	0.27	1,459	0.603	
Lability × Condition × Time of day	1.29	1,459	0.256	
Lability × Day × Time of day	0.11	1,459	0.737	
Lability × Condition × Day × Time of day	<0.01	1,459	<0.999	
Protocol	**6.16**	**2,459**	**0.002**	**0.03**
Sex	0.04	1,459	0.849	

Note. Bold indicates p < 0.05.

may have failed to observe a significant effect of TSD on SCL because we considered only the daytime measurements shared between the TSD and rested control conditions. Separately, we did not find that participants' baseline lability classification significantly moderated the effect of TSD on the frequency of NSSCR, as the interaction of lability, condition, and day was not significant. However, lability did moderate the effect of day in the study, such that regardless of whether participants were sleep-deprived, stable participants' frequency of NSSCR did not significantly change across days, whereas labile participants had fewer NSSCR on the intervention day than at baseline. As the study that originally reported a moderating influence of lability on the effect of TSD on NSSCR (Michael et al., 2012) did not have a rested control condition, it is possible that the investigators misattributed a non-specific effect of day on NSSCR to increasing time awake. Alternatively, the lack of a moderating effect of lability classification on TSD may reflect differences in the dose of sleep deprivation in our study, which measured EDA until around 30 h awake, vs. the original work that did find a moderation effect, which measured EDA until around 51 h awake (Michael et al., 2012).

Critically, across individuals, the change in frequency of NSSCR was not significantly related to TSD participants' self-reported affect. We expected EDA to be associated with participants' self-reported affect, as SCL and frequency of NSSCR have been linked to emotion regulation (Gross and Levenson, 1993; Gross, 1998; Egloff et al., 2006; Duijndam et al., 2020) and to ratings of arousal in response to emotional stimuli (Gomez et al., 2016; Rattel et al., 2020; Sato et al., 2020). Yet all of these studies included an emotional induction through picture or film stimuli, whereas we measured changes in affect over time spent awake. While TSD did influence participants' affect, it is not necessarily a reliable form of emotion induction. As emotions consist of shorter-lived, specific experiences elicited from a given stimulus, our lack of a relationship at rested baseline between frequency of NSSCR and affect may reflect a difference between measuring affect and measuring emotion (Russell, 2009). It would be of interest to investigate whether TSD would alter EDA and experienced emotion responses to emotional induction stimuli (cf. Franzen et al., 2008; Stenson et al., 2021).

Studies that observed a relationship between the frequency of NSSCR and experienced emotion under rested conditions (Gomez et al., 2016; Rattel et al., 2020; Sato et al., 2020) generally found a relationship with the arousal but not the valence dimension of emotion. Our use of the PANAS, which has arousal and valence intertwined, may not have been optimal to detect the relationship between the frequency of NSSCR and the arousal dimension of emotion. The much smaller effect of TSD on negative affect as compared to positive affect may have also contributed to that issue. However, we also did not find a change in frequency of NSSCR to be significantly related to the TSD effects on self-reported sleepiness and vigilant attention performance, our well-established subjective and objective correlates of the reduction in physiological arousal during sleep deprivation (Doran et al., 2001; Åkerstedt et al., 2014). This is in contrast to significant correlations obtained in previous studies of EDA and sleep deprivation (Miró et al., 2002; Posada-Quintero et al., 2018), which collected EDA measures during (rather than before or after) the performance of a vigilance task (Miró et al., 2002; Posada-Quintero et al., 2018). This likely increased physiological arousal and may have exposed a possible relationship between EDA and vigilant attention performance during sleep deprivation that remained concealed in our investigation based on a more passive measurement of EDA. Our findings are also at odds with research that has repeatedly found differences in vigilant attention performance by lability classification (Crider and Adgenbraun, 1975; Sostek, 1978; Munro et al., 1987). Although these studies measured EDA before engaging in a vigilance task, they focused on group-level analyses. It is unclear whether these same effects would be observed at the individual level.

This study represents an advancement in the understanding of how TSD effects on physiological arousal relate to TSD effects on affective and cognitive outcomes. Our findings are largely consistent with previous work when examining group

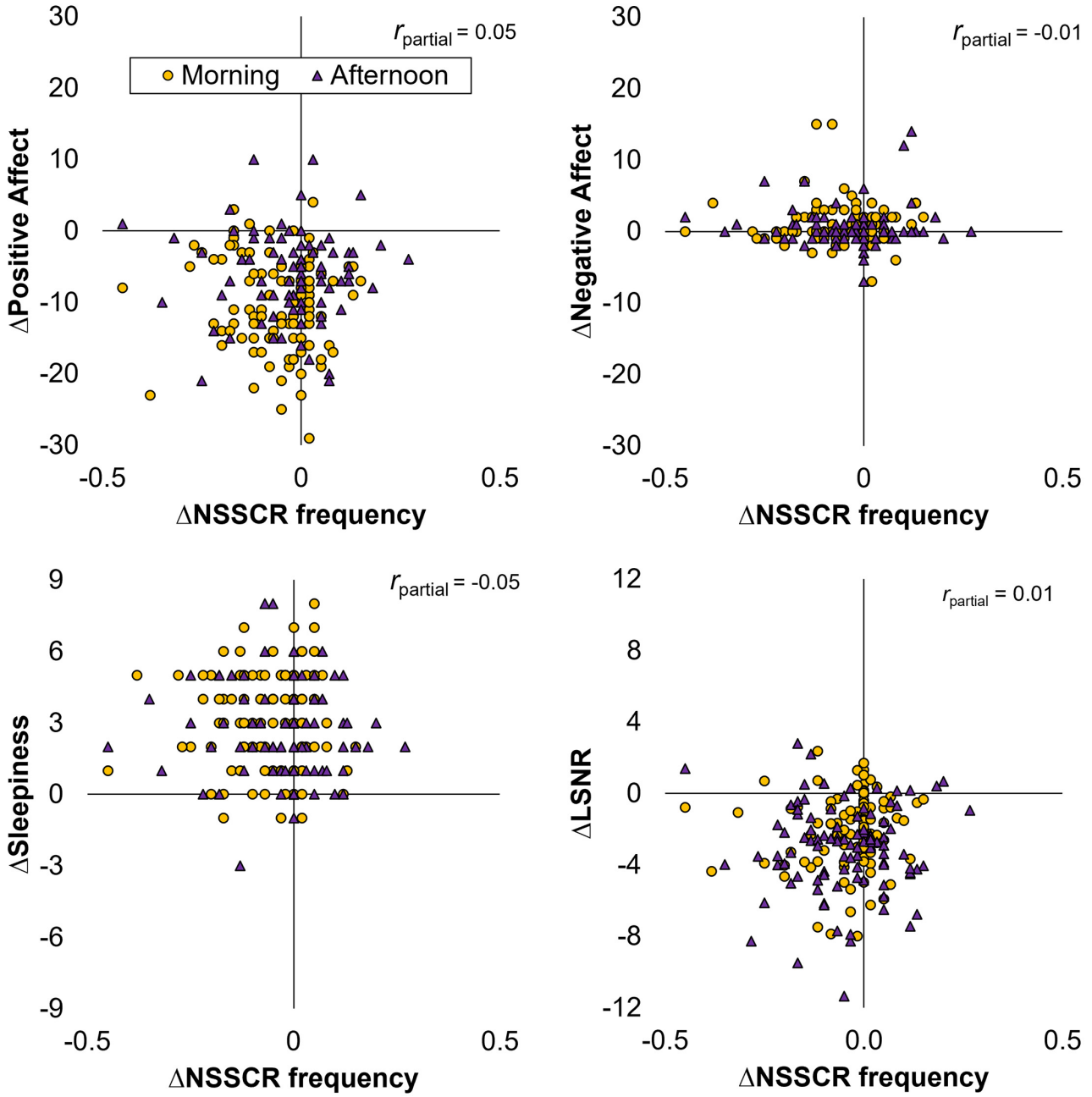

FIGURE 3 | Scatter plots of the change across days (Δ) in the frequency of NSSCR vs. positive affect (top left), negative affect (top right), subjective sleepiness (bottom left), and LSNR (bottom right) for participants in the TSD condition.

differences, but we do not find any significant relationship between the frequency of NSSCR and self-reported affect, sleepiness, or vigilant attention at the level of individuals at baseline or during TSD. Our findings suggest that the well-documented TSD effects on physiological arousal on the one hand and affect, sleepiness, and vigilant attention, on the other hand, are not reflections of a single underlying phenomenon, despite being conceptually linked. While sleep deprivation has been shown to influence both sympathetic and parasympathetic arousal (McEwen, 2006), EDA reflects changes in sympathetic arousal specifically. Therefore, it is possible that TSD changes in parasympathetic arousal may be related to affect, which would explain the dissociation between affect and EDA.

At first glance, it seems problematic that the frequency of NSSCR did not account for significant variance in any of the measures that have been previously associated with EDA, but subjective and cognitive measures obtained under conditions of sleep deprivation often do not cluster with physiological

measures across individuals (Leproult et al., 2003; Van Dongen et al., 2004a; Franzen et al., 2008). That we did not find a relationship during TSD between physiological arousal and affect in particular, and also no significant moderating effect of lability classification, does not support the proposition by some that lability is related to individuals' ability to regulate their emotions (Crider, 2008). TSD has been found to reduce available cognitive resources at an individual's disposal for given cognitive processes (Drummond et al., 2001; Chee and Van Dongen, 2013; Sullan et al., 2021). It would be reasonable, then, to assume that those individuals whose frequency of NSSCR is more strongly diminished by TSD may have fewer resources to regulate their mood. That should be reflected in their self-reported positive and negative affect, which is not what we found. However, it is important to note that this study was not specifically designed to assess the relationship between lability and emotion regulation.

Overall, NSSCR may be a useful tool for assessing sleep deprivation effects on non-specific arousal, particularly for those interested in monitoring arousal in operational settings and remote environments where decreases in alertness may have negative impacts on productivity or health and safety. However, this measure is unlikely to be predictive of TSD-related changes in an individual's subjective emotional state or subjective sleepiness, or vigilant attention. Organizations interested in using physiological measures to detect negative emotions or other mental states in their employees (e.g., commanders monitoring warfighters, or flight surgeons monitoring astronauts) should be aware of the limitations of using EDA to this end. Further, our finding that physiological arousal as measured by EDA was not associated with multiple measures expected to be sensitive to arousal reduction during sleep deprivation suggests that measures of physiological arousal are dissociable from affective and cognitive measures during TSD. There is a need for more research into the role of sleep and sleep loss with regard to neurophysiological mechanisms underlying experienced emotion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Washington State University Institutional Review Board. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH, CK, PW, AS, and HVD contributed to the conception and design of the study. JH and CK organized the database, and CK performed the statistical analyses. CK and AS wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Åkerstedt, T., Anund, A., Axelsson, J., and Kecklund, G. (2014). Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. *J. Sleep Res.* 23, 242–254. doi: 10.1111/jsr.12158

Åkerstedt, T., and Gillberg, M. (1990). Subjective and objective sleepiness in the active individual. *Int. J. Neurosci.* 52, 29–37. doi: 10.3109/00207459008994241

Bari, D. S. (2019). Psychological correlates of nonspecific electrodermal responses. *J. Electr. Bioimpedance* 10, 65–72. doi: 10.2478/joeb-2019-0010

Barontini, M., Lázzari, J. O., Levin, G., Armando, I., and Basso, S. J. (1997). Age-related changes in sympathetic activity: biochemical measurements and target organ responses. *Arch. Gerontol. Geriatr.* 25, 175–186. doi: 10.1016/s0167-4943(97)00008-3

Borbély, A. A., Daan, S., Wirz-Justice, A., and Deboer, T. (2016). The two-process model of sleep regulation: a reappraisal. *J. Sleep Res.* 25, 131–143. doi: 10.1111/jsr.12371

Chavali, V. P., Riedy, S. M., and Van Dongen, H. P. A. (2017). Signal-to-noise ratio in PVT performance as a cognitive measure of the effect of sleep deprivation on the fidelity of information processing. *Sleep* 40:zsx016. doi: 10.1093/sleep/zsx016

Chee, M. W. L., and Van Dongen, H. P. A. (2013). "Functional imaging of inter-individual differences in response to sleep deprivation," in *Neuroimaging of Sleep and Sleep Disorders*, eds E. Nofzinger, P. Maquet and M. J. Thorpy (Cambridge, UK: Cambridge University Press), 154–162.

Choi, A., de Melo, C. M., Khooshabeh, P., Woo, W., and Gratch, J. (2015). Physiological evidence for a dual process model of the social effects of emotion in computers. *Int. J. Hum. Comput. Studies* 74, 41–53. doi: 10.1016/j.ijhcs.2014.10.006

Choi, A., Melo, C. D., Woo, W., and Gratch, J. (2012). Affective engagement to emotional facial expressions of embodied social agents in a decision-making game. *Comput. Animation Virtual Worlds* 23, 331–342. doi: 10.1002/cav.1458

Crawford, J. R., and Henry, J. D. (2004). The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br. J. Clin. Psychol.* 43, 245–265. doi: 10.1348/0144665031752934

Crider, A. (1993). Electrodermal response lability-stability: individual difference correlates. *Prog. Electroder. Res.* 249, 173–186. doi: 10.1007/978-1-4615-2864-7_12

Crider, A. (2008). Personality and electrodermal response lability: an interpretation. *Appl. Psychophysiol. Biofeedback* 33, 141–148. doi: 10.1007/s10484-008-9057-y

Crider, A., and Adgenbraun, C. B. (1975). Auditory vigilance correlates of electrodermal response habituation speed. *Psychophysiology* 12, 36–40. doi: 10.1111/j.1469-8986.1975.tb03056.x

Crider, A., Kremen, W. S., Xian, H., Jacobson, K. C., Waterman, B., Eisen, S. A., et al. (2004). Stability, consistency and heritability of electrodermal response lability in middle-aged male twins. *Psychophysiology* 41, 501–509. doi: 10.1111/j.1469-8986.2004.00189.x

Daan, S., Beersma, D. G., and Borbély, A. A. (1984). Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.* 246, R161–R183. doi: 10.1152/ajpregu.1984.246.2.R161

Danker-Hopfe, H., Kraemer, S., Dorn, H., Schmidt, A., Ehlert, I., and Herrmann, W. M. (2001). Time-of-day variations in different measures of sleepiness (MSLT, pupillography, and SSS) and their interrelations. *Psychophysiology* 38, 828–835. doi: 10.1111/1469-8986.3850828

Dawson, M. E., Schell, A. M., and Filion, D. L. (2017). "The electrodermal system," in *Handbook of Psychophysiology*, 4th Edn., eds J. T. Cacioppo, L. G. Tassinary and G. G. Berntson (New York, NY: Cambridge University Press), 217–243.

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep* 20, 267–277. doi: 10.1093/sleep/20.4.267

Dinges, D. F., and Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav. Res. Methods Instrum. Comput.* 17, 652–655. doi: 10.3758/BF03200977

Doran, S. M., Van Dongen, H. P. A., and Dinges, D. F. (2001). Sustained attention performance during sleep deprivation: Evidence of state instability. *Arch. Ital. Biol.* 139, 253–276. doi: 10.4449/aib.v139i3.503

Drummond, S. P. A., Gillin, J. C., and Brown, G. G. (2001). Increased cerebral response during a divided attention task following sleep deprivation. *J. Sleep Res.* 10, 85–92. doi: 10.1046/j.1365-2869.2001.00245.x

Duijndam, S., Karreman, A., Denollet, J., and Kupper, N. (2020). Emotion regulation in social interaction: physiological and emotional responses associated with social inhibition. *Int. J. Psychophysiol.* 158, 62–72. doi: 10.1016/j.ijpsycho.2020.09.013

Egloff, B., Schmukle, S. C., Burns, L. R., and Schwerdtfeger, A. (2006). Spontaneous emotion regulation during evaluated speaking tasks: associations with negative affect, anxiety expression, memory and physiological responding. *Emotion* 6, 356–366. doi: 10.1037/1528-3542.6.3.356

Franzen, P. L., Siegle, G. J., and Buysse, D. J. (2008). Relationships between affect, vigilance and sleepiness following sleep deprivation. *J. Sleep Res.* 17, 34–41. doi: 10.1111/j.1365-2869.2008.00635.x

Goldstein, J. M., Jerram, M., Poldrack, R., Ahern, T., Kennedy, D. N., Seidman, L. J., et al. (2005). Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. *J. Neurosci.* 25, 9309–9316. doi: 10.1523/JNEUROSCI.2239-05.2005

Gomez, P., von Gunten, A., and Danuser, B. (2016). Autonomic nervous system reactivity within the valence-arousal affective space: modulation by sex and age. *Int. J. Psychophysiol.* 109, 51–62. doi: 10.1016/j.ijpsycho.2016.10.002

Gómez-Amor, J., Martínez-Selva, J. M., Román, F., Zamora, S., and Sastre, J. F. (1990). Electrodermal activity, hormonal levels and subjective experience during the menstrual cycle. *Biol. Psychol.* 30, 125–139. doi: 10.1016/0301-0511(90)90022-o

Gross, J. J. (1998). The emerging field of emotion regulation: an integrative review. *Rev. Gen. Psychol.* 2, 271–299. doi: 10.1037/1089-2680.2.3.271

Gross, J. J., and Levenson, R. W. (1993). Emotional suppression: physiology, self-report and expressive behavior. *J. Pers. Soc. Psychol.* 64, 970–986. doi: 10.1037//0022-3514.64.6.970

Honn, K. A., Hinson, J. M., Whitney, P., and Van Dongen, H. P. A. (2019). Cognitive flexibility: a distinct element of performance impairment due to sleep deprivation. *Accid. Anal. Prev.* 126, 191–197. doi: 10.1016/j.aap.2018.02.013

Horne, J. A. (1978). A review of the biological effects of total sleep deprivation in man. *Biol. Psychol.* 7, 55–102. doi: 10.1016/0301-0511(78)90042-x

Iacono, W. G., Peloquin, L. J., Lykken, D. T., Haroian, K. P., Valentine, R. H., and Tuason, V. B. (1984). Electrodermal activity in euthymic patients with affective disorders: one-year retest stability and the effects of stimulus intensity and significance. *J. Abnorm. Psychol.* 93, 304–311. doi: 10.1037/0021-843X.93.3.304

Isen, J. D., Iacono, W. G., Malone, S. M., and McGue, M. (2012). Examining electrodermal hyporeactivity as a marker of externalizing psychopathology: a twin study. *Psychophysiology* 49, 1039–1048. doi: 10.1111/j.1469-8986.2012.01394.x

Juniper, K., and Dykman, R. A. (1967). Skin resistance, sweat-gland counts, salivary flow and gastric secretion: age, race and sex differences and intercorrelations. *Psychophysiology* 4, 216–222. doi: 10.1111/j.1469-8986.1967.tb02759.x

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., and Killgore, W. D. S. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med.* 8, 215–221. doi: 10.1016/j.sleep.2006.08.007

Kaida, K., Takahashi, M., Åkerstedt, T., Nakata, A., Otsuka, Y., Haratani, T., et al. (2006). Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin. Neurophysiol.* 117, 1574–1581. doi: 10.1016/j.clinph.2006.03.011

Ketterer, M. W., and Smith, B. D. (1977). Bilateral electrodermal activity, lateralized cerebral processing and sex. *Psychophysiology* 14, 513–516. doi: 10.1111/j.1469-8986.1977.tb01190.x

Kopacz, F. M., II, and Smith, B. D. (1971). Sex differences in skin conductance measures as a function of shock threat. *Psychophysiology* 8, 293–303. doi: 10.1111/j.1469-8986.1971.tb00459.x

Korol, B., Bergfeld, G. R., and Mclaughlin, L. J. (1975). Skin color and autonomic nervous system measures. *Physiol. Behav.* 14, 575–578. doi: 10.1016/0031-9384(75)90184-5

Kredlow, A. M., Pineles, S. L., Inslicht, S. S., Marin, M.-F., Milad, M. R., Otto, M. W., et al. (2017). Assessment of skin conductance in African American and Non-African American participants in studies of conditioned fear. *Psychophysiology* 54, 1741–1754. doi: 10.1111/psyp.12909

Kreibig, S. D., Wilhelm, F. H., Roth, W. T., and Gross, J. J. (2007). Cardiovascular, electrodermal and respiratory response patterns to fear- and sadness-inducing films. *Psychophysiology* 44, 787–806. doi: 10.1111/j.1469-8986.2007.00550.x

Kurinec, C. A., Whitney, P., Hinson, J. M., Hansen, D. A., and Van Dongen, H. P. A. (2021). Sleep deprivation impairs binding of information with its context. *Sleep* 44:zsab113. doi: 10.1093/sleep/zsab113

Lawrence-Sidebottom, D., Hinson, J. M., Whitney, P., Van Dongen, H. P. A., and Honn, K. A. (2020). Reversal learning deficits during sleep deprivation: investigating the role of information acquisition failures. *Chronobiol. Int.* 37, 1445–1451. doi: 10.1080/07420528.2020.1819306

Leproult, R., Colecchia, E. F., Berardi, A. M., Stickgold, R., Kosslyn, S. M., and Van Cauter, E. (2003). Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 284, R280–R290. doi: 10.1152/ajpregu.00197.2002

Lim, J., and Dinges, D. F. (2008). Sleep deprivation and vigilant attention. *Ann. N. Y. Acad. Sci.* 1129, 305–322. doi: 10.1196/annals.1417.002

Lim, J., and Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136, 375–389. doi: 10.1037/a0018883

Liu, J. C. J., Verhulst, S., Massar, S. A. A., and Chee, M. W. L. (2015). Sleep deprived and sweating it out: The effects of total sleep deprivation on skin conductance reactivity to psychosocial stress. *Sleep* 38, 155–159. doi: 10.5665/sleep.4346

Lundholm, K. R., Honn, K. A., Skeiky, L., Muck, R. A., and Van Dongen, H. P. A. (2021). Trait interindividual differences in the magnitude of subjective sleepiness from sleep inertia. *Clocks Sleep* 3, 298–311. doi: 10.3390/clockssleep3020019

Lustig, K. (2021). *The Interaction of Sleep and Hormones on Emotion Functioning. [Dissertation]*. St. Catharines, ON: Brock University.

Lustig, K. A., Cote, K. A., and Willoughby, T. (2021). The role of pubertal status and sleep satisfaction in emotion reactivity and regulation in children and adolescents. *SLEEP Adv.* 2:zpab003. doi: 10.1093/sleepadvances/zpab003

McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. *Metabolism* 55, S20–S23. doi: 10.1016/j.metabol.2006.07.008

Michael, L., Passmann, S., and Becker, R. (2012). Electrodermal lability as an indicator for subjective sleepiness during total sleep deprivation. *J. Sleep Res.* 21, 470–478. doi: 10.1111/j.1365-2869.2011.00984.x

Miró, E., Cano-Lozano, M. C., and Buela-Casal, G. (2002). Electrodermal activity during total sleep deprivation and its relationship with other activation and performance measures. *J. Sleep Res.* 11, 105–112. doi: 10.1046/j.1365-2869.2002.00286.x

Munro, L. L., Dawson, M. E., Schell, A. M., and Sakai, L. M. (1987). Electrodermal lability and rapid vigilance decrement in a degraded stimulus continuous performance task. *J. Psychophysiol.* 1, 249–257.

Nikula, R. (1991). Psychological correlates of nonspecific skin conductance responses. *Psychophysiology* 28, 86–90. doi: 10.1111/j.1469-8986.1991.tb03392.x

Oken, B. S., Salinsky, M. C., and Elsas, S. M. (2006). Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clin. Neurophysiol.* 117, 1885–1901. doi: 10.1016/j.clinph.2006.01.017

Pilcher, J. J., and Huffcutt, A. I. (1996). Effects of sleep deprivation on performance: a meta-analysis. *Sleep* 19, 318–326. doi: 10.1093/sleep/19.4.318

Podsakoff, P. M., MacKenzie, S. B., Lee, J.-Y., and Podsakoff, N. P. (2003). Common method biases in behavioral research: a critical review of the literature and recommended remedies. *J. Appl. Psychol.* 88, 879–903. doi: 10.1037/0021-9010.88.5.879

Posada-Quintero, H. F., Bolkhovsky, J. B., Qin, M., and Chon, K. H. (2018). Human performance deterioration due to prolonged wakefulness can be accurately detected using time-varying spectral analysis of electrodermal activity. *Hum. Factors* 60, 1035–1047. doi: 10.1177/0018720818781196

Posada-Quintero, H. F., Bolkhovsky, J. B., Reljin, N., and Chon, K. H. (2017). Sleep deprivation in young and healthy subjects is more sensitively identified by higher frequencies of electrodermal activity than by skin conductance level evaluated in the time domain. *Front. Physiol.* 8:409. doi: 10.3389/fphys.2017.00409

Posner, J., Russell, J. A., and Peterson, B. S. (2005). The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development and psychopathology. *Dev. Psychopathol.* 17, 715–734. doi: 10.1017/S0954579405050340

Ratcliff, R., and Van Dongen, H. P. A. (2011). Diffusion model for one-choice reaction-time tasks and the cognitive effects of sleep deprivation. *Proc. Natl. Acad. Sci. U S A* 108, 11285–11290. doi: 10.1073/pnas.1100483108

Rattel, J. A., Mauss, I. B., Liedlgruber, M., and Wilhelm, F. H. (2020). Sex differences in emotional concordance. *Biol. Psychol.* 151:107845. doi: 10.1016/j.biopsycho.2020.107845

Riedy, S., Grant, D., and Van Dongen, H. P. A. (2013). Comparison of the SPANE and PANAS scales for measuring self-reported affect during total sleep deprivation. *NSWO* 24, 102–105. Available online at: https://labs.wsu.edu/sprc/documents/2021/02/2013swr-riedy-etal.pdf/.

Russell, J. A. (1980). A circumplex model of affect. *J. Pers. Soc. Psychol.* 39, 1161–1178. doi: 10.1037/h0077714

Russell, J. A. (2009). Emotion, core affect, and psychological construction. *Cogn. Emotion* 23, 1259–1283. doi: 10.1080/02699930902809375

Sato, W., Kochiyama, T., and Yoshikawa, S. (2020). Physiological correlates of subjective emotional valence and arousal dynamics while viewing films. *Biol. Psychol.* 157:107974. doi: 10.1016/j.biopsycho.2020.107974

Schell, A. M., Dawson, M. E., Nuechterlein, K. H., Subotnik, K. L., and Ventura, J. (2002). The temporal stability of electrodermal variables over a one-year period in patients with recent-onset schizophrenia and in normal subjects. *Psychophysiology* 39, 124–132. doi: 10.1017/S0048577202010193

Schwerdtfeger, A., and Rosenkaimer, A. -K. (2011). Depressive symptoms and attenuated physiological reactivity to laboratory stressors. *Biol. Psychol.* 87, 430–438. doi: 10.1016/j.biopsycho.2011.05.009

Scott, J. P. R., McNaughton, L. R., and Polman, R. C. J. (2006). Effects of sleep deprivation and exercise on cognitive, motor performance and mood. *Physiol. Behav.* 87, 396–408. doi: 10.1016/j.physbeh.2005.11.009

Seidel, W. F., Stephen, B., Cohen, S., Patterson, N., Yost, D., and Dement, W. C. (1984). Daytime alertness in relation to mood, performance and nocturnal sleep in chronic insomniacs and noncomplaining sleepers. *Sleep* 7, 230–238. doi: 10.1093/sleep/7.3.230

Skeiky, L., Hudson, A. N., and Van Dongen, H. P. A. (2021). "Circadian rhythms in sleepiness, alertness and performance," in *Principles and Practice of Sleep Medicine*, 7th Edn., eds M. H. Kryger, T. Roth and W. C. Dement (Philadelphia, PA: Elsevier), 38–44.

Society for Psychophysiological Research Ad Hoc Committee on Electrodermal Measures (2012). Publication recommendations for electrodermal measurements. *Psychophysiology* 49, 1017–1034. doi: 10.1111/j.1469-8986.2012.01384.x

Sostek, A. J. (1978). Effects of electrodermal lability and payoff instructions on vigilance performance. *Psychophysiology* 15, 561–568. doi: 10.1111/j.1469-8986.1978.tb03110.x.

Stenson, A. R., Kurinec, C. A., Hinson, J. M., Whitney, P., and Van Dongen, H. P. A. (2021). Total sleep deprivation reduces top-down regulation of emotion without altering bottom-up affective processing. *PLoS One* 16:e0256983. doi: 10.1371/journal.pone.0256983

Sullan, M. J., Drummond, S. P. A., and Granholm, E. (2021). Sleep deprivation and compensatory cognitive effort on a visual information processing task. *Sleep* 44:zsaa177. doi: 10.1093/sleep/zsaa177

Surwillo, W. W., and Quilter, R. E. (1965). The relation of frequency of spontaneous skin potential responses to vigilance and to age. *Psychophysiology* 1, 272–276. doi: 10.1111/j.1469-8986.1965.tb03245.x

Talbot, L. S., McGlinchey, E. L., Kaplan, K. A., Dahl, R. E., and Harvey, A. G. (2010). Sleep deprivation in adolescents and adults: changes in affect. *Emotion* 10, 831–841. doi: 10.1037/a0020138

Vaidyanathan, U., Isen, J. D., Malone, S. M., Miller, M. B., McGue, M., and Iacono, W. G. (2014). Heritability and molecular genetic basis of electrodermal activity: a genome-wide association study. *Psychophysiology* 51, 1259–1271. doi: 10.1111/psyp.12346

Van Dongen, H. P. A., Baynard, M. D., Maislin, G., and Dinges, D. F. (2004a). Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 27, 423–433. doi: 10.1093/sleep/27.3.423

Van Dongen, H. P. A., Maislin, G., and Dinges, D. F. (2004b). Dealing with inter-individual differences in the temporal dynamics of fatigue and performance: importance and techniques. *Aviat. Space and Environ. Med.* 75, A147–A154.

Van Dongen, H. P. A., Maislin, G., Mullington, J. M., and Dinges, D. F. (2003). The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26, 117–126. doi: 10.1093/sleep/26.2.117

Vossel, G. (1988). Electrodermal lability, errors and reaction times: an examination of the motor impulsivity hypothesis. *Int. J. Psychophysiol.* 6, 15–24. doi: 10.1016/0167-8760(88)90031-1

Watson, D., Clark, L. A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063–1070. doi: 10.1037//0022-3514.54.6.1063

Watson, D., and Tellegen, A. (1985). Toward a consensual structure of mood. *Psychol. Bull.* 98, 219–235. doi: 10.1037//0033-2909.98.2.219

Whitney, P., Hinson, J. M., Satterfield, B. C., Grant, D. A., Honn, K. A., and Van Dongen, H. P. A. (2017). Sleep deprivation diminishes attentional control effectiveness and impairs flexible adaptation to changing conditions. *Sci. Rep.* 7:16020. doi: 10.1038/s41598-017-16165-z

Wilson, K. G., and Graham, R. S. (1989). Electrodermal lability and visual information processing. *Psychophysiology* 26, 321–328. doi: 10.1111/j.1469-8986.1989.tb01926.x

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Contrasting Effects of Sleep Restriction, Total Sleep Deprivation, and Sleep Timing on Positive and Negative Affect

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Laboratory-based sleep manipulations show asymmetries between positive and negative affect, but say little about how more specific moods might change. We report extensive analyzes of items from the Positive and Negative Affect Scale (PANAS) during days following nights of chronic sleep restriction (6 h sleep opportunity), during 40 h of acute sleep deprivation under constant routine conditions, and during a week-long forced desynchrony protocol in which participants lived on a 28-h day. Living in the laboratory resulted in medium effects sizes on all positive moods (Attentiveness, General Positive Affect, Joviality, Assuredness), with a general deterioration as the days wore on. These effects were not found with negative moods. Sleep restriction reduced some positive moods, particularly Attentiveness (also General Positive), and increased Hostility. A burden of chronic sleep loss also led to lower positive moods when participants confronted the acute sleep loss challenge, and all positive moods, as well as Fearfulness, General Negative Affect and Hostility were affected. Sleeping at atypical circadian phases resulted in mood changes: all positive moods reduced, Hostility and General Negative Affect increased. Deteriorations increased the further participants slept from their typical nocturnal sleep. In most cases the changes induced by chronic or acute sleep loss or mistimed sleep waxed or waned across the waking day, with linear or various non-linear trends best fitting these time-awake-based changes. While extended laboratory stays do not emulate the fluctuating emotional demands of everyday living, these findings demonstrate that even in controlled settings mood changes systematically as sleep is shortened or mistimed.

Keywords: mood, emotion, sleep restriction, sleep deprivation, circadian rhythm, forced desynchrony, affect

INTRODUCTION

The contribution of sleep and circadian rhythmicity to "mood" and cognition has been documented in many studies in healthy participants and people living with mood and cognitive disturbances (Musiek and Holtzman, 2016; Hertenstein et al., 2019). This summary of many important findings conceals a range of conceptual and methodological shortcomings. Our intention here is to clarify what we know about sleep loss and emotion in the laboratory, as well as identifying some limitations of the approaches typically used when investigating these relationships. Specifically, through extensive re-analysis of several datasets, we aim to quantify differences in feelings (Joviality, Self-assurance, Attentiveness, Fear, Hostility and Guilt, as well as less specific aspects of General Positive and Negative Affect), assessed at various times of day during standard sleep restriction, total sleep deprivation and forced desynchrony protocols. Before considering these in detail, we address some of the conventions which influence the design and conduct of studies in this area.

For very sound reasons, our studies of the effects of sleep restriction, total sleep deprivation or mistimed sleep (i.e., circadian effects), on cognition and "emotion" require repeated measurement throughout protocols. This inevitably constrains the tasks which can be used, and as a consequence, the conclusions that can be drawn about the effects of reducing, removing, or re-scheduling sleep on waking functioning are limited to tasks with particular characteristics (i.e., brief, have no or known learning effects, maintain participant motivation, avoid task related fatigue, or any of a variety of other confounds). These necessary methodological constraints may have undesirable theoretical consequences, which is a particular issue for the measurement of states which are themselves, by definition, transient. Furthermore, few studies have used identical tools across protocols designed to assess effects of repeated sleep restriction, acute total sleep loss and desynchrony between circadian rhythmicity and sleep-wake timing.

As may be clear from the previous paragraph, the terms "affect," "mood," and even "emotion," are sometimes used interchangeably. This does little to establish conceptual clarity (Barrett and Russell, 1999; Kaufmann et al., 2020). DSM-V (American Psychiatric Association, 2013) defines "affect" as "a pattern of observable behaviors that is the expression of a subjectively experienced feeling state (emotion)," examples of which include "sadness, elation, and anger. (p.817)." Affect is contrasted with "mood," which is a "pervasive and sustained emotion that colors the perception of the world. Common examples of mood include depression, elation, anger, and anxiety" (p.824). Mood and affect are also distinguished in terms the time course over which they both typically change from "seconds and minutes" in the case of affect, to days, weeks, or months, in the case of mood (see Kaufmann et al., 2020). Of course, affect and mood will both be readily impacted by life circumstances, but typically our constant routines are designed to avoid such challenges, and thus we are more likely to observe changes in affect, rather than mood in our laboratory studies.

It is also important to recognize that conceptual space described by the terms affect, emotion and mood has long been considered to be a combination of bi-polar dimensions. Beginning with Wundt (1912/1924), one of these dimensions has tended to reflect a feeling of, or lack of, activation or energy, and almost evert theorist since includes an "arousal" component in their construal of mood. Gold-standard measures of subjective sleepiness (Akerstedt et al., 2013), show that sleepiness increases with time awake, and is also strongly modulated by circadian phase. Given this, the 'energetic' aspect of affect would be expected to change systematically when sleep is restricted, completely lost, or permitted at different circadian phases. Whether this is a change in mood, *per se*, or a change in perceived alertness/sleepiness, is obviously problematical, and the difficulty of interpreting results is compounded where only a single measure of whatever is currently-felt this "mood" is available.

There is greater diversity in how the second general dimension of affect has been understood. For Russell (1980) the bi-polar dimensions are Arousal-Sleep and Misery-Pleasure; for Larsen and Diener (1992) they are High Activation-Low Activation and Unpleasant-Pleasant, while for Thayer (1989) these reflect Energy-Tiredness and Tension-Calmness. The first dimension in each case has clear conceptual overlap with sleep loss and reduced arousal. The second dimensions are not obviously related to these, except, perhaps Tension-Calmness. A fourth influential approach, as represented by PANAS, also invokes a bi-polar structure with poles based on Positive Affect, a combination of Pleasantness and High Activation, and Negative Affect, a combination of Unpleasantness and High Activation. That is, both dimensions are in principle affected by activation-level. Despite this, Watson and Tellegen (1985), make explicit that these two dimensions are orthogonal, which is more implicit in the other frameworks. These accounts suggest alternative predictions. If the two dimensions are truly orthogonal, it is unclear why the dimension construed as Misery-Pleasure, Unpleasant-Pleasant or Tension-Calmness should change when people are under-slept or awake when they would typically be asleep. In contrast, because activation is intrinsic to both Positive and Negative Affect in the Watson and Tellegan approach, both dimensions of affect might be expected to change.

In our previous studies, data from some of which are re-analyzed below, we have shown that acoustic suppression of Slow Wave Activity results increased daytime sleepiness and reduced Positive Affect (Dijk et al., 2010; Groeger et al., 2014), as does sleep restriction and sleep deprivation (Lo et al., 2012), and rescheduling sleep and wakefulness to take place at atypical circadian phases (Santhi et al., 2016). None of these manipulations resulted in a change in Negative Affect. These findings provide an important confirmation of the orthogonality of Positive and Negative Affect, given that one of the dimensions changes while the other does not. However, these findings are also problematical for the PANAS framework, since lowered energy levels might be expected to influence both Positive

and Negative Affect, rather than just one dimension. However, it is also possible that the measurement of Negative Affect is simply insensitive to changes brought about by sleep loss. Other studies, described below, using alternative measurement techniques report increases in what might be regarded as negative mood as a function of sleep loss. For this reason, the sensitivity, or otherwise, of negative affect to sleep manipulations is a particular focus of this paper.

Studies have typically adopted one of two broad measures of affective state, such as PANAS or POMS[1], or used bespoke single item rating scales. Although the latter are convenient, inter- and intra-individual differences in how different words are construed, and the lack of information about how each construal might relate to other states, make findings difficult to interpret within larger theoretical frameworks.

Perhaps because of their length, there is a dearth of information regarding the effects of accumulating sleep loss on more specific aspects of mood using measures which have the scope to elucidate more nuanced changes in mood such as the full versions of PANAS or POMS. There are exceptions, certainly, such as Meney et al. (1988) who showed that the effect of one night of sleep loss increased Confusion and Fatigue and reduced Vigor, i.e., there were effects of sleep loss on both negative and positive affect. Similar findings were reported by Dinges et al. (1997), as well as increased Tension, when sleep was restricted to 5 h per night for one week. Notably these results were consistent across Morning, Afternoon or Evening testing- implying that circadian influences on mood are weak or absent when sleep is restricted, although no assessment were obtained during the nighttime. Consistent with this there were no time-of-day effects in a similar 5-h restriction study reported recently by Harous et al. (2021), but in their case only Fatigue-Inertia, but no other aspects of negative mood increased. Other studies, also using PANAS (e.g., Saksvik-Lehouillier et al., 2020) show no effect of sleep restriction (2 h less than normal sleep duration) on Negative Affect, but, as in our own work, a reduction in Positive Affect.

There are fewer studies which use either of the major pan-mood measures when investigating the effects of total sleep loss. Li et al. (2021) is an important recent exception. After 36 h awake, between 08:00 and late evening the following day, POMS measured mood showed significant deterioration in mood. Specifically, anxiety, anger, fatigue and confusion increased, although depression did not change, whereas vitality decreased significantly. Moreover, fMRI data collected by Li and colleagues show that changes observed in subjective mood were reflected in changes in thalamic and inferior frontal activity-brain areas which are consistently implicated after acute sleep loss (e.g., Vandewalle et al., 2009). Similarly, an earlier acute sleep deprivation study by Kaida and Niki (2014), also shows an increase in negative affect (POMS: Sleepiness, Confusion, Fatigue, and Anger) and a decrease in positive affect (i.e., Vitality), when mood was assessed at 8AM and 10PM the following day. Unfortunately, a 36-h delay between the collection of mood data inevitably confounds what might be independent and interacting effects of extended wakefulness and circadian phase.

Time of day effects are also problematical, for similar reasons, in multi-day studies of mood and sleep conducted as people live their everyday lives. Thus, for example, Shen et al. (2022) report an impressive 28-day long study of adolescent sleep and mood, but while subjective sleep quality was assessed on waking, a shortened and adapted version of PANAS-X was administered only in the afternoon/early evening. While mood was assessed more frequently by Wong et al. (2021), the intriguing day-to-day bi-directional effects of mood and sleep across consecutive days cannot easily distinguish between what may be cumulative or compensatory circadian and homeostatic influences.

The examples of empirical studies cited above illustrate three consistent shortcomings of experimental studies of the relationship between sleep and mood. Firstly, within POMS and in studies using single item scales, positive mood is synonymous with energy, arousal, or activation, but is measured only with a single scale. In addition to being confounded with feelings of sleepiness or diminished alertness, a different measurement approach, such as that offered by PANAS, is required if the effects on more nuanced aspects of positive affect are to be explored. Secondly, there are inconsistencies in relation to which aspects of negative mood are affected by sleep loss. Finally, level of activation is intrinsic to understandings of mood, but it is also quintessentially circadian. Most studies of the mood-sleep relationship, if not all, confound time awake, time of day and circadian phase, each of which are known to affect subjective alertness.

The data reanalyzed below come from two separate studies which were carried out in order to assess the effects of sleep restriction, sleep deprivation (Lo et al., 2012) and misalignment of the sleep-wake cycle with the circadian system (Santhi et al., 2016), on repeated performance of tests of cognitive and affective functioning, and how any effects were modulated by a polymorphism of the Period3 gene. Overall these studies showed that measures of alertness and sustained attention were very sensitive to the sleep manipulations whereas tests which were more demanding on executive resources were not very sensitive to these manipulations, but were sensitive to the effects of the polymorphism (Groeger et al., 2008). With regard to measures of affect it was notable and that while Positive Affect, as measured with PANAS, reduced as sleep pressure increased, Negative Affect was at a low level and appeared impervious to the manipulations carried out. No attempt was made in those analyzes to decompose these broad measures of affect into more discrete components, and this paper seeks to redress this. We trust that comparative data from sleep restriction, total sleep deprivation and forced desynchrony protocols provide a unique insight into how different aspects of Positive and Negative Affect vary across waking states.

[1]The original PANAS (Positive and Negative Affect Schedule), was a formulation of 20 items (Watson et al., 1988) measuring but was later extended to 60 items (PANAS-X) allowing the measurement of Fear, Sadness, Guilt, Hostility (i.e., four Basic Negative Emotions), Joviality, Self-Assurance, Attentiveness (i.e., three Basic Positive Emotion scales) as well as four "Other Affective Scales": Shyness, Fatigue, Surprise, and Serenity. POMS (Profile of Mood States, McNair et al., 1971), comprises 65 items and yields a total mood index, together with a single index of positive mood (Vigor/Activity) and five indices of negative mood (Tension/Anxiety, Depression/Dejection, Anger/Hostility, Fatigue/Inertia, and Confusion/Bewilderment).

MATERIALS AND METHODS

Full methodological details are provided in the original reports of both studies, some of the more relevant details are rehearsed here for the reader's convenience.

Procedures

The sleep loss study (see **Figure 1** and Lo et al., 2012) required that participants visited the laboratory on two extended occasions at least 10 days apart. On the first or second occasion, depending on counterbalancing, after habituation and baseline nights (8h time in bed), participants were assigned to a seven-night regime allowing 6 or 10 h of sleep opportunity per night, followed by a 41- or 39-h period of extended waking, and a recovery night where 12 h of sleep was permitted. Over the restriction/extension week, an extensive battery of cognitive tests, including PANAS, was undertaken on five equally spaced occasions between sleeps; and every 2 h during sleep deprivation. The forced-desynchrony study (see **Figure 2** and Santhi et al., 2016) required a single extended visit to the laboratory, which, after normal days and nights (8 h in bed scheduled to participant's typical bedtime), required that participants experienced a 9 h:20 min sleep opportunity followed by a period of continuous wakefulness of 18 h:40 min, for seven consecutive cycles, meaning that participants would begin by sleeping and waking at a typical day/night time, and then sleep and wake progressively later until sleeping and waking once again at the original times. The same test battery was administered at approximately every 3 h after waking. Throughout both protocols all participants lived in light-controlled environments. During the forced desynchrony study and during the sleep-deprivation/constant routine segment of the sleep restriction/extension study light levels were low (i.e., lux < 10). During the other days of the sleep-extension/sleep restriction study participants were exposed to normal indoor ambient light.

Participants

Thirty-six healthy individuals (18 males; Mean age = 27.6, SD = 4.0 years) completed the sleep loss study protocol. A different group of 34 participants (34; 18 women; Mean age = 25.54, SD = 3.323 years) completed the forced-desynchrony protocol.

Measurement of Mood and Statistical Analyzes

The original 20-adjective version of PANAS was administered as part of the computerized test battery. Ten of these adjectives assess Positive and ten Negative Affect. However, these adjectives are all components of the more specific mood measurement possible with the much longer PANAS-X. The reanalysis reported below assigned the PANAS adjectives to the PANAS-X mood classifications (see **Table 1**), and then averaged responses to provide a single measure for each classification. The Cronbach alpha for each of these new components were calculated for each of these new scales, by timepoints across individuals, showing excellent reliabilities in each dataset. This allows us to assess change in three positive (Joviality, Self-Assurance, Attentiveness) and negative (Fear, Hostility, Guilt) moods reported upon below, as well as the for the now, far briefer, measures of General Negative and Positive Affect (see **Table 1**).

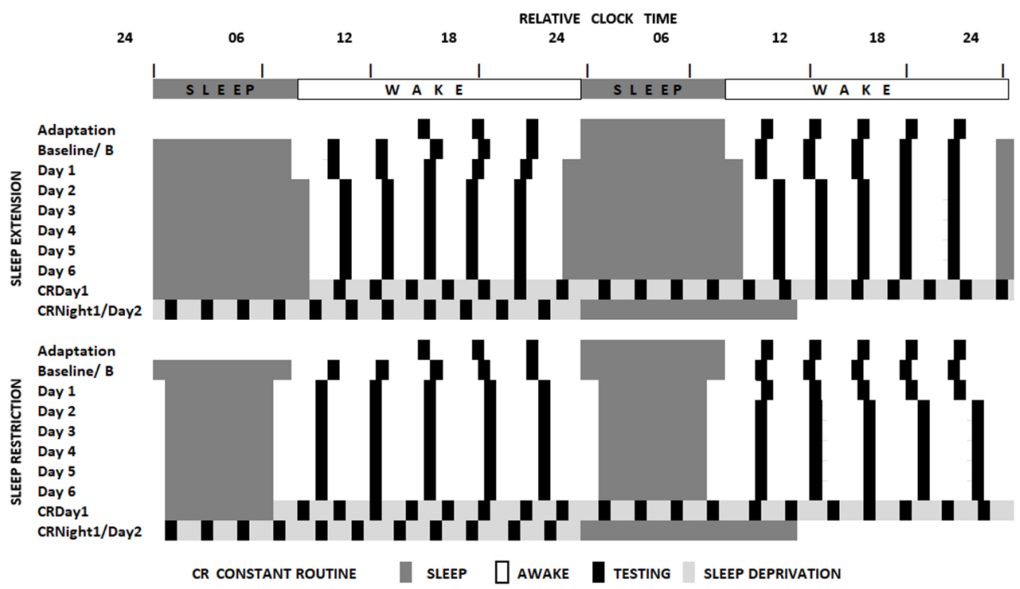

FIGURE 1 | Schematic representation of the sleep restriction-sleep extension protocol. All participants completed two sleep opportunity condition sessions. In both sessions, participants were scheduled to sleep at their habitual times for two consecutive nights and then to extended (10 h) or restricted (6 h) sleep opportunities for 7 consecutive days. This then was followed by a sleep deprivation under constant routine conditions (see Duffy and Dijk, 2002) and a recovery sleep opportunity. Black boxes indicate the timing of the cognitive assessments (Lo et al., 2012).

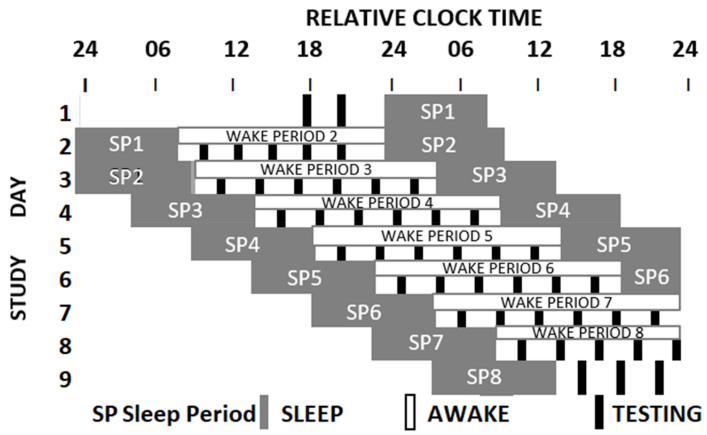

FIGURE 2 | Schematic representation of the Forced Desynchrony protocol. After two baseline days participants were scheduled to a 28-h sleep wake cycle by extending the sleep opportunity to 9h:20 min and the wake period to 18h:40 min. Light intensity was low during wake periods. During each wake period 6 assessments of cognition and mood (black boxes) were conducted. The melatonin rhythm (not shown) cannot follow the 28-h sleep-wake cycle and oscillates at it near 24-h intrinsic period. As a consequence, mood assessments occur at different circadian times (Santhi et al., 2016).

Repeated Measures ANOVA were carried out using SPSS v.28 (IBM Corp, 2021). For each of the eight moods defined in **Table 1**, separate analyzes contrasted mood changes as a function of (a) Sleep Restriction/Sleep Extension, with 5 time of day test-points for each of 8 days; (b) Total Sleep Deprivation following Sleep Extension or Sleep Restriction, with 18 or 19 time points reflecting the two-hourly test batteries across the sleep deprivation, and eight 28-h Forced Desynchrony "days", each with six equally spaced test battery administrations.

There were small amounts of missing PANAS data in each protocol (Sleep Restriction/Extension, 2.5%; Sleep Deprivation: 2.7%; Forced Desynchrony: 3.8%), which Missing Value Analyzes showed to be random. Multiple imputation based on linear regression was used to ensure participants missing minimal data could be included in the analyzes. Main effects and interactions were decomposed to simple effects and followed up with Bonferroni α-adjusted *post hoc* contrasts as appropriate. Time of day and Forced Desynchrony day simple effects were further assessed using linear or more complex contrasts in order to assess which shaped trend best represented any changes across the protocol. Effect sizes were quantified using partial-eta-squared (η_p^2, where 0.01 indicates a small effect; 0.06 indicates a medium effect and 0.14 indicates a large effect, Cohen, 1988).

RESULTS

The effects of sleep restriction, sleep deprivation and forced desynchrony of wake and sleep times on different aspects of positive and negative affect are considered in turn.

Sleep Restriction

Overall, consistent with what was reported previously, positive moods changed considerably across the week-long sleep restriction or extension (see **Table 2** and **Figure 3**), although extension or restriction *per se* had relatively little effect. However, two specific aspects of positive mood, do show main effects extension-restriction, such that participants reported being more Attentive (i.e., alert, attentive, determined) when a 10 h sleep opportunity was available, than when sleep restricted, and

TABLE 1 | Adjectives contributing to measurement of specific Negative and Positive moods and their reliabilities.

Valence	Mood	Adjectives included in 20-item PANAS	Cronbach's Alpha Reliabilities	Adjectives comprising PANAS-X
Negative	General Negative Affect	upset, distressed	SE:.98; SR:.97 SD:.99; FD:.99	*Included in negative moods (Fear, Hostility, Guilt)*
	Fear	afraid, scared, nervous, jittery	SE:.98; SR:.96 SD:.98; FD:.98	frightened, shaky
	Hostility	hostile, irritable	SE:.97; SR:.97 SD:.97; FD:.98	angry, scornful, disgusted, loathing
	Guilt	guilty, ashamed	SE:.97; SR:.90 SD:.96; FD:.99	blameworthy, angry at self, disgusted with self, dissatisfied with self
Positive	General Positive Affect	active, inspired, interested	SE:.99; SR:.99 SD:.99; FD:.98	*Included in positive moods (Joviality, Self-Assurance, Attentive)*
	Joviality	excited, enthusiastic	SE:.99; SR:.99 SD:.99; FD:.96	happy, joyful, delighted, cheerful, lively, energetic
	Self-Assurance	proud, strong	SE:.99; SR:.99 SD:.99; FD:.99	confident, bold, daring, fear
	Attentive	alert, attentive, determined	SE: .97; SR: .98 SD:.98; FD: .97	Concentrating

NB: Nota bene; SR/E: Sleep Restriction/Extension; SD: Sleep Deprivation; FD: Forced Desynchrony.

a small effect-size three-way interaction for General Positive Affect between day into protocol, time of day when tested and sleep opportunity condition. Negative moods, although relatively stronger or weaker than each other, show no effect of restricting sleep to 6 h per night over a week (see **Table 2** and **Figure 4**). This is also consistent with our previous reports.

Joviality, Assuredness and General Positive Affect, all showed large, statistically significant, effects of both day-into-protocol, and time of day when tested, generally there is a steady decline in each positive mood as individuals spent more days in the laboratory, and from earlier to later in the day (see **Figure 3**). Only in the case of Joviality did these effects interact significantly. Within subject contrasts showed that the decline is best characterized in each case by a quadratic function for General Positive Affect (Linear: $\eta_p^2 = 0.24$; Quadratic: $\eta_p^2 = 0.48$; only provided where contrast is statistically significant), Attentiveness (Quadratic: $\eta_p^2 = 0.54$), Joviality (Quadratic: $\eta_p^2 = 0.49$) and Assuredness (Quadratic: $\eta_p^2 = 0.34$). *Post hoc* testing for each of the positive moods showed that days 1, 2, and 3 were significantly more positive than the final three laboratory days, differing only in whether the third and fourth days themselves differed.

The four positive moods also differed significantly across the time of day when testing took place. There is a linear trend indicating a general decline across the day in positivity, which had the largest effect sizes (General Positive Affect: $\eta_p^2 = 0.72$; Joviality: $\eta_p^2 = 0.62$; Assuredness: $\eta_p^2 = 0.63$; Attentiveness: $\eta_p^2 = 0.77$). The consistency of these trends is evident in **Figure 3**, as is the more complex change in Assuredness, with most positivity in mid-morning, and a slight improvement in late afternoon of compared with a mid-day slump. Joviality is also subject to an interaction. Participants were more Jovial earlier in the day and less so at the end of the day. While Joviality declines across the protocol the difference between Joviality earlier and later in the day is more apparent as the protocol proceeds. For General Positive Affect, this time into protocol and time of day is also apparent, but is intensified toward the end of the protocol when sleep has been restricted. Within subject contrasts suggest that day into protocol is a quadratic, 4th Order or 6th Order trend combined with linear or quadratic effects of test-point trends (Quadratic-Quadratic: $\eta_p^2 = 0.16$; 4th Order -Quadratic: $\eta_p^2 = 0.12$; 6th Order-Linear: $\eta_p^2 = 0.15$, 6th Order-Quadratic: $\eta_p^2 = 0.14$, representing the effects of Day and Test-point, respectively).

It is important to recognize that these effects do not interact with the sleep restriction-extension manipulation, and thus reflect the constraints of being in the laboratory for an extended period or time of day, rather than the accumulation or depletion of any sleep debt or drive.

General Positive Affect is the exception to this. It also shows the general trends of time of day and day into protocol, but their combined effects are influenced by sleep restriction-sleep extension. Within subject contrasts suggest that this is best fit by a combination of linear and more complex trends (Linear-Linear-Cubic: $\eta_p^2 = 0.12$; Linear-Linear-4th Order: $\eta_p^2 = 0.11$; Linear-5th Order-4th Order: $\eta_p^2 = 0.12$, representing the effects of Extension-Restriction, Day and Test-point, respectively).

In summary, restricting sleep opportunity to 6 h per night has very little effect on mood, nor does the cumulative loss of sleep across the protocol. The number of days in the laboratory, and the time of day at which mood is assessed, does influence particular positive moods, but in a very similar way for each: generally declining within the day and declining from earlier days until part way through the

TABLE 2 | Effects of sleep restriction and time of day on Negative and Positive moods.

Source $_{(df,df)}$	F	η_p	F	η_p	F	η_p	F	η_p
Negative	**GNA**		**Fearful**		**Hostile**		**Guilty**	
Extension-Restriction $_{(1,35)}$	1.292	0.035	1.288	0.035	2.696	0.07	2.224	0.058
Day $_{(7,245)}$	1.653	0.044	1.171	0.032	1.594	0.042	1.604	0.043
Test-point $_{(4,140)}$	0.972	0.026	1.293	0.035	0.939	0.025	0.734	0.02
Extent-Restrict * Day $_{(7,245)}$	1.201	0.032	1.328	0.036	1.11	0.03	0.982	0.027
Extent-Restrict * Test-point $_{(4,140)}$	1.458	0.039	1.172	0.032	0.942	0.025	0.48	0.013
Day * Test-point $_{(28,245)}$	1.422	0.038	1.279	0.034	1.36	0.036	1.301	0.035
Extent-Restrict * Day * Test-point $_{(28,980)}$	1.368	0.037	1.252	0.034	0.746	0.02	0.492	0.013
Positive	**GPA**		**Jovial**		**Assured**		**Attentive**	
Extension-Restriction $_{(1,35)}$	3.746	0.094	2.127	0.056	0.663	0.018	11.388$^{\#}$	0.24
Day $_{(7,245)}$	19.092$^{\#}$	0.347	15.028$^{\#\#}$	0.295	7.812$^{\#}$	0.178	13.264$^{\#\#}$	0.269
Test-point $_{(4,140)}$	11.191$^{\#}$	0.237	10.724$^{\#\#}$	0.23	6.399$^{\#}$	0.151	12.18$^{\#\#}$	0.253
Extent-Restrict * Day $_{(7,245)}$	1.119	0.03	0.953	0.026	0.774	0.021	1.759	0.047
Extent-Restrict * Test-point $_{(4,140)}$	1.147	0.031	1.336	0.036	0.372	0.01	1.666	0.044
Day * Test-point $_{(28,245)}$	1.402	0.037	1.908$^{\#}$	0.05	1.39	0.037	1.454	0.039
Extent-Restrict * Day * Test-point $_{(28,980)}$	1.569*	0.042	1.177	0.032	0.849	0.023	1.272	0.034

KEY: GNA: General Negative Affect.; GPA: General Positive Affect.
$^{*}p<.05$, $^{**}p<01$, $^{\#}p<.005$, $^{\#\#}p<.001$.
η_p Partial-eta squared.

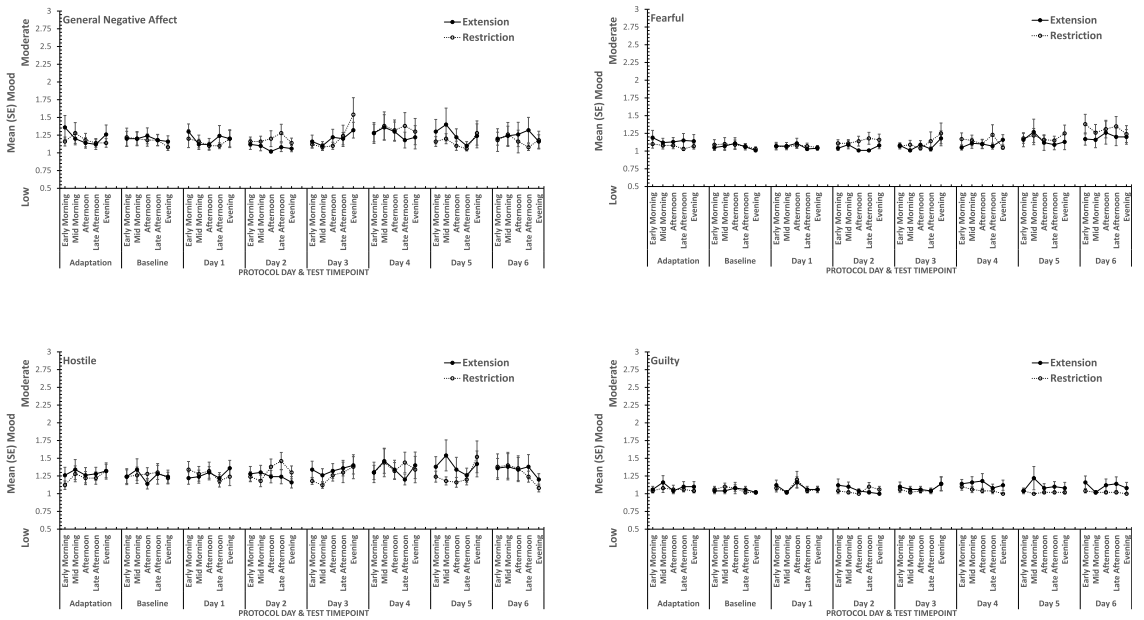

FIGURE 3 | Effects of sleep restriction and extension on Negative Mood (General Negative Affect, Fearfulness, Guilt, Hostility) across protocol days and mood assessment time points.

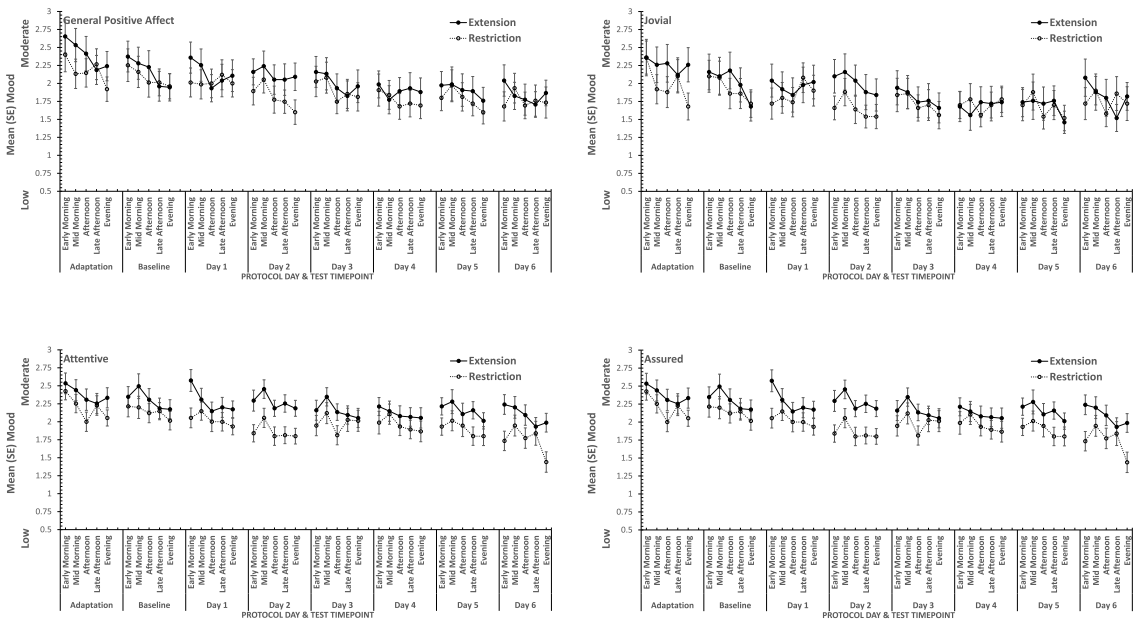

FIGURE 4 | Effects of sleep restriction and extension on Positive Mood (General Positive Affect, Assuredness, Joviality, Attentiveness) across protocol days and mood assessment time points.

protocol, and then flattening. Negative moods, on the other hand, remain stable, more or less, across time of day and days in the laboratory.

Sleep Deprivation

The same participants followed their period of sleep restriction or extension with 39/41 h continuous waking, during which PANAS was completed at fixed intervals. The data reported here are for 18 of the occasions on which they did so (matched for chronological time). Once again there are substantial effects on all four positive moods studied (see **Table 3** and **Figure 5**), but on this occasion, General Negative Affect and Hostility also changed systematically across the protocol (see **Table 3** and **Figure 6**).

TABLE 3 | Effects of sleep history (extension-restriction) and accumulating sleep loss (test point during sleep deprivation) on Negative and Positive moods.

	Extension-Restriction (1,35)		Test-point (17,595)		Extension-Restriction * Test-point (17,595)	
	F	η_p	F	η_p	F	η_p
Negative						
GNA	0.433	0.015	3.118**	0.1	1.085	0.037
Fearful	1.999	0.067	0.918	0.032	0.831	0.029
Hostile	5.216**	0.157	2.386**	0.079	1.009	0.035
Guilty	0.446	0.016	0.856	0.03	1.091	0.037
Positive						
GPA	4.279*	0.133	10.018#	0.264	2.343**	0.077
Jovial	3.878	0.122	4.376**	0.135	1.88*	0.063
Assured	3.758	0.118	7.181#	0.204	0.953	0.033
Attentive	2.844	0.092	16.683##	0.373	4.097##	0.128

KEY: GNA: General Negative Affect; GPA: General Positive Affect.
**p <.05, **p <01, #p <.005, ##p <.001.*
η_p *Partial-eta squared.*

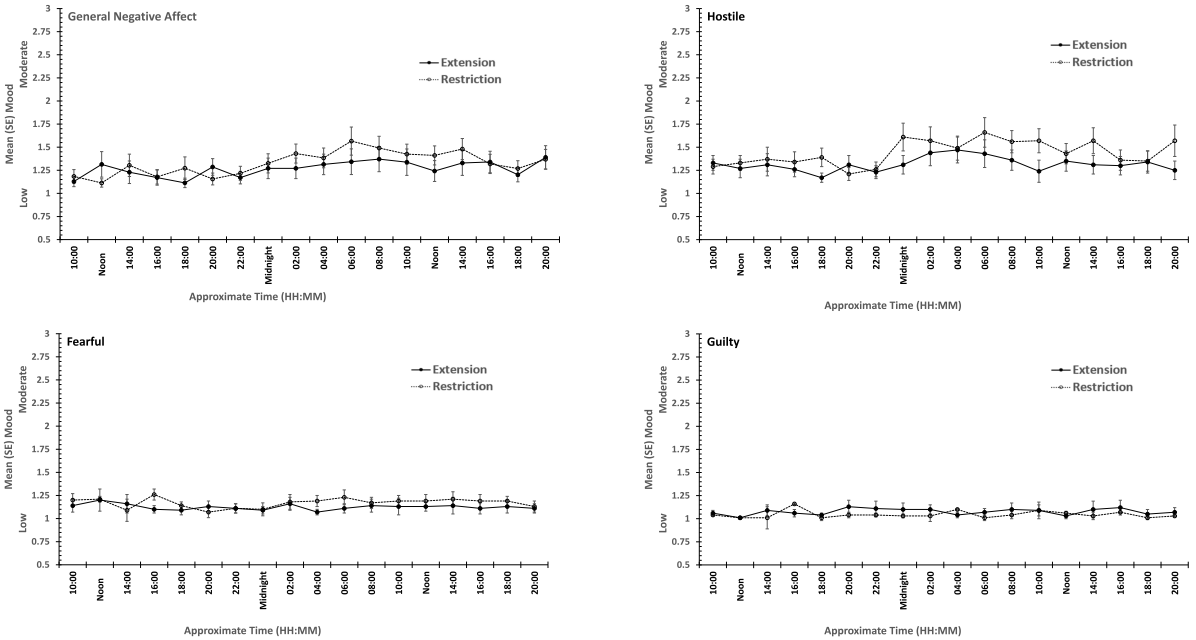

FIGURE 5 | Effects of prior sleep restriction and extension on Negative Mood (General Negative Affect, Fearfulness, Guilt, Hostility) across 38 h of wakefulness.

Participants were more Hostile when their sleep had been restricted the previous week. Statistically reliable effects of time awake across the protocol were present for both Hostility and General Negative Affect; both Hostility and General Negative Affect increase with time awake. Within subject contrasts of the main effect of time awake revealed that General Negative Affect had a strong linear trend, but also evidence of more complex trends (Linear: η_p^2 = 0.23; 5th order: η_p^2 = 0.20; 9th order: η_p^2 = 0.17). A linear trend was also evident for Hostility, but the change in Hostility with time awake was more complex, being relatively low and flat to begin with, then Hostility increases and remains at this higher level but varies from approximately in the second half of the sleep deprivation (Linear: η_p^2 = 0.13; Cubic: η_p^2 = 0.18; 8th order: η_p^2 = 0.13; 12th order: η_p^2 = 0.14; 15th order: η_p^2 = 0.23).

General Positive Affect was lower after a week of restricted sleep, but the effect of prior sleep loss was not statistically significant for any of the other positive moods. Each positive mood changed substantially as time awake increased (see **Table 3** and **Figure 5**). Within subject contrasts for this main effect showed that the change in positive mood is best characterized by a linear decline for General Positive Affect (Linear: η_p^2 = 0.53; Quadratic: η_p^2 = 0.36; Cubic: η_p^2 = 0.29), and Attentiveness (Linear: η_p^2 = 0.74; Quadratic: η_p^2 = 0.38;

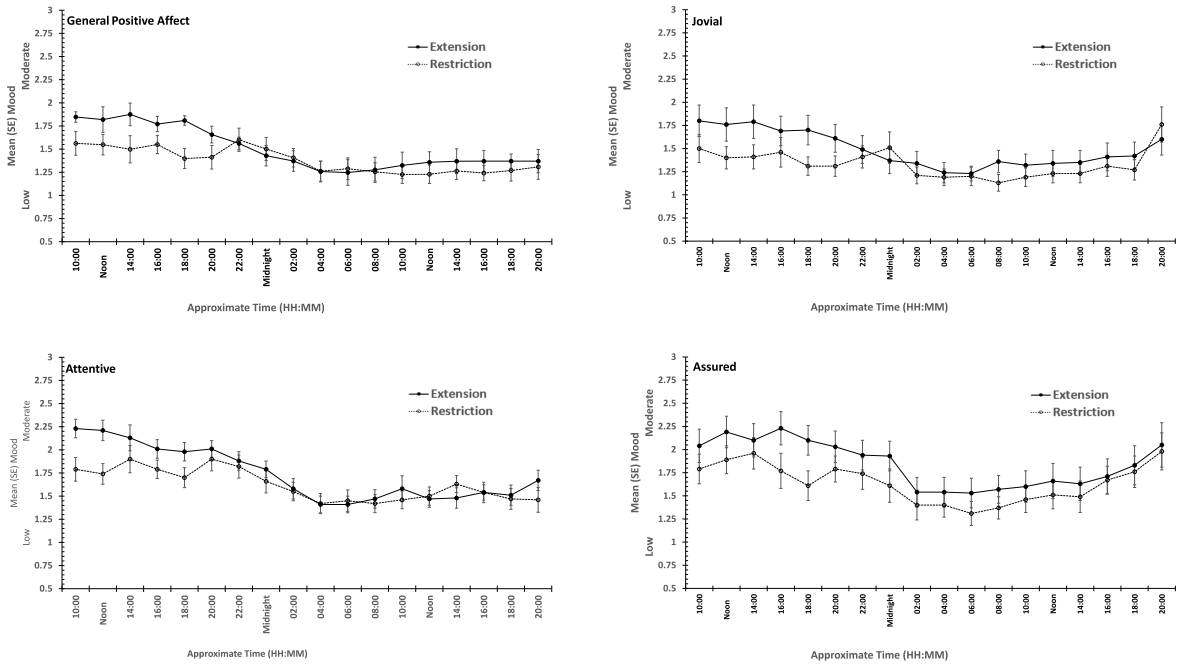

FIGURE 6 | Effects of prior sleep restriction and extension on Positive Mood (General Positive Affect, Assuredness, Joviality, Attentiveness) across 38 h of wakefulness.

Cubic: η_p^2 = 0.34), with substantially larger effect sizes for linear fits than for quadratic or more complex functions. In contrast, for Joviality (Linear: η_p^2 = 0.14; Quadratic: η_p^2 = 0.28; Cubic: η_p^2 = 0.33) and Assuredness (Linear: η_p^2 = 0.33; Quadratic: η_p^2 = 0.43; Cubic: η_p^2 = 0.44), non-linear trends dominate, with both Assurance and Joviality at higher levels during what would be the normal waking day, decreasing in the typical nighttime, and recovering almost to the early session levels. These main effects of time awake are subject to an interaction with prior sleep loss for General Positive Affect, Joviality and Attentiveness (see **Figure 5**). For General Positive Affect combination of linear and quadratic trends for sleep extension/restriction and test-point respectively has double the effect size that the only other statistically significant contrast (Linear-Linear: η_p^2 = 0.13; Linear-Quadratic: η_p^2 = 0.26). For each of the first five, and the final test-point, participants having had a week of sleep restriction were less positive than when they preceded the sleep deprivation with extended sleep opportunities. This pattern is similar for Joviality, except that the difference is at the penultimate rather than the final test-point, with a combination of linear trends the only statistically outcome for combination of trends (Linear-Linear: η_p^2 = 0.21). For Assuredness the increased positivity after sleep extension occurs at the second, fourth, and fifth test-points, and is only fit by a combination of Linear and 6th order functions (Linear-6th Order: η_p^2 = 0.11); while for Attentiveness, the statistically significant differences occur at the first, second and fifth test-points, and is again best represented by a combination of linear trends (Linear-Linear: η_p^2 = 0.36; Linear-Quadratic: η_p^2 = 0.18; Linear-11^{th} Order: η_p^2 = 0.17). The two-way interactions involving time Attentiveness and General Positive Affect are similar, in addition to the typical tendency of positive mood to decline with time awake, there is no improvement in these moods toward the end of the protocol, and mood is less positive early in the protocol when sleep has been restricted. For Joviality, unlike these other two positive moods, while the effect of prior sleep restriction is clear, so too in this case is an improvement toward the end of time awake approaches.

In summary, sleep deprivation leads to an increased negativity in mood, but only for General Negative Affect and Hostility, those who were well slept were less hostile across the sleep deprivation than when they had been sleep restricted. Positive moods were again more labile, some (Joviality and Assuredness) are more positive after sleep, become less positive as time awake increases reaching their lowest point in the morning of the next day, but then during the daytime recover to their initial levels. The same is true for General Positive Affect, but the recovery is not as complete, while Attentiveness declines steadily as time awake increases until the deterioration ceases mid-session with no recovery. These effects are exacerbated early in the session when sleep has been restricted. Thus, sleep deprivation has a far more profound effect on mood than does sleep restriction, at least at the extents studied here. However, when sleep at typical bedtimes is prevented, the accumulation of sleep loss over the previous week certainly does affect mood during extended waking. The deteriorations in at least some moods and subsequent recovery in others, raises the possibility that homeostatic sleep drive as well as circadian modulation, affect

some moods more than others. The next data set allow us to establish the effects of circadian change in the near absence of sleep loss.

Sleeping at Different Circadian Phases

Beginning at their typical sleep time, participants were scheduled to sleep 28 h later each day on seven successive occasions, with a maximum of 9.33 h of sleep permitted. Approximately every 3 h when awake, participants undertook the same battery of tests described above, including PANAS. **Table 4** summarizes the outcome of repeated measures anovas on each of the eight moods considered above.

There were main effects of study day for each of the four positive moods, and for General Negative Affect and for Hostility (see **Figures 7**, **8**). General Negative Affect increases as individuals' sleep and waking was displaced further from their typical timing, but neither individual comparisons of each day, nor within subject contrasts revealed significant differences or trends. Linear and quadratic contrasts for Hostility were statistically reliable for this same pattern of circadian displacement on negative affect (Linear: $\eta_p^2 = 0.12$; Quadratic: $\eta_p^2 = 0.12$). The point at which testing occurred in the 18.66-h period of waking in each study day also exerts a large additional influence. **Figure 7** also shows that while for days at or near typical sleep-wake timing there is a flat or erratic effect of time of day, Hostility increases across the day (days 2, 3, 4), and decreases across the later part of the day (days 5 and 6). This occurs as maximum displacement from typical sleep time approaches and recedes.

Strong quadratic trends are evident in the main effects of circadian displacement on General Positive Affect (Linear: $\eta_p^2 = 0.24$; Quadratic: $\eta_p^2 = 0.40$), Joviality (Linear: $\eta_p^2 = 0.10$ Quadratic: $\eta_p^2 = 0.49$), Assuredness (Linear: $\eta_p^2 = 0.10$; Quadratic: $\eta_p^2 = 0.32$) and Attentiveness (Linear: $\eta_p^2 = 0.10$; Quadratic: $\eta_p^2 = 0.54$), and no more complex trends were statistically reliable. Positive mood reduces the further from typical sleep timing the observations on a given study are made.

TABLE 4 | Effects of circadian phase on Negative and Positive moods.

	Day		Test-point		Day*Test-point	
	F(6,186)	η_p	F(5,198)	η_p	F(30,990)	η_p
Negative						
GNA	2.514*	0.073	1.11	0.034	0.908	0.028
Fearful	0.351	0.011	0.723	0.022	0.679	0.021
Hostile	2.859**	0.082	1.331	0.04	1.68**	0.05
Guilty	0.241	0.007	1.251	0.038	1.186	0.036
Positive						
GPA	10.265##	0.243	47.395##	0.597	6.001##	0.158
Jovial	8.698##	0.214	30.498##	0.488	4.08#	0.113
Assured	5.102#	0.138	25.06##	0.439	3.539#	0.1
Attentive	8.025##	0.2	54.348##	0.629	6.638##	0.172

KEY: GNA: General Negative Affect; GPA: General Positive Affect.
**p<.05, **p<01, #p<.005, ##p<.001.*
η_p Partial-eta squared.

In contrast, linear trends best represent the effect of test-point for each positive mood (General Positive Affect, Linear: $\eta_p^2 = 0.72$; 5th Order: $\eta_p^2 = 0.17$; Jovial, Linear: $\eta_p^2 = 0.62$; 5th Order: $\eta_p^2 = 0.29$; Assuredness, Linear: $\eta_p^2 = 0.63$; 5th Order: $\eta_p^2 = 0.41$; Attentiveness, Linear: $\eta_p^2 = 0.77$; Quadratic: $\eta_p^2 = 0.17$; 5th Order: $\eta_p^2 = 0.16$). Positive mood is higher soon after waking, and declines with time awake.

For each positive mood, the effects of circadian displacement and when in that day testing took place interacted significantly (see **Table 4** and **Figure 7**). The combined effects of both main effects on General Positive Affect and Attentiveness show very strong Quadratic-Linear trends for displacement and time of day respectively (Quadratic-Linear: $\eta_p^2 = 0.53$, Quadratic-Linear: $\eta_p^2 = 0.57$), with Cubic-Quadratic trends being the next largest effects sizes (General Positive Affect, Cubic-Quadratic: $\eta_p^2 = 0.39$; Attentiveness, Cubic-Quadratic: $\eta_p^2 = 0.46$). The Assuredness interaction reflects combinations of both 4th Order – Cubic trends ($\eta_p^2 = 0.46$), or Linear-Linear ($\eta_p^2 = 0.34$). Joviality is subject to Quadratic-Linear effects of displacement and test-point ($\eta_p^2 = 0.36$; 4th Order-Cubic, $\eta_p^2 = 0.25$). As is obvious from **Figure 7**, the effects of being awake on each positive mood intensify when the person sleep further away from their natural sleep time.

Summary

Figure 9 summarizes the effects on mood of the three paradigmatic sleep manipulations reported above, in terms of the relative scale of the effects sizes of each manipulation. There were small, but not necessarily significant, effects of each manipulation on each mood. The effects on positive moods were medium or large.

Hostility increased when sleep was restricted, when individuals were continuously awake for long periods having been sleep restricted, and when sleep was displaced from its typical timing. General Negative Affect and Hostility was unaffected by sleep restriction, but increased when time awake increased during sleep deprivation, when sleep was displaced from its typical timing. This suggests that the influence of circadian phase on General Negative Affect is particularly strong. Positive moods, particularly Attentiveness and General Positive Affect were reduced by sleep restriction, and when people were awake continuously there were large/medium effect of having been sleep restricted the previous week. In the absence of substantial sleep loss, but when the sleep opportunities available were out of phase with typical sleep, each of the four positive moods deteriorated substantially, with large/medium effects.

DISCUSSION

The re-analyzes reported above sought to address three issues that arise from previous literature: (a) previous studies provide little information about the specificity of any sleep manipulations with respect to particular positive mood states, beyond "vigor/energy" or "alertness"; (b) the effects on negative moods are inconsistent, but typically show an increase in

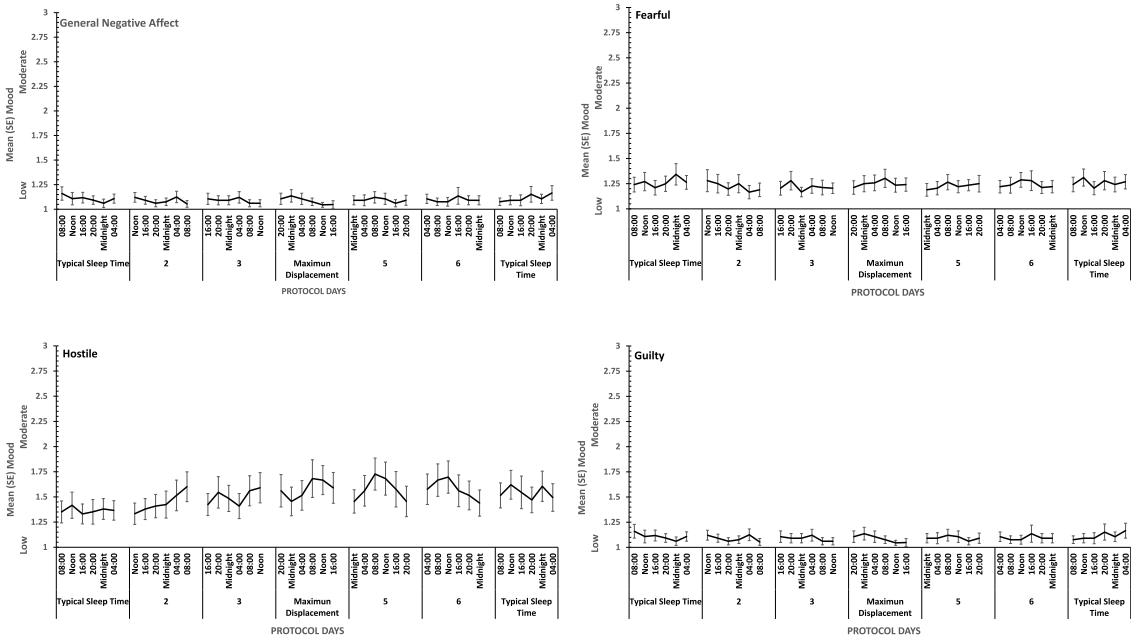

FIGURE 7 | Effects of circadian phase on Negative mood (General Negative Affect, Fearfulness, Guilt, Hostility) across a week-long 28 h Forced Desynchrony protocol.

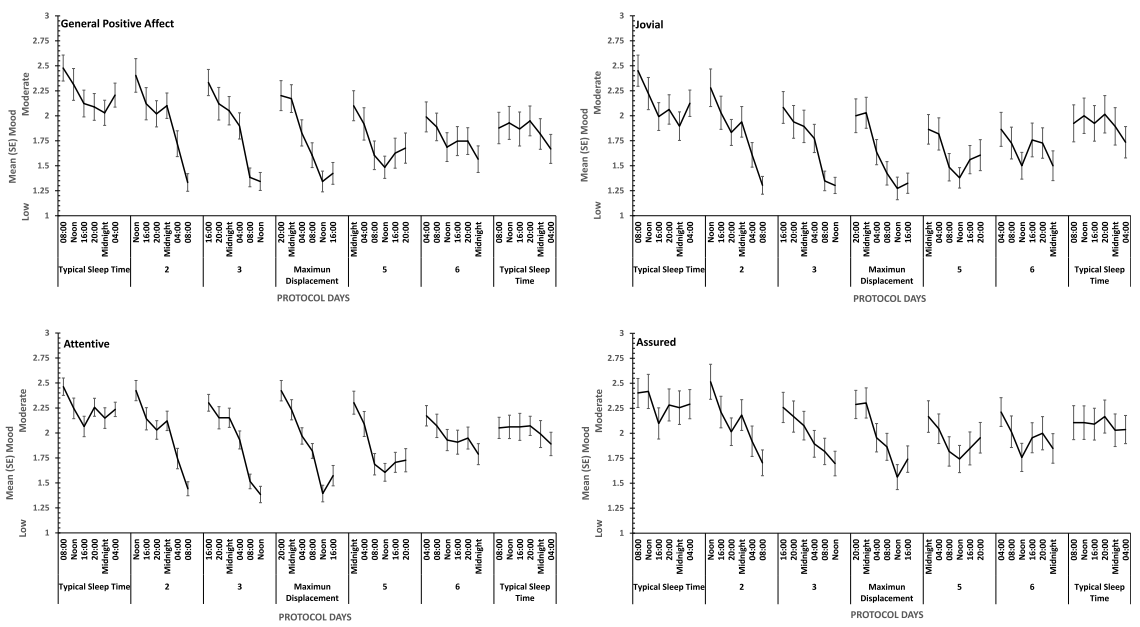

FIGURE 8 | Effects of circadian phase on Positive mood (General Positive Affect, Assuredness, Joviality, Attentiveness) across a week-long 28hr Forced Desynchrony protocol.

Confusion and Fatigue when there are any at all, and (c) many previous results might reflect effects of circadian phase, rather than sleep loss.

The studies above show that different aspects of positive mood are more or less affected by shortening, preventing and displacing sleep. General Positive Affect and Attentiveness, the latter perhaps an echo of the declines in energy/vigor reported by others (e.g., Dinges et al., 1997), are affected by each manipulation. Joviality, on the other hand, seems more prone to circadian disruption, which is also an inevitable confound of most sleep deprivation studies. Assuredness is perhaps the least affected by our sleep manipulations.

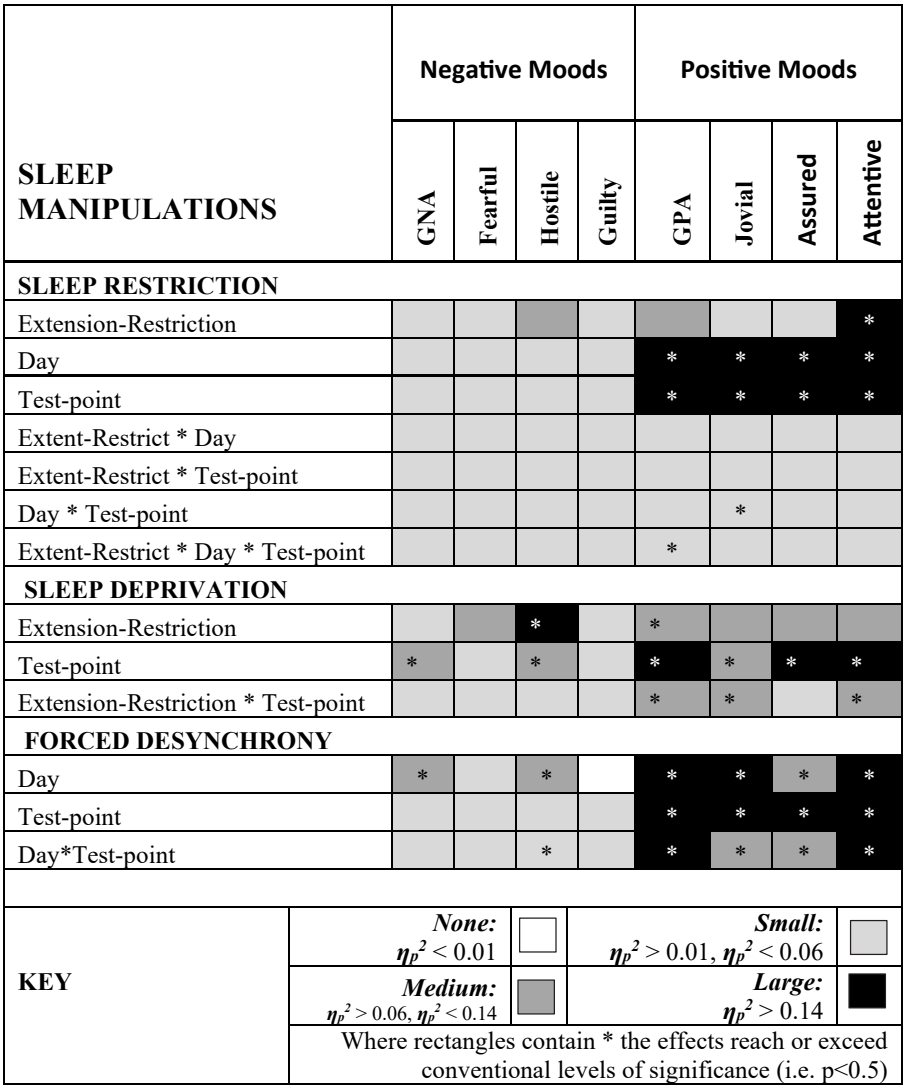

FIGURE 9 | Effect sizes of sleep manipulations on Negative and Positive moods. Where rectangles contain * the effects reach or exceed conventional levels of significance (i.e. $p < 0.5$).

Contrary to our previous reports, negative affect is influenced by sleep manipulations, but only particular aspects of negative affect- Hostility and General Negative Affect. PANAS adjectives do not easily translate to "Confusion," but both Hostility and General Negative Affect increase as fatigue is operationally manipulated. Of the other two negative moods studied, Fear increased when poorly slept individuals attempt to remain awake for extended periods, while Guilt is influenced by all manipulations, but only to a small extent. It is worth noting that negative affect is generally quite low, and while it does increase for some negative moods and not others, it is possible that these idiosyncratic patterns of change, when combined into the Negative Affect measure obscures change in negative mood, as we and others have reported (e.g., Boivin et al., 1997; Lo et al., 2012; Santhi et al., 2016).

Manipulating circadian phase, without substantial sleep loss, shows extensive large effects on positive mood, General Positive Affect, Attentiveness, but also Joviality, Assuredness. General Negative Affect and Hostility also show medium sized effects of forced desynchrony. This substantial influence of circadian disruption is hardly surprising, but we believe the results above provide the clearest demonstration of this reported anywhere.

While we believe the sleep manipulations reported about are very robust, the measurement of mood states was, as is typical in the literature, a compromise. The short-form PANAS used here is typically used to measure the more global Positive and Negative Affect. Here, as described above, we re-categorized these into the more specific moods measured by the much longer PANAS-X, and this might have reduced our sensitivity to more specific moods than the full PANAS-X measure would allow. However, the internal reliabilities are excellent for each newly-created subscale, and what was measured does seem differentially sensitive to different sleep manipulations. Replicating these effects with the longer version of PANAS would be very useful.

What we would caution against is the use of unvalidated single scales purporting to measure a specific mood. Inevitably, verbal items are interpreted in the context in which they occur, and may easily be suffused with irrelevant aspects of mood when these are not given the opportunity for expression. Studies that can only show that people express a lack of energy or vigor when we have deprived them of sleep can reveal very little about the subtleties of mood change as a function of sleep loss. We also question the usefulness of POMS in research contexts such as these, since it has little or no specificity with regard to positive moods.

We feel the re-analyzes reported above contribute substantial new insights to the literature: the relative insensitivity to chronic compared with acute sleep challenges; the very evident effects on mood of circadian phase without a substantial loss of sleep; the differential sensitivity of particular positive and negative moods to these challenges. However, we also need to emphasize that these effects are present in the relatively benign and highly controlled circumstances of the sleep laboratory, where there is no real emotional challenge- in contrast to what may be true of our everyday lives. The recent reports by Wong et al. (2021) and Shen et al. (2022), where moods are assessed repeatedly across weeks, provide a far more relevant insight into daily life. That acknowledged, without knowing what emotional challenges these individuals actually faced from day to day, it is difficult to be sure quite how helpful sleep might be in helping us to regulate our moods. What is clear from the present data is that even which consistently shortened sleep, people do not become more negative, and only do so when substantial sleep debt has been accumulated. People do, much more readily, become less positive in outlook. The data reported above also suggest that researchers need to be cautious when interpreting effects of time or day, or time awake, on mood- there are profound effects of circadian phase. Circadian markers would be an important addition to the very exciting ecological momentary analytic methods adopted in both studies, as would a more detailed investigation of the effects of menstrual phase. Several studies have reported sex differences in the effects of sleep-wake and circadian manipulations on measures of performance (e.g., Boivin et al., 2016; Santhi et al., 2016; Vidafar et al., 2018). In the present analyzes we have not explored these effects because, in contrast to the aforementioned studies, the current analyzes are based on only one assessment tool (i.e., PANAS). This and the relatively small number of men and women precludes a robust assessment of sex differences.

While the studies reported above both included similar numbers of people self-identifying as men or women, and carried out pregnancy tests to avoid unnecessary risk to participants or potential progeny, neither study was statistically powered to assess sex differences, nor was there any requirement on participants to report in which part of their menstrual cycle they were being tested. Far from ignoring the importance of possible sex differences on affect and mood, we believe without robust measures of hormonal changes typical of menstruating women, any serendipitous findings with regard to mood and sex are likely to understate, confuse or mislead.

Finally, the differentiation within and between positive and negative moods reported above has implications for theoretical accounts of affect and mood which rely on the orthogonality of both. Manipulations of sleep and circadian phase clearly demonstrate their independence, but the PANAS framework theorizes that low arousal can be reflected in lower levels of Positive or Negative Affect, the data reported above render this claim empirically questionable, adding to its conceptual confusion.

CONCLUSION

Reductions in nightly sleep duration, extended sleep deprivation and sleeping out of phase with one's normal sleep-wake routine, all influence mood in general, and particular mood states. Theoretical conceptualizations of mood which differentiate between an energetic and a more valence pleasant/positive state (or its opposite), are supported by the studies reported above, but when at least one of these dimensions is confounded with an essential and highly variable aspect of everyday life-sleep. Such theorizing on the structure of mood might benefit from considering what happens to mood when sleep is shifted, shortened, or removed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Surrey Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

D-JD and JG respectively were principal and co-investigators on the original studies, designed and oversaw the protocol, data collection, statistical analyzes, and reporting. JL, NS, and ASL collected most of the data reported. JG conceived the current study and carried out the statistical analyzes. All authors contributed to the article and approved the submitted version.

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REFERENCES

Akerstedt, T., Axelsson, J., Lekander, M., Orsini, N., and Kecklund, G. (2013). The daily variation in sleepiness and its relation to the preceding sleep episode–a prospective study across 42 days of normal living. *J. Sleep Res.* 22, 258–265. doi: 10.1111/jsr.12014

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders 5 th Edn*. Arlington, VA: American Psychiatric Publishing.

Barrett, L. F., and Russell, J. A. (1999). The structure of current affect: controversies and emerging consensus. *Curr. Dir. Psychol. Sci.* 8, 10–14. doi: 10.1088/1478-3975/10/4/040301

Boivin, D. B., Czeisler, C. A., Dijk, D. J., Duffy, J. F., Folkard, S., Minors, D. S., et al. (1997). Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Arch. Gen. Psychiatry* 54, 145–152. doi: 10.1001/archpsyc.1997.01830140055010

Boivin, D. B., Shechter, A., Boudreau, P., Begum, E. A., and Ng Ying-Kin, N. M. (2016). Diurnal and circadian variation of sleep and alertness in men vs. naturally cycling women. *Proc. Natl. Acad. Sci.* 113, 10980–10985. doi: 10.1073/pnas.1524484113

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: Routledge Academic.

Duffy, J. F., and Dijk, D. J. (2002). Getting through to circadian oscillators: why use constant routines? *J. Biol. Rhythms* 17, 4–13. doi: 10.1177/074873002129002294

Dijk, D. J., Groeger, J. A., Stanley, N., and Deacon, S. (2010). Age-related reduction in daytime sleep propensity and nocturnal slow wave sleep: Implications for insomnia. *Sleep* 33, 211–223. doi: 10.1093/sleep/33.2.211

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*. 20, 267–277.

Groeger, J. A., Stanley, N., Deacon, S., and Dijk, D. J. (2014). Dissociating effects of global SWS disruption and healthy aging on waking performance and daytime sleepiness. *Sleep* 37, 1127–1142. doi: 10.5665/sleep.3776

Groeger, J. A., Viola, A. U., Lo, J. C. Y., Archer, S. N., von Schantz, M., and Dijk, D. J. (2008). Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. *Sleep* 31, 1159–1167.

Harous, C., Roach, G. D., Kontou, T. G., Montero, A. J., Stuart, N., and Sargent, C. (2021). Consecutive nights of moderate sleep loss does not affect mood in healthy young males. *Clocks Sleep* 3, 442–448. doi: 10.3390/clockssleep3030031

Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalder, K., Johann, A., et al. (2019). Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Med. Rev.* 43, 96–105. doi: 10.1016/j.smrv.2018.10.006

IBM Corp. (2021). *IBM SPSS Statistics for Windows, Version 28.0.0*. Armonk, NY: IBM Corp.

Kaida, K., and Niki, K. (2014). Total sleep deprivation decreases flow experience and mood status. *Neuropsychiatr. Dis. Treat.* 10, 19–25. doi: 10.2147/NDT.S53633

Kaufmann, C., Agalawatta, N., Bell, E., and Malhi, G. S. (2020). Getting emotional about affect and mood. *Aust. N. Z. J. Psychiatry* 54, 850–852.

Larsen, R. J., and Diener, E. (1992). "Promises and problems with the circumplex model of emotion," in *Review of personality and social psychology: emotion*, ed. M. S. Clark (Newbury Park, CA: SAGE), 25–59. doi: 10.1177/0004867420943943

Li, B. Z., Cao, Y., Zhang, Y., Chen, Y., Gao, Y. H., Peng, J. X., et al. (2021). Relation of decreased functional connectivity between left thalamus and left inferior frontal gyrus to emotion changes following acute sleep deprivation. *Front. Neurol.* 12:642411. doi: 10.3389/fneur.2021.642411

Lo, C. Y., Groeger, J. A., Santhi, N., Arbon, E. L., Lazar, A. S., Hasan, S., et al. (2012). Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PLoS One* 7:e45987. doi: 10.1371/journal.pone.0045987

McNair, D. M., Lorr, M., and Droppelman, L. F. (1971). *Manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service.

Meney, I., Waterhouse, J., Atkinson, G., Reilly, T., and Davenne, D. (1988). The effect of one night's sleep deprivation on temperature, mood, and physical performance in subjects with different amounts of habitual physical activity. *Chronobiol. Int.* 15, 349–363. doi: 10.3109/07420529808998695

Musiek, E. S., and Holtzman, D. M. (2016). Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science.* 354, 1004–1008. doi: 10.1126/science.aah4968

Russell, J. A. (1980). A circumplex model of affect. *J. Pers. Soc. Psychol.* 39, 1161–1178. doi: 10.1037/h0077714

Saksvik-Lehouillier, I., Saksvik, S. B., Dahlberg, J., Tanum, T. K., Ringen, H., Karlsen, H. R., et al. (2020). Mild to moderate partial sleep deprivation is associated with increased impulsivity and decreased positive affect in young adults. *Sleep* 43:zsaa078. doi: 10.1093/sleep/zsaa078

Santhi, N., Lazar, A. S., McCabe, P. J., Lo, J. C., Groeger, J. A., and Dijk, D. J. (2016). Sex differences in the circadian regulation of sleep and waking cognition in humans. *PNAS* 113, E2730–E2739. doi: 10.1073/pnas.1521637113

Shen, L., Wiley, J. F., and Bei, B. (2022). Sleep and affect in adolescents: bidirectional daily associations over 28-day ecological momentary assessment. *J Sleep Res.* 31:e13491. doi: 10.1111/jsr.13491

Thayer, R. E. (1989). *The Biopsychology of Mood and Activation*. New York, NY: Oxford University Press.

Vandewalle, G., Archer, S. N., Wuillaume, C., Balteau, E., Degueldre, C., Luxen, A., et al. (2009). Functional magnetic resonance imaging-assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. *J. Neurosci.* 29, 7948–7956. doi: 10.1523/JNEUROSCI.0229-09.2009

Vidafar, P., Gooley, J. J., Burns, A. C., Rajaratnam, S. M. W., Rueger, M., Van Reen, E., et al. (2018). Increased vulnerability to attentional failure during acute sleep deprivation in women depends on menstrual phase. *Sleep* 41:zsy098. doi: 10.1093/sleep/zsy098

Watson, D., and Tellegen, A. (1985). Toward a consensual structure of mood. *Psychol. Bull.* 98, 219–235. doi: 10.1037//0033-2909.98.2.219

Watson, D., Clark, L. A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063–1070. doi: 10.1037/0022-3514.54.6.1063

Wong, P. M., Hasler, B. P., Kamarck, T. W., Wright, A. G. C., Hall, M., Carskadon, M. A., et al. (2021). Day-to-day associations between sleep characteristics and affect in community dwelling adults. *J. Sleep Res.* 30:e13297. doi: 10.1111/jsr.13297

Wundt, W. (1912/1924). *An Introduction to Psychology (R. Pintner, Trans.)*. London: Allen and Unwin.doi: 10.1037/13784-000

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Sleep architecture and emotional inhibition processing in adolescents hospitalized during a suicidal crisis

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Background: Suicide is the second leading cause of death in adolescents. Sleep disturbances could alter inhibitory processes and contribute to dangerous behaviors in this critical developmental period. Adolescents in suicidal crisis have been shown to have lighter sleep compared to healthy controls. Additionally, suicidal adolescents have lower neural resources mobilized by emotionally charged inhibition processing. The present exploratory study aimed to determine how sleep architecture in suicidal adolescents may relate to inhibition processing in response to emotional stimuli.

Methods: Ten adolescents between 12 and 17 years of age with a diagnosis of major depressive disorder and who attempted suicide were recruited while hospitalized for a suicidal crisis in a psychiatric inpatient unit. Event-related potentials (ERPs) were recorded prior to bedtime during a Go/NoGo task involving pictures of sad, happy, and neutral faces. Polysomnography was then recorded throughout the night. Pearson correlations were conducted to investigate how inhibition performance and ERP parameters reflecting inhibition processing (i.e., P3d and N2d derived from difference waveform calculated as NoGo minus Go trials) relate to sleep architecture.

Results: Poorer inhibition accuracy in response to emotional stimuli was significantly correlated with shorter REM sleep latency, higher REM sleep, and more frequent nocturnal awakenings. The P3d in response to sad faces was negatively correlated with NREM2 sleep and positively correlated with NREM3 sleep. No such association with the P3d was found for happy or neutral stimuli. There were no significant correlations for the N2d.

Conclusion: Altered sleep in adolescents with depression who are in a suicidal crisis is associated with behavioral inhibition difficulties and fewer neural resources mobilized by inhibitory processes in emotionally charged contexts. This highlights the importance of addressing sleep disturbances while managing suicidal crises in adolescents.

KEYWORDS

sleep, inhibition, suicide, emotional processing, adolescence, event related potentials

Introduction

Suicide is the second leading cause of death in adolescents worldwide (1). Adolescence brings physiological, social, and behavioral changes that can increase vulnerability to mental health problems and dangerous behaviors (2). Notably, from childhood to adolescence, changes in sleep co-occur with structural and functional brain changes (3–5), and sleep architecture is sensitive to mental disorders (6–8). Suicidal thoughts and behaviors have been associated with symptoms of sleep disorders among both adults and adolescents (9, 10). In fact, sleep alterations have been identified as a risk factor for suicidal ideations, suicidal behaviors, and death by suicide (11, 12). Although sleep is well known to alter mental health, which can in turn increase suicidality (13, 14), there are some indications that the link between sleep disruptions and suicidality cannot be solely explained by mental disorders (15–18). Notably, This may operate in part *via* sleep-induced alterations in cognitive and emotional processing linked to suicidality (9, 10). For instance, difficulties with inhibitory control, a cognitive function known to be sensitive to sleep loss (19), are thought to contribute to suicidal behaviors (20–23). Inhibitory processes reflect the ability to actively suppress unwanted thoughts or actions (24). This allows individuals to leverage cognitive efforts to suppress habits or impulses and can, therefore, be instrumental for the management of suicidal ideations and behaviors (20, 25, 26). Conversely, weakened inhibitory processes increase impulsivity (27), a phenomenon that can emerge with sleep difficulties (28, 29). From this perspective, the interactions between poor sleep and inhibitory control could possibly increase the risks of engaging in suicidal behaviors. Yet, the contribution of sleep disturbances toward neurocognitive factors underlying suicidality in adolescents remains to be investigated.

Emotional processing and inhibitory control in the context of suicide

Emotional processing is often altered in suicidal states (30–33). Individuals with suicidal thoughts and behaviors have an attentional bias toward emotionally negative suicide-related cues (30, 33). It has been suggested that vulnerability to suicidal ideations could be worsened by altered inhibitory control, which diminishes one's ability to inhibit intrusive thoughts (33). Alterations in inhibitory processes can also affect emotional regulation, which may make it more arduous to manage emotionally difficult situations (34–37).

The Go/NoGo task is one of the most commonly used paradigms to study inhibitory processing (38). In this task, participants are instructed to respond when presented with a "Go" stimulus and to withhold their response when presented with a "NoGo" stimulus. The "Go" trials prime the behavioral response while the "NoGo" trials elicit inhibitory processes. Accurate detection of the "Go" stimulus is associated with two main event-related potential (ERP) components [for reviews, see (37, 38)]: (a) the Go-N2, occurring at about 200–300 ms, reflecting the controlled detection of a stimulus event, and (b) the Go-P3, occurring at about 300–500 ms, reflecting decision making and memory updating processes. The "NoGo" stimulus, on the other hand, is associated with (a) the NoGo-N2, reflecting conflict monitoring and detection and, (b) the NoGo-P3, reflecting the actual inhibition process and the conscious decision to withhold a prepared response. These components are thought to reflect the extent of neuronal activity dedicated toward a particular cognitive process.

A larger increase in the amplitude of the N2 from "Go" to "NoGo" conditions has been reported in adults who attempted suicide compared to adults with suicidal ideation (39). Furthermore, we previously observed that adolescents with depression facing a suicidal crisis have a reduced P3d (i.e., difference waveform calculated as NoGo minus Go trials, a marker of inhibition processes isolated from more basic processes) in response to happy and neutral, but not sad stimuli, when compared to healthy controls (40). This suggests that depression/suicidal states may be characterized by difficulties recruiting neural resources to inhibit inadequate responses in certain emotional contexts. We also observed a negative correlation between the severity of suicidal symptoms and the amplitude of the P3d. Furthermore, other studies have shown that self-harming individuals commit more errors in a Stop Signal Task than controls, especially in a negative emotional context (41). Overall, these findings suggest that cognitive resources needed to inhibit negative thoughts in the context of emotional processing can be altered in suicidal individuals (40, 42).

Sleep, adolescence, and suicidality

Many changes in sleep take place during adolescence, including a reduction in total sleep time, and shortening of the latency to rapid eye movement (REM) sleep (3, 4, 43). The transition into adolescence is also accompanied by an increase in NREM2 sleep (44) with a progressive reduction in slow wave sleep (i.e., NREM3 sleep) and slow-wave activity (SWA, i.e., EEG spectral power in the delta frequency band) toward adult levels (4, 44, 45), and a delay in the sleep wake-cycle (43, 45). This delay in the sleep-wake cycle is often accompanied by circadian disruptions and social jetlag, and these sleep and chronobiologic factors have been shown to alter cognition and mental health (46, 47).

Beyond typical developmental changes, abnormal sleep features have been reported in suicidal adolescents. Notably, Dahl et al. (48) observed that, compared to depressed adolescents and healthy controls, suicidal adolescents exhibited longer sleep onset latency and a marginal increase in REM pressure as reflected by a shorter REM sleep latency with increased time spend in REM sleep and higher REM density. Also, we previously observed that, compared to healthy controls, adolescents in acute suicidal crisis have longer sleep onset latency, higher REM density, and a higher percentage of NREM1 sleep accompanied by a lower percentage of NREM3 sleep in the last third of the night (49). There are also indications that high scores of the suicide item of the Hamilton Depression Rating Scale significantly correlate with a lower percentage of NREM3 in adolescents (50).

To date, little research has been done on the relation between sleep, inhibitory control and suicidality in adolescents. Experimental studies in healthy individuals undergoing partial sleep restriction, a phenomenon akin to naturalistic sleep difficulties, demonstrated that partial sleep loss can lead to heightened impulsivity but would not change the ability to perform while inhibiting responses to negative stimuli on the emotional Go-NoGo task (51). Further work is required to decipher how sleep abnormalities emerging in the context of a suicidal crisis may interact with overt inhibitory control performance and underlying brain processes.

Objectives

The present report follows our recent findings that suicidal adolescents have altered sleep (49) and a distinct pattern of interactions between emotional and inhibition processing (40). We now aimed to determine how sleep architecture may relate to inhibitory processes in response to stimuli with neutral, positive, and negative emotional valence in these suicidal adolescents. This investigation is exploratory in nature. Nevertheless, based on previous work suggesting that sleep disruptions lead to difficulties in inhibitory control, as well as the typical increase in NREM2 with accompanying reductions in NREM3 occurring both in adolescence and adverse mental health states, it was hypothesized that higher NREM2 and lower NREM3 sleep would correlate with poorer response accuracy on NoGo trials and with a higher amplitude of P3d and N2d evoked by emotional stimuli.

Materials and methods

Participants

Participants were sourced from a dataset used in two previous reports (40, 49). The first report compared the sleep architecture of 17 suicidal adolescents to 17 age- and sex-matched controls. The second report assessed the influence of inhibition and emotional valence on behavioral responses and ERPs to the Go/NoGo task across both groups in a subset of participants. From this dataset, all participants with valid sleep and ERP data ($n = 10$) were included in the present report.

All participants were between the ages of 13 and 17 (80% females, mean age = 15.1, SD = 1.6 years) and were admitted to the inpatient psychiatric unit of a pediatric hospital due to an acute risk of suicide. The length of stay in this unit typically spans over 5–7 days. Suicidal risk was judged too high for these adolescents to live safely in the community. All participants had a diagnosis of major depression, reported a plan to kill themselves with the full intention of dying, and had made a suicide attempt. Within 24 h of admission, clinical interviews were conducted with the participant and their families by a board-certified psychiatrist to determine diagnosis based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; American Psychiatric Association, 2013). Exclusion criteria were: a diagnosis of schizophrenia or neurological or pervasive developmental disorder to limit the effects of sleep and inhibitory process alterations that are known to be associated with these conditions.

Written informed consent was obtained from all participants who were at least 16 years of age. Participant younger than 16 years of age provided assent and their parents provided consent for them to take part in this study. The University of Ottawa's Health and Sciences Research Ethics Board and the Children's Hospital of Eastern Ontario Research Institute's Research Ethics Board approved the study. The study was conducted according to the Declaration of Helsinki.

Psychological assessment

Depression symptom severity was assessed with the Children's Depression Inventory Second Edition (CDI-2) (52), which includes 27 items grouped into two major factors, each

comprised of two subscales assessing emotional problems (i.e., negative mood/physical symptoms and negative self-esteem) and functional problems (i.e., ineffectiveness and interpersonal problems). Furthermore, the presence and severity of suicidal thoughts and behaviors were assessed using the Suicidal Ideation Questionnaire-JR SIQ-JR; (53) and the Suicidal Behaviors Questionnaire-Revised (SBQ-R) (54). The SIQ-JR includes 15 items assessing thoughts and ideations about suicide. The SBQ-R includes four items addressing different dimensions of suicidality: (1) lifetime suicide ideation and suicide attempts, (2) frequency of suicide ideation over the past 12 months, (3) threat of suicidal behavior, and (4) the likelihood of suicidal behavior. Both the SIQ-JR and the SBQ-R have been found to have good reliability and validity (54, 55).

Polysomnography

Participants underwent two consecutive overnight polysomnography recordings, according to their habitual sleep-wake schedules. The first night served as an adaptation night while the second night was used for final analyses. Polysomnography was recorded at the patient's bedside in the inpatient psychiatric unit using the MediPalm 22-Channel polysomnography amplifier (Braebon Medical, Ottawa, ON). EEG data was collected from F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, O2, M1, M2, right, and left electrooculograms (EOG), two chins and two leg electromyograms (EMG), and two electrocardiogram (ECG) channels according to the 10/20 system of electrode placement. A registered sleep technologist manually scored sleep stages according to guidelines established by the American Academy of Sleep Medicine (56) on the Stellate Harmonie (Natus, Pleasanton, CA) analysis software. Total sleep time (TST), sleep onset latency, REM sleep latency, wake after sleep onset (WASO), and absolute and relative sleep stages (NREM1, NREM2, NREM3, REM) were computed. TST was defined as the time spent asleep between the "light off" and "lights on" markers. WASO was calculated as the total duration of all epochs following sleep onset that were scored as wake. Absolute sleep stages were calculated as the total number of minutes participants spent in each respective stage of sleep. Relative sleep stages were calculated as the percentage of time between the "lights off" and "lights on" markers scored as NREM1, NREM2, NREM3, and REM divided by the TST.

Go/NoGo task

Prior to bedtime on the second night of polysomnography, ERPs were recorded while participants completed an emotional Go/NoGo task. Full details of the task and detailed ERP profiles in the larger sample from which the current cohort is sourced are highlighted in a previous report (40). Briefly, stimuli included images of facial expressions showing happy, sad, and neutral emotions. Five images of males and fives images of females were cropped to an elliptical shape to eliminate hair and background cues. The stimuli were presented in four blocks. Equiprobable neutral and happy faces were presented in random order in two of the blocks. For the first block, participants were asked to press the space bar with their index finger of their dominant hand (Go trials) upon detection of happy faces and to withhold their response (NoGo trials) upon detection of neutral faces. For the following block, participants had to reverse their response procedure by pressing the space bar when seeing neutral faces and withholding their response when seeing happy faces. In the remaining two blocks, the same procedure was done with neutral and sad faces. Each block contained 124 total trials. Each stimulus was presented for 500 ms and the interstimulus interval was 2,000 ms. One block thus lasted approximately 5 min. The total duration of the Go/NoGo task was approximately 20 min. E-Prime software (Psychology Software Tools, Pittsburgh, United States) was used for stimulus presentation and recording of responses.

Event-related potential recording and analysis

ERPs were recorded during presentation of the Go/NoGo task using BrainAmp amplifiers and Recorder software (Brain Products, Gilching, Germany). The same electrodes used for polysomnography were also used for the ERP recording. The nose served as a reference for all ERP recording channels. Vertical eye movements were recorded from electrodes placed at infra- and supraorbital ridges of the left eye. Horizontal eye movements were recorded from electrodes placed on the outer canthus of each eye. Inter-electrode impedances were kept below 5 kΩ. High-frequency filter was set at 75 Hz. The time constant was set at 2 s. Electrical signals were digitized continuously using 500 Hz sampling rate.

Offline, data were reconstructed using Brain Products' Analyzer2 Software. The continuous EEG data was bandpass filtered at 0.5–20 Hz (24 dB/octave). A vertical EOG channel was computed by subtracting activity recorded at the supraorbital and the infraorbital ridges of the left eye. The horizontal EOG channel was computed by subtracting activity recorded at the outer canthus of each eye. Independent Component Analysis (57) was used to analyze eye movement and blink artifacts that were statistically independent of the EEG activity. These artifacts were then partialled out of the EEG traces. Continuous data was subsequently reconstructed into discrete single trial 900 ms segments beginning 100 ms before the stimulus onset and then baseline corrected. The segments in which EEG activity exceeded ± 100 μV relative to the baseline was excluded from further analyses. No more than 5% of total trials were rejected from further analyses per participant. Single trials

were then sorted and averaged based on stimulus type (Go or NoGo), emotional facial expression (happy, neutral, sad) and electrode site.

Quantification

The amplitude of all ERP components was quantified for each participant using the means of all the data points within ± 25 ms of the peak amplitude that was identified in the grand average (the average of all participants' averages). For both Go and NoGo trials, the N2 was identified as the most negative peak between 150 and 300 ms after stimulus onset while the P3 was identified as the most positive peak between 300 and 500 ms. N2 and P3 were identified at the Fz electrode site, where they both tend to be at maximum in amplitude.

Difference waveforms were then calculated by subtracting the ERP waveforms to Go trials from those of NoGo trials to isolate the unique processing following NoGo trials and examine the effects of inhibition (58). From these difference waveforms, the N2d was identified as the most negative-going peak between 150 and 350 ms and the P3d as the most positive-going peak in the window of 300–500 ms, for each emotion. Visual inspection of the ERP waveform revealed that both the N2d and P3d were largest at frontal sites. The data, were, therefore quantified at the Fz electrode site.

Statistical analyses

Kolmogorov-Smirnov tests confirmed that the data was normally distributed. Pearson correlations were used to assess whether the amplitudes of the N2d and P3d at Fz were associated with the following sleep architecture parameters: sleep onset latency, REM sleep latency, total sleep time, number of nocturnal awakenings, sleep efficiency, and absolute and relative sleep stages (NREM1, NREM2, NREM3, REM). Additional correlations were also conducted to assess potential associations between performance accuracy on NoGo trials (i.e., inhibition condition) and sleep architecture parameters. Subsequently, partial correlations were done for all significant findings to determine whether they survived adjustment for medication intake. Prior to all analyses, outlying values above and below 2SD were curtailed.

Results

The effects of inhibition and emotional valence on performance indices and ERPs were presented in a previous report based on the larger sample (40). Performance and ERP profiles on the specific subset of participants included in the current report are provided in **Supplementary materials**.

TABLE 1 Demographic and clinical characteristics.

Variables	Participants (n = 10)
Age: mean (*SD*)	15.1 (1.6)
Sex distribution [*n* (%) females]	8 (80%)
Medication intake [*n* (%)]	
Antidepressants	9 (90%)
Mood stabilizers/anticonvulsants	1 (10%)
Melatonin	2 (20%)
Stimulants	1 (10%)
Atypical antipsychotics	2 (20%)
CDI-2 [mean (*SD*)]	26.7 (10.5)
SBQ-R [mean (*SD*)]	15.6 (2.5)
SIQ-JR [mean (*SD*)]	43.8 (17.2)

CDI-2, Children's Depression Inventory Second Edition; SBQ-R, Suicidal Behavior Questionnaire Revised, cutoff > 8; SD, Standard Deviation; SIQ-JR, Suicidal Ideation Questionnaire-Junior, cutoff > 31.

Demographics

Participant's characteristics are listed in **Table 1**. In brief, depression symptoms severity on the CDI-2 ranged from 11 to 39 (mean = 26.7, *SD* = 10.5) which are within the "high average" or "elevated" severity range. All participants showed clinically significant suicidal thoughts and behaviors based on the standard cut-off score of 8 for the SBQ-R. Suicidal symptoms severity on the SIQ-JR ranged from 24 to 82, with an average score above the standard threshold of 31 (mean = 43.8; *SD* = 17.2), indicating overall significant levels of suicidal ideation.

Correlations between inhibition and sleep parameters

Performance accuracy on NoGo trials

Table 2 shows unadjusted correlation coefficients for the association between inhibition response accuracy (i.e., on NoGo trials) and sleep parameters. Lower response inhibition accuracy on NoGo trials with sad faces significantly correlated with more frequent nocturnal awakenings ($r = -0.76$, $p = 0.011$, **Figure 1A**). Furthermore, lower response inhibition accuracy on NoGo trials with happy faces significantly correlated with shorter REM sleep latency ($r = 0.64$, $p = 0.046$, **Figure 1B**) and higher absolute ($r = -0.72$, $p = 0.019$, **Figure 1C**) and relative ($r = -0.74$, $p = 0.014$, **Figure 1D**) amounts of REM sleep.

Event-related potentials

Conflict detection as reflected by N2d

Table 3 presents unadjusted correlation coefficients linking sleep parameters to N2d amplitudes. There was no significant correlation between sleep parameters and the amplitude of the

TABLE 2 Correlation coefficients for sleep and response inhibition accuracy.

	Sad		Neutral		Happy	
	r	*P*	*r*	*P*	*r*	*P*
Sleep latency (min)	0.32	0.368	0.27	0.445	0.14	0.700
REM latency (min)	0.10	0.788	0.00	0.996	0.64*	0.046
Total sleep time (min)	−0.11	0.756	−0.29	0.409	−0.01	0.990
Nocturnal Awakenings (nb)	−0.76*	0.011	−0.62	0.056	−0.56	0.093
Sleep efficiency (%)	0.32	0.361	0.13	0.711	0.26	0.462
Absolute sleep stages (min)						
NREM1	−0.62	0.056	−0.61	0.060	−0.48	0.157
NREM2	−0.32	0.365	−0.24	0.508	−0.30	0.407
NREM3	0.31	0.379	0.34	0.332	0.58	0.081
REM	−0.15	0.673	−0.47	0.176	−0.72*	0.019
Relative sleep stages (%)						
NREM1	−0.60	0.067	−0.59	0.072	−0.49	0.151
NREM2	−0.22	0.551	−0.08	0.829	−0.24	0.507
NREM3	0.33	0.352	0.38	0.283	0.61	0.059
REM	−0.14	0.708	−0.42	0.225	−0.74*	0.014

Inhibition response accuracy as reflected by the percentage of correct responses on NoGo trials in each emotional valence condition.
*Correlation is significant at the 0.05 level (2-tailed).

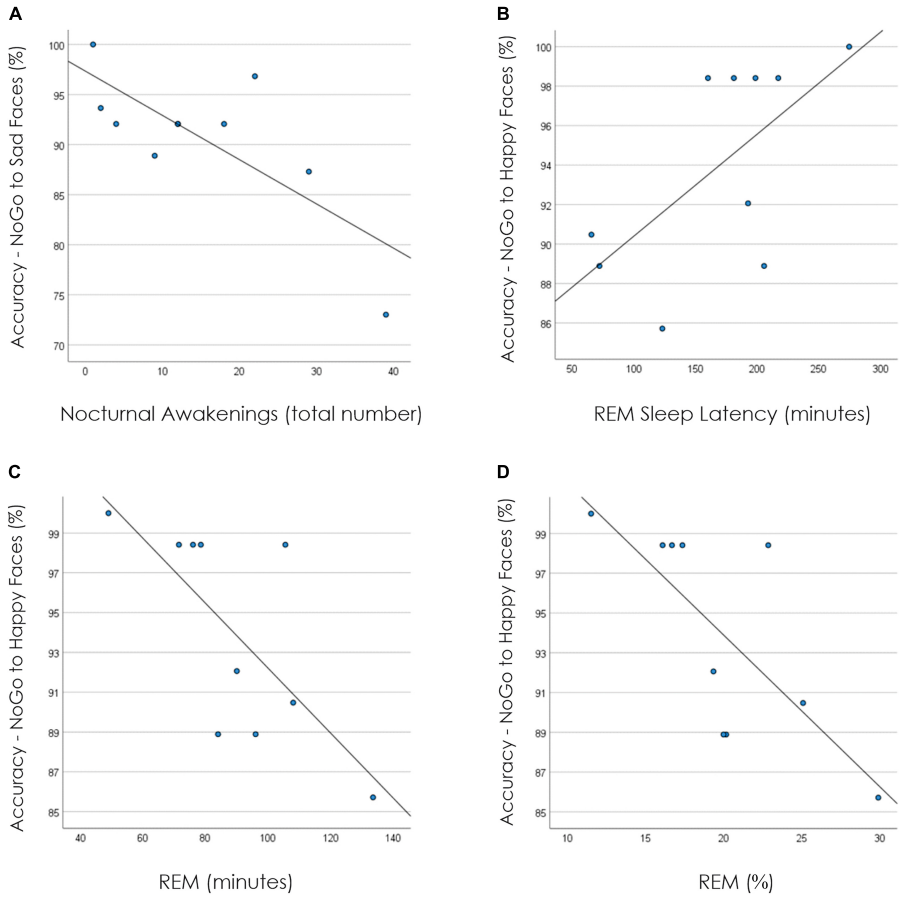

FIGURE 1
Correlation plots between sleep parameters and performance data. **(A)** Displays the correlation plot for response accuracy on NoGo trials to sad faces and nocturnal awakenings. **(B)** Displays the correlation plot for response accuracy on NoGo trials to happy faces and REM sleep latency (in minutes). **(C)** Displays the correlation plot for response accuracy on NoGo trials to happy faces and REM (in minutes). **(D)** Displays the correlation plot for response accuracy on NoGo trials to happy faces and REM (percentage).

TABLE 3 Correlation coefficients for sleep and conflict detection as reflected by the amplitude of the N2d, at Fz.

	Sad		Neutral		Happy	
	r	*P*	*r*	*P*	*r*	*P*
Sleep latency (min)	0.51	0.129	0.11	0.761	0.02	0.953
REM latency (min)	−0.35	0.328	−0.05	0.890	−0.10	0.778
Total sleep time (min)	−0.49	0.150	−0.62	0.057	−0.09	0.803
Sleep efficiency (%)	0.23	0.530	−0.32	0.367	−0.06	0.862
Absolute sleep stages (min)						
NREM1	−0.53	0.115	0.20	0.590	0.54	0.106
NREM2	0.02	0.967	0.44	0.200	0.26	0.471
NREM3	−0.10	0.780	−0.54	0.106	−0.36	0.309
REM	0.02	0.952	0.09	0.814	0.18	0.614
Relative sleep stages (%)						
NREM1	−0.48	0.161	0.23	0.523	0.54	0.110
NREM2	0.18	0.619	0.54	0.105	0.22	0.544
NREM3	−0.07	0.847	−0.49	0.155	−0.35	0.329
REM	0.11	0.758	0.18	0.627	0.19	0.599

No correlation reached the significance threshold at the 0.05 level (2-tailed).

N2d in response to any type of emotional stimuli (all $p > 0.050$; Table 3).

Inhibition as reflected by the P3d

Table 4 presents unadjusted correlation coefficients linking sleep parameters to P3d amplitudes. The amplitude of the P3d to sad stimuli was significantly negatively correlated with both absolute ($r = -0.77$, $p = 0.010$; Figure 2A) and relative ($r = -0.71$, $p = 0.022$; Figure 2B) amounts of NREM2 sleep. The P3d amplitude to sad stimuli also significantly correlated with higher absolute amounts of NREM3 sleep ($r = 0.64$, $p = 0.045$; Figure 2C), with a similar trend for relative NREM3 sleep ($r = 0.62$, $p = 0.055$; Figure 2D). When controlling for psychotropic medication use, these results remained significant with the exception of the correlation between absolute NREM3 and the P3d to sad stimuli, which became a non-significant trend ($r = 0.63$, $p = 0.072$). Sleep onset latency, REM sleep latency, total sleep time, sleep efficiency, and the time spent in NREM1 and REM sleep were not significantly correlated with the P3d elicited by any type of emotional stimuli.

Discussion

The present study is the first to investigate parallels between brain activity during sleep and brain activity in the wake state during emotionally charged inhibition processing in adolescents undergoing a suicidal crisis. Physiological measures of sleep and inhibitory brain processes were measured in acutely suicidal adolescents while they were hospitalized after attempting suicide, thereby providing information about this critical time window. Findings suggest that lighter sleep, as reflected by higher levels of NREM2 and lower levels of NREM3, is associated with fewer neural resources mobilized by inhibitory processing, as reflected by the amplitude of the P3d in a Go/NoGo task. This was especially prominent in the context of negative emotional valence.

Task performance and event-related potentials across inhibition and emotional valence conditions

The adolescent brain undergoes significant developmental changes (59) affecting emotional regulation (60–62) and executive functions such as inhibitory control (63–66). As observed in the current subsample, our previous report revealed that adolescents in suicidal crisis take longer time and make more mistakes when processing negative compared to positive emotional stimuli (40), a finding consistent with those reported in another similar study (67). In other words, it may be especially difficult for suicidal adolescents to inhibit inadequate responses when confronted with information with a negative emotional tone, a factor likely to contribute to increased impulsivity (27) in emotionally charged contexts. These cognitive difficulties could notably arise if insufficient neural resources are mobilized to support performance during emotional tasks, a phenomenon that can be appraised using ERPs. As was the case in our previous report based on the larger sample of suicidal adolescents from which the current participants were sourced (40), the subsample of participants

TABLE 4 Correlation coefficients for sleep and inhibition as reflected by the amplitude of Pd3, at Fz.

	Sad		Neutral		Happy	
	r	*P*	*r*	*P*	*r*	*P*
Sleep latency (min)	−0.03	0.927	0.02	0.954	−0.16	0.658
REM latency (min)	0.09	0.811	−0.59	0.071	−0.29	0.419
Total sleep time (min)	0.33	0.357	0.02	0.950	0.11	0.770
Sleep efficiency (%)	0.29	0.413	−0.03	0.927	−0.15	0.686
Absolute sleep stages (min)						
NREM1	−0.32	0.373	0.05	0.897	0.38	0.285
NREM2	−0.77**	0.010	−0.52	0.120	−0.52	0.123
NREM3	0.64*	0.045	0.27	0.449	0.15	0.676
REM	−0.15	0.684	−0.02	0.952	0.16	0.661
Relative sleep stages (%)						
NREM1	−0.32	0.363	0.07	0.849	0.40	0.258
NREM2	−0.71*	0.022	−0.42	0.233	−0.46	0.179
NREM3	0.62	0.055	0.26	0.471	0.15	0.687
REM	−0.20	0.584	−0.01	0.984	0.15	0.683

**Correlation significant at the 0.01 level (2-tailed).

*Correlation significant at the 0.05 level (2-tailed).

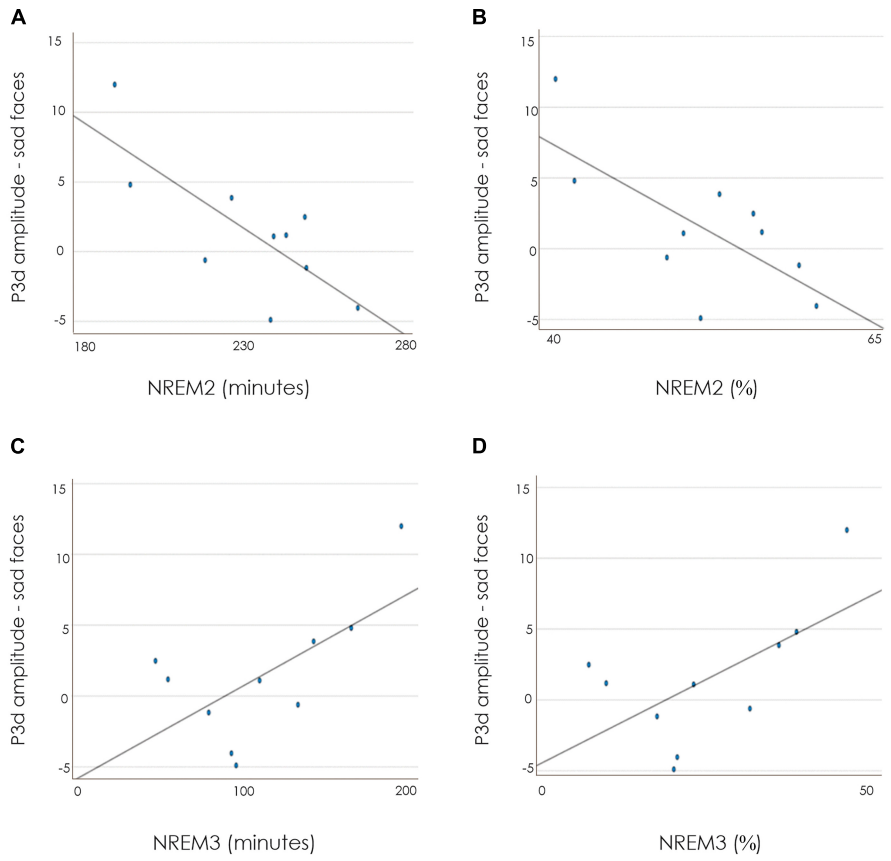

FIGURE 2
Correlation plots between the amplitude of the P3d to sad faces (at Fz) and NREM2 in minutes **(A)**; NREM in percentage **(B)**; NREM3 in minutes **(C)**; NREM3 in percentage **(D)**.

included in the current report showed no evidence that conflict monitoring in the early stages of inhibition processing (as reflected by the N2 ERP) varied across emotional conditions. However, the P3 (reflecting later stages of inhibition processing) was significantly larger for negative compared to positive stimuli. This larger P3 could suggest that suicidal adolescents require more neural resources dedicated to withholding a response to negative stimuli compared to positive stimuli. It is important to note that, this larger P3 elicited by negative stimuli compared to neutral or positive stimuli was accompanied by lower inhibition response accuracy. It is thus possible that the extent of neural resources dedicated to the inhibition of negative stimuli was not sufficient to maintain performance levels similar to those observed for positive and neutral stimuli. Overall, the subsample included in the current report had similar performance and ERP profiles than the larger sample of suicidal adolescents included in our previous report (40).

Association between emotionally charged inhibition and sleep

The novel findings issued from the present report are that inhibition behaviors and underlying neural processes are associated with the extent of sleep abnormalities occurring during a suicidal crisis. From a behavioral perspective, correlations between performance measures and sleep parameters revealed that increased REM pressure and indices of sleep disruptions correlated with poorer inhibition accuracy in the context of emotional processing. More specifically, shorter REM sleep latency and higher amounts of REM sleep were associated with increased failures to inhibit inappropriate response to stimuli with positive emotional valence. This profile of increased REM pressure is a characteristic feature of depression and suicidality in adults [for reviews, see (68, 69)]. Furthermore, higher nocturnal awakenings, a sleep feature previously linked to suicidal states in adolescents (70), were associated with more failures to inhibit inappropriate responses to stimuli with negative emotional valence. Hence, features of sleep alterations commonly emerging in the context of suicidality could possibly influence behavioral inhibition differentially according to the valence of the emotional context. This suggests that poor sleep may be a factor contributing to the difficulties to inhibit suicide-related cues previously reported in suicidal adolescents (30, 33).

These cognitive challenges emerging at the behavioral level co-occurred with signs of altered neural processing. Reduced P3d amplitudes elicited by negative stimuli correlated with higher levels of NREM2 and lower levels of NREM3. A reduced amplitude P3d indicates less differentiation in the amplitudes of the Go- and NoGo-P3 from the raw ERP waveforms and thus suggests that the inhibitory control processes associated with the NoGo-P3 are attenuated. It may be proposed that sleep-related alterations in the recruitment of neural resources for the inhibition of emotionally negative content may diminish the ability to inhibit intrusive suicidal thoughts. More specifically, shallower sleep may be associated with lower resources to inhibit intrusive, negative information.

Although causality cannot be inferred from the present study, these results align with previous experimental sleep deprivation studies demonstrating that sleep plays a casual role in cognitive functions (71, 72) and emotional regulation (73, 74). Notably, research has shown a complex interplay between sleep, emotions and cognition whereby poor sleep leads to increased emotional reactivity and impulsivity, while these daytime experiences can, in turn, affect sleep (75). The current results further reinforce previous knowledge that impaired sleep hampers cognitive inhibitory control (51), a phenomenon also highlighted in the ERP literature. For instance, research has shown a reduction in the amplitude of the P3 component on cognitive control tasks following sleep deprivation (76–78). Furthermore, research examining emotionally charged stimuli has shown enhanced amplitudes of P3/late positive complex (LPP) to negative stimuli following sleep deprivation (79). This suggests greater attention allocation to emotionally negative stimuli following sleep deprivation. It may be postulated that this could be one of the mechanisms *via* which sleep disturbances fuel impulsivity and increase the risk of enacting suicidal behaviors. Increased attention toward negative stimuli may result in an inability to attend to other relevant information. This may be especially problematic for suicidal adolescents who are vulnerable to emotional regulation difficulties. Furthermore, since alterations of inhibitory processes can affect emotional regulation (34), sleep-related alterations in cognitive processing could also indirectly hinder emotional management in the context of a suicidal crisis. Overall, the effects of poor sleep on both inhibitory processes and emotional regulation may heighten the risk for suicidal thoughts and behaviors in adolescents. Further research is warranted to investigate whether reductions in cognitive resources, as a result of disturbed sleep, could affect coping and resilience mechanisms, and ultimately lead to increased difficulties inhibiting suicidal thoughts and behaviors.

The results obtained in this study may also relate to maturational brain changes in the adolescent prefrontal cortex, a brain region highly involved in both inhibitory control (59, 63) and slow wave sleep (i.e., NREM3; 84). Firstly, synaptic pruning in the frontal cortex during adolescence may contribute to the alteration of neural resources available for inhibition processes (80). For instance, inhibition failures in emotional contexts could notably result from a competition

between heightened activity in subcortical emotional processing systems and immature top-down prefrontal systems (66, 81). Secondly, the maturational increase in NREM2 sleep (44) and decrease in NREM3 sleep (4, 44, 45) typically observed during adolescence, and commonly associated with adverse mental health states, may contributed to the shallower sleep profile associated with altered inhibition processing. During adolescence, considerable sex differences may influence sleep and inhibition alterations linked to suicidality. For instance, a previous study reported that, compared to their female counterparts, depressed male adolescents had more sleep disturbances characterized by a shorter REM sleep latency, more time spent in NREM1, and less NREM3, especially in the first NREM period (82). In addition, although healthy male adolescents tend to be more impulsive than healthy female adolescents (83), this trend does not seem to apply in depressed adolescents, suggesting that interactions between adverse mental health and sex-related developmental processes may influence impulsivity (84). Also, previous studies reported an association between depression symptoms severity and impulsivity in depressed male adolescents but not in depressed female adolescents (84, 85). The exploration of these sex-based variations may be especially helpful in the context of suicidality in adolescence, a period of sex-specific changes. Although the current study sample had a higher proportion of females and was too small to address this, future studies should assess potential sex differences in the relationship between sleep disturbances and cognitive challenges faced by suicidal adolescents.

Altogether, the combined patterns of performance and brain responses observed in the present study suggest that REM sleep and nocturnal awakenings may be linked to overt inhibition failures during emotional processing, whereas the depth of NREM sleep may be linked to the underlying neural resources involved in emotionally tainted inhibition processing. Overall, suicidal adolescents with lighter sleep may have less neural resources available to inhibit negative intrusive thoughts. This calls for further work assessing whether increased impulsivity following sleep disruptions, particularly in the face of negative emotional information, may increase the risk of enacting suicide behaviors.

Limitations

This study presents certain limitations. Firstly, the sample size was limited by challenges inherent to this vulnerable population. This small sample size notably prevented the use of multiple regression and sex-based analyses. Nonetheless, previous studies examining the P3 component in depressed and suicidal participants have used similar sample sizes (86–90).

Furthermore, females were overrepresented in this sample (i.e., 80% of all participants). This aligns with expected sex differences in youth hospitalized for suicidal crisis, since it has been estimated that between 10 and 19 years of age, females are 4 times more likely to attempt suicide than males (91). Nevertheless, these sex difference may be influenced by biases inherent to help-seeking behaviors and hospitalizations, and there is a need to further investigate suicidality in adolescent males.

Additionally, the present study cannot dissociate the effects of suicidality from those of depression or other psychiatric comorbidities. Also, this sample was mostly medicated with drugs likely to influence both sleep and ERPs. Nevertheless, depression, comorbidities, and psychotropic medications are highly common in adolescents with suicidal behavior and as such, the results obtained from the present study are likely to be representative of this population.

Considering the high variability in sleep profiles previously observed in youth with mental disorders (6), a single night of polysomnography does not capture potential changes in sleep patterns. Furthermore, the sleep profiles recorded in this study confounds the state of a suicidal crisis with the context of sleeping in a foreign environment. Alterations in sleep patterns could present themselves differently when individuals are sleeping in an inpatient ward compared to when they are sleeping at home. Nonetheless, this study provides a first glimpse of the interaction between cognitive processes and objective sleep metrics within a psychiatric ward, which enables a better understanding of the clinical journey of these individuals.

Although the aim of the present study was to investigate sleep and inhibition control in adolescents with known suicide attempts, future work should assess this association in adolescents who may be at risk, but have not yet attempted suicide. Notably, subsequent longitudinal investigations are required to identify if sleep-related changes in inhibitory control may precede worsening suicidal thoughts and behaviors.

Conclusion

The present results highlight the relationship between emotionally charged inhibitory control and sleep architecture in adolescents facing a suicidal crisis. This unveils potential mechanisms *via* which poor sleep could possibly worsen neurocognitive processes involved in suicidality. Although they need to be replicated in larger samples, these findings stress the importance of future sleep intervention studies in suicidal youth. Notably, there is a need to assess whether strategies such as adapted pharmacotherapy, psychotherapy, creating a restful environment, limiting daytime naps, and increasing daytime activities could be beneficial to improve sleep, with potential downstream effects on cognitive inhibition that could translate

in better management of suicidal ideations and behaviors in hospitalized adolescents.

Data availability statement

Proposals to access data from this study can be submitted to the corresponding author and may be made available upon data sharing agreement.

Ethics statement

This study was reviewed and approved by the University of Ottawa's Health and Sciences Research Ethics Board and the Children's Hospital of Eastern Ontario Research Institute's Research Ethics Board. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

AB, JD, and RR contributed to the rationale and the design of the study. PT and ML wrote the manuscript. AB carried out the psychiatric assessments. PT and RR contributed to the data collection. PT, ML, RR, and MP conducted analysis of the data. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.920789/full#supplementary-material

References

1. World Health Organization. *An Implementation Guide for Suicide Prevention in Countries*. Geneva: World Health Organization (2021).

2. World Health Organization. *Adolescent Mental Health [Internet]*. (2021). Available online at: https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health (accessed January 23, 2021).

3. Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics.* (2003) 111:302–7. doi: 10.1542/peds.111.2.302

4. Gaudreau H, Carrier J, Montplaisir J. Age-related modifications of NREM sleep EEG: from childhood to middle age. *J Sleep Res.* (2001) 10:165–72. doi: 10.1046/j.1365-2869.2001.00252.x

5. Wright L, Kutcher S. *Adolescent Brain Development. Colloquium Series on The Developing Brain*. (Vol. 5). San Rafael, CA: Morgan & Claypool Publishers LLC (2016). p. 1–104. doi: 10.4199/C00133ED1V01Y201602DBR012

6. Robillard R, Hermens DF, Naismith SL, White D, Rogers NL, Ip TKC, et al. Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders. *J Psychiatry Neurosci.* (2015) 40:28–37. doi: 10.1503/jpn.130247

7. Forbes EE, Bertocci MA, Gregory AM, Ryan ND, Axelson DA, Birmaher B, et al. Objective sleep in pediatric anxiety disorders and major depressive disorder. *J Am Acad Child Adolesc Psychiatry.* (2008) 47:148–55. doi: 10.1097/chi.0b013e31815cd9bc

8. Roybal DJ, Chang KD, Chen MC, Howe ME, Gotlib IH, Singh MK. Characterization and factors associated with sleep quality in adolescents with bipolar I disorder. *Child Psychiatry Hum Dev.* (2011) 42:724–40. doi: 10.1007/s10578-011-0239-0

9. Bernert RA, Joiner TE, Joiner T. Sleep disturbances and suicide risk: a review of the literature. *Neuropsychiatr Dis Treat.* (2007) 3:735–43. doi: 10.2147/NDT.S1248

10. Drapeau C, Nadorff M. Suicidality in sleep disorders: prevalence, impact, and management strategies. *Nat Sci Sleep.* (2017) 9:213–26. doi: 10.2147/NSS.S125597

11. Bernert RA, Kim JS, Iwata NG, Perlis ML. Sleep disturbances as an evidence-based suicide risk factor. *Curr Psychiatry Rep.* (2015) 17:15. doi: 10.1007/s11920-015-0554-4

12. Goldstein TR, Bridge JA, Brent DA. Sleep disturbance preceding completed suicide in adolescents. *J Consult Clin Psychol.* (2008) 76:84–91. doi: 10.1037/0022-006X.76.1.84

13. Hawton K, van Heeringen K. Suicide. *Lancet.* (2009) 373:1372–81. doi: 10.1016/S0140-6736(09)60372-X

14. Høier NK, Madsen T, Spira AP, Hawton K, Eriksen Benros M, Nordentoft M, et al. Association between hospital-diagnosed sleep disorders and suicide: a nationwide cohort study. *Sleep.* (2022) 45:zsac069. doi: 10.1093/sleep/zsac069

15. Wojnar M, Ilgen MA, Wojnar J, McCammon RJ, Valenstein M, Brower KJ. Sleep problems and suicidality in the National Comorbidity Survey Replication. *J Psychiatr Res.* (2009) 43:526–31. doi: 10.1016/j.jpsychires.2008.07.006

16. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry.* (2012) 73:e1160-7. doi: 10.4088/JCP.11r07586

17. Sarchiapone M, Mandelli L, Carli V, Iosue M, Wasserman C, Hadlaczky G, et al. Hours of sleep in adolescents and its association with anxiety, emotional concerns, and suicidal ideation. *Sleep Med.* (2014) 15:248–54. doi: 10.1016/j.sleep.2013.11.780

18. Liu X. Sleep and adolescent suicidal behavior. *Sleep.* (2004) 27:1351–8. doi: 10.1093/sleep/27.7.1351

19. Anderson C, Platten CR. Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. *Behav Brain Res.* (2011) 217:463–6. doi: 10.1016/j.bbr.2010.09.020

20. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological dysfunction in depressed suicide attempters. *Am J Psychiatry.* (2001) 158:735–41. doi: 10.1176/appi.ajp.158.5.735

21. Medeiros T, Lopes E, Macedo G, Monteiro L. Coping, executive functioning, inhibitory control and decision-making in a sample of depressed suicidal patients. *Clin Biomed Res.* (2014) 34:287–96.

22. Miranda R, Gallagher M, Bauchner B, Vaysman R, Marroquín B. Cognitive inflexibility as a prospective predictor of suicidal ideation among young adults with a suicide attempt history. *Depress Anxiety.* (2012) 29:180–6. doi: 10.1002/da.20915

23. Loyo Sánchez LM, Salvador Martínez-Velázquez E, Ramos-Loyo J. Influence of emotions on executive functions in suicide attempters. *Suicidol Online.* (2013) 4:42–55.

24. Rey-Mermet A, Singh KA, Gignac GE, Brydges CR, Ecker UKH. Interference control in working memory: evidence for discriminant validity between removal and inhibition tasks. *PLoS One.* (2020) 15:e0243053. doi: 10.1371/journal.pone.0243053

25. Malhi GS, Das P, Outhred T, Gessler D, John Mann J, Bryant R. Cognitive and emotional impairments underpinning suicidal activity in patients with mood disorders: an fMRI study. *Acta Psychiatr Scand.* (2019) 139:454–63. doi: 10.1111/acps.13022

26. Richard-Devantoy S, Gorwood P, Annweiler C, Olié JP, le Gall D, Beauchet O. Suicidal behaviours in affective disorders: a defcit of cognitive inhibition? *Can J Psychiatry.* (2012) 57:254–62. doi: 10.1177/070674371205700409

27. Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clin Psychol Rev.* (2006) 26:379–95. doi: 10.1016/j.cpr.2006.01.001

28. Kamphuis J, Dijk DJ, Spreen M, Lancel M. The relation between poor sleep, impulsivity and aggression in forensic psychiatric patients. *Physiol Behav.* (2014) 123:168–73. doi: 10.1016/j.physbeh.2013.10.015

29. Zhu J, Jiang Y, Chen Y, Huang L, Bao Z, Zhang W. High impulsivity, low self-control and problematic mobile phone use: the effect of poor sleep quality. *Curr Psychol.* (2021) 40:3265–71. doi: 10.1007/s12144-019-00259-0

30. Cha CB, Najmi S, Park JM, Finn CT, Nock MK. Attentional bias toward suicide-related stimuli predicts suicidal behavior. *J Abnorm Psychol.* (2010) 119:616–22. doi: 10.1037/a0019710

31. Becker ES, Strohbach D, Rinck MA. Specific attentional bias in suicide attempters. *J Nerv Ment Dis.* (1999) 187:730–5. doi: 10.1097/00005053-199912000-00004

32. Lynch TR, Cheavens JS, Morse JQ, Rosenthal MZ. A model predicting suicidal ideation and hopelessness in depressed older adults: the impact of emotion inhibition and affect intensity. *Aging Ment Health.* (2004) 8:486–97. doi: 10.1080/13607860412331303775

33. Richard-Devantoy S, Ding Y, Turecki G, Jollant F. Attentional bias toward suicide-relevant information in suicide attempters: a cross-sectional study and a meta-analysis. *J Affect Disord.* (2016) 196:101–8. doi: 10.1016/j.jad.2016.02.046

34. Joormann J. Cognitive inhibition and emotion regulation in depression. *Curr Direct Psychol Sci.* (2010) 19:161–6. doi: 10.1177/0963721410370293

35. Joormann J, Siemer M, Gotlib IH. Mood regulation in depression: differential effects of distraction and recall of happy memories on sad mood. *J Abnorm Psychol.* (2007) 116:484–90. doi: 10.1037/0021-843X.116.3.484

36. Kudinova AY, Owens M, Burkhouse KL, Barretto KM, Bonanno GA, Gibb BE. Differences in emotion modulation using cognitive reappraisal in individuals with and without suicidal ideation: an ERP study. *Cognit Emot.* (2016) 30:999–1007. doi: 10.1080/02699931.2015.1036841

37. Rajappa K, Gallagher M, Miranda R. Emotion dysre.gulation and vulnerability to suicidal ideation and attempts. *Cogn Ther Res.* (2012) 36:833–9. doi: 10.1007/s10608-011-9419-2

38. Falkenstein M, Hoormann J, Hohnsbein J. ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychol.* (1999) 101:267–91. doi: 10.1016/S0001-6918(99)00008-6

39. Albanese BJ, Macatee RJ, Gallyer AJ, Stanley IH, Joiner TE, Schmidt NB. Impaired conflict detection differentiates suicide attempters from ideating nonattempters: evidence from event-related potentials. *Biol Psychiatry.* (2019) 4:902–12. doi: 10.1016/j.bpsc.2019.05.015

40. Porteous M, Tavakoli P, Campbell K, Dale A, Boafo A, Robillard R. Emotional modulation of response inhibition in adolescents during acute suicidal crisis: event-related potentials in an emotional Go/NoGo task. *Clin EEG Neurosci.* (2021) [Online ahead of print].. doi: 10.1177/15500594211063311

41. Allen KJD, Hooley JM. Inhibitory control in people who self-injure: evidence for impairment and enhancement. *Psychiatry Res.* (2015) 225:631–7. doi: 10.1016/j.psychres.2014.11.033

42. Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. The neural basis of mood-congruent processing biases in depression. *Arch General Psychiatry.* (2002) 59:597. doi: 10.1001/archpsyc.59.7.597

43. Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta-analysis of age, region, and sleep. *Sleep Med.* (2011) 12:110–8. doi: 10.1016/j.sleep.2010.11.008

44. Jenni OG, Carskadon MA. Spectral analysis of the sleep electroencephalogram during adolescence. *Sleep.* (2004) 27:774–83.

45. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep.* (2004) 27:1255–73. doi: 10.1093/sleep/27.7.1255

46. Robillard R, Naismith SL, Smith KL, Rogers NL, White D, Terpening Z, et al. Sleep-wake cycle in young and older persons with a lifetime history of mood disorders. *PLoS One* (2014) 9:e87763. doi: 10.1371/journal.pone.0087763

47. Taillard J, Sagaspe P, Philip P, Bioulac S. Sleep timing, chronotype and social jetlag: impact on cognitive abilities and psychiatric disorders. *Biochem Pharmacol.* (2021) 191:114438. doi: 10.1016/j.bcp.2021.114438

48. Dahl RE, Puig-Antich J, Ryan ND, Nelson B, Dachille S, Cunningham SL, et al. EEG sleep in adolescents with major depression: the role of suicidality and inpatient status. *J Affect Disord.* (1990) 19:63–75. doi: 10.1016/0165-0327(90)90010-6

49. Boafo A, Armitage R, Greenham S, Tavakoli P, Dale A, Nixon A, et al. Sleep architecture in adolescents hospitalized during a suicidal crisis. *Sleep Med.* (2019) 56:41–6. doi: 10.1016/j.sleep.2018.12.018

50. McCracken JT, Poland RE, Lutchmansingh P, Edwards C. Sleep electroencephalographic abnormalities in adolescent depressives: effects of scopolamine. *Biol Psychiatry.* (1997) 42:577–84. doi: 10.1016/S0006-3223(96)00431-3

51. Rossa KR, Smith SS, Allan AC, Sullivan KA. The effects of sleep restriction on executive inhibitory control and affect in young adults. *J Adolesc Health.* (2014) 55:287–92. doi: 10.1016/j.jadohealth.2013.12.034

52. Kovacs M. Children's depression inventory (CDI and CDI 2. In: Cautin RL, Lilienfeld SO editors. *The Encyclopedia of Clinical Psychology*. Hoboken, NJ: John Wiley & Sons, Inc (2015). p. 1–5. doi: 10.1002/9781118625392.wbecp419

53. Reynolds WM. *Suicidal Ideation Questionnaire-Junior*. Odessa, FL: Psychological Assessment Resources (1987).

54. Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The suicidal behaviors questionnaire-revised (SBQ-R):validation with clinical and nonclinical samples. *Assessment.* (2001) 8:443–54. doi: 10.1177/107319110100800409

55. Reynolds WM, Mazza JJ. Assessment of suicidal ideation in inner-city children and young adolescents: reliability and validity of the suicidal ideation questionnaire-JR. *Sch Psychol Rev.* (1999) 28:17–30. doi: 10.1080/02796015.1999.12085945

56. Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger MM, Hirshkowitz, et al. The visual scoring of sleep in adults. *J Clin Sleep Med.* (2007). 3:121–31.

57. Chaumon M, Bishop DVM, Busch NA. A practical guide to the selection of independent components of the electroencephalogram for artifact correction. *J Neurosci Methods.* (2015) 250:47–63. doi: 10.1016/j.jneumeth.2015.02.025

58. Falkenstein M, Hoormann J, Hohnsbein J. Inhibition-related ERP components: variation with modality, age, and time-on-task. *J Psychophysiol.* (2002) 16:167–75. doi: 10.1027//0269-8803.16.3.167

59. Luciana M, Bjork JM, Nagel BJ, Barch DM, Gonzalez R, Nixon SJ, et al. Adolescent neurocognitive development and impacts of substance use: overview of the adolescent brain cognitive development (ABCD) baseline neurocognition battery. *Dev Cognit Neurosci.* (2018) 32:67–79. doi: 10.1016/j.dcn.2018.02.006

60. Arnett JJ. Adolescent storm and stress, reconsidered. *Am Psychol.* (1999) 54:317–26. doi: 10.1037/0003-066X.54.5.317

61. Kilford EJ, Garrett E, Blakemore SJ. The development of social cognition in adolescence: an integrated perspective. *Neurosci Biobehav Rev.* (2016) 70:106–20. doi: 10.1016/j.neubiorev.2016.08.016

62. Tottenham N, Hare TA, Casey BJ. Behavioral assessment of emotion discrimination, emotion regulation, and cognitive control in childhood, adolescence, and adulthood. *Front Psychol.* (2011):2:39. doi: 10.3389/fpsyg.2011.00039

63. Blakemore SJ, Choudhury S. Development of the adolescent brain: implications for executive function and social cognition. *J Child Psychol Psychiatry.* (2006) 47:296–312. doi: 10.1111/j.1469-7610.2006.01611.x

64. Constantinidis C, Luna B. Neural substrates of inhibitory control maturation in adolescence. *Trends Neurosci.* (2019) 42:604–16. doi: 10.1016/j.tins.2019.07.004

65. Lo SL. A meta-analytic review of the event-related potentials (ERN and N2) in childhood and adolescence: providing a developmental perspective on the conflict monitoring theory. *Dev Rev.* (2018) 48:82–112. doi: 10.1016/j.dr.2018.03.005

66. Luna B, Thulborn KR, Munoz DP, Merriam EP, Garver KE, Minshew NJ, et al. Maturation of widely distributed brain function subserves cognitive development. *Neuroimage.* (2001) 13:786–93. doi: 10.1006/nimg.2000.0743

67. Aral A, Say GN, Gerdan G, Usta MB, Aral AE. The role of sociodemographic, clinical and neuropsychological variables in suicide attempts in depressed adolescents. *Arch Neuropsychiatry.* (2020) 57:312–7.

68. Riemann D, Krone LB, Wulff K, Nissen C. Sleep, insomnia, and depression. *Neuropsychopharmacology.* (2020) 45:74. doi: 10.1038/s41386-019-0411-y

69. Steiger A, Pawlowski M. Depression and sleep. *Int J Mol Sci.* (2019) 20:607. doi: 10.3390/ijms20030607

70. Lopes M, Boronat AC, Wang Y, Fu IL. Sleep complaints as risk factor for suicidal behavior in severely depressed children and adolescents. *CNS Neurosci Therapeut.* (2016) 22:915–20. doi: 10.1111/cns.12597

71. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull.* (2010) 136:375–89. doi: 10.1037/a0018883

72. Killgore WDS. Effects of sleep deprivation on cognition. *Progr Brain Res.* (2010) 185:105–29. doi: 10.1016/B978-0-444-53702-7.00007-5

73. Kahn M, Sheppes G, Sadeh A. Sleep and emotions: bidirectional links and underlying mechanisms. *Int J Psychophysiol.* (2013) 89:218–28. doi: 10.1016/j.ijpsycho.2013.05.010

74. Palmer CA, Alfano CA. Sleep and emotion regulation: an organizing, integrative review. *Sleep Med Rev.* (2017) 31:6–16. doi: 10.1016/j.smrv.2015.12.006

75. Gruber R, Cassoff J. The interplay between sleep and emotion regulation: conceptual framework empirical evidence and future directions. *Curr Psychiatry Rep.* (2014) 16:500. doi: 10.1007/s11920-014-0500-x

76. Kusztor A, Raud L, Juel BE, Nilsen AS, Storm JF, Huster RJ. Sleep deprivation differentially affects subcomponents of cognitive control. *Sleep.* (2019) 42:zsz016. doi: 10.1093/sleep/zsz016

77. Jin X, Ye E, Qi J, Wang L, Lei Y, Chen P, et al. Recovery sleep reverses impaired response inhibition due to sleep restriction: evidence from a visual event related potentials study. *PLoS One* (2015) 10:e0142361. doi: 10.1371/journal.pone.0142361

78. Xu L, Song T, Peng Z, Dai C, Wang L, Shao Y, et al. Acute sleep deprivation impairs motor inhibition in table tennis athletes: an ERP study. *Brain Sci.* (2022) 12:746. doi: 10.3390/brainsci12060746

79. Cote K, Jancsar C, Hunt B. Event-related neural response to emotional picture stimuli following sleep deprivation. *Psychol Neurosci.* (2015) 8:102–13. doi: 10.1037/h0100354

80. Gorgoni M, D'Atri A, Scarpelli S, Reda F, de Gennaro L. Sleep electroencephalography and brain maturation: developmental trajectories and the relation with cognitive functioning. *Sleep Med.* (2020) 66:33–50. doi: 10.1016/j.sleep.2019.06.025

81. Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ. Biological substrates of emotional reactivity and regulation in adolescence during an emotional Go-Nogo Task. *Biol Psychiatry.* (2008) 63:927–34. doi: 10.1016/j.biopsych.2008.03.015

82. Robert JJT, Hoffman RF, Emslie GJ, Hughes C, Rintelmann J, Moore J, et al. Sex and age diferrences in sleep macroarchitecture in childhood and adolescent depression. *Sleep.* (2006) 29:351–8. doi: 10.1093/sleep/29.3.351

83. Chapple CL, Johnson KA. Gender differences in impulsivity. *Youth Viol Juvenile Justice.* (2007) 5:221–34. doi: 10.1177/1541204007301286

84. Royuela-Colomer E, Fernández-González L, Orue I. Longitudinal associations between internalizing symptoms, dispositional mindfulness, rumination and impulsivity in adolescents. *J Youth Adolesc.* (2021) 50:2067–78. doi: 10.1007/s10964-021-01476-2

85. Regan T, Harris B, Fields SA. Are relationships between impulsivity and depressive symptoms in adolescents sex-dependent? *Heliyon.* (2019) 5:e02696. doi: 10.1016/j.heliyon.2019.e02696

86. Hansenne M, Pitchot W, Gonzalez Moreno A, Zaldua IU, Ansseau M. Suicidal behavior in depressive related potential study disorder: an event. *Biol Psychiatry.* (1996) 40:116–22. doi: 10.1016/0006-3223(95)00372-X

87. Tavakoli P, Boafo A, Jerome E, Campbell K. Active and passive attentional processing in adolescent suicide attempters: an event-related potential study. *Clin EEG Neurosci.* (2021) 52:29–37. doi: 10.1177/1550059420933086

88. Tavakoli P, Boafo A, Dale A, Robillard R, Greenham SL, Campbell K. Event-related potential measures of attention capture in adolescent inpatients with acute suicidal behavior. *Front Psychiatry.* (2018) 9:85. doi: 10.3389/fpsyt.2018.00085

89. Hansenne M, Pitchot W, Moreno AG, Torrecilas JG, Mirel J, Ansseau M. Psychophysiological correlates of suicidal behavior in depression. A preliminary study. *Neuropsychobiology.* (1994) 30:1–3. doi: 10.1159/000119125

90. Jandl M, Steyer J, Kaschka WP. Suicide risk markers in major depressive disorder: a study of electrodermal activity and event-related potentials. *J Affect Disord.* (2010) 123:138–49. doi: 10.1016/j.jad.2009.09.011

91. Government of Canada. *Suicide in Canada: Key Statistics (Infographic) [Internet]*. (2020). Available online at: https://www.canada.ca/en/public-health/services/publications/healthy-living/suicide-canada-key-statistics-infographi tml (accessed January 23, 2022).

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Investigating the effects of sleep and sleep loss on the different stages of episodic emotional memory: A narrative review and guide to the future

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For two decades, sleep has been touted as one of the primary drivers for the encoding, consolidation, retention, and retrieval of episodic emotional memory. Recently, however, sleep's role in emotional memory processing has received renewed scrutiny as meta-analyses and reviews have indicated that sleep may only contribute a small effect that hinges on the content or context of the learning and retrieval episodes. On the one hand, the strong perception of sleep's importance in maintaining memory for emotional events may have been exacerbated by publication bias phenomena, such as the "winner's curse" and "file drawer problem." On the other hand, it is plausible that there are sets of circumstances that lead to consistent and reliable effects of sleep on emotional memory; these circumstances may depend on factors such as the placement and quality of sleep relative to the emotional experience, the content and context of the emotional experience, and the probes and strategies used to assess memory at retrieval. Here, we review the literature on how sleep (and sleep loss) influences each stage of emotional episodic memory. Specifically, we have separated previous work based on the placement of sleep and sleep loss in relation to the different stages of emotional memory processing: (1) prior to encoding, (2) immediately following encoding during early consolidation, (3) during extended consolidation, separated from initial learning, (4) just prior to retrieval, and (5) post-retrieval as memories may be restructured and reconsolidated. The goals of this review are three-fold: (1) examine phases of emotional memory that sleep may influence to a greater or lesser degree, (2) explicitly identify problematic overlaps in traditional sleep–wake study designs that are preventing the ability to better disentangle the potential role of sleep in the different stages of emotional memory processing, and (3) highlight areas for future research by identifying the stages of emotional memory processing in which the effect of sleep and sleep loss remains under-investigated. Here,

we begin the task of better understanding the contexts and factors that influence the relationship between sleep and emotional memory processing and aim to be a valuable resource to facilitate hypothesis generation and promote important future research.

KEYWORDS

sleep, emotion, memory, consolidation, retrieval, encoding, reconsolidation, emotional memory

Introduction

For nearly 100 years, investigators have researched sleep in the context of memory performance (Jenkins and Dallenbach, 1924; Ekstrand, 1967). Substantial evidence over this time has indicated that sleep before and after both learning and retrieval benefits multiple forms of declarative and non-declarative memories compared to matched periods of active wakefulness or sleep deprivation (Stickgold, 2005; Walker and Stickgold, 2006; Stickgold and Walker, 2007; Walker, 2008; Alger et al., 2014), though the exact mechanisms underlying this effect continue to be debated (see Nadel et al., 2000; Hobson and Pace-Schott, 2002; Ellenbogen et al., 2006; Squire et al., 2015; Yonelinas et al., 2019; Zadra and Stickgold, 2021). Around the turn of the millennium, an interest in the role of sleep in the preferential processing, retention, and retrieval of emotional episodic memories developed and continues on through today. Specifically, a series of notable studies indicated sleep, and perhaps rapid eye movement (REM) sleep in particular, retains or enhances memory for arousing or emotional information above and beyond neutral information of the same kind (e.g., words, pictures, etc.; Wagner, 2001; Hu et al., 2006; Holland and Lewis, 2007; Nishida et al., 2009).

More recently, however, a series of comprehensive meta-analyses and reviews exploring this preferential processing of emotional content during sleep, perhaps considered settled science by many, have called this effect into question (Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021). With regard to the purported benefit that sleep during the early consolidation period has on the specific retention of emotional information, a recent sweeping review of the literature revealed that while a few studies do support this effect, the majority of studies *do not* support an interaction between sleep and emotion on long-term declarative memory processing (Davidson et al., 2021). In an effort to prevent the loss of the baby with the bathwater, rather than arguing against the role of sleep in emotional memory processing entirely, this review and others have noted a list of factors that need to be taken into consideration and controlled for in a stepwise manner in future research that will ultimately help to reveal the strength and limitations of this effect. These include factors such as the placement and quality of sleep in relation to the encoding, consolidation and retrieval of an emotional memory; the amount of time that has passed between encoding and retrieval; the content, context, and intensity of an emotional experience or stimuli; the types of probes and strategies used to assess memory at retrieval; whether there is pre- as well as post-sleep testing; the type of sleep manipulation employed (e.g., nap vs. full nights of sleep); and the macro- and microarchitecture of the studied sleep period (Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021).

The goal of the present review is to initiate this deeper exploration of the relationship between sleep and emotional memory processing by outlining the current state of the literature with regard to just one of the factors noted above: the *placement* of sleep (or sleep loss) in relation to the encoding, consolidation and retrieval of an emotional memory (i.e., when does the manipulated sleep period occur with relation to the different phases of memory processing). To do so, we have identified and defined five different stages during which sleep can be manipulated that may have overlapping or distinct effects on the formation, evolution, and retrieval of an emotional memory (see **Box 1** and **Figure 1**):

(1) Prior to encoding emotional information[1],

(2) Immediately following encoding during early consolidation,

(3) During extended consolidation away from initial learning,

(4) Just prior to retrieval of emotional memory[2], and

(5) Post-retrieval as an emotional memory may be restructured and reconsolidated.

We briefly review some of the previous literature that falls primarily under each category with the hope of shedding light on how sleep influences may differ in strength across these five stages. Perhaps more importantly, however, the additional objectives of this review are to (1) identify problematic overlaps between memory stages in commonly used sleep and emotional memory protocols and make suggestions to prioritize certain study designs in the future that will provide the opportunity to better disentangle the distinct role of sleep at each phase of

1 Of course, manipulations of sleep pre-encoding can also be considered to affect the encoding phase itself (i.e., someone who is sleep-deprived pre-encoding enters the encoding phase in that state).

2 As with pre-encoding manipulations, sleep manipulations that occur just prior to retrieval will necessarily affect the retrieval phase itself.

BOX 1 Operationalized definitions for each phase of emotional memory processing that may be influenced by sleep.

Pre-encoding	The period prior to the encoding of emotional information or the experience of an emotional event.
Early consolidation	The period just following encoding of an emotional event, during which memories are thought to be highly labile and susceptible to additional modulation via factors such as sleep and stress. The precise amount of time that this period lasts before it enters into the next phase (extended consolidation) remains an open question, especially with regard to emotional memories.
Extended consolidation	Any additional consolidation processing that occurs to a memory after it transitions from its labile state during the early consolidation phase into a more stable memory trace. This phase of memory processing extends all the way until the memory is retrieved, reactivated, or forgotten.
Pre-retrieval	The period just prior to the activation of a memory trace in response to a cue to call to mind a specific item or event or to perform a specific task (i.e., the period just prior to memory testing)
Post-retrieval/reconsolidation	Immediately after a memory is retrieved or reactivated it enters the reconsolidation phase of memory processing, during which it returns to a labile state that again makes it more prone to influence, modulation, and forgetting, much like the period of early consolidation. This phase can lead to updates to an already-existing memory trace or can lead to the creation of an additional memory trace that may interfere with the originally created trace. Similar to the early consolidation period, the exact amount of time that a memory spends in this labile phase post-retrieval remains an open investigation.

emotional memory processing[3] (see **Box 2** for a demonstration), and (2) highlight areas for future research by identifying the stages of emotional memory processing that remain under-investigated with respect to their relationship with sleep.

Of note, while the primary focus of this review is emotional episodic memory processing in humans, some of the identified stages of memory processing remain nearly or entirely unexplored in the context of human sleep. In these instances, examples from the animal literature are used to provide readers with the extent of our current knowledge and in the hopes of inspiring additional research. It is important to acknowledge, however, that emotional episodic memory in humans and animal models of "emotional memory" – typically fear conditioning – may be vastly different in both expression and underlying mechanisms. We also limited the scope of our review here specifically to the effect of sleep at each stage of long-term episodic memory processing for emotional vs. neutral information. This is not because we think that the placement of sleep is disproportionately important for emotional episodic memories: Substantial evidence suggests that other forms of declarative and non-declarative memories may also be affected by when sleep is present (Stickgold et al., 2000; Fischer et al., 2002; Walker et al., 2002, 2003; Stickgold, 2005; Walker and Stickgold, 2005). However, the role of sleep in emotional memory processing may have particular clinical relevance. Remembering negative events that we experience can be critically important to our ability to make adaptive decisions and even to survive, but it can be detrimental to re-experience too much emotion and stress each time these past events are recalled. It has been hypothesized that sleep helps to protect or boost memory for the content of an emotional experience while simultaneously allowing for or assisting with the reduction in emotional tone associated with the event (Walker and van Der Helm, 2009; Goldstein and Walker, 2014). As such, it has been suggested that sleep not only plays a critical part in the healthy processing of our day-to-day emotional experiences, but also of traumatic experiences as well (Walker and van Der Helm, 2009; Tempesta et al., 2010; van der Helm et al., 2011; Motomura et al., 2013; Stickgold and Walker, 2013; Cunningham et al., 2014a; Goldstein and Walker, 2014; Thormar et al., 2014; Harrington and Cairney, 2021; Zeng et al., 2021). Regardless of the severity of the emotional experience, this adaptive processing is thought to be highly beneficial for our overall well-being and mental health (Walker and van Der Helm, 2009; Cunningham et al., 2014b; Cunningham and Payne, 2017). This theory is in striking contrast to a separate line of research that has suggested depriving sleep following a traumatic experience with the goal of preventing the onset of PTSD symptoms (Kuriyama et al., 2010; Cohen et al., 2017). The juxtaposition between these competing theories is apparent and of potentially grave importance. Thus, while our goal here is to initially promote future research aimed at taking a dedicated, stepwise approach to determining how sleep affects each phase of emotional episodic memory processing, ultimately we believe this treatment should be extended to all forms of human memory consolidation.

3 Critically, in most cases there is no "perfect" study design in which all sleep and circadian influences are entirely limited to a single stage of emotional memory processing. Our goal here is to motivate future work that makes intentional effort either to minimize the overlap between stages or to embed conditions that control for differences in stages that are not the intended target, with the ultimate goal of better understanding some of the influences that might account for the mixed findings in the field.

Process S vs. Process C

When considering the placement of sleep and wakefulness, it is important to note that more than just the order and proximity of the next sleep episode needs to be taken into consideration,

FIGURE 1
Schematic of the five stages of long-term episodic memory processing during which sleep can be manipulated: (1) prior to encoding, (2) immediately following encoding during early consolidation, (3) during extended consolidation away from initial learning, (4) just prior to retrieval of emotional memory, and (5) post-retrieval/reconsolidation.

BOX 2 Demonstration of the issue*.

Je'Rell is a budding graduate student interested in how sleep loss affects emotional memory consolidation. In his first study, Je'Rell had participants come into the sleep lab at 9pm. They were then either allowed a normal night of sleep or were totally sleep deprived. In the morning, Je'Rell had participants view negative and neutral scenes, and an hour later they completed a recognition memory test for the scenes. Je'Rell found that not only did sleep deprived participants have poorer memory overall, but that memory for both scene types deteriorated equally. Participants in the sleep condition, however, showed greater memory for the negative scenes compared to the neutral scenes. From this, Je'Rell concluded that sleep *prior to encoding* allows for the preferential memory processing of emotional over neutral information.

Excited, Je'Rell turned to his lab mate Hachirô to tell him the news but was only met with muted enthusiasm. Hachirô told Je'Rell that he too had just finished his study on sleep and emotional memory. In his study, Hachirô also had his participants come into the sleep lab at 9pm. However, Hachirô had his participants do the encoding of the negative and neutral scenes shortly after arriving that evening. Immediately following encoding, Hachirô's participants were either allowed a normal night of sleep or were totally sleep deprived. The next morning, participants also completed a recognition memory for the scenes. Just like Je'Rell, Hachirô found that participants in the sleep deprived group had poorer memory overall and that memory for both scene types deteriorated at the same rate, while those in the sleep condition showed better overall memory and a preference in memory for negative over neutral scenes. From this, Hachirô concluded that it was sleep during the *early consolidation* phase that was the critical process for the enhancement of emotional over neutral memories.

After heated debate over a number of pints and Diet Cokes, Je'Rell and Hachirô finally turned to the lab postdoc, Luisa, to settle the debate. Before they could, Luisa excitedly told them about her recent findings. In her study, Luisa had all of her participants view negative and neutral scenes at 9pm, followed by a normal night of sleep. Seventy-two hours later, Luisa had her participants return to the sleep lab and half of the participants were allowed a normal night of sleep while the other half were sleep deprived for the night. In the morning, the participants completed a recognition memory test for the scenes, and you guessed it. Once again, sleep deprived participants showed poorer retention for memory overall with both types of memory deteriorating at the same rate, while those that slept showed superior memory overall and enhanced memory for negative compared to neutral scenes. From this, Luisa concluded that sleep *prior to retrieval* was critical for the enhancement of emotional over neutral memories. The silence is deafening as the three friends look at each other. Who is right?

We would argue that across these scenarios, while none of the interpretations can be definitively determined to be incorrect, the study design used by Luisa allows us to be the most confident in her results, as she did the best job isolating the phase of memory that she was targeting (sleep and sleep loss prior to retrieval). In contrast, multiple phases of memory processing were affected in the study designs employed by Je'Rell (encoding, consolidation, retrieval) and Hachirô (consolidation, retrieval). While all three studies are helpful in developing our understanding of the contexts and circumstances that sleep and sleep loss can affect emotional memory performance, only Luisa's was designed in such a way that allows substantial confidence in the specific *stage* of emotional memory processing that was directly influenced.

*Note the results here are hypothetical to help illustrate our point and may not reflect the majority of the current state of the literature.

and this may be particularly true when emotional processing is involved. Two critical components that are inextricably embedded into every sleep and memory study are Process S and Process C (see **Figure 2**; Borbély and Achermann, 1999; Carskadon et al., 2004; Stiller and Postolache, 2005; Borbély, 2009). Process S (or Process H) refers to the homeostatic sleep pressure that builds up over time spent awake. From the moment we rise in the morning, Process S begins to accumulate until our next bout of sleep. This sleep-dependent process reflects the growing need to recover from the wear and tear of wakefulness through the buildup of sleep-promoting hormones, like adenosine, driving the need for sleep, and especially slow wave activity (SWA) during sleep, to restore optimal functioning (Carskadon et al., 2004; Landolt, 2008). Quite simply, the longer you are awake, the more your brain craves sleep.

Working in tandem with Process S is Process C. Process C is our internal body clock that is kept in sync with the Earth's ∼24-h cycle primarily via light exposure through the suprachiasmatic nucleus (SCN; Czeisler and Klerman, 1999; Carskadon et al., 2004; Mistlberger, 2005). Process C can favor sleep or wakefulness at different times of day depending on our own internal daily oscillations. In addition to promoting sleep and wakefulness, Process C exerts influence on a host of different endogenous physiological functions, including body temperature, metabolism, immune system function, and melatonin, cortisol, and other hormone production, just to name a few (Czeisler and Klerman, 1999; Carskadon et al., 2004). As demonstrated in **Figure 2**, under normal circumstances with a typically entrained circadian rhythm, Process C has a vastly different influence at 8am as compared to 8pm.

With regard to exploring the role of sleep in emotional memory processing, taking Process S and Process C into careful consideration may be even more critical than when investigating other forms of memory. This is because both extended periods of wakefulness (i.e., sleep deprivation) and different periods in our circadian rhythm have both been shown to affect cognitive

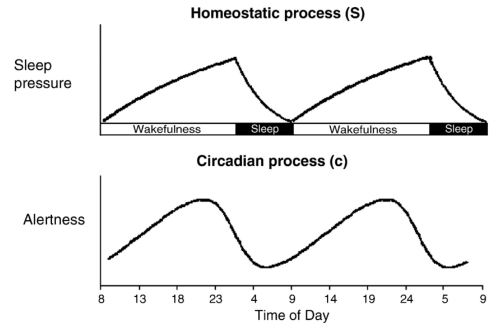

FIGURE 2
Process S is a sleep-dependent process that reflects the homeostatic sleep pressure that builds up linearly as long as we are awake (i.e., the extent of time that has passed since our previous bout of sleep). Process C is a sleep-independent process that reflects our internal daily rhythms kept in sync with the Earth's near 24-h cycle through the suprachiasmatic nucleus (SCN). Adapted from Stiller and Postolache (2005).

function (Dijk et al., 1992; Drummond et al., 2004; Durmer and Dinges, 2005; Blatter and Cajochen, 2007; Goel et al., 2009; Killgore, 2010; Lim and Dinges, 2010; Krause et al., 2017) and emotional perception (Paradee et al., 2008; Walker and van Der Helm, 2009; Kahn et al., 2013; McClung, 2013; Prather et al., 2013; Goldstein and Walker, 2014; Stolarski and Jankowski, 2015). If the expectation is that our emotion and memory systems interact in such a way that drives preferential long-term declarative memory for arousing over neutral information (van der Helm and Walker, 2011; Cunningham et al., 2014b; Cunningham and Payne, 2017) and both Process S and Process C individually exert influence on these systems, then in order to understand the independent effects of sleep on emotional memory processing, Process S and Process C must both be taken into consideration.

While Process S and Process C cannot be completely controlled in many study designs, there are some elements or groups that can be added to most study protocols that can help. One of these additions is to conduct an initial memory test after just a short delay, immediately following encoding[4]. Not only does comparing pre-sleep to post-sleep memory performance better isolate the effects of sleep manipulations that occur following encoding (e.g., during early consolidation), but potential "time of day" effects can be determined and controlled for statistically. For instance, if encoding takes place at different times of day (e.g., 9am and 9pm) then the homeostatic pressure (Process S) by definition is going to be substantially different between groups as the 9pm group has 12 additional hours of sleep pressure built up compared to the 9am group. If this immediate test reflects no initial performance differences between groups, it provides some support that Process S is not substantially altering the encoding of the material (though does not eliminate the possibility entirely), and if there is a difference, then it can be added to the analysis as a covariate.

Use of circadian control groups is another technique that can be implemented to help to account for the influences of Process S and Process C, especially if investigators have concerns that immediate testing may influence the long-term memory performance they plan to test (see *Footnote 4*). As described above, if encoding and retrieval are conducted at different times of day (e.g., wake: encoding 9am, retrieval 9pm vs. sleep: encoding 9pm, retrieval 9am) then in addition to the presence and absence of sleep between sessions, the innate circadian rhythms of the groups are exerting very different physiological influences at the time of encoding, initial consolidation, and retrieval. Circadian control groups can be recruited to complete emotional memory encoding and retrieval tasks after a shorter delay (e.g., 30–60 min) such that the entire protocol can be conducted in a single session. Again, while it does not completely eliminate the possibility that circadian influences might account for some of the effect, if there is no difference between the circadian control groups then it does provide support that the circadian influences during encoding, early consolidation, and retrieval do not completely account for the differences found between the sleep and wake conditions, and if there are differences they can potentially be controlled for statistically. Moreover, collaborations between sleep and circadian researchers could lead to the implementation of even more intensive, elegant study designs that disentangle the effects of Process S from Process C at the neurophysiological level (see Discussion section).

A final biological rhythm that may be particularly important in the discussion of emotional memory processing is the regulation of rapid eye movement (REM) sleep. While the need and intensity for slow wave activity (SWA) during non-REM (NREM) seems to largely increase linearly over time spent awake (Dijk et al., 1990), REM sleep seems to have its own regulatory mechanisms. For one, depriving REM sleep, as might happen during a sleep-restriction protocol in which participants are only allowed to sleep the first half of the night, leads to an immediate REM sleep rebound and reduction in the intensity of NREM sleep in the subsequent sleep periods (Beersma et al., 1990; Brunner et al., 1990). Unlike SWA, however, propensity for REM sleep has also been shown to be closely coupled to circadian rhythm (Czeisler et al., 1980), and the relationship between REM sleep and learning has been shown to be affected by the circadian phase during which the REM sleep occurs (Cajochen et al., 2004). Importantly, it has been hypothesized

4 While this design fixes some problems, it may introduce others. First, this design requires the use of "intentional encoding" designs, whereby participants know their memory will be tested; otherwise, the comparison of the short- and long-delay performance would be like comparing apples (a surprise short-delay memory task) and oranges (an expected long-delay memory task). Second, asking participants to retrieve a subset of items on a short-delay task may initiate other phenomena (e.g., retrieval-induced forgetting effects), which could in turn affect performance on the long-delay task.

that REM sleep may play a particularly important role in the processing of emotional memories (Walker and van Der Helm, 2009; van der Helm and Walker, 2011; Cunningham et al., 2014b), yet – to our knowledge – the timing of its effectiveness with regard to circadian phase has never been investigated in the context of emotional memory. Thus, relative to other stages of sleep, the distinct and complex regulation of REM sleep may be particularly important in the investigation of sleep's effect in emotional memory. As we now move into discussion of the current state of the field and dissect the literature based on the placement of the sleep manipulation with regard to emotional memory processing, we encourage innovative thought as to how some of these REM-related factors may be better accounted for in future research.

Sleep placement and emotional memory processing

Sleep prior to encoding

Sleep can be manipulated in the period prior to the encoding of emotional information or the experience of an emotional event. This includes both the presence or absence of sleep (e.g., sleep vs. sleep deprivation or nap vs. no nap designs), as well as the duration of time since the previous bout of sleep leading to differences in the magnitude of homeostatic sleep pressure at encoding (e.g., nocturnal sleep vs. daytime wakefulness designs).

Sleep prior to emotional experiences may be particularly important for the initial experience of emotionality that shapes the development of the subsequent memory, as the absence of sleep has been shown to heavily affect our mood (Carskadon and Dement, 1979; Reddy et al., 2017; Feng et al., 2018; Ben Simon et al., 2020; Tomaso et al., 2021), alter our perception of and response to emotional information (van der Helm et al., 2010; Minkel et al., 2011; Alfarra et al., 2015; Killgore et al., 2017; Tomaso et al., 2021), and inhibit our ability to regulate our emotional response when perceiving or experiencing emotional events (Killgore et al., 2008a; Killgore, 2013; Baum et al., 2014; Miller et al., 2015; Tomaso et al., 2021). Intriguingly, a growing body of evidence has indicated that sleep loss prior to viewing emotional stimuli may lead to hyperactivity of limbic regions such as the amygdala (Yoo et al., 2007a; Goldstein et al., 2013; Motomura et al., 2013; Goldstein-Piekarski et al., 2015), altered amygdala-prefrontal cortex (PFC) connectivity (Chuah et al., 2010; Killgore, 2013; Motomura et al., 2013), impaired or blunted behavioral responses to aversive stimuli (van der Helm et al., 2010; Alfarra et al., 2015; Pilcher et al., 2015; Killgore et al., 2017), and increased emotional responses to neutral stimuli (Tempesta et al., 2010; Simon et al., 2015). It has been suggested that these features may lead the sleep-deprived brain to treat all stimuli as potentially aversive, possibly due to a decreased threshold for emotional activation (Goldstein et al., 2013; Simon et al., 2015), which would likely have an impact on the subsequent memory processing for both emotional and neutral stimuli. It is also worth noting that animal models have indicated that substantial sleep loss in rodents prior to operant conditioning leads to impaired contextual memory (but not cued memory; McDermott et al., 2003). The authors further provide evidence that this may be due to cellular-level alterations in membrane excitability leading to reduced hippocampal long-term potentiation (LTP), thus impairing hippocampal-dependent learning performance.

With regard to declarative memory in humans, studies using neutral stimuli only have consistently shown an impairment in subsequent memory when sleep is deprived or impaired prior to encoding (Drummond et al., 2000; Yoo et al., 2007b; Chuah et al., 2009; Van Der Werf et al., 2009; Saletin et al., 2016), though certain structural brain morphology (Saletin et al., 2016) and compensatory activation (Drummond et al., 2000; Chuah et al., 2009) may limit the negative effects that sleep loss at encoding has on memory performance. Similar detrimental effects have been reported in studies testing emotional declarative memory (see **Table 1**). In one study, participants were sleep deprived for 36 h prior to encoding negative, neutral, and positive words, and then were allowed two nights of recovery sleep before testing (Walker and Stickgold, 2006). They found that sleep-deprived participants had a 40% reduction in overall memory with the magnitude of the deficit differing across emotional categories. Specifically, retention was especially poor for neutral and positive words, with the retention in memory for positive words reaching a 59% deficit, while negative words had a smaller, non-significant decrease (19%). Another study either allowed normal sleep or totally sleep-deprived participants prior to viewing negative, neutral, and positive videos (Tempesta et al., 2016). With total sleep deprivation (TSD), recognition memory for video images was once again impaired for positive and neutral scenes, while recognition for negative scenes was similar between rested and TSD participants. With regard to contextual memory (i.e., temporal order of scenes), TSD impaired performance overall, independent of emotional valence (Tempesta et al., 2016).

Kaida et al. (2015) had participants encode positive, neutral, and negative scenes following TSD, targeted rapid eye movement sleep deprivation (REMD), or normal sleep. Following the sleep manipulation, participants completed a recognition task for half of the previously viewed material[5], and returned 1 week later to complete an identical recognition task for the other half of the material. TSD led to impaired overall memory performance,

5 While sleep was manipulated pre-encoding, in this design, TSD would also affect the retrieval of material on the short-delay test. Thus, the Condition × Design interaction could be considered a comparison of the effect of TSD on retrieval (TSD would affect short-delay but not long-delay retrieval).

TABLE 1 Studies aimed at investigating the effect of sleep on the pre-encoding phase of emotional memory processing.

Study	Human subjects (Y/N)	Genders	Age (M ± SD)	N	Between-groups/Within-groups	Sleep manipulation	Stimulus material	Emotions	Immediate test (Y/N)	Time of day control (Y/N)	Main effect of sleep manipulation (effect size)	Interaction sleep × emotion (effect size)
Cellini et al., 2016	Y	Mixed	23.81 ± 2.63 years	46	Between	Nap	Pictures	NNP	N	N	Y ($\eta 2 = 0.15$)	N (NR)
Kaida et al., 2015	Y	Men	21.4 ± 1.65 years	14	Within	TSD/S	Pictures	NNP	N	N	Y ($\varepsilon = 1.00$)	N (NR)
Kaida et al., 2015	Y	Men	22.0 ± 2.09 years	18	Within	REMD/S	Pictures	NNP	N	N	N (NR)	N (NR)
Tempesta et al., 2016	Y	Mixed	21.6 ± 2.1 years	48	Between	TSD/S	Videos	NNP	N	N	Y (NR)	Y (NR)
Walker and Stickgold, 2006	Y	NR	NR	NR	Between	TSD/S	Words	NNP	N	N	Y (NR)	NR

Style of Tables adapted from Davidson et al. (2021). Table includes studies included as part of this narrative review, and is not necessarily a comprehensive list of all published works. Immediate test, test prior to sleep manipulation; Y, yes; N, no, Mixed, not restricted to a single reported gender; DW/NS, daytime wake vs. nocturnal sleep; TSD/S, total sleep deprivation vs. sleep; REMD/S, REM sleep deprivation vs. sleep; Nap, daytime nap vs. no nap protocol; NNP, negative, neutral, positive stimuli; NR, not reported.

independent of emotional valence; while the decrease between testing sessions appeared more pronounced in the TSD condition, the Condition × Day interaction did not reach significance. Compared to the control condition, REMD had no significant impact on overall picture recognition, although an exploratory analysis of just negative pictures found that REMD participants remembered slightly more negative pictures on Day 1 and slightly fewer negative pictures on Day 8, leading to a significant Condition × Day interaction for negative picture memory (Kaida et al., 2015). A nap study manipulated sleep both prior to encoding and during early consolidation by having participants encode two sets of pleasant, unpleasant, and neutral images, one prior to nap or wake and another after nap or wake, followed by a memory test for all images 30 min after encoding the second set (Cellini et al., 2016). Participants that napped had better overall memory for both sets of images, indicating that sleep both pre- and post-encoding facilitates learning. While the images encoded pre-sleep showed an effect of valence (neutral and unpleasant stimuli were better discriminated than pleasant stimuli), the effect of valence did not reach significance for the images that were encoded immediately following sleep (Cellini et al., 2016).

The pre-encoding phase in emotional memory processing can begin to be targeted in study designs by manipulating sleep prior to the encoding of emotional information (e.g., sleep vs. sleep deprivation) and allowing normal periods of sleep to occur immediately following encoding and before testing (**Figure 3A**). Given that the early consolidation phase begins *immediately* after the cessation of the encoding task, disentangling the effects of sleep prior to encoding from lingering effects of the sleep manipulation during the early consolidation phase may be one of the most challenging distinctions to make. Moreover, the micro- and macro-architecture of the sleep period immediately following encoding would also need to be taken into consideration. Polysomnography (PSG) sleep recordings (particularly with high-density capabilities; Cox et al., 2012, 2017, 2018a; Cox and Fell, 2020; Cunningham et al., 2021a; Denis et al., 2021) and an immediate test directly following encoding may help to at least partially account for some of these influences. Nap studies could also be conducted that either permit or deny a nap period prior to encoding, and then delay testing until subsequent nocturnal sleep is obtained in both groups (**Figure 3B**). In study designs that are unable to keep the encoding and testing sessions consistent between conditions, differences in circadian rhythm, time of day effects, and duration of time since the previous sleep episode may be controlled for using immediate testing or circadian control groups, as described above.

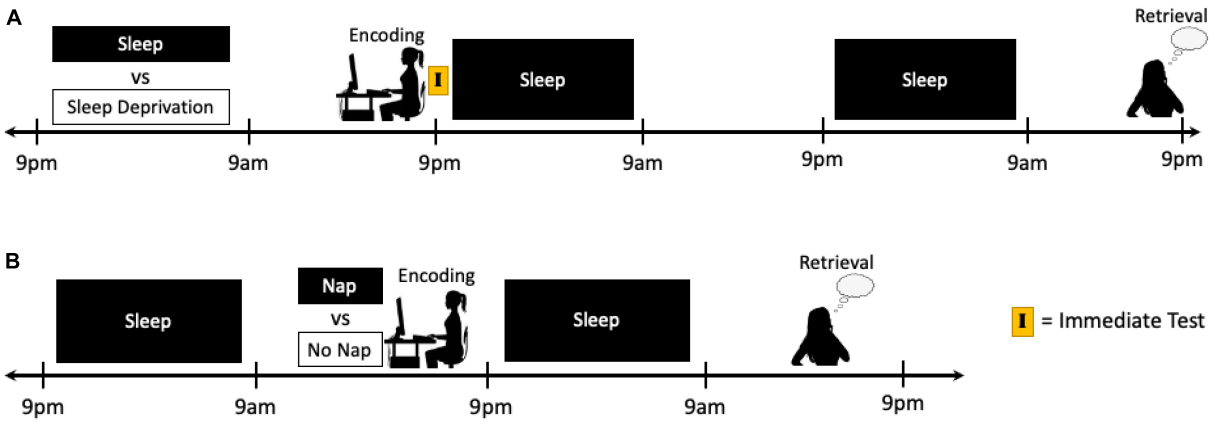

FIGURE 3
Schematics of two potential study protocols designed to target the effects of sleep manipulation on the pre-encoding period of emotional memory processing. **(A)** Following a night of sleep or sleep deprivation, participants can complete an encoding task just prior to the next night of sleep, thus manipulating sleep prior to encoding while allowing both groups to sleep during the early consolidation phase and be rested again prior to final retrieval. **(B)** Typically rested participants can remain awake or be given a nap opportunity prior to an encoding task, and then all participants can be given a normal night of sleep prior to testing the next day. The primary challenge in targeting the pre-encoding phase of memory processing is distinguishing the specific effects of the sleep manipulation on the encoding of information from any lingering effects that the sleep manipulation may have during the early consolidation period.

Sleep during early consolidation

The early consolidation period just following encoding of an emotional event is a period during which memories are thought to be highly labile and susceptible to additional modulation via factors such as sleep and stress (McGaugh, 2000, 2004, 2018; Dudai et al., 2015; Squire et al., 2015). Withholding sleep (i.e., sleep deprivation) during this critical period has been shown to prevent long term memory storage for some types of memories (Stickgold et al., 2000; Stickgold, 2005; Walker and Stickgold, 2006). Likely because seminal models of emotional memory focused on the role of emotional arousal in modulating consolidation processes (McGaugh, 2000, 2004), the vast majority of sleep and emotional memory research has focused on the manipulation of sleep during this critical period with early evidence suggesting that the sleeping brain is able to specifically target emotional content for preferential memory processing (Wagner, 2001; Hu et al., 2006; Holland and Lewis, 2007; Nishida et al., 2009).

Recent reviews and meta-analyses have extensively reviewed the literature focusing on this stage of emotional memory consolidation and highlighted other factors that may influence the effect of sleep during this period (see Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021; for review). The quick synopsis, however, is that while several studies do report an interaction between sleep and emotion during the early consolidation period (Hu et al., 2006; Wagner et al., 2006; Nishida et al., 2009; Prehn-Kristensen et al., 2009, 2013; McKeon et al., 2012; Chambers and Payne, 2014; van Heugten-van der Kloet et al., 2015; Bolinger et al., 2018; Cox et al., 2018b), most do not (e.g., Wagner et al., 2007; Baran et al., 2012; Morgenthaler et al., 2014; Ackermann et al., 2015, 2019; Göder et al., 2015; Tempesta et al., 2015, 2017; Gilson et al., 2016; Jones et al., 2016, 2018; Lehmann et al., 2016b; Harrington et al., 2018; Ashton et al., 2019; Bolinger et al., 2019; Huguet et al., 2019; Kurz et al., 2019; Schoch et al., 2019; Cross et al., 2020; Huan et al., 2020; for Tables detailing the current state of the literature on the effect of sleep during the early consolidation stage of emotional memory processing see recent open access publication Davidson et al., 2021). A potential confound in a number of these studies, however, is that sleep is frequently manipulated at multiple stages of memory processing, such as during early consolidation *and* prior to retrieval. Recent models of emotional memory have highlighted that the effects of emotion on memory are not constrained to the consolidation phase, with emotion robustly affecting retrieval processes (e.g., Bowen et al., 2018; Talmi et al., 2019). Thus, manipulations that simultaneously target both consolidation and retrieval may be blending effects that could plausibly be working in opposition to one another. As such, two studies in particular are worth noting as their study designs allowed for above average isolation of the sleep manipulation during the early consolidation period.

Tempesta et al. (2017) had participants view six films (two negative, two positive, two neutral) before either TSD or a normal night of sleep. They were then allowed multiple nights of recovery sleep before returning to the lab 48 h later for a surprise recognition test of scenes from the videos. They found that the sleep deprived participants had poorer overall memory, regardless of film valence. Similarly, Wagner et al. (2007) had

participants view happy, angry, and neutral faces prior to a night of TSD or normal sleep in a within-subject, crossover design. They were then allowed a night of recovery sleep before returning for the memory test. They too found that while sleep deprivation impaired overall memory accuracy, there was no interaction with stimuli valence.

The one exception to this growing trend of null results are studies that utilize emotional trade-off paradigms as the assessment for memory (Davidson et al., 2021). In these study designs, images are created that display either a negative or neutral central object overlayed over a neutral background (Kensinger et al., 2007; Cunningham et al., 2014a,c, 2021b). During encoding, participants view the entire scene (e.g., a spider on a fence), but at recognition the scene components are separated and presented one at a time (e.g., participants see just the spider and just the fence on different trials). Unlike studies using other types of emotional memory probes, a majority of these studies have demonstrated an interaction with sleep and emotional memory, such that the magnitude of the difference between negative objects and their paired backgrounds is larger after sleep than after similar periods of wakefulness (e.g., Payne et al., 2008, 2012, 2015; Payne and Kensinger, 2011; Alger et al., 2018). What is remembered about these types of complex emotional scenes has also been shown to be affected by the way memories must be retrieved (Madan et al., 2020), suggesting the possibility that sleep's exaggeration of emotional memory trade-offs may be reflecting effects on both consolidation and retrieval. However, in at least one study using a 24-h delay (Payne et al., 2012), the effect of sleep on the emotional memory trade-off was greatest when sleep occurred soon after learning (disproportionately affecting early consolidation) rather than when it was shifted in time to occur during extended consolidation, just before retrieval. Interestingly, while the pattern of these results was similar for both a strict, specific assessment of memory performance and a more lenient, general memory performance measure, the strength of the effect was stronger in the stricter measure of veridical memory (Payne et al., 2012). Other studies that probe different aspects of emotional memory or different strengths of the emotional memory trace (e.g., specific vs. gist memory, direct vs. associative memory, "Remember" vs. "Know," etc.) have also demonstrated differences in the magnitude or even direction of the sleep effect depending on which aspect of memory performance was assessed (e.g., Hu et al., 2006; McKeon et al., 2012; Goldschmied et al., 2015; Alger and Payne, 2016; Schoch et al., 2017; Kurz et al., 2019). Thus, the type of probe or the inclusion of false alarm rates in the calculation of memory performance (e.g., hit rate vs. d-prime) may interact with the placement of sleep and is in need of careful consideration to add precision to our understanding of sleep's relationship with emotional memory processing (see section "Discussion").

In summary, recent reviews and meta-analyses have indicated that the specific memory enhancement of emotional over neutral information due to sleep during the early consolidation stage may not be as strong as initially indicated (i.e., sleep may more frequently benefit both emotional and neutral memories), and may depend on a variety of additional factors, such as the type of emotional stimuli used, the use of pre- and post-sleep testing to determine changes from baseline memory, and the type of memory probe, such as free recall vs. recognition testing (Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021). This phase of memory processing may also be subject to time of day and circadian influences as hormones and emotional reactivity fluctuate significantly throughout the day. Moreover, additional research is needed to determine the exact duration of this "critical labile period" where memories can be more easily influenced compared to the extended consolidation period (see below) at which time memories may be less influenced to modulation unless reactivated. Recent research exploring forgetting curves have indicated that this labile period may last up to 12 h or more in the absence of sleep for some types of memory (Radvansky et al., 2022), and this may be subject to individual differences as well.

Critically, a majority of studies that have sought to explore the role of sleep during early consolidation on the long-term formation of emotional memories have inadvertently manipulated sleep prior to retrieval as well. For example, in many nap vs. no nap and nocturnal sleep vs. daytime wakefulness protocols, the buildup of sleep homeostatic pressure at retrieval also differs between groups. Similarly, in sleep vs. sleep deprivation studies, sleep at retrieval is directly influenced unless recovery sleep is obtained. As such, the impact of sleep during early consolidation can be isolated by manipulating sleep immediately following exposure to emotional information (e.g., nap vs. no nap design, sleep vs. sleep deprivation design) and then allowing all participants to obtain subsequent night(s) of recovery sleep prior to testing (**Figure 4**). These designs would also control for circadian rhythm, time of day effects, and duration of time since previous sleep episodes by keeping the encoding and retrieval sessions consistent between groups.

Another intriguing line of research that has thus far primarily been implemented during the early consolidation phase of memory processing is the use of non-invasive stimulation techniques during sleep, such as targeted memory reactivation (TMR; Oudiette and Paller, 2013), closed- and open-loop auditory stimulation (Weigenand et al., 2016; Baxter et al., 2020), and transcranial direct current stimulation (tDCS; Marshall et al., 2004; Zhang and Gruber, 2019). Generally, the goal of these techniques is to affect or enhance sleep in such a way that it will ultimately boost its effect on both emotional and non-emotional types of memory. While a complete review of studies utilizing these techniques is beyond the scope of the current review, TMR and other non-invasive stimulation

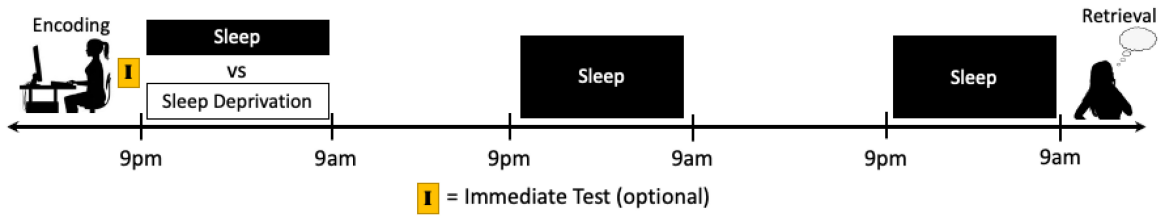

FIGURE 4
Schematics of a potential study protocol designed to target the effects of sleep manipulation on the early consolidation stage of emotional memory processing. Participants can complete an encoding task immediately prior to a period of sleep or sleep deprivation. By allowing multiple nights of recovery sleep prior to retrieval, the effects of the sleep manipulation can be limited primarily to the early consolidation period. Moreover, an immediate test directly after encoding can be used to determine within-subject memory changes due to the different conditions. However, it must be kept in mind that the testing of memory itself may influence subsequent memory performance (see Footnote 4 and section "Discussion").

techniques could be similarly employed at various stages of emotional memory processing and may be a valuable tool for increasing the precision of our understanding of sleep's effect on different stages of memory processing (see **Box 3** for additional discussion).

Sleep during extended consolidation

Following the early consolidation phase, emotional memories enter into a period of extended consolidation. This stage in memory formation refers to any additional consolidation processes that occur to a memory after it transitions from its labile state during the early consolidation phase into a more stable memory trace and extends all the way until the memory is retrieved, reactivated, or forgotten. With regard to emotional memory, this period remains one of the least studied involving sleep manipulations, though memory studies using non-emotional tasks indicate that sleep may expedite the transition of memories from the early to extended consolidation phase (Walker et al., 2002, 2003; Stickgold, 2005) and that interference training or manipulating sleep after a memory enters this phase of memory formation appears to have little influence on later retrieval (Stickgold et al., 2000; Walker et al., 2003; Ellenbogen et al., 2006; Alger et al., 2012). Still, an important question continues to be in the absence of sleep, at what point (or does) the waking brain transition a memory from the early to extended consolidation phase so that it might be less influenced by other processes such as sleep and stress.

While substantial research has aimed at the early consolidation stage of emotional memory processing, very few studies have explored this extended consolidation period (see **Table 2**), and, to our knowledge, only three studies have utilized protocols meant to specifically target this stage. In a final sample of 265 Dutch children, Vermeulen et al. (2017) had participants encode 30-word pairs (10 positive, 10 negative, 10 neutral) at 7am or 7pm, followed by an immediate recall test. Participants then either had a 12-h delay of daytime wakefulness or nocturnal sleep (targeting early consolidation) or a 24-h delay in which sleep occurred either shortly after encoding (7 pm condition) or after a normal day spent awake (7 am condition), targeting the extended consolidation period. They found that while more arousing words did result in better immediate and delayed recall, there was no main effect or interaction of sleep for any of the conditions. They also reported no deterioration in memory from immediate to delayed recall across both the 12-h and 24-h periods, regardless of sleep placement (Vermeulen et al., 2017). Another study utilized essentially the same sleep manipulation protocol (12-h delay of sleep vs. wake and 24 h delay of sleep-first vs. wake-first), but used the emotional memory trade-off paradigm in young adults (Payne et al., 2012). As noted above, the sleep effect was strongly diminished in the wake-first group compared to the sleep-first condition, suggesting that sleep may have less of an impact on emotional memory processing once the memory reaches this stage, at least for some paradigms. A final study recently utilized a similar sleep-first vs. wake-first protocol, but memory was tested for negative and neutral scenes on three separate occasions across the protocol: immediately following encoding, 12-h after encoding, and 24-h after encoding (Carollo et al., 2022). While immediate testing showed no differences, at the 12-h mark memory was clearly benefited by a sleep period, though this effect was generalized and not limited to negative pictures. Interestingly, testing after the 24-h delay showed that the sleep-first group showed deterioration in memory in the subsequent 12-h of wakefulness, while memory was largely preserved from the 12- to 24-h test in the wake-first group after receiving their opportunity for sleep in the second half of the protocol (Carollo et al., 2022). Importantly, while the authors clearly state that the intention was to assess delayed sleep-dependent consolidation on emotional memory, it is likely that the 12-h testing session reactivated memory traces for the stimuli that had been set aside for the 24-h assessment. Thus, in this design elements of reactivation and reconsolidation may have been in effect as well.

BOX 3 Targeted memory reactivation (TMR) and non-invasive stimulation.

A valuable addition to the conversation of creative study design is recent innovations in the modulation of the sleep periods. Determining performance changes following the enhancement or suppression of certain elements of sleep microarchitecture (e.g., slow waves, spindles, REM density, etc.) or by otherwise affecting the processing occurring during the sleep period may be another way to not only help us distinguish the impact of sleep on emotional memory processing, but also may help to reveal what elements of sleep play a primary role. As noted, the primary goal of some of these recent strategies — such as closed/open-loop auditory stimulation (Weigenand et al., 2016; Baxter et al., 2020) and transcranial direct current stimulation (tDCS; Marshall et al., 2004; Zhang and Gruber, 2019) — is simply to affect the sleep architecture to enhance or suppress certain elements of sleep. As we make suggestions for different study designs geared toward isolating the effects of sleep on the different stages of emotional processing, it is certainly worth consideration of how these techniques might also be implemented within each protocol to further our understanding of sleep's effect.

Another relatively novel technique, Targeted Memory Reactivation (TMR), may be particularly relevant in the context of the present review. In TMR protocols, stimuli during encoding are typically either presented audibly or are paired with an auditory or olfactory cue. Then, *during* the subsequent sleep period, previously experienced auditory stimuli or paired cues may or may not be presented again along with novel foils at a level that is designed to be processed by the brain without waking the participant. The goal of this stimulation is to artificially trigger the memory engram for replay during the sleep period. In this way, TMR has elements of encoding, consolidation, and reconsolidation all occurring within a sleep period, and in particular may be a way to enhance the consolidation or expedite the reconsolidation phase of emotional memory processing. TMR has already generated some very interesting findings in the overall sleep and memory field (see Oudiette and Paller, 2013; Schouten et al., 2017; Cellini and Capuozzo, 2018) and we are beginning to understand more about the underlying mechanisms that promote memory enhancement through TMR (Lewis and Bendor, 2019). TMR has been shown to reliably enhance declarative memory (e.g., Rasch et al., 2007; Diekelmann et al., 2011; Donohue and Spencer, 2011; Van Dongen et al., 2012), procedural memory (e.g., Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014), and creative performance (Ritter et al., 2012), with a recent meta-analysis indicating that TMR is highly effective, particularly when implemented during NREM sleep (Hu et al., 2020).

TMR has also been implemented at an encouraging rate with emotional stimuli, though the findings remain unsurprisingly mixed. Studies using fear extinction memory in humans have found that TMR may facilitate fear extinction learning (Hauner et al., 2013; He et al., 2015). Intriguingly, some animal literature suggests that TMR may also weaken or interfere with extinction learning (Rolls et al., 2013). With regard to emotional picture recognition, TMR has been shown to both benefit (Cairney et al., 2014; Lehmann et al., 2016a; Groch et al., 2017) and have no effect on (Ashton et al., 2018) subsequent memory performance. One final study found that TMR had no effect on the emotional memory trace, but did influence the affective tone (Rihm and Rasch, 2015). Overall, substantial evidence indicates that TMR is effective at modulating a variety of memory traces. While the unique effects of TMR protocols make it difficult to fit it cleanly within any single category discussed here, it is clearly another exciting new tool available to sleep researchers that may aid in the continued dissection of sleep's effect on emotional memory processing.

Given the uncertainty surrounding the timing at which memories may transition from the early to extended consolidation stage in the absence of sleep, there are two additional studies that may have some relevance in this investigation. Atienza and Cantero (2008) had participants encode negative, neutral, and positive pictures either at 11 am or 5 pm prior to a normal night of sleep or TSD. Participants returned a week later for a recognition test using a Remember/Know memory assessment (Tulving, 1985). They found a main effect of sleep on Remember judgments such that TSD participants had poorer overall recall. They also report that while Remember judgments for neutral images were more impaired by sleep deprivation (41%) compared to emotional information, the interaction between sleep and emotion was not significant (Atienza and Cantero, 2008). While additional information might be able to be gleaned from the different consolidation periods prior to the first bout of sleep or sleep deprivation, the authors used the different encoding times as a means to take circadian influences into consideration and collapsed the groups for analysis. Similarly, Sterpenich et al. (2007, 2009) had participants encode negative, neutral, and positive pictures between 3:30 pm and 8:30 pm before sleep or TSD, and participants were allowed two nights and 6 months of recovery sleep prior to testing. Memory was poorer overall for TSD participants at both testing sessions. After the three-day delay, "Remember" judgments specifically deteriorated for neutral and positive images while memory for negative images was not impacted by lack of sleep, though this effect was not present at the 6 months delay, possibly due to high variability in memory capacity at that time (Sterpenich et al., 2007, 2009). Interestingly, less vividly retained memories as indicated by "Know" judgments did not show as strong of a sleep effect even after the short delay (see section "Discussion"). Of relevance to this review, however, while the authors did isolate the consolidation period in their design, the differential consolidation periods prior to the first bout of sleep or sleep deprivation were not a factor in their analysis.

Future studies that aim to differentiate the effects of full nights of sleep on the early and extended consolidation periods of emotional memory would benefit from the use of 24- or 48-h study designs. In these studies, there is at least a 24-h delay between the encoding and retrieval of emotional information, and sleep or sleep deprivation is scheduled to occur either shortly after encoding or after an extended delay. In cases where the encoding sessions take place at different times of day (e.g., 9am and 9pm), it is critical to attempt to control for differences in circadian rhythm, time of day effects, and homeostatic sleep pressure using immediate tests and/or circadian control groups (**Figure 5A**). Nap protocols may also be used to gain better understanding of the amount of time that needs to pass before the early consolidation period transitions into the extended consolidation period. In such a design, comparisons can be made between participants that (1) nap shortly after encoding, (2) nap at variable, substantial delays after encoding,

TABLE 2 Studies aimed at investigating the effect of sleep on the extended consolidation phase of emotional memory processing.

Study	Human subjects (Y/N)	Genders	Age (M ± SD)	N	Between-groups/Within-groups	Sleep manipulation	Stimulus material	Emotions	Immediate test (Y/N)	Time of day control (Y/N)	Main effect of sleep (effect size)	Interaction sleep × emotion (effect size)
Atienza and Cantero, 2008	Y	Mixed	21 ± NR years	28	Between	TSD/S	Pictures	NNP	N	N	Y (NR)	N (NR)
Carollo et al., 2022	Y	Mixed	23.6 ± 3.2 years	40	Between	SF/WF	Pictures	NN	Y	N	Y*($\eta_p 2 = 0.10$)	N ($\eta_p 2 < 0.01$)
Payne et al., 2012	Y	NR	18-25 years (M ± SD: NR)	71	Between	SF/WF	Pictures (ETO)	NN	N	N	NR	Y (NR), negative objects better remembered in sleep-first compared to wake-first conditions indicating larger influence in early compared to extended consolidation
Sterpenich et al., 2007	Y	Mixed	22.3 ± 2.7 years	40	Within	TSD/S	Pictures	NNP	N	N	Y (NR)	N (NR)
Sterpenich et al., 2009	Y	Mixed	22.3 ± 2.7 years	40	Within	TSD/S	Pictures	NNP	N	N	N (NR)	N (NR)
Vermeulen et al., 2017	Y	Mixed	10.5 ± 0.8 years	265	Between	SF/WF	Words	NNP	Y	N	N (OR = 1.06)	N (OR = 1.10)

Style of Tables adapted from Davidson et al. (2021). Table includes studies included as part of this narrative review, and is not necessarily a comprehensive list of all published works. Y, yes; N, no; Mixed, not restricted to a single reported gender; ETO, emotional trade-off task; SF/WF, 24 h protocol with sleep-first vs. wake-first groups; TSD/S, total sleep deprivation vs. sleep; NN, negative and neutral; NNP, negative, neutral, and positive; NR, not reported.
*For "hit rate" but not d-prime calculation of memory performance.

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and (3) remain awake until testing. This design would have the added benefit of keeping circadian and time of day influences consistent between groups (**Figure 5B**).

Sleep prior to retrieval

Memory retrieval refers to the process of activating the neural memory trace of our previous experiences to call to mind a specific item or event or to perform a specific task. With regard to declarative emotional memory, it is at this phase of memory that enhancements in memory for emotional vs. neutral information following sleep or wake are tested. Importantly, retrieval of emotional memory has been tested in a variety of different ways (e.g., free recall, cued recall, recognition, forced choice, etc.), and recent evidence has indicated that certain tasks and types of testing (e.g., free recall, emotional memory trade-off) may be more sensitive to picking up on selective benefits of sleep for emotional content (Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021). Additionally, for some tasks (including emotional memory) the effects of sleep may be more pronounced when examining changes in pre-sleep to post-sleep testing rather than comparing memory performance following the sleep manipulation alone (Lipinska et al., 2019; Schäfer et al., 2020).

To our knowledge, no human studies have *specifically* targeted the influence of sleep on this pre-retrieval stage of emotional declarative memory processing. This paucity of data is quite surprising given relatively robust animal models that not only indicate that sleep loss prior to retrieval of emotionally laden information most certainly does impair memory performance, but there might be sex differences in the degree of impact as well (Fernandes-Santos et al., 2012), and also given recent models of emotional memory that emphasize effects operating at retrieval (e.g., Bowen et al., 2018; Talmi et al., 2019). As such, there is an obvious need for human research that intentionally utilizes sleep manipulations to specifically target the retrieval stage of emotional memory processing.

This lack of targeted research is in sharp contrast with the fact that a majority of sleep and emotional memory studies do ultimately manipulate sleep prior to retrieval by shifting the occurrence of sleep in relation to learning. Thus, as part of this manipulation, the proximity of sleep to retrieval has also been shifted (i.e., when sleep is shifted further away from encoding, it is also shifted closer to retrieval), but the results are not discussed as such. For instance, in typical nocturnal sleep vs. daytime wakefulness and nap vs. no nap study designs, when memory is tested immediately following the sleep manipulation there is a difference in homeostatic sleep pressure during retrieval. Additionally, in sleep vs. sleep deprivation or sleep restriction protocols, if recovery sleep is not permitted prior to the memory assessment then sleep loss is having an active effect on retrieval processes as well. Some of these influences can again be accounted for via immediate tests and circadian control groups. To specifically target this phase in memory processing, however, longer study protocols would need to be employed. For instance, participants could all complete the encoding session at the same time of day on Day 1, and then return several days later, after the memory has reached the extended consolidation phase, to have their memory tested directly following a night of sleep deprivation or sleep or directly following a nap or no nap (**Figure 6**). Such a protocol would also benefit by keeping the encoding and testing sessions at the same time of day for both conditions, thereby eliminating time of day and circadian effects.

Sleep post-retrieval/during reconsolidation

The evolution of a memory is not complete after retrieval. Instead, once a memory is retrieved or reactivated (i.e., a brief reminder of the memory content), it has been shown to return to a labile state that again makes it more prone to influence, modulation, and forgetting[6] (Stickgold and Walker, 2007; Tronson and Taylor, 2007; Nader and Einarsson, 2010; Alberini and LeDoux, 2013; Agren, 2014; Cassini and Lee, 2018; Simon et al., 2020), much like the period of early consolidation. Several studies have suggested that sleep plays an important role in re-stabilizing declarative episodic memories following reactivation (Klinzing et al., 2016; Moyano et al., 2019; Bryant et al., 2020). For instance, in one study that used retrieval-induced forgetting as a way to ascertain whether a memory was in a labile state (Moyano et al., 2019), results led the authors to propose that 90 min of sleep may be sufficient to accelerate memory re-stabilization, shortening the time over which memories are susceptible to interference. Joensen et al. (2022) recently reported that targeted memory reactivation during sleep can lead to retrieval induced forgetting – but not for memories that had been reactivated just prior to sleep, perhaps consistent with other evidence (Klinzing et al., 2016) that a brief sleep epoch can specifically improve retention of recently reactivated memories.

To our knowledge, only a single study has directly examined the effect that sleep may have on the reconsolidation of emotional episodic memories (see **Table 3**). Azza et al. (2022) asked participants to undergo an "imagery rescripting" manipulation in which they retrieved an autobiographical memory and reinterpreted it so as to make it less aversive. After

6 By "forgetting," we refer to the failure to retrieve a previously accessible memory (e.g., if you remember what you ate for breakfast yesterday morning but can no longer recall that information 2 weeks from now, that would be an instance of forgetting). Recent evidence suggests that this may occur via either passive or active processes and likely involves the deterioration of molecular and cellular memory traces or erosion of the memory cell circuit that would make it unresponsive to recall mechanisms (Davis and Zhong, 2017; Anderson and Hulbert, 2021).

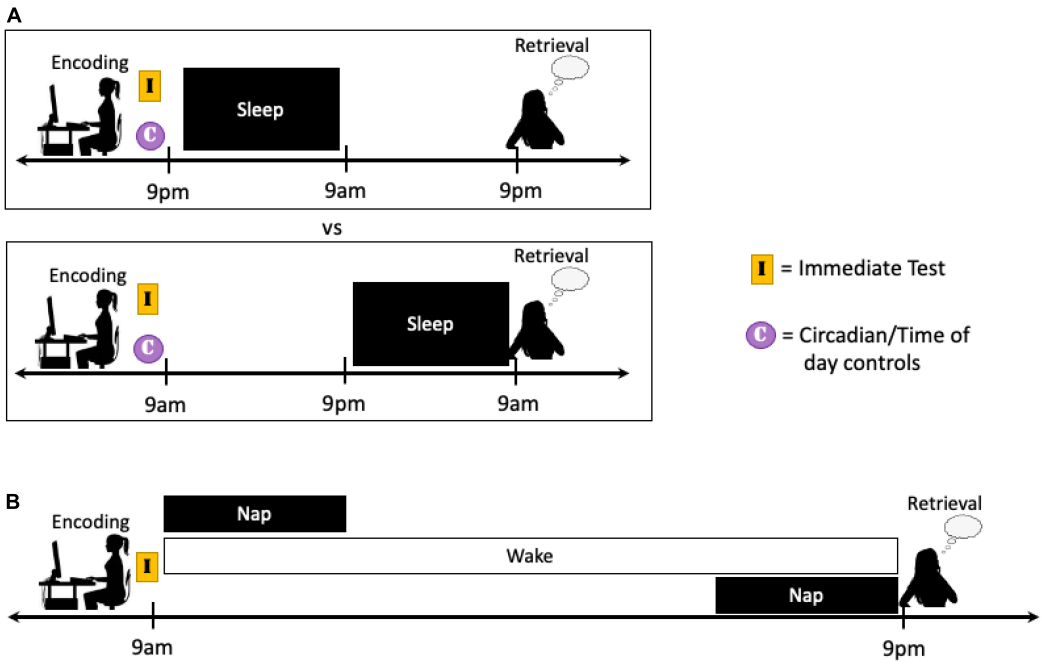

FIGURE 5
Schematics of two potential study protocols designed to target the effects of sleep manipulation on the extended consolidation period. **(A)** Similar to the studies described in the text, longer protocols can be implemented so the sleep manipulation occurs after either a short or extended delay following encoding. In cases where encoding takes place at different times of day, immediate testing and/or circadian controls should be employed when possible to account for differences in sleep pressure and circadian phase. **(B)** Nap studies could also be utilized to better distinguish the point at which a memory transitions from the early to the extended consolidation stage. In these designs, a nap can occur either shortly following encoding or after an extended delay and performance can be compared to participants that remain awake the entire consolidation period. Modulating the placement of the extended nap in a systemic fashion could help determine when this transition occurs in the waking brain, or if sleep is necessary.

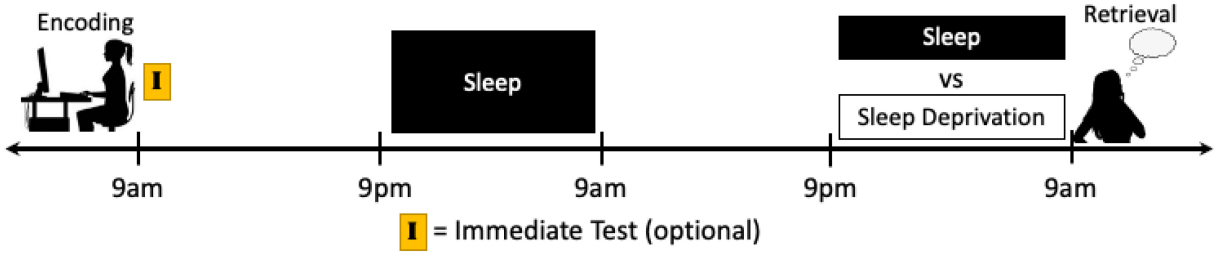

FIGURE 6
Schematics of a potential study protocol designed to isolate the influence of sleep just prior to retrieval on emotional memory performance. Participants can complete an encoding task and after a night, or multiple nights, of sleep to ensure that memories have transitioned to the extended consolidation stage, sleep can be manipulated just prior to retrieval. In this way, sleep vs. sleep loss can specifically target the retrieval of emotional memories while also controlling for circadian rhythm and time of day effects. Moreover, an immediate test directly after encoding can be used to determine within-subject memory changes due to the different conditions, however it must be kept in mind that the testing of memory itself may influence subsequent memory performance (see Footnote 4 and section "Discussion").

this retrieval of the memory, half of the participants were given a nap opportunity while the others stayed awake. 90 min later, the nap group showed a reduced heart rate response to the negative memory script as compared to the wake group, and spindle density was correlated with this reduced arousal response. The authors argued that their results provided the first evidence of a beneficial role for sleep in the adaptive reconsolidation of aversive memories, though the effect did not persist after a 1 week delay (Azza et al., 2022).

While this is the only study to directly examine the reconsolidation phase for emotional memories, there is other suggestive evidence that sleep may affect the way that emotional

TABLE 3 Studies aimed at investigating the effect of sleep on the post-retrieval/reconsolidation phase of emotional memory processing.

Study	Human subjects (Y/N)	Genders	Age (M ± SD)	N	Between-groups/Within-groups	Sleep manipulation	Stimulus material	Emotions	Immediate test (Y/N)	Time of day control (Y/N)	Main effect of sleep (effect size)	Interaction sleep × emotion (effect size)
Azza et al., 2022	Y	Mixed	23.2 ± 3.3 years	44	Between	Nap	Autobiographical Memory*	NN	N	N	NR	Y (η_p2 = 0.12)
Gui et al., 2019**	Y	Mixed	Young: 18–25 Older: 58–78 (M ± SD: NR)	119	Between	DW/NS	Pictures	NNP	Y	N	Y (η2 = 0.07)	N (η2 = 0.02)

Style of Tables adapted from Davidson et al. (2021). Table includes studies included as part of this narrative review, and is not necessarily a comprehensive list of all published works. Y, yes; N, no; Mixed, not restricted to a single reported gender; DW/NS, daytime wake vs. nocturnal sleep; Nap, daytime nap vs. no nap protocol; NN, negative and neutral; NNP, negative, neutral, and positive; NR, not reported.
*Memory was tested as heart rate reactivity to rescripted negative autobiographical memory after nap manipulation. Effect did not persist at retests 1 week later.
**Only reporting results from the second memory task after reactivation during the first memory task.

memories are reconsolidated after initial retrieval. In particular, the effects of sleep on emotional memory can unfold over time and across retrievals – a pattern broadly consistent with the proposal that sleep is affecting the way that memories are reconsolidated after retrieval. For instance, upon a short-delay retrieval task, sleep primarily boosted young adults' neutral memory, whereas after a longer delay, benefits were revealed for young adults' positive memory as well (Gui et al., 2019).

Fortunately, the gold-standard study protocols designed to target the effects of sleep during this post-retrieval, reconsolidation period are typically proficient at isolating the effect of sleep specifically on this phase of memory processing. In many of these studies, the encoding session, the reactivation manipulation (e.g., reactivation vs. no reactivation), and the retrieval session each take place days apart, with sleep being manipulated immediately following reactivation (e.g., nap vs. no nap or sleep vs. sleep deprivation protocols; **Figure 7**). By providing multiple nights between each study session, it can be assured that the memories have entered (or re-entered) the extended consolidation phase before manipulation or testing and that the effects of the sleep manipulation are no longer active at the time of retrieval. Additionally, the encoding task, reactivation task, and retrieval task can all be scheduled at the same time of day between conditions, minimizing time of day and circadian effects and controlling homeostatic sleep pressure at the time of each assessment. As noted, an important future direction will be to intentionally add emotional elements into these designs to differentiate the impact of sleep on the reconsolidation of emotional and neutral aspects of memory. However, a number of studies to date that have conducted multiple memory tests on information encoded in a single session may have unintentionally or inexplicitly included reconsolidation into their study design. For instance, in studies in which emotional and neutral pictures and words are encoded and memory for half of the material is tested 12 h later and memory for the other half of the stimuli is tested days or weeks later, it is possible that the material not presented during the initial 12 h test was reactivated and reconsolidated prior to the final test session.

Discussion

The primary motivation for this review was the recent surge in comprehensive publications describing the rise in mixed findings with regard to sleep and emotional episodic memory processing (Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021). The long-standing belief that sleep interacts with emotionally arousing information to prioritize it in long-term declarative memory over neutral information has been called into question after it was determined that a *majority* of investigations were unable to replicate this effect. As it stands, it is important to reassess the current literature with regard to

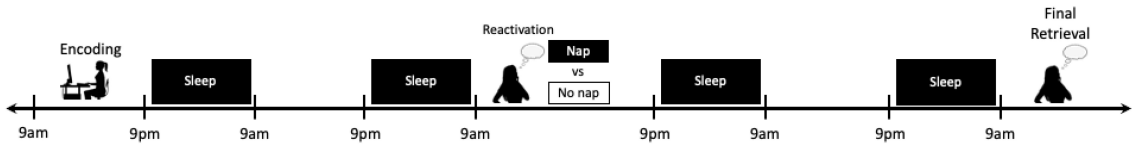

FIGURE 7
Schematics of a potential study protocol designed to target the effects of sleep manipulation on post-retrieval, reconsolidation processing of emotional memory. In the typical reconsolidation study design, the encoding, reactivation, and retrieval sessions typically take place days apart with full nights of sleep in between, allowing for the investigation into the specific effects of sleep manipulation after reactivation using nap or sleep deprivation protocols. While sleep has been shown to be an important component of the reconsolidation process in other forms of declarative memory, investigations into the effects on emotional episodic memory remain scarce.

different factors that may be responsible for generating these mixed findings (e.g., type of stimuli and testing, intensity of stimuli, amount of time between encoding and retrieval, the type of sleep manipulation, etc.). Here, we contribute to this work by reviewing the literature in the context of the placement of sleep with regard to the formation and evolution of an emotional memory.

In general, the extreme absence of sleep through manipulations such as TSD appears to have a near ubiquitous negative effect on overall memory performance compared to normal sleeping behavior, regardless of what memory stage it is introduced (Drummond et al., 2000; Stickgold et al., 2000; Walker and Stickgold, 2006; Sterpenich et al., 2007; Wagner et al., 2007; Fernandes-Santos et al., 2012; Tempesta et al., 2016, 2017). Moreover, a period of sleep frequently has a beneficial effect on overall memory as compared to a matched period of daytime wakefulness (e.g., Prehn-Kristensen et al., 2009; Baran et al., 2012; Alger and Payne, 2016; Lehmann et al., 2016b; Whitehurst et al., 2016; Bolinger et al., 2018), though this is not always the case (e.g., Ashton et al., 2019; Bolinger et al., 2019; Huan et al., 2020). With regard to sleep prior to encoding, TSD seems to impair memory for all valences (Kaida et al., 2015), though may have the *least* detrimental effect on subsequent memory for aversive stimuli (Walker and Stickgold, 2006; Tempesta et al., 2016) resulting in what may appear to be a prioritization of negative information. As previously reviewed (Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021), the literature on the effects of sleep on the early consolidation period of emotional memory processing is quite mixed. While a majority of studies indicate that sleep does have a positive effect on overall memory, regardless of valence, only a small portion of studies indicate that it specifically prioritizes emotionally arousing information during this period (Davidson et al., 2021). The exception to this general trend has been studies that use the emotional memory trade-off paradigm (Kensinger et al., 2007), which has indicated that sleep during the early consolidation period reliably leads to enhanced memory for negative central details over neutral peripheral details (Payne et al., 2008, 2012, 2015; Payne and Kensinger, 2011; Alger et al., 2018).

Studies specifically targeting the effects of sleep and sleep loss on emotional episodic memory during the extended consolidation, pre-retrieval, and post-retrieval stages of memory processing remain particularly scarce. For extended consolidation, one study of word pairs in children found no sleep effects on memory regardless of whether sleep occurred during early or extended consolidation (Vermeulen et al., 2017), while a study using the emotional trade-off paradigm found that delaying sleep to the extended consolidation period resulted in less of an impact than sleep obtained during the early consolidation period (Payne et al., 2012). Finally, the sole study that investigated the impact of sleep on the reconsolidation of emotional episodic memories found that participants that napped after imagery rescripting ended up with a reduced heart rate response to the negative memory script the next time it was presented (Azza et al., 2022). Notably, most of the work cited here was not able to completely eliminate all potential overlap between sleep stages and confounding circadian and sleep pressure effects, motivating future work that continues to work toward isolating the effects of sleep on each stage of emotional memory processing.

Targets for future research

Given the lack of research in some of these windows of episodic emotional memory development, we also aim to support future research by identifying the least studied memory stages with regard to the effects of sleep and emotional declarative memory processing and seek to re-initiate a discussion on the best protocol practices to attempt to target each memory phase with minimal overlap with other phases. The vast majority of research has been on the effects of sleep during the early consolidation phase. One possible explanation for the hyper-focus on this stage of emotional memory processing with regard to sleep is that much of the foundational research has indicated that sleep (Stickgold et al., 2000; Walker et al., 2003; Stickgold, 2005) and emotion (McGaugh, 2000, 2004) each individually have major influences on memory during this period, making it a prime target when searching for the interaction between these two factors. Given the increase in mixed findings of this effect, however, it would be worthwhile

to broaden the search and isolate the impact of sleep manipulations on other, less studied stages of emotional episodic memory development.

The extended consolidation and post-retrieval periods currently remain two of the least studied periods of emotional memory processing. Further, while sleep is manipulated prior to retrieval in many commonly used study designs, especially when the effects of Process S and Process C are taken into consideration, essentially no human research has been done with the explicit goal of targeting this phase of emotional episodic memory processing. This is rather surprising given that it is a period that can be relatively well isolated from the other phases of memory processing, animal models suggest that the absence of sleep pre-retrieval impacts memory performance, and recent models of emotional memory that emphasize effects operating at retrieval (e.g., Bowen et al., 2018; Talmi et al., 2019). Thus, while the vast majority of sleep and emotional memory research has targeted the early consolidation phase of memory processing, recent reviews indicate that the findings have been quite mixed with small effects at best. By broadening the scope of the different ways that sleep can influence an emotional memory and researching each phase in a deliberate, stepwise manner, we may identify confounding influences leading to this surge in mixed results and better understand the strengths and limitations of this effect.

Need for novel protocol development

Research in this area would also benefit from increased ingenuity with regard to protocol development. As discussed above, many of the traditional sleep vs. wake, sleep vs. sleep deprivation, and nap vs. no nap study designs manipulate sleep and wake at multiple phases of memory processing, especially when Process S and Process C are taken into consideration. Additionally, several studies in this area have used "early sleep vs. late sleep" paradigms to try to target differential effects of slow wave sleep and REM sleep on emotional memory processing (Wagner, 2001; Wagner et al., 2006; Groch et al., 2013, 2015; Sopp et al., 2017). While these studies do successfully manipulate the makeup of the sleep macroarchitecture during the early consolidation period, there are also group differences in sleep homeostasis and circadian effects during encoding and retrieval in action as well. This overlap in memory phases may be particularly confounding when considering emotional memory as any differential processing between emotional declarative memory and other forms of declarative memory is predicated on the fact that the experience and processing of an emotionally arousing event triggers unique neurophysiological responses that tag that information as being particularly relevant and worth prioritization in our memory (Payne and Kensinger, 2018; Payne, 2020). As such, any change along the pipeline of emotional memory processing may have substantial impact on how it is ultimately remembered and retrieved, and factors like sleep pressure and circadian phase likely interact with the initial experience and early consolidation of an emotional event.

We have highlighted some potential protocol designs above aimed at better dissociating the different memory phases from one another, but even several of these fail to completely control for all potential sleep-related effects and overlap between memory phases. Beyond our suggestions, there are also substantial opportunities – and frankly a need – for collaboration between sleep and circadian researchers. For instance, while circadian control groups may aid in statistically controlling for circadian effects, a forced desynchrony experiment could systematically disentangle the contributions of sleep from circadian rhythm at a neurophysiological level (Dijk et al., 1992, 1999; Zhou et al., 2011). In these protocols, participants are scheduled to live on days that are substantially shorter or longer than the typical, free-running 24.1–24.2 h circadian period (Borbély and Achermann, 1999). Sleep episodes are thereby scheduled at different periods within the circadian phase. In this way, the effects of sleep and circadian phase can be disassociated and compared. Not only has this protocol been used to isolate EEG components driven by Process S and Process C (Dijk and Czeisler, 1995), but it has also already been used to distinguish differential effects of homeostatic sleep pressure and circadian phase on non-emotional cognitive tasks involving planning and sequence learning (Dijk et al., 1992; Cajochen et al., 2004). While herculean in nature, it is this type of elegant study design that is going to ultimately allow us to distinguish the effects between Process S and C on emotional memory consolidation with certainty, and by piggybacking on a study by circadian sleep researchers, both the cost and effort of the memory study can become minimal.

While our goal here is to encourage the field to move further with collaboration and study design innovation, we also acknowledge that several of the protocols that we have proposed suggest taking a study design that can typically occur in a single visit (e.g., encoding and testing immediately pre- and post-sleep or sleep deprivation) and stretches it out across multiple visits. These additions would increase logistical complexity, could reduce the range of participants able to participate, and cost and may become prohibitive. Given these barriers, we are not suggesting that there is no knowledge to be gained from the standard study designs. However, the limitations of these designs should be openly discussed and understood, and ideally immediate testing and/or circadian controls can be employed to help account for these additional influences when longer protocols are not possible. Ultimately, our goal is to promote increased deliberateness with which we conduct our studies to intentionally isolate the memory phase that we are studying and acknowledge the potential influence of overlap between phases when that is not possible.

Practical considerations

As part of this call for protocol development, there are several open questions that merit further investigation of their own. To begin, there are a number of practical elements that would benefit from heightened consideration in this line of research. For instance, it is important to understand how sleep placement might interact with some of the other elements that have been identified as possibly important for emotional memory processing, such as stimulus intensity and the type of encoding and retrieval assessment used. One challenge faced by researchers is the substantial diversity in tasks and assessments used to assess episodic emotional memory, which makes it difficult to track trends across the literature. The lack of standardization in the field is likely due to the fact that both episodic memory and the human experience of emotion are sufficiently complex that there can be no single task that captures all of their canonical features and interactions. As such, a variety of tasks have been developed in an attempt to capture the different components of emotional memory that can be reasonably measured within a laboratory space. While this does inevitably lead to a 'weakness,' in that there are a number of mixed findings that must be sorted out to try to make sense of the literature, it is also a potential 'strength' in that when results do begin to consistently coalesce around a common effect, our confidence that the effect is legitimate increases, especially when there is slight variability in tasks and stimuli used.

The field of sleep and emotional memory is currently at a crossroads as a growing number of studies fail to replicate the preferential retention of emotional memory elements associated with sleep. Similar to our focus on the "placement of sleep" here, we are in need of additional task-centric conversations in order to make better sense of the field as it stands and to help guide future research. To begin, it will be imperative that effect sizes are reported in this line of research. Comparing the magnitude of effect for different emotional memory probes will be invaluable in disentangling where the effects of sleep are consistent. With the normalization of this level of data transparency moving forward, similar reviews and meta-analyses can be conducted at regular intervals with a focus on how task designs, stimuli, retrieval probes, and calculations of memory relate to the effect of sleep, an effort that has already been initiated by some of our colleagues (e.g., Lipinska et al., 2019; Schäfer et al., 2020; Davidson et al., 2021).

An example of task type interacting with the effect of sleep on emotional memory consolidation is the relatively consistent success of studies finding a sleep effect when utilizing the emotional memory trade-off (ETO) paradigm (Kensinger et al., 2007; Payne et al., 2008). One element of the memory trade-off design that may be essential for revealing sleep x emotion interactions on memory is that encoding is *incidental*, and even in cases where participants might suspect a memory test, no participant reports that they expected their memory to be tested for *components* of scenes. This design may therefore mirror some of the most important aspects of real-world episodic memories: Events are multifaceted, we tend to be processing those events for reasons other than memorizing what is happening to us, and we are almost never re-presented with an entire event (a standard old/new recognition test) nor asked to recall with no cues everything that we experienced (a standard recall test). The incidental nature of the memory task may be particularly important, as a study by Bennion et al. (2016) found that when trade-off stimuli were presented under conditions in which people either knew that their memory would be tested or were unaware of the subsequent memory test, sleep prioritized emotional vs. neutral content when studied in the incidental condition, but not when studied in the intentional encoding condition. Another benefit of the ETO task is that some versions assess both strict veridical memory and more lenient general or gist memory. Importantly, assessing specific, veridical memory for previously viewed stimuli is just one way that memory can be assessed, and the ETO paradigm is just one example of a task that assesses memory at different levels of specificity. A number of the studies highlighted above distinguish between the strength (e.g., Remember vs. Know paradigms; Sterpenich et al., 2007, 2009; Atienza and Cantero, 2008) or resolution of memory (e.g., veridical vs. gist memory in ETO task or Deese–Roediger–McDermott task; McKeon et al., 2012; Payne et al., 2012; Kurz et al., 2019), which may be more ecologically similar to how emotional events are actually retained in our memory. Both the type of probe and the strength of the memory trace may be important elements that interact with the placement of sleep leading to more or less reliable findings and warrant further investigation and subsequent reviews aimed specifically at their contributions to this relationship. Ultimately, there may be a certain set of factors that generate the most reliable effects of sleep on emotional memory processing.

Another practical question is the effect of multiple memory tests in longer sleep and memory protocols. For example, some studies have had participants test on half of the material that they encoded after a 12-h period of sleep or wake, and then return to the lab several days or a week later for a second memory test on the other half of the materials. These memory tests are frequently viewed as being equivalent in nature, just over longer delay intervals. Critically, however, many memory reconsolidation periods can use a similar protocol in which memory for some of the items or just the task itself may be activated, followed by another delay before final testing. In studies that utilize these multiple tests, it is important to understand how an initial memory test (and whether it is followed by sleep or wakefulness) might reactivate and reconsolidate the material that has yet to be tested.

A related point is that cognitive models of memory are increasingly recognizing the importance of context effects at retrieval in predicting what information comes to mind and what information is not able to be accessed. Context can refer

to the match between the encoded context and the retrieved context or to fluctuations in context across the retrieval epoch that may be related to the earlier information that has been brought to mind (see Bowen et al., 2018; Talmi et al., 2019). As we noted earlier, many sleep-wake designs that attribute their effects to influences on consolidation are, in fact, also manipulating sleep pre-retrieval. Future work will be well served to consider how this may affect results. For instance, if sleep enhances consolidation, this benefit could be masked when those in the sleep condition are experiencing a change in context from pre-encoding (no sleep) to pre-retrieval (sleep) while those in the wake condition are not.

Beyond these considerations that relate to the placement of sleep within the context of the memory experiment, there is the challenge of considering sleep history and individual differences as well. Pre-encoding sleep could be thought to include the aggregation of multiple nights of sleep or sleep loss leading up to the experience of an emotional event, and it is likely that all stages of emotional memory processing are affected in those that have consistent difficulty sleeping. Moreover, research has indicated that individual differences (Chuah et al., 2009) and demographic factors such as sex (Killgore et al., 2008b; Fernandes-Santos et al., 2012; Goldstein et al., 2013) and age (Philip et al., 2004; Duffy et al., 2009; Talbot et al., 2010) may also impact the degree to which we are affected by sleep loss. While tools such as actigraphy and sleep logs can give us a peek into the typical sleeping habits of our participants, it is likely that more than a single night of sleep influences our interpretation of and interaction with emotional events. More research into these individual differences will contribute to our broader understanding of the effects of sleep on emotional perception and memory processing.

Theoretical considerations

Beyond these practical considerations, there are a number of broader, theoretical questions that need to be addressed as well. For instance, one consideration particularly relevant to this review is that "sleep's effect" on emotional memory may highly depend on the cognitive and affective processing that is engaged surrounding the placement of the sleep manipulation. As noted, a majority of sleep and emotional memory research has focused on the early consolidation stage of memory processing. This stage has been particularly tantalizing for researchers given evidence that suggests distinct neurophysiological responses rise during the experience of arousing events that tag that experience for prioritized processing during the early consolidation period, thereby enhancing long-term retention (Payne and Kensinger, 2018; Payne, 2020). However, isolating the effects of the sleep manipulation on the different stages of memory processing could reveal other co-occurring mechanisms that add to the overall variability of the sleep effect. For instance, perhaps the most established impact of sleep deprivation is its negative effect on attentional resources (Durmer and Dinges, 2005). If the effect of a sleep manipulation could be isolated to the pre-encoding stage of memory processing, we may find that a lack of attentional resources leads to an increased focus on emotional information (i.e., emotional content grabs our attention even when tired). Thus, the prioritization of this information being preserved long-term may begin even before any preferential processing can occur during early consolidation. Taking a step-wise approach to investigating the effects of different placements of sleep manipulations across the stages of emotional memory processing identified here would help us to better understand the different effects that contribute to the impact of sleep on emotional memory and their magnitude.

Another factor that remains unclear is how long it takes for a memory of any kind, let alone an emotional memory, to transition from the "early" to "extended" consolidation period. Indeed, many things about the time course of a memory that might have seemed to be settled science – such as the exponential forgetting curve discovered by Ebbinghaus – have recently been drawn into question (Radvansky et al., 2022). It seems as though sleep itself expedites this transition into "extended" consolidation, but it remains to be determined if the waking brain can make this transition alone, and if so, how long it takes. If the waking brain can make this transition alone, then the question remains about the differential impact of manipulating sleep at these different periods.

More generally, most frameworks for understanding the effects of sleep and emotional memory consolidation seem to build from models that assume a similar hippocampal-dependency for emotional and neutral memory consolidation, perhaps motivated by models of emotional memory that focused on synergistic relations between the amygdala and hippocampus (e.g., McGaugh, 2000, 2004). Yet other models of emotional memory propose diminished roles for hippocampal-dependent processes, and increased roles for amygdala-dependent processes, in long-term retention of emotional components of episodic experiences (e.g., Yonelinas and Ritchey, 2015; Bisby et al., 2016). Framing effects of sleep within the context of these models may lead to different predictions for how sleep influences emotional memory vs. neutral memory consolidation.

Beyond emotional memory

Finally, we want to reiterate that here we solely focused on the relationship between sleep placement and declarative memory for the content of emotional experiences. One of the major challenges in the human sleep and memory field in general is that there is extensive variability in the research that may have substantial impact on the results that continues to be poorly understood. These include factors such as the placement

and type of the sleep manipulation, the type of task or memory test used, and the type and intensity of the emotional stimuli. As such, doing similar breakdowns of different types of memories (e.g., working memory, procedural memory, fear memory, autobiographical memory, etc.) would be a worthwhile endeavor that would ultimately lead to a greater understanding of the strength and limitations of the effect of sleep on overall memory processing. Additionally, this review exclusively focused on sleep's role in memory retention for the content of emotional experience. Substantial research has indicated that sleep may also play an active role in modulating the emotional tone or affectivity associated with emotional experiences (Walker and van Der Helm, 2009; van der Helm et al., 2011; Baran et al., 2012; Cunningham et al., 2014a; Bolinger et al., 2019). As such, the relationship between sleep and affective modulation of emotional experiences would benefit from a similar discussion on the effects of sleep placement, especially given the additional clinical implications of this effect.

Conclusion

In summary, initial evidence suggests that sleep and sleep loss has differential effects depending on what phase in the evolution of an emotional memory it is manipulated. Here, we operationalized these stages as (1) prior to encoding, (2) immediately following encoding during early consolidation, (3) during extended consolidation away from initial learning, (4) just prior to retrieval, and (5) post-retrieval/reconsolidation. While some of these phases have been extensively studied with regard to the impact of sleep (i.e., sleep during early consolidation), others remain under-researched, particularly in the context of intentional research targeting that phase of emotional memory processing (i.e., extended consolidation, prior to retrieval, reconsolidation). Moreover, the absence or presence of sleep is often manipulated in multiple phases of emotional memory processing in a number of the typical study designs used in the field, with factors such as sleep pressure, time of day, and circadian effects not always taken into consideration. Given the recent surge of mixed findings with regard to the role of sleep in emotional memory processing, future research should aim to disentangle the effects of sleep on these different components in the evolution of an emotional memory, and memory in general, through intentional, targeted study protocols that do their best to account for sleep homeostatic and circadian influences.

Author contributions

TC was primary author responsible for drafting initial manuscript with EK and RS providing additional comments, edits, feedback, material, and direction. All authors contributed to the concept and major elements of the review.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Ackermann, S., Cordi, M., La Marca, R., Seifritz, E., and Rasch, B. (2019). Psychosocial stress before a nap increases sleep latency and decreases early slow-wave activity. *Front. Psychol.* 10:20. doi: 10.3389/fpsyg.2019.00020

Ackermann, S., Hartmann, F., Papassotiropoulos, A., de Quervain, D. J. F., and Rasch, B. (2015). No associations between interindividual differences in sleep parameters and episodic memory consolidation. *Sleep* 38, 951–959. doi: 10.5665/sleep.4748

Agren, T. (2014). Human reconsolidation: A reactivation and update. *Brain Res. Bull.* 105, 70–82. doi: 10.1016/j.brainresbull.2013.12.010

Alberini, C. M., and LeDoux, J. E. (2013). Memory reconsolidation. *Curr. Biol.* 23, R746–R750. doi: 10.1016/j.cub.2013.06.046

Alfarra, R., Fins, A. I., Chayo, I., and Tartar, J. L. (2015). Changes in attention to an emotional task after sleep deprivation: Neurophysiological and behavioral findings. *Biol. Psychol.* 104, 1–7. doi: 10.1016/j.biopsycho.2014.11.001

Alger, S. E., Chambers, A. M., Cunningham, T., and Payne, J. D. (2014). "The role of sleep in human declarative memory consolidation," in *Sleep, Neuronal Plasticity and Brain Function*, Vol. 25, eds P. Meerlo, R. M. Benca, and T. Abel (Berlin: Springer), 269–306. doi: 10.1007/7854_2014_341

Alger, S. E., Kensinger, E. A., and Payne, J. D. (2018). Preferential consolidation of emotionally salient information during a nap is preserved in middle age. *Neurobiol. Aging* 68, 34–47. doi: 10.1016/j.neurobiolaging.2018.03.030

Alger, S. E., Lau, H., and Fishbein, W. (2012). Slow wave sleep during a daytime nap is necessary for protection from subsequent interference and long-term retention. *Neurobiol. Learn. Mem.* 98, 188–196. doi: 10.1016/j.nlm.2012.06.003

Alger, S. E., and Payne, J. D. (2016). The differential effects of emotional salience on direct associative and relational memory during a nap. *Cogn. Affect. Behav. Neurosci.* 16, 1150–1163. doi: 10.3758/s13415-016-0460-1

Anderson, M. C., and Hulbert, J. C. (2021). Active forgetting: Adaptation of memory by prefrontal control. *Annu. Rev. Psychol.* 72, 1–36. doi: 10.1146/annurev-psych-072720-094140

Antony, J. W., Gobel, E. W., O'hare, J. K., Reber, P. J., and Paller, K. A. (2012). Cued memory reactivation during sleep influences skill learning. *Nat. Neurosci.* 15, 1114–1116.

Ashton, J. E., Cairney, S. A., and Gaskell, M. G. (2018). No effect of targeted memory reactivation during slow-wave sleep on emotional recognition memory. *J. Sleep Res.* 27, 129–137. doi: 10.1111/jsr.12542

Ashton, J. E., Harrington, M. O., Guttesen, A. Á. V., Smith, A. K., and Cairney, S. A. (2019). Sleep preserves physiological arousal in emotional memory. *Sci. Rep.* 9:5966. doi: 10.1038/s41598-019-42478-2

Atienza, M., and Cantero, J. L. (2008). Modulatory effects of emotion and sleep on recollection and familiarity. *J. Sleep Res.* 17, 285–294. doi: 10.1111/j.1365-2869.2008.00661.x

Azza, Y., Wilhelm, F. H., Seifritz, E., Junghanns, K., Kleim, B., and Wilhelm, I. (2022). Sleep's role in updating aversive autobiographical memories. *Transl. Psychiatry* 12:117. doi: 10.1038/s41398-022-01878-1

Baran, B., Pace-Schott, E. F., Ericson, C., and Spencer, R. M. C. (2012). Processing of emotional reactivity and emotional memory over sleep. *J. Neurosci.* 32, 1035–1042. doi: 10.1523/JNEUROSCI.2532-11.2012

Baum, K. T., Desai, A., Field, J., Miller, L. E., Rausch, J., and Beebe, D. W. (2014). Sleep restriction worsens mood and emotion regulation in adolescents. *J. Child Psychol. Psychiatry* 55, 180–190. doi: 10.1111/jcpp.12125

Baxter, B., Kwok, K., Talbot, C., Zhu, L., Mylonas, D., Stickgold, R., et al. (2020). Evaluating closed-loop auditory stimulation during sleep as an intervention to improve memory consolidation deficits in schizophrenia. *Biol. Psychiatry* 87, S283–S284.

Beersma, D. G. M., Dijk, D. J., Blok, C. G. H., and Everhardus, I. (1990). REM sleep deprivation during 5 hours leads to an immediate REM sleep rebound and to suppression of non-REM sleep intensity. *Electroencephalogr. Clin. Neurophysiol.* 76, 114–122. doi: 10.1016/0013-4694(90)90209-3

Ben Simon, E., Vallat, R., Barnes, C. M., and Walker, M. P. (2020). Sleep loss and the socio-emotional brain. *Trends Cogn. Sci.* 24, 435–450. doi: 10.1016/j.tics.2020.02.003

Bennion, K. A., Payne, J. D., and Kensinger, E. A. (2016). The impact of napping on memory for future-relevant stimuli: Prioritization among multiple salience cues. *Behav. Neurosci.* 130, 281–289. doi: 10.1037/bne0000142

Bisby, J. A., Horner, A. J., Hørlyck, L. D., and Burgess, N. (2016). Opposing effects of negative emotion on amygdalar and hippocampal memory for items and associations. *Soc. Cogn. Affect. Neurosci.* 11, 981–990. doi: 10.1093/scan/nsw028

Blatter, K., and Cajochen, C. (2007). Circadian rhythms in cognitive performance: Methodological constraints, protocols, theoretical underpinnings. *Physiol. Behav.* 90, 196–208. doi: 10.1016/j.physbeh.2006.09.009

Bolinger, E., Born, J., and Zinke, K. (2018). Sleep divergently affects cognitive and automatic emotional response in children. *Neuropsychologia* 117, 84–91. doi: 10.1016/j.neuropsychologia.2018.05.015

Bolinger, E., Cunningham, T. J., Payne, J. D., Bowman, M. A., Bulca, E., Born, J., et al. (2019). Sleep's benefits to emotional processing emerge in the long term. *Cortex* 120, 457–470. doi: 10.1016/j.cortex.2019.07.008

Borbély, A. A. (2009). Refining sleep homeostasis in the two-process model. *J. Sleep Res.* 18, 1–2. doi: 10.1111/j.1365-2869.2009.00750.x

Borbély, A. A., and Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *J. Biol. Rhythms* 14, 559–570.

Bowen, H. J., Kark, S. M., and Kensinger, E. A. (2018). NEVER forget: Negative emotional valence enhances recapitulation. *Psychon. Bull. Rev.* 25, 870–891. doi: 10.3758/s13423-017-1313-9

Brunner, D. P., Dijk, D. J., Tobler, I., and Borbély, A. A. (1990). Effect of partial sleep deprivation on sleep stages and EEG power spectra: Evidence for non-REM and REM sleep homeostasis. *Electroencephalogr. Clin. Neurophysiol.* 75, 492–499. doi: 10.1016/0013-4694(90)90136-8

Bryant, N. B., Nadel, L., and Gómez, R. L. (2020). Associations between sleep and episodic memory updating. *Hippocampus* 30, 794–805. doi: 10.1002/hipo.23178

Cairney, S. A., Durrant, S. J., Hulleman, J., and Lewis, P. A. (2014). Targeted memory reactivation during slow wave sleep facilitates emotional memory consolidation. *Sleep* 37, 701–707.

Cajochen, C., Blatter, K., and Wallach, D. (2004). Circadian and sleep-wake dependent impact on neurobehavioral function. *Psychol. Belg.* 44, 59–80.

Carollo, G., Degasperi, G., and Cellini, N. (2022). The role of sleep and wakefulness in the recognition of emotional pictures. *J. Sleep Res.* 31, 1–13. doi: 10.1111/jsr.13695

Carskadon, M. A., Acebo, C., and Jenni, O. G. (2004). Regulation of adolescent sleep: Implications for behavior. *Ann. N. Y. Acad. Sci.* 1021, 276–291. doi: 10.1196/annals.1308.032

Carskadon, M. A., and Dement, W. C. (1979). Effects of total sleep loss on sleep tendency. *Percept. Mot. Skills* 48, 495–506. doi: 10.2466/pms.1979.48.2.495

Cassini, L., and Lee, J. (2018). On the synaptic tagging and capture hypothesis and the process of memory reconsolidation. *Eur. Neuropsychopharmacol.* 28:S56. doi: 10.1016/j.euroneuro.2017.12.087

Cellini, N., and Capuozzo, A. (2018). Shaping memory consolidation via targeted memory reactivation during sleep. *Ann. N. Y. Acad. Sci.* 1426, 52–71. doi: 10.1111/nyas.13855

Cellini, N., Torre, J., Stegagno, L., and Sarlo, M. (2016). Sleep before and after learning promotes the consolidation of both neutral and emotional information regardless of REM presence. *Neurobiol. Learn. Mem.* 133, 136–144. doi: 10.1016/j.nlm.2016.06.015

Chambers, A. M., and Payne, J. D. (2014). Laugh yourself to sleep: Memory consolidation for humorous information. *Exp. Brain Res.* 232, 1415–1427. doi: 10.1007/s00221-013-3779-7

Chuah, L. Y. M., Chong, D. L., Chen, A. K., Rekshan, W. R. III, Tan, J.-C., Zheng, H., et al. (2009). Donepezil improves episodic memory in young individuals vulnerable to the effects of sleep deprivation. *Sleep* 32, 999–1010. doi: 10.1093/sleep/32.8.999

Chuah, L. Y. M., Dolcos, F., Chen, A. K., Zheng, H., Parimal, S., and Chee, M. W. L. (2010). Sleep deprivation and interference by emotional distracters. *Sleep* 33, 1305–1313. doi: 10.1093/sleep/33.10.1305

Cohen, S., Kaplan, Z., Zohar, J., and Cohen, H. (2017). Preventing sleep on the first resting phase following a traumatic event attenuates anxiety-related responses. *Behav. Brain Res.* 320, 450–456. doi: 10.1016/j.bbr.2016.10.039

Cousins, J. N., El-Deredy, W., Parkes, L. M., Hennies, N., and Lewis, P. A. (2014). Cued memory reactivation during slow-wave sleep promotes explicit knowledge of a motor sequence. *J. Neurosci.* 34, 15870–15876. doi: 10.1523/JNEUROSCI.1011-14.2014

Cox, R., and Fell, J. (2020). Analyzing human sleep EEG: A methodological primer with code implementation. *Sleep Med. Rev.* 54:101353. doi: 10.1016/j.smrv.2020.101353

Cox, R., Hofman, W. F., and Talamini, L. M. (2012). Involvement of spindles in memory consolidation is slow wave sleep-specific. *Learn. Mem.* 19, 264–267. doi: 10.1101/lm.026252.112

Cox, R., Mylonas, D. S., Manoach, D. S., and Stickgold, R. (2018a). Large-scale structure and individual fingerprints of locally coupled sleep oscillations. *Sleep* 41:zsy175. doi: 10.1093/sleep/zsy175

Cox, R., van Bronkhorst, M. L. V., Bayda, M., Gomillion, H., Cho, E., Parr, M. E., et al. (2018b). Sleep selectively stabilizes contextual aspects of negative memories. *Sci. Rep.* 8:17861. doi: 10.1038/s41598-018-35999-9

Cox, R., Schapiro, A. C., Manoach, D. S., and Stickgold, R. (2017). Individual differences in frequency and topography of slow and fast sleep spindles. *Front. Hum. Neurosci.* 11:433. doi: 10.3389/fnhum.2017.00433

Cross, Z. R., Santamaria, A., Corcoran, A. W., Chatburn, A., Alday, P. M., Coussens, S., et al. (2020). Individual alpha frequency modulates sleep-related emotional memory consolidation. *Neuropsychologia* 148:107660. doi: 10.1016/j.neuropsychologia.2020.107660

Cunningham, T. J., Chambers, A. M., and Payne, J. D. (2014c). Prospection and emotional memory: How expectation affects emotional memory formation following sleep and wake. *Front. Psychol.* 5:862. doi: 10.3389/fpsyg.2014.00862

Cunningham, T. J., Crowell, C. R., Alger, S. E., Kensinger, E. A., Villano, M. A., Mattingly, S. M., et al. (2014a). Psychophysiological arousal at encoding leads to reduced reactivity but enhanced emotional memory following sleep. *Neurobiol. Learn. Mem.* 114, 155–164. doi: 10.1016/j.nlm.2014.06.002

Cunningham, T. J., Pardilla-Delgado, E., Alger, S., and Payne, J. (2014b). "The role of REM sleep in emotional memory and affective reactivity in humans," in *REM Sleep: Characteristics, disorders and physiological effects*, ed. C. L. Saylor (Hauppauge, NY: Nova Science Publishers), 1–28. doi: 10.13140/2.1.1609.0560

Cunningham, T. J., Bottary, R., Denis, D., and Payne, J. D. (2021a). Sleep spectral power correlates of prospective memory maintenance. *Learn. Mem.* 28, 291–299. doi: 10.1101/lm.053412.121

Cunningham, T. J., Mattingly, S. M., Tlatenchi, A., Wirth, M. M., Alger, S. E., Kensinger, E. A., et al. (2021b). Higher post-encoding cortisol benefits the selective consolidation of emotional aspects of memory. *Neurobiol. Learn. Mem.* 180:107411. doi: 10.1016/j.nlm.2021.107411

Cunningham, T. J., and Payne, J. D. (2017). "Emotional memory consolidation during sleep," in *Cognitive neuroscience of memory consolidation*, eds N. Axmacher and B. Rasch (Cham: Springer International Publishing), 133–159. doi: 10.1007/978-3-319-45066-7_9

Czeisler, C. A., and Klerman, E. B. (1999). Circadian and sleep-dependent regulation of hormone release in humans. *Recent Prog. Horm. Res.* 54, 97–130; discussion 130–132.

Czeisler, C. A., Weitzman, E. D., Moore-Ede, M. C., Zimmerman, J. C., and Knauer, R. S. (1980). Human sleep: Its duration and organization depend on its circadian phase.. *Science* 210, 1264–1267. doi: 10.1126/science.7434029

Davidson, P., Jönsson, P., Carlsson, I., and Pace-Schott, E. (2021). Does sleep selectively strengthen certain memories over others based on emotion and perceived future relevance? *Nat. Sci. Sleep* 13, 1257–1306. doi: 10.2147/NSS.S286701

Davis, R. L., and Zhong, Y. (2017). The biology of forgetting—a perspective. *Neuron* 95, 490–503. doi: 10.1016/j.neuron.2017.05.039

Denis, D., Mylonas, D., Poskanzer, C., Bursal, V., Payne, J. D., and Stickgold, R. (2021). Sleep spindles preferentially consolidate weakly encoded memories. *J. Neurosci.* 41, 4088–4099. doi: 10.1523/JNEUROSCI.0818-20.2021

Diekelmann, S., Büchel, C., Born, J., and Rasch, B. (2011). Labile or stable: Opposing consequences for memory when reactivated during waking and sleep. *Nat. Neurosci.* 14, 381–386.

Dijk, D. J., Brunner, D. P., Beersma, D. G., and Borbély, A. A. (1990). Electroencephalogram power density and slow wave sleep as a function of prior waking and circadian phase. *Sleep* 13, 430–440.

Dijk, D. J., and Czeisler, C. A. (1995). Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J. Neurosci.* 15, 3526–3538. doi: 10.1523/JNEUROSCI.15-05-03526.1995

Dijk, D.-J., Duffy, J. F., and Czeisler, C. A. (1992). Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J. Sleep Res.* 1, 112–117. doi: 10.1111/j.1365-2869.1992.tb00021.x

Dijk, D. J., Duffy, J. F., Riel, E., Shanahan, T. L., and Czeisler, C. A. (1999). Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *J. Physiol.* 516(Pt 2), 611–627. doi: 10.1111/j.1469-7793.1999.0611v.x

Donohue, K. C., and Spencer, R. M. (2011). Continuous re-exposure to environmental sound cues during sleep does not improve memory for semantically unrelated word pairs. *J. Cogn. Educ. Psychol.* 10, 167–177. doi: 10.1891/1945-8959.10.2.167

Drummond, S. P. A., Brown, G. G., Gillin, J. C., Stricker, J. L., Wong, E. C., and Buxton, R. B. (2000). Altered brain response to verbal learning following sleep deprivation. *Nature* 403, 655–657.

Drummond, S. P. A., Brown, G. G., Salamat, J. S., and Gillin, J. C. (2004). Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. *Sleep* 27, 445–451. doi: 10.1093/sleep/27.3.445

Dudai, Y., Karni, A., and Born, J. (2015). The consolidation and transformation of memory. *Neuron* 88, 20–32. doi: 10.1016/j.neuron.2015.09.004

Duffy, J. F., Willson, H. J., Wang, W., and Czeisler, C. A. (2009). Healthy older adults better tolerate sleep deprivation than young adults. *J. Am. Geriatr. Soc.* 57, 1245–1251. doi: 10.1111/j.1532-5415.2009.02303.x

Durmer, J. S., and Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Semin. Neurol.* 25:13.

Ekstrand, B. R. (1967). Effect of sleep on memory. *J. Exp. Psychol.* 75, 64–72. doi: 10.1037/h0024907

Ellenbogen, J. M., Payne, J. D., and Stickgold, R. (2006). The role of sleep in declarative memory consolidation: Passive, permissive, active or none? *Curr. Opin. Neurobiol.* 16, 716–722. doi: 10.1016/j.conb.2006.10.006

Feng, P., Becker, B., Zheng, Y., and Feng, T. (2018). Sleep deprivation affects fear memory consolidation: Bi-stable amygdala connectivity with insula and ventromedial prefrontal cortex. *Soc. Cogn. Affect. Neurosci.* 13, 145–155. doi: 10.1093/scan/nsx148

Fernandes-Santos, L., Patti, C. L., Zanin, K. A., Fernandes, H. A., Tufik, S., Andersen, M. L., et al. (2012). Sleep deprivation impairs emotional memory retrieval in mice: Influence of sex. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 38, 216–222. doi: 10.1016/j.pnpbp.2012.03.014

Fischer, S., Hallschmid, M., Elsner, A. L., and Born, J. (2002). Sleep forms memory for finger skills. *Proc. Natl. Acad. Sci. U.S.A.* 99, 11987–11991. doi: 10.1073/pnas.182178199

Gilson, M., Deliens, G., Leproult, R., Bodart, A., Nonclercq, A., Ercek, R., et al. (2016). REM-enriched naps are associated with memory consolidation for sad stories and enhance mood-related reactivity. *Brain Sci.* 6:1. doi: 10.3390/brainsci6010001

Göder, R., Graf, A., Ballhausen, F., Weinhold, S., Baier, P. C., Junghanns, K., et al. (2015). Impairment of sleep-related memory consolidation in schizophrenia: Relevance of sleep spindles? *Sleep Med.* 16, 564–569. doi: 10.1016/j.sleep.2014.12.022

Goel, N., Rao, H., Durmer, J. S., and Dinges, D. F. (2009). Neurocognitive consequences of sleep deprivation. *Semin. Neurol.* 29, 320–339. doi: 10.1055/s-0029-1237117

Goldschmied, J. R., Cheng, P., Kim, H. S., Casement, M., Armitage, R., and Deldin, P. J. (2015). Slow-wave disruption enhances the accessibility of positive memory traces. *Neurobiol. Learn. Mem.* 125, 168–175. doi: 10.1016/j.nlm.2015.09.006

Goldstein, A. N., Greer, S. M., Saletin, J. M., Harvey, A. G., Nitschke, J. B., and Walker, M. P. (2013). Tired and apprehensive: Anxiety amplifies the impact of sleep loss on aversive brain anticipation. *J. Neurosci.* 33, 10607–10615. doi: 10.1523/JNEUROSCI.5578-12.2013

Goldstein, A. N., and Walker, M. P. (2014). The role of sleep in emotional brain function. *Annu. Rev. Clin. Psychol.* 10, 679–708. doi: 10.1146/annurev-clinpsy-032813-153716

Goldstein-Piekarski, A. N., Greer, S. M., Saletin, J. M., and Walker, M. P. (2015). Sleep deprivation impairs the human central and peripheral nervous system discrimination of social threat. *J. Neurosci.* 35, 10135–10145. doi: 10.1523/JNEUROSCI.5254-14.2015

Groch, S., Preiss, A., McMakin, D. L., Rasch, B., Walitza, S., Huber, R., et al. (2017). Targeted reactivation during sleep differentially affects negative memories in socially anxious and healthy children and adolescents. *J. Neurosci.* 37, 2425–2434. doi: 10.1523/JNEUROSCI.1912-16.2017

Groch, S., Wilhelm, I., Diekelmann, S., and Born, J. (2013). The role of REM sleep in the processing of emotional memories: Evidence from behavior and event-related potentials. *Neurobiol. Learn. Mem.* 99, 1–9. doi: 10.1016/j.nlm.2012.10.006

Groch, S., Zinke, K., Wilhelm, I., and Born, J. (2015). Dissociating the contributions of slow-wave sleep and rapid eye movement sleep to emotional item and source memory. *Neurobiol. Learn. Mem.* 122, 122–130. doi: 10.1016/j.nlm.2014.08.013

Gui, W., Wang, P., Lei, X., Lin, T., Horta, M., Liu, X., et al. (2019). Sleep facilitates consolidation of positive emotional memory in healthy older adults. *Memory* 27, 387–396. doi: 10.1080/09658211.2018.1513038

Harrington, M. O., and Cairney, S. A. (2021). Sleep loss gives rise to intrusive thoughts. *Trends Cogn. Sci.* 25, 434–436. doi: 10.1016/j.tics.2021.03.001

Harrington, M. O., Nedberge, K. M., and Durrant, S. J. (2018). The effect of sleep deprivation on emotional memory consolidation in participants reporting depressive symptoms. *Neurobiol. Learn. Mem.* 152, 10–19. doi: 10.1016/j.nlm.2018.04.013

Hauner, K. K., Howard, J. D., Zelano, C., and Gottfried, J. A. (2013). Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nat. Neurosci.* 16, 1553–1555. doi: 10.1038/nn.3527

He, J., Sun, H. Q., Li, S. X., Zhang, W. H., Shi, J., Ai, S. Z., et al. (2015). Effect of conditioned stimulus exposure during slow wave sleep on fear memory extinction in humans. *Sleep* 38, 423–431.

Hobson, J. A., and Pace-Schott, E. F. (2002). The cognitive neuroscience of sleep: Neuronal systems, consciousness and learning. *Nat. Rev. Neurosci.* 3, 679–693. doi: 10.1038/nrn915

Holland, P., and Lewis, P. A. (2007). Emotional memory: Selective enhancement by sleep. *Curr. Biol.* 17, R179–R181. doi: 10.1016/j.cub.2006.12.033

Hu, P., Stylos-Allan, M., and Walker, M. P. (2006). Sleep facilitates consolidation of emotional declarative memory. *Psychol. Sci.* 17, 891–898. doi: 10.1111/j.1467-9280.2006.01799.x

Hu, X., Cheng, L. Y., Chiu, M. H., and Paller, K. A. (2020). Promoting memory consolidation during sleep: A meta-analysis of targeted memory reactivation. *Psychol. Bull.* 146, 218–244. doi: 10.1037/bul0000223

Huan, S.-Y., Liu, K.-P., Lei, X., and Yu, J. (2020). Age-related emotional bias in associative memory consolidation: The role of sleep. *Neurobiol. Learn. Mem.* 171:107204. doi: 10.1016/j.nlm.2020.107204

Huguet, M., Payne, J. D., Kim, S. Y., and Alger, S. E. (2019). Overnight sleep benefits both neutral and negative direct associative and relational memory. *Cogn. Affect. Behav. Neurosci.* 19, 1391–1403. doi: 10.3758/s13415-019-00746-8

Jenkins, J. G., and Dallenbach, K. M. (1924). Obliviscence during sleep and waking. *Am. J. Psychol.* 35, 605–612.

Joensen, B. H., Harrington, M., Berens, S., Cairney, S., Gaskell, M. G., and Horner, A. J. (2022). Targeted memory reactivation during sleep can induce forgetting of overlapping memories. *PsyArXiv [Preprint]* doi: 10.31234/osf.io/bx3ew

Jones, B. J., Mackay, A., Mantua, J., Schultz, K. S., and Spencer, R. M. C. (2018). The role of sleep in emotional memory processing in middle age. *Neurobiol. Learn. Mem.* 155, 208–215. doi: 10.1016/j.nlm.2018.08.002

Jones, B. J., Schultz, K. S., Adams, S., Baran, B., and Spencer, R. M. C. (2016). Emotional bias of sleep-dependent processing shifts from negative to positive with aging. *Neurobiol. Aging* 45, 178–189. doi: 10.1016/j.neurobiolaging.2016.05.019

Kahn, M., Sheppes, G., and Sadeh, A. (2013). Sleep and emotions: Bidirectional links and underlying mechanisms. *Int. J. Psychophysiol.* 89, 218–228. doi: 10.1016/j.ijpsycho.2013.05.010

Kaida, K., Niki, K., and Born, J. (2015). Role of sleep for encoding of emotional memory. *Neurobiol. Learn. Mem.* 121, 72–79. doi: 10.1016/j.nlm.2015.04.002

Kensinger, E. A., Garoff-Eaton, R. J., and Schacter, D. L. (2007). Effects of emotion on memory specificity: Memory trade-offs elicited by negative visually arousing stimuli. *J. Mem. Lang.* 56, 575–591. doi: 10.1016/j.jml.2006.05.004

Killgore, W. D. S. (2010). Effects of sleep deprivation on cognition. *Prog. Brain Res.* 185, 105–129. doi: 10.1016/B978-0-444-53702-7.00007-5

Killgore, W. D. S. (2013). Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. *Sleep* 36, 1597–1608. doi: 10.5665/sleep.3106

Killgore, W. D. S., Balkin, T. J., Yarnell, A. M., and Capaldi, V. F. (2017). Sleep deprivation impairs recognition of specific emotions. *Neurobiol. Sleep Circadian Rhythms* 3, 10–16. doi: 10.1016/j.nbscr.2017.01.001

Killgore, W. D. S., Kahn-Greene, E. T., Lipizzi, E. L., Newman, R. A., Kamimori, G. H., and Balkin, T. J. (2008a). Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Med.* 9, 517–526. doi: 10.1016/j.sleep.2007.07.003

Killgore, W. D. S., Muckle, A. E., Grugle, N. L., Killgore, D. B., and Balkin, T. J. (2008b). Sex differences in cognitive estimation during sleep deprivation: Effects of stimulant countermeasures. *Int. J. Neurosci.* 118, 1547–1557. doi: 10.1080/00207450802323970

Klinzing, J. G., Rasch, B., Born, J., and Diekelmann, S. (2016). Sleep's role in the reconsolidation of declarative memories. *Neurobiol. Learn. Mem.* 136, 166–173. doi: 10.1016/j.nlm.2016.10.004

Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., et al. (2017). The sleep-deprived human brain. *Nat. Rev. Neurosci.* 18, 404–418. doi: 10.1038/nrn.2017.55

Kuriyama, K., Soshi, T., and Kim, Y. (2010). Sleep deprivation facilitates extinction of implicit fear generalization and physiological response to fear. *Biol. Psychiatry* 68, 991–998. doi: 10.1016/j.biopsych.2010.08.015

Kurz, E.-M., Conzelmann, A., Barth, G. M., Hepp, L., Schenk, D., Renner, T. J., et al. (2019). Signs of enhanced formation of gist memory in children with autism spectrum disorder – a study of memory functions of sleep. *J. Child Psychol. Psychiatry* 60, 907–916. doi: 10.1111/jcpp.13048

Landolt, H.-P. (2008). Sleep homeostasis: A role for adenosine in humans? *Biochem. Pharmacol.* 75, 2070–2079. doi: 10.1016/j.bcp.2008.02.024

Lehmann, M., Schreiner, T., Seifritz, E., and Rasch, B. (2016a). Emotional arousal modulates oscillatory correlates of targeted memory reactivation during NREM, but not REM sleep. *Sci. Rep.* 6:39229. doi: 10.1038/srep39229

Lehmann, M., Seifritz, E., and Rasch, B. (2016b). Sleep benefits emotional and neutral associative memories equally. *Somnologie* 20, 47–53. doi: 10.1007/s11818-015-0034-4

Lewis, P. A., and Bendor, D. (2019). How targeted memory reactivation promotes the selective strengthening of memories in sleep. *Curr. Biol.* 29, R906–R912.

Lim, J., and Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136, 375–389. doi: 10.1037/a0018883

Lipinska, G., Stuart, B., Thomas, K. G. F., Baldwin, D. S., and Bolinger, E. (2019). Preferential consolidation of emotional memory during sleep: A meta-analysis. *Front. Psychol.* 10:1014. doi: 10.3389/fpsyg.2019.01014

Madan, C. R., Knight, A. G., Kensinger, E. A., and Mickley Steinmetz, K. R. (2020). Affect enhances object-background associations: Evidence from behaviour and mathematical modelling. *Cogn. Emot.* 34, 960–969. doi: 10.1080/02699931.2019.1710110

Marshall, L., Mölle, M., Hallschmid, M., and Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *J. Neurosci.* 24, 9985–9992.

McClung, C. A. (2013). How might circadian rhythms control mood? Let me count the ways. *Biol. Psychiatry* 74, 242–249. doi: 10.1016/j.biopsych.2013.02.019

McDermott, C. M., LaHoste, G. J., Chen, C., Musto, A., Bazan, N. G., and Magee, J. C. (2003). Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. *J. Neurosci.* 23, 9687–9695. doi: 10.1523/JNEUROSCI.23-29-09687.2003

McGaugh, J. L. (2000). Memory—a century of consolidation. *Science* 287, 248–251. doi: 10.1126/science.287.5451.248

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.* 27, 1–28. doi: 10.1146/annurev.neuro.27.070203.144157

McGaugh, J. L. (2018). Emotional arousal regulation of memory consolidation. *Curr. Opin. Behav. Sci.* 19, 55–60. doi: 10.1016/j.cobeha.2017.10.003

McKeon, S., Pace-Schott, E. F., and Spencer, R. M. (2012). Interaction of sleep and emotional content on the production of false memories. *PLoS One* 7:e49353. doi: 10.1371/journal.pone.0049353

Miller, A. L., Seifer, R., Crossin, R., and Lebourgeois, M. K. (2015). Toddler's self-regulation strategies in a challenge context are nap-dependent. *J. Sleep Res.* 24, 279–287. doi: 10.1111/jsr.12260

Minkel, J., Htaik, O., Banks, S., and Dinges, D. (2011). Emotional expressiveness in sleep-deprived healthy adults. *Behav. Sleep Med.* 9, 5–14. doi: 10.1080/15402002.2011.533987

Mistlberger, R. E. (2005). Circadian regulation of sleep in mammals: Role of the suprachiasmatic nucleus. *Brain Res. Rev.* 49, 429–454. doi: 10.1016/j.brainresrev.2005.01.005

Morgenthaler, J., Wiesner, C. D., Hinze, K., Abels, L. C., Prehn-Kristensen, A., and Göder, R. (2014). Selective REM-sleep deprivation does not diminish emotional memory consolidation in young healthy subjects. *PLoS One* 9:e89849. doi: 10.1371/journal.pone.0089849

Motomura, Y., Kitamura, S., Oba, K., Terasawa, Y., Enomoto, M., Katayose, Y., et al. (2013). Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PLoS One* 8:e56578. doi: 10.1371/journal.pone.0056578

Moyano, M. D., Diekelmann, S., Pedreira, M. E., and Forcato, C. (2019). Sleep accelerates re-stabilization of human declarative memories. *Neurobiol. Learn. Mem.* 162, 1–8. doi: 10.1016/j.nlm.2019.04.012

Nadel, L., Samsonovich, A., Ryan, L., and Moscovitch, M. (2000). Multiple trace theory of human memory: Computational, neuroimaging, and neuropsychological results. *Hippocampus* 10, 352–368. doi: 10.1002/1098-1063(2000)10:4<352::AID-HIPO2>3.0.CO;2-D

Nader, K., and Einarsson, E. Ö. (2010). Memory reconsolidation: An update. *Ann. N. Y. Acad. Sci.* 1191, 27–41. doi: 10.1111/j.1749-6632.2010.05443.x

Nishida, M., Pearsall, J., Buckner, R. L., and Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cereb. Cortex* 19, 1158–1166. doi: 10.1093/cercor/bhn155

Oudiette, D., and Paller, K. A. (2013). Upgrading the sleeping brain with targeted memory reactivation. *Trends Cogn. Sci.* 17, 142–149. doi: 10.1016/j.tics.2013.01.006

Paradee, C. V., Rapport, L. J., Lumley, M. A., Hanks, R. A., Langenecker, S. A., and Whitman, R. D. (2008). Circadian preference and facial emotion recognition among rehabilitation inpatients. *Rehabil. Psychol.* 53, 46–53. doi: 10.1037/0090-5550.53.1.46

Payne, J., Chambers, A. M., and Kensinger, E. A. (2012). Sleep promotes lasting changes in selective memory for emotional scenes. *Front. Integr. Neurosci.* 6:108. doi: 10.3389/fnint.2012.00108

Payne, J. D. (2020). "Stress and sleep interact to selectively consolidate and transform negative emotional memories," in *Neuroscience of enduring change: Implications for psychotherapy*, eds R. Lane and L. Nadel (Oxford: Oxford University Press).

Payne, J. D., and Kensinger, E. A. (2011). Sleep leads to changes in the emotional memory trace: Evidence from fMRI. *J. Cogn. Neurosci.* 23, 1285–1297. doi: 10.1162/jocn.2010.21526

Payne, J. D., and Kensinger, E. A. (2018). Stress, sleep, and the selective consolidation of emotional memories. *Curr. Opin. Behav. Sci.* 19, 36–43. doi: 10.1016/j.cobeha.2017.09.006

Payne, J. D., Kensinger, E. A., Wamsley, E. J., Spreng, R. N., Alger, S. E., Gibler, K., et al. (2015). Napping and the selective consolidation of negative aspects of scenes. *Emotion* 15, 176–186. doi: 10.1037/a0038683

Payne, J. D., Stickgold, R., Swanberg, K., and Kensinger, E. A. (2008). Sleep preferentially enhances memory for emotional components of scenes. *Psychol. Sci.* 19, 781–788. doi: 10.1111/j.1467-9280.2008.02157.x

Philip, P., Taillard, J., Sagaspe, P., Valtat, C., Sanchez-Ortuno, M., Moore, N., et al. (2004). Age, performance and sleep deprivation. *J. Sleep Res.* 13, 105–110. doi: 10.1111/j.1365-2869.2004.00399.x

Pilcher, J. J., Callan, C., and Posey, J. L. (2015). Sleep deprivation affects reactivity to positive but not negative stimuli. *J. Psychosom. Res.* 79, 657–662. doi: 10.1016/j.jpsychores.2015.05.003

Prather, A. A., Bogdan, R., Ahmad, R., and Hariri, P. (2013). Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. *Psychosom. Med.* 75, 350–358. doi: 10.1097/PSY.0b013e31828ef15b

Prehn-Kristensen, A., Göder, R., Chirobeja, S., Breßmann, I., Ferstl, R., and Baving, L. (2009). Sleep in children enhances preferentially emotional declarative but not procedural memories. *J. Exp. Child Psychol.* 104, 132–139. doi: 10.1016/j.jecp.2009.01.005

Prehn-Kristensen, A., Munz, M., Molzow, I., Wilhelm, I., Wiesner, C. D., and Baving, L. (2013). Sleep promotes consolidation of emotional memory in healthy children but not in children with attention-deficit hyperactivity disorder. *PLoS One* 8:e65098. doi: 10.1371/journal.pone.0065098

Radvansky, G. A., Doolen, A. C., Pettijohn, K. A., and Ritchey, M. (2022). A new look at memory retention and forgetting. *J. Exp. Psychol. Learn. Mem. Cogn.* [Epub ahead of print]. doi: 10.1037/xlm0001110

Rasch, B., Büchel, C., Gais, S., and Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* 315, 1426–1429.

Reddy, R., Palmer, C. A., Jackson, C., Farris, S. G., and Alfano, C. A. (2017). Impact of sleep restriction versus idealized sleep on emotional experience, reactivity and regulation in healthy adolescents. *J. Sleep Res.* 26, 516–525. doi: 10.1111/jsr.12484

Rihm, J. S., and Rasch, B. (2015). Replay of conditioned stimuli during late REM and stage N2 sleep influences affective tone rather than emotional memory strength. *Neurobiol. Learn. Mem.* 122, 142–151. doi: 10.1016/j.nlm.2015.04.008

Ritter, S. M., Strick, M., Bos, M. W., Van Baaren, R. B., and Dijksterhuis, A. P. (2012). Good morning creativity: Task reactivation during sleep enhances beneficial effect of sleep on creative performance. *J. Sleep Res.* 21, 643–647. doi: 10.1111/j.1365-2869.2012.01006.x

Rolls, A., Makam, M., Kroeger, D., Colas, D. D., De Lecea, L., and Heller, H. C. (2013). Sleep to forget: Interference of fear memories during sleep. *Mol. Psychiatry* 18, 1166–1170. doi: 10.1038/mp.2013.121

Saletin, J. M., Goldstein-Piekarski, A. N., Greer, S. M., Stark, S., Stark, C. E., and Walker, M. P. (2016). Human hippocampal structure: A novel biomarker predicting mnemonic vulnerability to, and recovery from, sleep deprivation. *J. Neurosci.* 36, 2355–2363. doi: 10.1523/JNEUROSCI.3466-15.2016

Schäfer, S. K., Wirth, B. E., Staginnus, M., Becker, N., Michael, T., and Sopp, M. R. (2020). Sleep's impact on emotional recognition memory: A meta-analysis of whole-night, nap, and REM sleep effects. *Sleep Med. Rev.* 51:101280. doi: 10.1016/j.smrv.2020.101280

Schoch, S. F., Cordi, M. J., and Rasch, B. (2017). Modulating influences of memory strength and sensitivity of the retrieval test on the detectability of the sleep consolidation effect. *Neurobiol. Learn. Mem.* 145, 181–189.

Schoch, S. F., Cordi, M. J., Schredl, M., and Rasch, B. (2019). The effect of dream report collection and dream incorporation on memory consolidation during sleep. *J. Sleep Res.* 28:e12754. doi: 10.1111/jsr.12754

Schönauer, M., Geisler, T., and Gais, S. (2014). Strengthening procedural memories by reactivation in sleep. *J. Cogn. Neurosci.* 26, 143–153.

Schouten, D. I., Pereira, S. I., Tops, M., and Louzada, F. M. (2017). State of the art on targeted memory reactivation: Sleep your way to enhanced cognition. *Sleep Med. Rev.* 32, 123–131. doi: 10.1016/j.smrv.2016.04.002

Simon, E. B., Oren, N., Sharon, H., Kirschner, A., Goldway, N., Okon-Singer, H., et al. (2015). Losing neutrality: The neural basis of impaired emotional control without sleep. *J. Neurosci.* 35, 13194–13205. doi: 10.1523/JNEUROSCI.1314-15.2015

Simon, K. C., Gómez, R. L., and Nadel, L. (2020). Sleep's role in memory reconsolidation. *Curr. Opin. Behav. Sci.* 33, 132–137. doi: 10.1016/j.cobeha.2020.04.001

Sopp, M. R., Michael, T., Weeß, H.-G., and Mecklinger, A. (2017). Remembering specific features of emotional events across time: The role of REM sleep and prefrontal theta oscillations. *Cogn. Affect. Behav. Neurosci.* 17, 1186–1209. doi: 10.3758/s13415-017-0542-8

Squire, L. R., Genzel, L., Wixted, J. T., and Morris, R. G. (2015). Memory consolidation. *Cold Spring Harb. Perspect. Biol.* 7:a021766. doi: 10.1101/cshperspect.a021766

Sterpenich, V., Albouy, G., Boly, M., Vandewalle, G., Darsaud, A., Balteau, E., et al. (2007). Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLoS Biol.* 5:e282. doi: 10.1371/journal.pbio.0050282

Sterpenich, V., Albouy, G., Darsaud, A., Schmidt, C., Vandewalle, G., Vu, T. T. D., et al. (2009). Sleep promotes the neural reorganization of remote emotional memory. *J. Neurosci.* 29, 5143–5152. doi: 10.1523/JNEUROSCI.0561-09.2009

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature* 437, 1272–1278. doi: 10.1038/nature04286

Stickgold, R., James, L., and Hobson, J. A. (2000). Visual discrimination learning requires sleep after training. *Nat. Neurosci.* 3, 1237–1238. doi: 10.1038/81756

Stickgold, R., and Walker, M. P. (2007). Sleep-dependent memory consolidation and reconsolidation. *Sleep Med.* 8, 331–343. doi: 10.1016/j.sleep.2007.03.011

Stickgold, R., and Walker, M. P. (2013). Sleep-dependent memory triage: Evolving generalization through selective processing. *Nat. Neurosci.* 16, 139–145. doi: 10.1038/nn.3303

Stiller, J., and Postolache, T. (2005). Sleep-wake and other biological rhythms: Functional neuroanatomy. *Clin. Sports Med.* 24, 205–235, vii. doi: 10.1016/j.csm.2004.12.008

Stolarski, M., and Jankowski, K. S. (2015). Morningness–eveningness and performance-based emotional intelligence. *Biol. Rhythm Res.* 46, 417–423. doi: 10.1080/09291016.2015.1020199

Talbot, L. S., McGlinchey, E. L., Kaplan, K. A., Dahl, R. E., and Harvey, A. G. (2010). Sleep deprivation in adolescents and adults: Changes in affect. *Emotion* 10, 831–841. doi: 10.1037/a0020138

Talmi, D., Lohnas, L. J., and Daw, N. D. (2019). A retrieved context model of the emotional modulation of memory. *Psychol. Rev.* 126, 455–485. doi: 10.1037/rev0000132

Tempesta, D., Alessandro, C., Giuseppe, C., Fabio, M., Cristina, M., Luigi, D. G., et al. (2010). Lack of sleep affects the evaluation of emotional stimuli. *Brain Res. Bull.* 82, 104–108. doi: 10.1016/j.brainresbull.2010.01.014

Tempesta, D., De Gennaro, L., Natale, V., and Ferrara, M. (2015). Emotional memory processing is influenced by sleep quality. *Sleep Med.* 16, 862–870. doi: 10.1016/j.sleep.2015.01.024

Tempesta, D., Socci, V., Coppo, M., Dello Ioio, G., Nepa, V., De Gennaro, L., et al. (2016). The effect of sleep deprivation on the encoding of contextual and non-contextual aspects of emotional memory. *Neurobiol. Learn. Mem.* 131, 9–17. doi: 10.1016/j.nlm.2016.03.007

Tempesta, D., Socci, V., Dello Ioio, G., De Gennaro, L., and Ferrara, M. (2017). The effect of sleep deprivation on retrieval of emotional memory: A behavioural study using film stimuli. *Exp. Brain Res.* 235, 3059–3067. doi: 10.1007/s00221-017-5043-z

Thormar, S. B., Gersons, B. P., Juen, B., Djakababa, M. N., Karlsson, T., and Olff, M. (2014). The impact of disaster work on community volunteers: The role of peri-traumatic distress, level of personal affectedness, sleep quality and resource loss, on post-traumatic stress disorder symptoms and subjective health. *J. Anxiety Disord.* 28, 971–977. doi: 10.1016/j.janxdis.2014.10.006

Tomaso, C. C., Johnson, A. B., and Nelson, T. D. (2021). The effect of sleep deprivation and restriction on mood, emotion, and emotion regulation: Three meta-analyses in one. *Sleep* 44:zsaa289. doi: 10.1093/sleep/zsaa289

Tronson, N. C., and Taylor, J. R. (2007). Molecular mechanisms of memory reconsolidation. *Nat. Rev. Neurosci.* 8, 262–275. doi: 10.1038/nrn2090

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi: 10.1037/h0080017

van der Helm, E., Gujar, N., and Walker, M. P. (2010). Sleep deprivation impairs the accurate recognition of human emotions. *Sleep* 33, 335–342. doi: 10.1093/sleep/33.3.335

van der Helm, E., and Walker, M. P. (2011). Sleep and emotional memory processing. *Sleep Med. Clin.* 6, 31–43. doi: 10.1016/j.jsmc.2010.12.010

van der Helm, E., Yao, J., Dutt, S., Rao, V., Saletin, J. M., and Walker, M. P. (2011). REM sleep depotentiates amygdala activity to previous emotional experiences. *Curr. Biol.* 21, 2029–2032. doi: 10.1016/j.cub.2011.10.052

Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W., et al. (2009). Sleep benefits subsequent hippocampal functioning. *Nat. Neurosci.* 12, 122–123. doi: 10.1038/nn.2253

Van Dongen, E. V., Takashima, A., Barth, M., Zapp, J., Schad, L. R., Paller, K. A., et al. (2012). Memory stabilization with targeted reactivation during human slow-wave sleep. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10575–10580.

van Heugten-van der Kloet, D., Giesbrecht, T., and Merckelbach, H. (2015). Sleep loss increases dissociation and affects memory for emotional stimuli. *J. Behav. Ther. Exp. Psychiatry* 47, 9–17. doi: 10.1016/j.jbtep.2014.11.002

Vermeulen, M. C. M., van der Heijden, K. B., Benjamins, J. S., Swaab, H., and van Someren, E. J. W. (2017). Memory effects of sleep, emotional valence, arousal and novelty in children. *J. Sleep Res.* 26, 309–317. doi: 10.1111/jsr.12506

Wagner, U. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learn. Mem.* 8, 112–119. doi: 10.1101/lm.36801

Wagner, U., Hallschmid, M., Rasch, B., and Born, J. (2006). Brief sleep after learning keeps emotional memories alive for years. *Biol. Psychiatry* 60, 788–790. doi: 10.1016/j.biopsych.2006.03.061

Wagner, U., Kashyap, N., Diekelmann, S., and Born, J. (2007). The impact of post-learning sleep vs. Wakefulness on recognition memory for faces with different facial expressions. *Neurobiol. Learn. Mem.* 87, 679–687. doi: 10.1016/j.nlm.2007.01.004

Walker, M. P. (2008). Sleep-dependent memory processing. *Harv. Rev. Psychiatry* 16, 287–298. doi: 10.1080/10673220802432517

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., and Stickgold, R. (2002). Practice with sleep makes perfect: Sleep-dependent motor skill learning. *Neuron* 35, 205–211. doi: 10.1016/S0896-6273(02)00746-8

Walker, M. P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J. A., and Stickgold, R. (2003). Sleep and the time course of motor skill learning. *Learn. Mem.* 10, 275–284. doi: 10.1101/lm.58503

Walker, M. P., and Stickgold, R. (2005). It's practice, with sleep, that makes perfect: Implications of sleep-dependent learning and plasticity for skill performance. *Clin. Sports Med.* 24, 301–317. doi: 10.1016/j.csm.2004.11.002

Walker, M. P., and Stickgold, R. (2006). Sleep, memory, and plasticity. *Annu. Rev. Psychol.* 57, 139–166. doi: 10.1146/annurev.psych.56.091103.070307

Walker, M. P., and van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135:731. doi: 10.1037/a0016570

Weigenand, A., Mölle, M., Werner, F., Martinetz, T., and Marshall, L. (2016). Timing matters: Open-loop stimulation does not improve overnight consolidation of word pairs in humans. *Eur. J. Neurosci.* 44, 2357–2368. doi: 10.1111/ejn.13334

Whitehurst, L. N., Cellini, N., McDevitt, E. A., Duggan, K. A., and Mednick, S. C. (2016). Autonomic activity during sleep predicts memory consolidation in humans. *Proc. Natl. Acad. Sci. U.S.A.* 113, 7272–7277. doi: 10.1073/pnas.1518202113

Yonelinas, A. P., Ranganath, C., Ekstrom, A. D., and Wiltgen, B. J. (2019). A contextual binding theory of episodic memory: Systems consolidation reconsidered. *Nat. Rev. Neurosci.* 20, 364–375. doi: 10.1038/s41583-019-0150-4

Yonelinas, A. P., and Ritchey, M. (2015). The slow forgetting of emotional episodic memories: An emotional binding account. *Trends Cogn. Sci.* 19, 259–267. doi: 10.1016/j.tics.2015.02.009

Yoo, S.-S., Gujar, N., Hu, P., Jolesz, F. A., and Walker, M. P. (2007a). The human emotional brain without sleep—A prefrontal amygdala disconnect. *Curr. Biol.* 17, R877–R878. doi: 10.1016/j.cub.2007.08.007

Yoo, S.-S., Hu, P. T., Gujar, N., Jolesz, F. A., and Walker, M. P. (2007b). A deficit in the ability to form new human memories without sleep. *Nat. Neurosci.* 10, 385–392. doi: 10.1038/nn1851

Zadra, A., and Stickgold, R. (2021). *When brains dream: Exploring the science and mystery of sleep*. New York, NY: W. W. Norton.

Zeng, S., Lau, E. Y. Y., Li, S. X., and Hu, X. (2021). Sleep differentially impacts involuntary intrusions and voluntary recognitions of lab-analogue traumatic memories. *J. Sleep Res.* 30:e13208. doi: 10.1111/jsr.13208

Zhang, Y., and Gruber, R. (2019). Focus: Attention science: Can slow-wave sleep enhancement improve memory? A review of current approaches and cognitive outcomes. *Yale J. Biol. Med.* 92, 63–80.

Zhou, X., Ferguson, S. A., Matthews, R. W., Sargent, C., Darwent, D., Kennaway, D. J., et al. (2011). Sleep, wake and phase dependent changes in neurobehavioral function under forced desynchrony. *Sleep* 34, 931–941.

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Treatment with morning blue light increases left amygdala volume and sleep duration among individuals with posttraumatic stress disorder

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Background: Posttraumatic stress disorder (PTSD) is associated with numerous cognitive, affective, and psychophysiological outcomes, including problems with sleep and circadian rhythms. We tested the effectiveness of a daily morning blue-light exposure treatment (BLT) versus a matched amber light treatment (ALT) to regulate sleep in individuals diagnosed with PTSD. Moreover, PTSD is also associated with reliable findings on structural neuroimaging scans, including reduced amygdala volumes and other differences in cortical gray matter volume (GMV) that may be indicative of underlying neurobehavioral dysfunctions. We examined the effect of BLT versus ALT on GMV and its association with sleep outcomes.

Methods: Seventy-six individuals (25 male; 51 female) meeting DSM-V criteria for PTSD (*Age* = 31.45 years, *SD* = 8.83) completed sleep assessments and structural neuroimaging scans, followed by random assignment one of two light groups, including BLT (469 nm; *n* = 39) or placebo ALT (578 nm; *n* = 37) light therapy daily for 30-min over 6-weeks. Participants wore a wrist actigraph for the duration of the study. After treatment, participants returned to complete sleep assessments and a structural neuroimaging scan. Neuroimaging data were analyzed using the Computational Anatomy Toolbox (CAT12) and Voxel-Based Morphometry (VBM) modules within the Statistical Parametric Mapping (SPM12) software.

Results: The BLT condition produced significant increases in total time in bed and total sleep time from actigraphy compared to the ALT condition, while ALT improved wake after sleep onset and sleep efficiency compared to BLT. Additionally, BLT led to an increase in left amygdala volume compared to ALT but did not affect hypothesized medial prefrontal regions. Finally, within group correlations showed that improvements in sleep quality and nightmare severity were correlated with increases in left amygdala volume over the course of treatment for the BLT group but not the ALT group.

Conclusion: In individuals with PTSD, daily exposure to morning blue light treatment was associated with improvements in objective sleep duration

and increased volume of the left amygdala compared to amber placebo light treatment, and changes in amygdala volume correlated with subjective improvement in sleep. These findings suggest that daily morning BLT may provide an important non-pharmacologic adjunctive approach for facilitating sleep and neurobehavioral recovery from PTSD.

KEYWORDS

PTSD, blue light treatment, sleep, voxel based morphometry (VBM), neuroimaging (anatomic)

Introduction

Exposure to a traumatic event can produce significant cognitive, emotional, and physiological changes within an individual. When severe and persistent, these changes may lead to stress-related outcomes, such as posttraumatic stress disorder (PTSD), a condition characterized by frequent re-experiencing symptoms, avoidance of situations or thoughts related to the trauma, negative mood, cognitive alterations, and increased arousal and reactivity (American-Psychiatric-Association, 2013). These recurrent symptoms are emotionally distressing and often interfere with normal social and occupational functioning. While most traumatic experiences do not lead to PTSD, the disorder remains prevalent and will affect up to 7% of the general population at some point over their lifespan (Kessler et al., 2005). Moreover, the prevalence of PTSD is even greater among certain groups such as combat Veterans (Hoge et al., 2004; Tanielian and Jaycox, 2008) who are at increased risk of exposure to traumatic events.

Posttraumatic stress disorder has also been associated with structural and functional changes within the brain. While the neurophysiological response to traumatic stress is complex and affects myriad systems throughout the central nervous system, several brain regions have been consistently identified as particularly relevant to the etiology and maintenance of PTSD, including the amygdala, medial prefrontal cortex, and hippocampus (Bremner, 2006; Liberzon and Martis, 2006). Among these, the amygdala, a brain region associated with the evaluation of affective valence and emotional salience, has often emerged as one of the most consistently implicated brain structures in the neuropathology of PTSD. Early functional magnetic resonance imaging (fMRI) studies repeatedly demonstrated that PTSD is often characterized by hyperresponsive activation of the amygdala to emotional or trauma-related stimuli (Rauch et al., 1996, 2000; Liberzon et al., 1999; Shin et al., 2004, 2005). Furthermore, the exaggerated amygdala responses have often been found to co-occur with reduced activation within areas of the medial prefrontal cortex, such as the anterior cingulate, subcallosal cortex, and medial orbitofrontal regions (Liberzon et al., 1999; Shin et al., 2004, 2005; Bremner et al., 2005), brain regions believed to be critical to emotional evaluation and regulation. Not only do these brain regions show significant functional differences between patients with PTSD and healthy controls, but these regions also appear to show corresponding differences in gray matter volume (GMV). While there is some inconsistency across studies, the most common findings includes reduced GMV in several structures including the amygdala (Morey et al., 2012; Starcevic et al., 2014; Logue et al., 2018; Ousdal et al., 2020), medial prefrontal cortex, and hippocampus (Franz et al., 2020; Del Casale et al., 2022). Decreased volume of the amygdala appears to be a particularly common finding, but there is uncertainty as to whether this represents a stable pre-existing risk factor for PTSD or if volume reductions emerge as a result of the stress response to trauma. Moreover, there is ample evidence to suggest that GMV is somewhat plastic and can be modified with experience (Ditye et al., 2013; Sun et al., 2016; Wenger et al., 2017, 2021; Ueno et al., 2018) or treatment (Perini et al., 2017; Butler et al., 2018; Mancke et al., 2018; Husain et al., 2019; Wang et al., 2019; Brancati et al., 2021; Schading et al., 2021; Soshi et al., 2021; Yang et al., 2021). Nevertheless, there has been relatively little research examining longitudinal changes in GMV over a course of treatment or with measured changes in relevant PTSD symptoms. The present study will attempt to address this gap by evaluating GMV changes in PTSD and their association with sleep outcomes.

In the present study, we focus on sleep disruption as it is one of the most common symptoms of PTSD. Sleep disruption is so closely linked with PTSD that it is sometimes called the "hallmark" symptom of the disorder, with prevalence rates for sleep problems ranging from 70% to 91% across studies. Among those with PTSD, self-reported sleep quality is often described as poor and fragmented (Van Liempt, 2012) and often includes problems falling asleep, staying asleep, early morning awakening, and frequent and severe nightmares (Neylan et al., 1998; Ohayon and Shapiro, 2000). Insomnia in the period prior to a traumatic event has been shown to increase vulnerability to developing PTSD (Gehrman et al., 2013). Similarly, sleep disruption, particularly rapid eye movement (REM) sleep, in the

acute period following a trauma has also been associated with the development of PTSD (Mellman et al., 2002). Sleep is critical for healthy social and emotional functioning (Goldstein and Walker, 2014; Ben Simon et al., 2020). When people lack sleep, emotional stability is adversely affected (Kahn-Greene et al., 2007; Killgore et al., 2008). Neuroimaging research has shown that sleep deprivation weakens the functional connectivity between the medial prefrontal cortex regions involved in emotional regulation and the emotionally reactive amygdala, leading to hyperresponsiveness of the amygdala to emotional stimuli (Yoo et al., 2007). One theoretical model proposes that REM sleep provides the ideal neurochemical balance of adrenergic to cholinergic activity in cortical modules to allow the brain to strip away unhealthy affective tone from memories, allowing them to be reconsolidated at a more manageable emotional intensity over time (Walker and Van Der Helm, 2009). According to this model, the sleep disruption common to PTSD may impair this normal affective balancing process, preventing full recovery. The important role of sleep in healthy emotional functioning and its disruption in PTSD has prompted many researchers to propose a primary focus of treatment toward sleep problems as a vehicle for bringing about effective recovery from the disorder (Gilbert et al., 2015; Miller et al., 2019).

The most common approaches for treating sleep disorders in people with PTSD include pharmacotherapy or cognitive behavioral therapy for insomnia (CBT-I) (Weber and Wetter, 2021). While treatment with hypnotic medications or benzodiazepines can initially facilitate a soporific state, there are many health and performance related drawbacks to the regular use of pharmacologic treatments for insomnia, and patients and their providers are often dissatisfied with the treatment (Hermes et al., 2013). Studies have suggested improvements in sleep with CBT-I for this population, but the majority still do not achieve full remission of insomnia (Talbot et al., 2014). Consequently, further research into alternative approaches is warranted.

Circadian disruption is common following exposure to a trauma and has even been proposed as a "core feature" of trauma-related disorders (Agorastos and Olff, 2020). Consequently, optimizing the underlying circadian rhythm is another potential approach that could be applied to facilitate sleep in people with PTSD. The human propensity for sleep is directly linked with the diurnal circadian rhythm of melatonin secretion by the pineal gland. For humans, the most efficient and restorative sleep occurs when the individual's sleep/wake pattern closely aligned with the circadian day and night (Lavie, 2001; Arendt, 2006). The circadian rhythm of sleep and melatonin production is most powerfully affected by ocular exposure to light (Cajochen et al., 2003). Because the retina contains melanopsin-based intrinsically photosensitive retinal ganglion cells (ipRGCs) that are primarily stimulated by blue-wavelength light, even brief periods of blue light exposure can significantly affect melatonin and the timing of the circadian rhythm (Provencio et al., 2000; Panda et al., 2005; Qiu et al., 2005). Morning exposure to blue-wavelength light has the effect of phase advancing the rhythm (i.e., shifting the sleep period earlier in the evening), while light in the evening will produce a phase delay (i.e., shifting the sleep period later into the night). Accordingly, we have successfully applied morning blue light treatment (BLT) to improve the sleep and circadian functioning of individuals with mild traumatic brain injury (mTBI) (Killgore et al., 2020; Raikes et al., 2021). Using a simple light-box device for 30-min each morning, we were able to shift the circadian rhythm of sleep/wake, improve cognitive performance, and influence brain structure and functional connectivity in these individuals (Bajaj et al., 2017, 2021; Killgore et al., 2020; Raikes et al., 2020, 2021). Two recent studies have examined the potential for bright light exposure treatment in PTSD, with promising preliminary outcomes suggesting reductions in symptoms (Zalta et al., 2019; Youngstedt et al., 2021). However, those studies used either bright white light or a weaker green light than in our prior work, and findings did not focus on sleep or brain structure. So, it remains to be determined whether sleep problems associated with PTSD could be modified by blue light and whether this would relate directly to changes in critical brain structures commonly implicated in the disorder.

For the present study, we conducted a 6-week clinical trial using the same light intensity and wavelength as in our prior mTBI studies described above. Participants completed a baseline assessment of subjective and objective sleep followed by 6-weeks of daily morning BLT or an identical treatment with an amber light treatment (ALT) as a placebo control, and a final post-treatment assessment of sleep. Moreover, each assessment also included a structural neuroimaging scan to assess gray matter volume (GMV) in segmented regions of the brain. Based on prior research described above, we hypothesized that BLT would increase objective sleep duration and subjective sleep quality relative to ALT and that these improvements would correlate with increased GMV of the amygdala and medial prefrontal cortex.

Materials and methods

Participants

A total of 90 individuals meeting DSM-V criteria for PTSD were initially recruited and randomized to one of the treatment conditions (30 male; 60 female; 47 BLT; 23 ALT) with an average age of 31.09 years (*SD* = 8.72). As shown in **Figure 1**, participant drop-out and missing data reduced the final complete dataset by 14 participants. Thus, for the complete dataset, a total of 76 individuals (25 male; 51 female) completed the light exposure treatment and underwent pre- and post-treatment assessments and structural neuroimaging

scans. Participants in the complete dataset ranged from 20 to 49 years of age (M = 31.45, SD = 8.83). These participants self-identified as White (61.8%), Hispanic/Latino (22.4%), Black/African American (3.9%), Native-American/American Indian (2.6%), Asian/Pacific Islander (1.3%), Other (7.9%), and there were no significant differences in the racial/ethnic breakdown between light conditions, $\chi^2(df = 5) = 4.03$, $p = 0.545$. Most participants indicated that they had used marijuana at some point in their lifetime, but this did not differ between groups [BLT: 71.8%; ALT: 83.8%, $\chi^2(df = 1) = 1.57$, $p = 0.21$]. Furthermore, most participants reported using marijuana fewer than 100 times during their lifetime, with no differences between groups (BLT: 58.1%; ALT: 57.2%). A total of 28% of those in the BLT group reported using marijuana in the month prior to their baseline session, while 16.1% of those in the ALT had done so, but this difference was not significant, $\chi^2(df = 1) = 1.33$, $p = 0.25$, Demographic breakdown for the two conditions is provided in Table 1.

Participants were recruited from the local Tucson and surrounding metropolitan areas *via* posted flyers, radio advertisements, and internet campaigns. Interested individuals completed a telephone screening interview to determine initial eligibility. Those meeting eligibility requirements were invited to complete an in-person laboratory assessment session (i.e., Visit 1) that included a Structured Clinical Interview for DSM-V (SCID-V) administered by a trained researcher. Selected participants were required to meet criteria for PTSD and be between the ages of 18 and 50 years, right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), and be a primary English speaker. Exclusionary criteria included any history of head injury with loss of consciousness exceeding 30 min or post-traumatic amnesia lasting longer than 24 h. Individuals were also excluded if they had any history of neurological illness, chronic medical condition, or comorbid psychiatric condition (excluding depression), or an index trauma event occurring before the age of 18 years or an index trauma that occurred longer than 10 years prior to

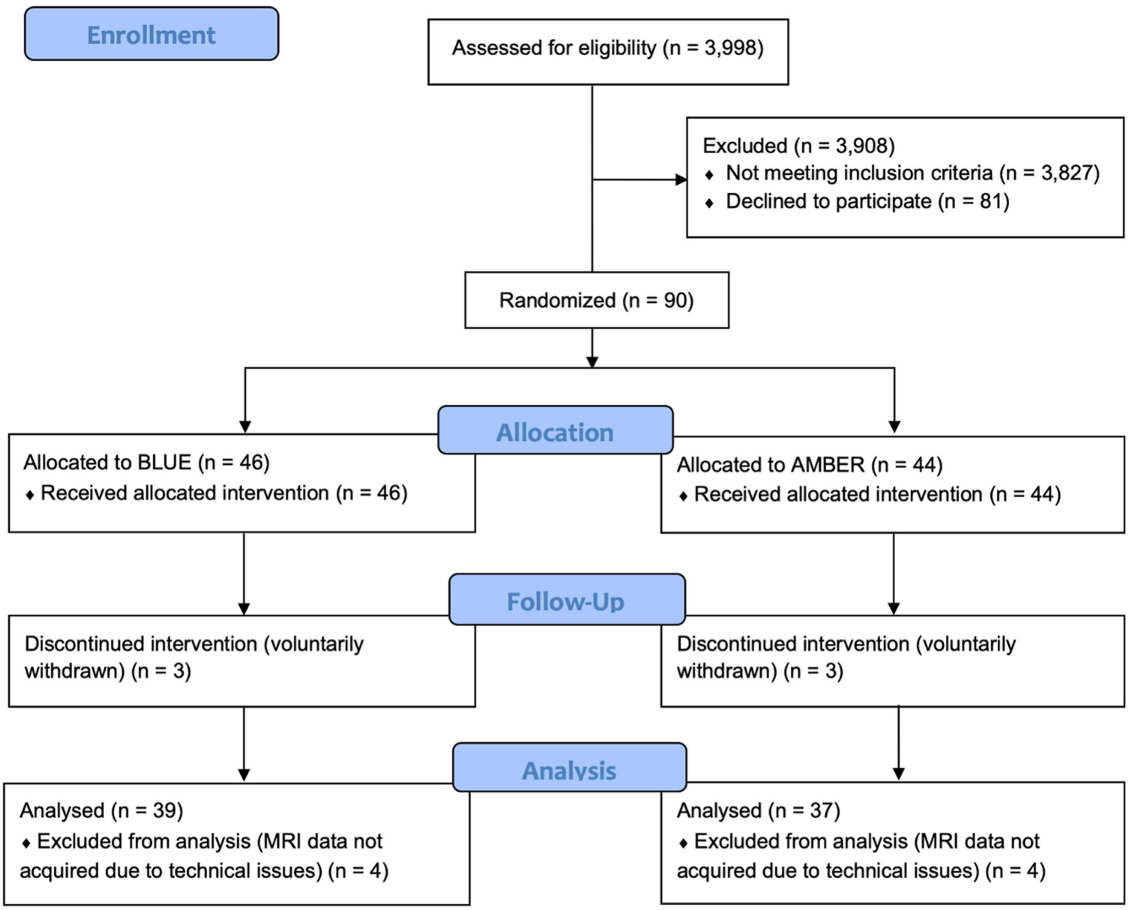

FIGURE 1
CONSORT diagram showing the assignment of participants to each condition. Following an intention-to-treat approach, all participants who were randomly assigned to a treatment condition were analyzed, with the exception of participants who withdrew from the trial prematurely (n = 3 per condition) or did not have usable neuroimaging scans at both sessions (n = 4) per condition.

TABLE 1 Baseline demographic characteristics.

Baseline demographics	Blue (active)$n = 39$		Amber (placebo)$n = 37$		*P*-value
	M	SD	M	SD	
Male/Female (n)	14/25	–	11/26	–	0.63
Age	32.08	9.01	30.78	8.72	0.53
Education	14.00	1.86	13.71	1.67	0.49
Full Scale IQ	100.08	10.22	102.97	13.65	0.30
Age at Index Trauma	28.33	8.65	27.58	8.30	0.70
Years since Index Trauma	3.38	2.36	3.12	2.23	0.60
Baseline PCL-5	48.38	12.97	44.51	12.48	0.19
Baseline CAPS-5 Number of Symptoms	13.33	2.68	12.35	3.42	0.17
Baseline CAPS-5 Symptom Severity	35.41	8.12	32.57	10.09	0.18
% With Direct Trauma Exposure	89.7%	–	78.4%	–	0.17
Trauma Type (within light group)					0.27
Physical Abuse/Assault	41.0%	–	32.4%	–	
Sexual Abuse/Assault	20.5%	–	27.0%	–	
Accident (e.g., car, work-related)	10.3%	–	2.7%	–	
Natural Disaster	2.6%	–	2.7%	–	
War/Combat	17.9%	–	10.8%	–	
Other	7.7%	–	24.3%	–	
PSQI Total	10.06	2.90	9.38	3.43	0.35
DDNSI Total	13.84	5.38	14.66	4.82	0.49
ISI Total	15.28	4.61	14.41	6.11	0.48

the current study. Potential participants were also excluded if there was evidence of ongoing trauma (e.g., currently in an abusive relationship), or an index trauma that was considered to be non-qualifying based on current diagnostic standards (e.g., emotional/verbal abuse, exposure to natural deaths due to age or illness). Volunteers were also excluded for abnormal visual acuity that could not be corrected with contact lenses, prior history of light treatment, history of light induced conditions (e.g., epilepsy, migraine) or other medical conditions that could be affected by light, measured intelligence below 70, metal in the body, pregnancy, or other contraindications for MRI, and use of medications that might affect neuroimaging outcomes (e.g., beta-blockers, mood stabilizers, etc.), current or upcoming use of sleep-inducing medications (e.g., zolpidem) or sleep altering supplements (e.g., melatonin), evidence of lower than 6th grade reading comprehension, or use of illicit substances (although marijuana was permitted). A total of 90 participants were enrolled, however, eight participants failed to complete the study and six other participants did not have complete neuroimaging scans due to technical issues. **Figure 1** presents the CONSORT flow diagram.

All interested individuals were briefed on the study procedures and requirements and provided written informed consent prior to enrollment. Study procedures were evaluated and approved by the Institutional Review Board of the University of Arizona College of Medicine and the United States Army Human Research Protections Office.

Procedure

Over a 7-week protocol, each participant attended three visits to the laboratory, including an intake (Visit 1), baseline assessment and scan (Visit 2), and post-treatment assessment and scan (Visit 3). After Visit 2, participants were randomly assigned to complete a daily half-hour morning light exposure regimen of either blue light treatment (BLT) or amber light treatment (ALT) for 6 weeks.

Visit 1: intake

The intake visit involved completion of the informed consent process and administration of the SCID by a trained research technician. Individuals meeting criteria for PTSD were fitted with a wrist actigraph device to assess sleep and wake over the course of the study (see below).

Visit 2: baseline assessment and MRI scan

Following 1 week of baseline sleep assessment, participants returned to the lab to complete a baseline cognitive assessment and a series of neuroimaging scans. Participants completed an extensive battery of assessments, some of which are discussed

in other publications. The present article focuses on subjective sleep assessments and actigraphy measures and their association with structural neuroimaging findings. Neuroimaging scans were initiated at 9:00 a.m. Daily assessment activities were highly scheduled throughout the day. Upon completion of the assessments and scans, each participant received a light exposure device (described below). The use of the device was demonstrated to the participant, and they were provided with a printed instruction brochure that provided detailed information about its use.

Six-week light therapy period

Based on a computer-generated randomization scheme, participants were randomly assigned to receive either a BLT or ALT light device. Treatment was administered double-blind (i.e., participants were not informed that there were different colors of lights being used and all study staff with direct participant contact were blind to the color of the light device assigned). Participants were instructed to use the assigned device every morning for 30-min, within 2 h of awakening, but no later than 11:00 a.m. This was done to ensure that the light exposure occurred within time-window generally associated with phase advancement of the circadian rhythm, while still allowing some flexibility of use within a naturalistic home setting. At each treatment session, the lightbox was set at approximately arm's length (20–30 in. from the face) at a slight angle (20–40°), so that both sides of the face would be exposed to the light. To minimize visual discomfort, participants were encouraged to refrain from looking directly at the light panel. The device automatically deactivated after 30 min of continuous use. Participants were also instructed to log their light use and previous night's sleep each morning *via* a secure online portal.

Visit 3: post-treatment assessment and MRI scan

After 6 weeks of daily treatment with morning light exposure, participants returned to the lab for a final assessment session (Visit 3). This final session involved essentially the same assessments and procedures as the baseline visit (Visit 2). Upon completion, all equipment was returned and participants were released from the study.

Equipment and assessment measures

Light exposure devices

Each participant was provided with a small light therapy device, fitted with either blue or amber light emitting diodes (LEDs). The devices were manufactured by Philips Electronics (Stamford, CT, United States), and were identical in design, except for the color wavelength emitted by the LEDs. The devices consisted of a 13.5 × 14 cm plastic-encased flat box that was table-mounted and included a 10 × 6 panel array of LEDs. A commercially available Philips goLITE BLU® Energy Light device (Model HF3321/60) was used for the active BLT condition. This device has a narrow bandwidth [peaking at λ = 469 nm, at 214 Lux, and single panel irradiance (mW/cm^2) = 0.11 at 80 cm]. The ALT condition was provided by an identical appearing device that was fitted LEDs that emitted amber wavelength light [peaking at λ = 578 nm, at 188 Lux, and panel irradiance (mW/cm^2) = 0.04 at 80 cm]. Amber light was selected as a control condition as prior research has used it successfully as a placebo (Raikes and Killgore, 2018), and evidence suggests that it has a significantly lower effect on melatonin phase shifting (Geerdink et al., 2016), and brain connectivity (Killgore et al., 2022), than blue light, but still provides a plausible and believable light condition. Participants were required to log into a secure website each day to record the time when the light was used.

Posttraumatic stress disorder assessments

The Structured Clinical Interview for DSM-V (SCID) (First, 2015) was administered at Visit 1 to ensure individuals met diagnostic criteria for a current PTSD diagnosis. For those who were enrolled in the study, the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2018) was administered at Visit 2 and Visit 3 to assess PTSD total symptom severity and the number of symptoms meeting threshold.

Subjective sleep assessments

Participants completed several subjective sleep assessments, including the Pittsburg Sleep Quality Index (PSQI), a measure of sleep habits and sleep quality in the past month (Buysse et al., 1989), the Disturbing Dreams and Nightmares Severity Index (DDNSI), a measure of the frequency and severity of nightmares (Krakow et al., 2002), and the Insomnia Severity Index (ISI), a measure of both nighttime and daytime insomnia components (Bastien et al., 2001).

Objective sleep assessments

Throughout the course of the study, participants wore an Actiwatch Spectrum Pro® (Philips Respironics, Bend, Oregon) on their dominant hand. Sleep was scored using the automated algorithms of the Actiware 6® program with further hand editing to ensure accuracy compared to sleep diaries. For the present analysis, we averaged the minutes of sleep obtained for each overnight sleep opportunity for the first six nights of the baseline week (i.e., between Visit 1 and 2) and the final six nights preceding the post-treatment visit (Visit 3). Actigraphic data were first scored for all sleep during each 24-h period (i.e., including nap periods), and again when only nocturnal sleep was included (i.e., excluding daytime naps). For the present report, we only used the nocturnal sleep scores. These included standard scores for total Time in Bed (TIB; the total amount of time spend in the rest period from bed-time to rise time), Total Sleep Time (TST; the total number of minutes scored as sleep

during the rest period once the individual had fallen asleep), Sleep Onset Latency (SOL; the number of minutes between the initiation of the rest period and first scored minute of sleep), Wake After Sleep Onset (WASO; the number of minutes of wake during the rest period scored after the first minute of scored sleep), and Sleep Efficiency (SE; defined as TST divided by TIB).

Structural neuroimaging

Structural magnetic resonance imaging (MRI) data were collected at 3T (Siemens Skyra) using a 32-channel head coil. Head movement was restricted using foam cushions during all image acquisition. Anatomical data were acquired with a high-resolution T1-weighted weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE/flip angle = 2,100 ms, 2.33 ms, 12°) comprising 176 axial slices (256 × 256 matrix) with a slice thickness of 1 mm and voxel size of 1 mm × 1 mm × 1 mm.

Statistical analysis

As this study reflects the first of its type examining the effects of a 6-week trial of BLT versus placebo ALT on sleep and recovery from PTSD, we present findings from two analytic approaches, including the per-protocol analysis (i.e., analysis of all participants who completed the study with valid data), as well as a more conservative intention-to-treat analysis (i.e., analysis of all participants who were randomized to a treatment condition, regardless of completion status or data availability). Because some participants who were initially randomized did not complete the study and there was also some loss of data due to technical difficulties in a few cases (see **Figure 1**), we replaced missing data in the intention-to-treat analysis with a multiple imputation approach. The multiple imputation analysis was implemented with 5 iterations using the Missing Values module in SPSS 28 and the pooled mean was imputed as the final value for missing scores. Imputed values were calculated for the following variables: PSQI Baseline Bedtime (3 missing values), PSQI Total Baseline (5 missing values), DDNSI Total Baseline (5 missing values), ISI Total Post-treatment (7 missing values), PSQI Total Post-treatment (8 missing values), Actigraphy TIB Baseline (9 missing values), Actigraphy TST Baseline (9 missing values), Actigraphy SOL Baseline (9 missing values), Actigraphy WASO Baseline (9 missing values), Actigraphy SE Baseline (9 missing values), Actigraphy TIB Post-treatment (11 missing values), Actigraphy TST Post-treatment (11 missing values), Actigraphy SOL Post-treatment (11 missing values), Actigraphy WASO Post-treatment (11 missing values), Actigraphy SE Post-treatment (11 missing values), Intracranial Volume Mean (14 missing values), Left Amygdala Volume Baseline (14 missing values), Left Amygdala Volume Post-treatment (14 missing values), DDNSI Total Post-treatment (15 missing values).

Sleep outcomes

Each sleep metric was scored according to standard published criteria. The effects of light condition on each sleep metric were tested using a 2 (light condition) × 2 (baseline versus post-treatment) mixed analysis of covariance (ANCOVA), with age, sex, baseline bedtime, and total PTSD symptom severity from the CAPS-5 entered as covariates. Significant interactions were decomposed with Bonferroni protected *post hoc* tests ($p < 0.05$).

Voxel based morphometry

T1 weighted structural images were preprocessed using the Computational Anatomy Toolbox (CAT12, version 12.8)[1] in SPM12[2]. Images were realigned to the anterior-posterior commissure axis and then segmented using the longitudinal pipeline into gray matter, white matter, and cerebrospinal fluid using CAT12. Segmented images were used to create a custom DARTEL template and then the images were normalized to the stereotaxic coordinate space of the Montreal Neurological Institute (MNI). Smoothing of normalized images was performed with an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

First, processed GMV data from CAT12 were analyzed in SPM12. For determining the effect of light conditions, a 2 between (BLT vs. ALT) × 2 within (baseline vs. post-treatment) mixed analysis of variance (ANOVA) was specified within SPM12 using the flexible factorial option, controlling for age, sex, and total intracranial volume. From this analysis, we focused specifically on the planned comparison between the magnitude of pre-to-post change for the BLT versus ALT conditions. Maps were initially thresholded for peak intensity at $p < 0.001$, with correction for multiple comparisons using a family wise error (FWE) cluster threshold of $p < 0.05$ (Woo et al., 2014). The statistical maps were constrained to two bilateral search territories defined by the AAL atlas (Tzourio-Mazoyer et al., 2002), including (1) bilateral amygdala, and (2) bilateral medial prefrontal cortex (i.e., gyrus rectus, medial orbitofrontal cortex, and anterior cingulate cortex).

To analyze the associations between sleep-related metrics and brain volume, we first calculated the difference score between the baseline and post-treatment sleep scores and the difference in GMV from baseline to post-treatment. Then, we ran a series of separate multiple regression analyses in SPM12 predicting change in GMV from the change in each sleep measure. In addition to the primary sleep measure difference scores, we also included covariates to control for age, sex, and total intracranial volume. The image maps were initially thresholded for peak intensity at $p < 0.001$, with a cluster threshold of $p < 0.05$, FWE corrected within each of the two

1 http://www.neuro.uni-jena.de/cat/

2 http://www.fil.ion.ucl.ac.uk/spm/software/spm12/

search territories corresponding to the amygdala and medial prefrontal cortex, as described above. The first eigenvariate from significant clusters was extracted and plotted against the relevant sleep metric for visualization. To determine the potential moderating effects of light condition, these data were examined using a regression analysis for categorical moderators.

Results

Condition blinding

It was important to determine whether participants believed they were receiving the active condition or the placebo condition. Therefore, at the end of treatment, all participants indicated their perceived treatment group. In the present sample, 71.1% of the BLT participants believed they were receiving the active treatment, while 75.0% of the ALT participants believed they had received the active treatment, $\chi^2(1) = 0.146$, $p = 0.702$. Thus, there was no difference between groups with regard to their perception of which treatment they received.

Treatment adherence

The treatment groups showed similar levels of treatment adherence, as determined by their valid daily logging of the times that they used the light device. One participant in each group failed to complete the daily logging of light use times. The BLT group recorded use of the light device on 40.65 days (SD = 5.30) and the ALT group recorded use of the light device on 41.57 days (SD = 7.40), which did not differ significantly between groups, $t(86) = 0.67$, $p = 0.502$.

Light condition effects

This initial set of analyses aimed to determine the effect of BLT versus ALT on (1) subjective and objective sleep outcomes and (2) GMV within the amygdala and prefrontal regions of interest.

Sleep outcomes

Pittsburg sleep quality index

Per-protocol analysis: After controlling for covariates, light condition did not significantly affect changes in PSQI Total scores, as indicated by a non-significant interaction, $F(1,64) = 0.008$, $p = 0.929$. Intention-to-treat analysis: Similarly, light condition did not influence changes in PSQI Total scores when all participants, regardless of adherence or completion status (including imputed scores for missing values), were included for the intention-to-treat analysis, $F(1,84) = 0.018$, $p = 0.895$.

Disturbing dreams and nightmares severity index

Per-protocol analysis: After controlling for covariates, light condition did not significantly affect changes in DDNSI scores, as indicated by a non-significant interaction, $F(1,59) = 0.29$, $p = 0.592$. Intention-to-treat analysis: Light condition also did not influence changes in DDNSI scores when all participants, regardless of adherence or completion status (including imputed scores for missing values), were included for the intention-to-treat analysis, $F(1,84) = 2.62$, $p = 0.109$.

ISI

Per-protocol analysis: After controlling for covariates, light condition did not significantly affect changes in ISI Total scores, as indicated by a non-significant interaction, $F(1,66) = 0.57$, $p = 0.454$. Intention-to-treat analysis: Similarly, light condition did not influence changes in ISI scores in the intention-to-treat analysis, $F(1,84) = 0.51$, $p = 0.479$.

Time in bed

Per-protocol analysis: With covariates controlled, there was a significant light condition by session interaction for actigraphically measured TIB, $F(1,59) = 6.24$, $p = 0.015$ (see **Figure 2**), suggesting that TIB increased for BLT while decreasing for ALT. Bonferroni protected *post hoc* comparisons revealed that the interaction was primarily driven by a decline in TIB for the ALT group ($p < 0.05$), while BLT was associated with a non-significant increase in TIB over the same time period. Although groups did not differ at baseline, the BLT group showed significantly higher TIB than the ALT group after 6-weeks of treatment ($p < 0.05$). Intention-to-treat analysis: When all participants, regardless of adherence or completion status (including imputed scores for missing values), were included for the intention-to-treat analysis, the outcomes remained significant, suggesting that TIB increased for BLT while decreasing for ALT $F(1,84) = 4.61$, $p = 0.035$.

Total sleep time

Per-protocol analysis: With covariates controlled, there was a significant light condition by session interaction for actigraphically measured TST, $F(1,59) = 4.33$, $p = 0.042$ (see **Figure 3**). Similar to the findings for TIB, Bonferroni protected *post hoc* comparisons revealed that the interaction was primarily driven by a decline in TST for the ALT group ($p < 0.05$), while BLT was associated with a non-significant increase in TST over the same time period. Although groups did not differ at baseline, the BLT group showed significantly higher TST than the ALT group after 6-weeks of treatment ($p < 0.05$). Intention-to-treat

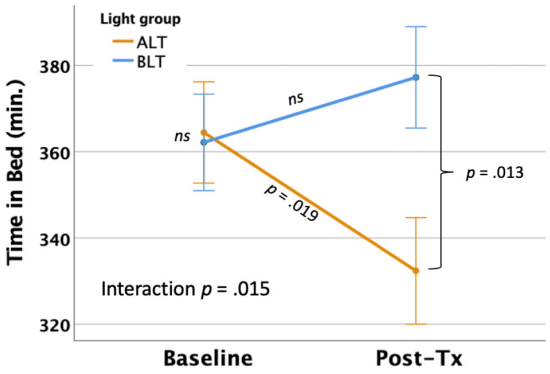

FIGURE 2
Six weeks of blue light treatment (BLT) was associated with significantly greater actigraphically measured time in bed (TIB) than an equal period of amber light treatment (ALT), $p = 0.015$. Orange line = ALT; Blue line = BLT. Error bars = ± 1 SE. *Post hoc* comparisons are Bonferroni corrected.

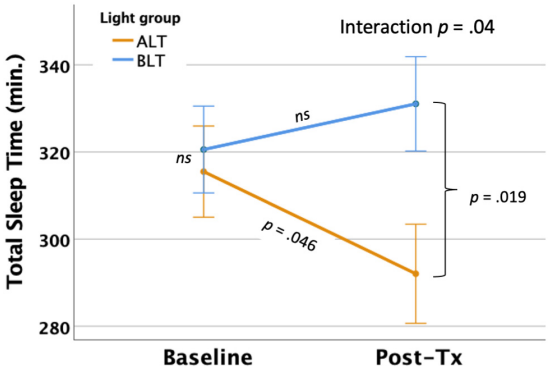

FIGURE 3
Six weeks of blue light treatment (BLT) was associated with significantly greater actigraphically measured total sleep time (TST) than an equal period of amber light treatment (ALT), $p = 0.042$. Orange line = ALT; Blue line = BLT. Error bars = ± 1 SE. *Post hoc* comparisons are Bonferroni corrected.

analysis: In contrast to the per-protocol analysis, when imputed data for all participants, regardless of adherence or completion status, were included for the intention-to-treat analysis, the light condition × assessment session interaction no longer reached statistical significance $F(1,84) = 2.56$, $p = 0.114$.

Sleep onset latency

Per-protocol analysis: After controlling for covariates, light condition did not significantly affect changes in actigraphically measured SOL Total scores, as indicated by a non-significant interaction, $F(1,59) = 1.54$, $p = 0.219$. Intention-to-treat analysis: Similarly, light condition did not influence changes in SOL scores in the intention-to-treat analysis, $F(1,84) = 0.087$, $p = 0.768$.

Wake after sleep onset

Per-protocol analysis: After controlling for covariates, there was a significant light condition by session interaction for actigraphically measured WASO, $F(1,59) = 7.73$, $p = 0.007$ (see Figure 4), suggesting that WASO declined significantly for the ALT group but did not change for the BLT group. Bonferroni protected *post hoc* comparisons revealed that the interaction was primarily driven by a decline in WASO for the ALT group ($p < 0.05$), while BLT was associated with a non-significant increase in WASO over the same time period. Nonetheless, groups did not differ significantly in total WASO at baseline or after 6-weeks of treatment. Intention-to-treat analysis: When all participants, regardless of adherence or completion status (including imputed scores for missing values), were included for the intention-to-treat analysis, the interaction remained significant, suggesting that WASO did not change for BLT but did decrease for ALT $F(1,84) = 8.78$, $p = 0.004$.

Sleep efficiency

Per-protocol analysis: Once covariates were controlled, there was a significant interaction between light condition and session for SE as measured by actigraphy, $F(1,59) = 5.35$ $p = 0.024$ (see Figure 5). This finding suggests that overall sleep efficiency was improved for the ALT group relative to the BLT group. Bonferroni protected *post hoc* comparisons revealed that the interaction was primarily driven by an increase in SE for the ALT group ($p < 0.05$), while BLT was associated with a non-significant decline over the same time period. Groups did not differ in SE at baseline or after 6-weeks of treatment. Intention-to-treat analysis: When all participants, regardless of adherence or completion status (including imputed scores for missing values), were included for the intention-to-treat analysis, the

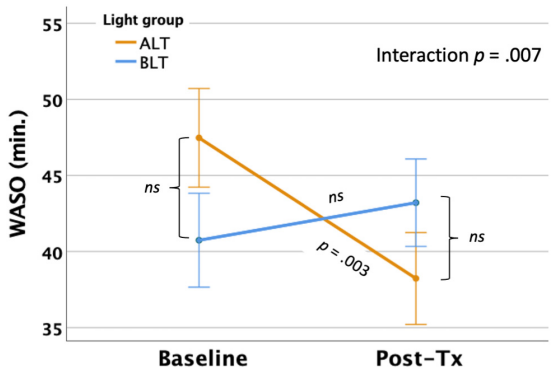

FIGURE 4
Six weeks of amber light treatment (ALT) was associated with significantly greater decrease in actigraphically measured wake after sleep onset (WASO) than an equal period of blue light treatment (BLT), $p = 0.007$. Orange line = ALT; Blue line = BLT. Error bars = ± 1 SE. *Post hoc* comparisons are Bonferroni corrected.

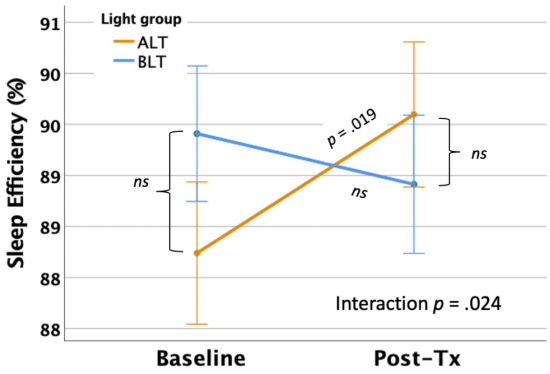

FIGURE 5
Six weeks of amber light treatment (ALT) was associated with significantly greater increase in actigraphically measured percentage sleep efficiency (SE) than an equal period of blue light treatment (BLT), $p = 0.024$. Orange line = ALT; Blue line = BLT. Error bars = ± 1 SE. *Post hoc* comparisons are Bonferroni corrected.

interaction remained significant, suggesting that SE did not change for BLT but decreased for ALT $F(1,84) = 8.12$, $p = 0.005$.

Gray matter volume

Amygdala

First, we applied a bilateral amygdala ROI mask from the AAL atlas and compared the magnitude of pre- to post-treatment GMV change within the bilateral amygdalae for the BLT versus the ALT group, using a peak threshold at $p < 0.001$ (uncorrected) and correction for multiple comparisons at the cluster level ($p < 0.05$, FWE corrected). This analysis yielded a significant cluster ($k = 18$ voxels) in the left amygdala [MNI: $x = -28$, $y = -8$, $z = -12$] where volume increased for the BLT group relative to the ALT group over the course of treatment (see **Figure 6**).

Medial prefrontal cortex

Using the same approach described above, we also examined the effects of light condition on changes in GMV within the medial prefrontal cortex (i.e., defined by a bilateral ROI comprising the gyrus rectus, medial orbitofrontal cortex, and anterior cingulate cortex from the AAL atlas). At an initial peak threshold of $p < 0.001$ (uncorrected), with cluster correction at $p < 0.05$ (FWE), there were no regions in which GMV change was moderated by light condition over the treatment period.

Gray matter volume correlations with sleep outcomes

Because the volume increases following 6 weeks of BLT were localized to the left amygdala, we conducted follow-up analyses within this same search territory to examine the potential associations between GMV changes and sleep-related outcomes.

Pittsburg sleep quality index

The primary subjective measure for sleep quality was the Total PSQI score collected at baseline and immediately after 6 weeks of light treatment. As evident in **Figure 7**, there was a significant negative association, suggesting that greater reductions (i.e., improvement) in PSQI scores over 6 weeks of treatment were significantly correlated with greater increases in volume within in a cluster ($k = 50$; MNI: −26, 2, −27) within the left amygdala (peak $p < 0.001$, uncorrected, cluster corrected $p < 0.05$, FWE). Because this association was for the sample as a whole, we extracted the significant voxels and assessed the influence of light condition as a moderator. However, when the interaction term for light condition × PSQI score was added to the regression, it did not account for significant variance (Change in $R^2 = 0.000$, $p = 0.92$), suggesting that light did not moderate the effect. Nonetheless, this association was statistically significant for the BLT group ($r = -0.388$, $p = 0.016$) but showed only a trend level association for the ALT group ($r = -0.339$, $p = 0.058$).

Disturbing dreams and nightmares severity index

We also examined disturbing dreams and nightmare severity with the DDNSI. Initial examination of the DDNSI change data suggested a positively skewed distribution, so a cube root transformation was applied to minimize the effects of outliers. As shown in **Figure 8**, greater declines (i.e., improvement) in DDNSI scores over the treatment period were significantly correlated with greater volume increases in a cluster ($k = 16$; MNI: −28, −4, −24) within the left amygdala (peak $p < 0.001$, uncorrected, cluster corrected $p < 0.05$, FWE). To test moderation by light condition, we extracted the significant voxels and examined the interaction term for the light condition × DDNSI scores. This analysis suggested a trend level interaction (Change in $R^2 = 0.057$, $p = 0.084$), but did not reach conventional levels of statistical significance. Nonetheless, the association was statistically significant for the BLT group ($r = -0.650$, $p = 0.00004$) but not for the ALT group ($r = -0.016$, $p = 0.928$). This suggests that nightmare severity may improve in concert with increases in left amygdala volume, which shows a trend toward greater increases with BLT than ALT.

ISI

There was no correlation between changes in ISI scores and changes in GMV within the left amygdala.

Time in bed

There was no correlation between changes in actigraphically measured TIB and changes in GMV within the left amygdala.

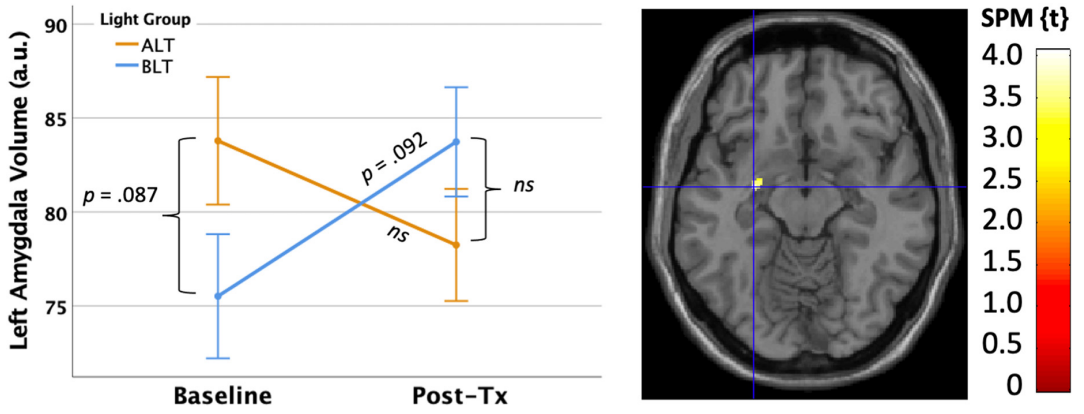

FIGURE 6
Six weeks of blue light treatment (BLT) was associated with significantly greater increase on left amygdala volume than an equal period of amber light treatment (ALT), $p < 0.05$ FWE corrected. The left side of the figure shows the mean (± SE) for amygdala volume. The right side of the figure shows the spatial location of this change [MNI: $x = -28$, $y = -8$, $z = -12$]. The color bar shows the magnitude of the t-value. Error bars = ± 1 SE. *Post hoc* comparisons are Bonferroni corrected.

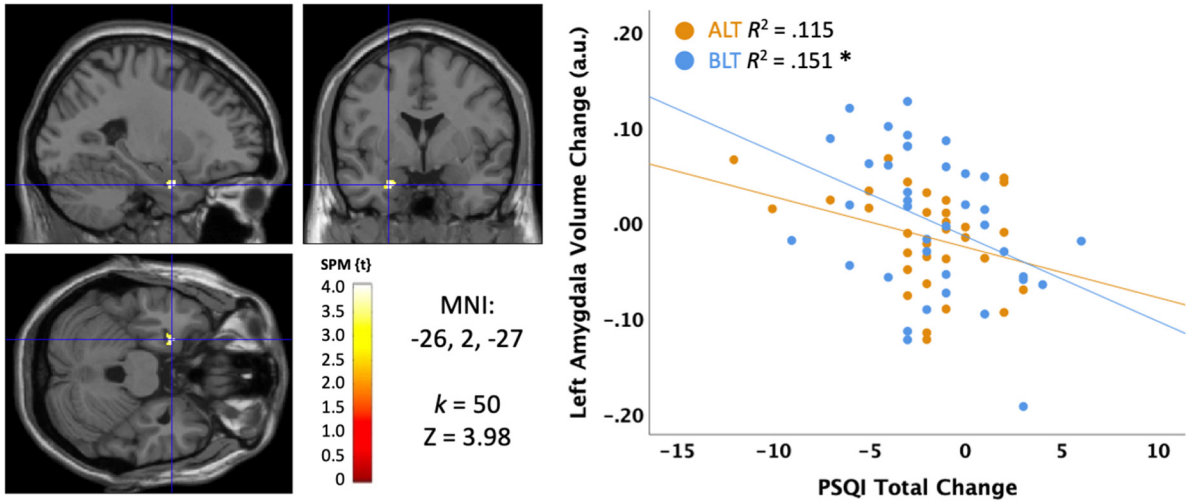

FIGURE 7
Correlation between sleep quality change on the Pittsburgh Sleep Quality Index (PSQI) and the change in left amygdala volume after 6 weeks of treatment with blue light treatment (BLT) or amber light treatment (ALT). The left panel shows the location of the significant cluster in the amygdala for the entire sample, $p < 0.05$ FWE cluster corrected. The right panel shows the scatterplot for the BLT and ALT samples separately. MNI, Montreal Neurologic Institute stereotaxic coordinates. *$p < 0.05$.

Total sleep time

There was no correlation between changes in actigraphically measured TST and changes in GMV within the left amygdala.

Sleep onset latency

There was no correlation between changes in actigraphically measured SOL and changes in GMV within the left amygdala.

Wake after sleep onset

There was no correlation between changes in actigraphically measured WASO and changes in GMV within the left amygdala.

Sleep efficiency

There was no correlation between changes in actigraphically measured SE and changes in GMV within the left amygdala.

Discussion

Three primary findings emerged from this study of individuals with PTSD. First, when analyzed per-protocol, 6 weeks of daily morning BLT led to significantly greater objectively measured time-in-bed (TIB) and total sleep time

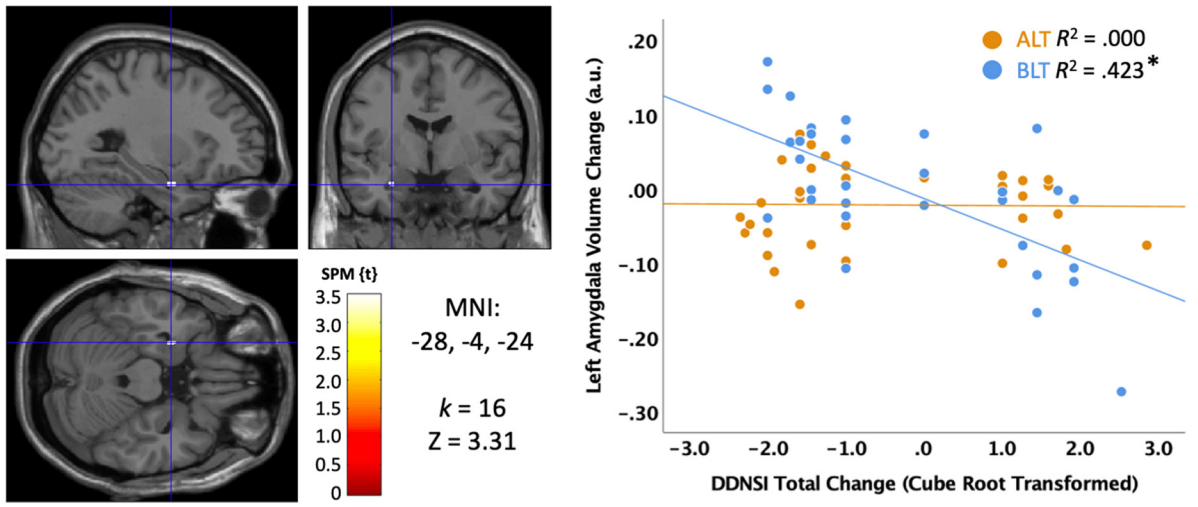

FIGURE 8
Correlation between sleep quality change on the Disturbing Dream and Nightmare Severity Index (DDNSI) and the change in left amygdala volume after 6 weeks of treatment with blue light treatment (BLT) or amber light treatment (ALT). The left panel shows the location of the significant cluster in the amygdala for the entire sample, $p < 0.05$ FWE cluster corrected. The right panel shows the scatterplot for the BLT and ALT samples separately. DDNSI change data were cube root transformed to ensure assumptions of normality. MNI, Montreal Neurologic Institute stereotaxic coordinates. *$p < 0.05$.

(TST) compared to an equivalent period of ALT. This suggests that BLT was effective at modifying objective sleep parameters to improve the amount of sleep obtained in people meeting diagnostic criteria for PTSD (although the TST finding did not hold when analyzed with missing values imputed in an intent-to-treat approach). However, there was no significant effect of BLT on subjective measures of sleep outcomes regardless of the approach. Second, over the course of treatment, the BLT group showed the hypothesized increase in the volume of the left amygdala compared to the ALT group. However, the predicted increase in medial prefrontal cortex volume was not observed. Finally, we found that the observed increases in left amygdala volume over the 6 weeks of treatment were correlated with improvements in sleep quality and nightmare severity, while no associations were found for objective measures of sleep. Each of these findings are discussed in turn below.

Importantly, we found that 6 weeks of daily morning BLT led to improvements in actigraphically measured sleep (when analyzed per protocol). As shown in **Figure 2**, BLT was associated with about a quarter of an hour more time in bed during the last week of treatment compared to the baseline week, while those who received the placebo treatment showed the opposite pattern. **Figure 3** shows that this resulted in a modest (but non-significant) increase in TST for the BLT group relative to the ALT group (who showed a significant decline over the same time frame) as well. This outcome was hypothesized based on the rationale that an earlier phase shift of melatonin onset (Cajochen et al., 2003) and regular entrainment of the circadian day would allow participants to maintain greater wakefulness during the day and fall asleep at an earlier time, which would maximize sleep by better aligning the biological night with the external environment (Lavie, 2001; Arendt, 2006). Our prior work with individuals who were recovering from an mTBI showed that BLT was effective at phase advancing the circadian rhythm of sleep by about 1 h (Killgore et al., 2020), although TST was not significantly changed. Research on the effects of light on TST has yielded mixed outcomes (Figueiro et al., 2014; Saxvig et al., 2014; Richardson et al., 2018; Wu et al., 2018) and has often been plagued by small sample sizes. Our prior mTBI study that failed to find TST effects had fewer participants than in the present PTSD study, so we had greater statistical power here to detect increases in sleep time, which may account for the differences in outcomes across studies. Further, while we found that actigraphic TST was increased by BLT relative to ALT, we did not find any effects on other objective metrics including SOL or WASO, suggesting that daily BLT did not significantly reduce the time to fall asleep or the amount of wakefulness observed after sleep onset, while this was improved for the ALT group. However, the lack of finding for WASO needs to also be considered in the context of the increased time in bed for the BLT group as well. With greater overall time in bed, there is also more opportunity for more or longer waking periods to occur, which may have contributed to the lack of improvement in WASO, despite an increase in TST. This is further supported by the lack of improvement in SE for the BLT group compared to the ALT group. Of course, wrist actigraphy is only a proxy for actual sleep and future studies would benefit from utilizing polysomnography to determine actual sleep.

In our prior studies of mTBI, we observed that BLT led to significant improvements in subjective sleep measures, such as daytime sleepiness (Killgore et al., 2020; Raikes et al., 2020, 2021) and subjective sleep quality (Raikes et al., 2020). Overall, we did not find a significant improvement in total sleep quality or nightmare severity here among those who received BLT versus ALT. When considered in light of the prior findings on objective sleep, this suggests that while individuals in the BLT condition did obtain more sleep overall, they did not self-report subjective differences in the quality of that sleep or a notable decline in the severity of nightmares. This is important and points to a potential limitation of the intervention in this group, as the subjective perception of sleep quality is an important aspect of wellbeing.

A primary objective of the current study was to examine the effect of BLT on GMV within the primary affective regulation network that has been implicated in PTSD, which includes the amygdala and medial prefrontal cortex (Rauch et al., 1996, 2000; Shin et al., 2004, 2005; Bremner et al., 2005). Prior work in PTSD samples has pointed to dysfunctional regulation of the functional responses of the amygdala by medial prefrontal regions (Rauch et al., 1996, 2000; Liberzon et al., 1999; Shin et al., 2004, 2005). This dysfunction of emotional regulation has been postulated to lead to exaggerated amygdala responses to emotional stimuli, which are remarkably similar to the prefrontal-amygdala disconnection findings that emerge during sleep deprivation (Yoo et al., 2007). When considered in light of volumetric MRI studies that have repeatedly demonstrated reduced amygdala and prefrontal volume in people with PTSD (Rogers et al., 2009; Morey et al., 2012), and evidence that amygdala volumes increase with successful treatment (Laugharne et al., 2016), we expected that our treatment with BLT would be associated with corresponding increases in amygdala (and perhaps medial prefrontal cortex) volumes. As predicted, we found that 6-weeks of BLT led to a significant increase in GMV within the left amygdala. However, the expected increase in GMV within the medial prefrontal cortex was not found. Together, these findings suggest that BLT plays an important role in normalizing amygdala volume in PTSD, perhaps *via* enhanced sleep, circadian alignment, or direct stimulation that affects amygdala responses. Recent findings suggest that light exposure suppresses acute responses within the amygdala but may increase the functional connectivity between the amygdala and prefrontal cortex (Alkozei et al., 2021; Mcglashan et al., 2021; Killgore et al., 2022). Thus, repeated exposures to BLT may lead to altered patterns of activity within the amygdala that facilitate volumetric increases. On the other hand, we did not find the expected increase in medial prefrontal cortex with BLT compared to ALT. Since the medial prefrontal cortex is critical to the assessment and understanding of emotions, and the ability to regulate emotional responses, our findings suggest that most of the effect of BLT on emotion may involve bottom-up changes to the emotion responsive regions of the amygdala rather than enhancement of top-down regulatory regions of the prefrontal cortex. This should be an area for further study.

To further explore the relevance of these volumetric changes to sleep outcomes in PTSD, we examined the associations between the changes in left amygdala GMV and sleep outcomes separately for the BLT and ALT groups. Overall, we found that increases in the volume of the left amygdala were associated with improvements in subjective sleep quality and reductions in the severity of nightmares, but these associations only held as significant for the BLT group and not the ALT group. Thus, while BLT did not lead to improvements in subjective sleep quality compared to placebo overall, within the BLT group specifically, greater increases in amygdala volume were clearly associated with improvements in self-reported sleep outcomes. In other words, the associations are complex and improvement in subjective sleep appears to be related to the changes in left amygdala volume that are enhanced by BLT. Conversely, no associations were generally found between amygdala volume and objective sleep outcomes as assessed by wrist actigraphy. The only exception to this was a general association between greater increases in WASO that corresponded to increases in left amygdala volume. However, as pointed out above, WASO scores were also associated with greater time in bed, which could account for part of the association.

Together, the findings suggest that daily BLT increased time in bed, total sleep time, and left amygdala volume relative to ALT, and that within the BLT group only, greater increases in amygdala volume were associated with subjective improvements in sleep quality and nightmares. Of course, these findings should be interpreted in the context of several limitations. First, we analyzed the data using a per-protocol approach as well as a more conservative intent-to-treat approach, and found that TST was significantly improved when only those who completed the project were analyzed. However, when missing values were imputed and the larger sample was analyzed with an intent-to-treat approach, these findings were no longer significant. This suggests that the effects of BLT on TST may be a best-case scenario and may not be observed in real-life trials when participants may or may not reliably complete treatment. Further work will be needed to clarify these outcomes. Second, the sleep patterns of the participants were quite variable, which led to significant difficulties in scoring the actigraphic sleep data. To minimize the error associated with frequent daytime naps, we chose to include only data from the nocturnal sleep periods. Consequently, it is possible that different outcomes would emerge if multiple brief naps were also incorporated into the findings. Third, wrist actigraphy only provides a proxy for sleep based on activity measurements. While actigraphy correlates well with the gold standard of polysomnography, future work would benefit from full polysomnographic assessments of sleep. Fourth, the samples were smaller than initially planned due to institutional and

funding agency requirements to discontinue data collection at the outset of the COVID-19 pandemic, so the modest size of the groups may have limited statistical power to detect some effects. Future research with larger sample sizes will be necessary and important to replicate and extend these findings. Fifth, the sample of participants with PTSD was quite heterogeneous with regard to their trauma histories. This made it impossible to validly compare subgroups based on trauma type. It is likely that the findings would be more telling in homogeneous groups that focused on a specific trauma exposure type (e.g., combat; sexual trauma; assault; etc.). Sixth, there was a trend toward group differences in many of the outcome measures at baseline, suggesting that the randomization process may not have completely equated the groups prior to light treatment. It is possible that some interactions may have been driven by simple regression to the mean. Alternatively, it is possible that the baseline differences may obscure even larger effects of treatment that would have been observed had the groups been equated at baseline. Finally, it is important to consider that voxel based morphometry (VBM) techniques provide only limited information about brain volume. Future work may benefit by incorporating additional anatomical approaches for gray matter (e.g., Freesurfer; metrics for gyrification, cortical thickness) or white matter integrity (e.g., diffusion tensor imaging). Nonetheless, we believe that with appropriate consideration of these limitations, the present findings demonstrate that blue-wavelength light treatment approaches may provide adjunctive non-pharmacologic intervention options that could be beneficial for enhancing some aspects of sleep and facilitating changes in critical emotional brain systems that contribute to recovery from PTSD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of Arizona Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WK designed the study, obtained the funding, oversaw the collection and archiving of the data, conducted the primary statistical analyses, wrote the initial draft of the manuscript, and revised the manuscript. JV assisted in data collection, archiving of the data, preprocessing of the neuroimaging data, and contributed to draft revisions of the manuscript. ND assisted in archiving and preprocessing of the data, management of lab resources and personnel, and contributed to draft revisions of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Agorastos, A., and Olff, M. (2020). Traumatic stress and the circadian system: Neurobiology, timing and treatment of posttraumatic chronodisruption. *Eur. J. Psychotraumatol.* 11:1833644. doi: 10.1080/20008198.2020.1833644

Alkozei, A., Dailey, N. S., Bajaj, S., Vanuk, J. R., Raikes, A. C., and Killgore, W. D. S. (2021). Exposure to Blue Wavelength Light Is Associated With Increases in Bidirectional Amygdala-DLPFC Connectivity at Rest. *Front. Neurol.* 12:625443. doi: 10.3389/fneur.2021.625443

American-Psychiatric-Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association. doi: 10.1176/appi.books.9780890425596

Arendt, J. (2006). Melatonin and human rhythms. *Chronobiol. Int.* 23, 21–37. doi: 10.1080/07420520500464361

Bajaj, S., Raikes, A. C., Razi, A., Miller, M. A., and Killgore, W. D. (2021). Blue-Light Therapy Strengthens Resting-State Effective Connectivity within Default-Mode Network after Mild TBI. *J. Cent. Nerv. Syst. Dis.* 13:11795735211015076. doi: 10.1177/11795735211015076

Bajaj, S., Vanuk, J. R., Smith, R., Dailey, N. S., and Killgore, W. D. S. (2017). Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. *Front. Neurol.* 8:616. doi: 10.3389/fneur.2017.00616

Bastien, C. H., Vallieres, A., and Morin, C. M. (2001). Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med.* 2, 297–307.

Ben Simon, E., Vallat, R., Barnes, C. M., and Walker, M. P. (2020). Sleep Loss and the Socio-Emotional Brain. *Trends Cogn. Sci.* 24, 435–450. doi: 10.1016/j.tics.2020.02.003

Brancati, G. E., Brekke, N., Bartsch, H., Evjenth Sorhaug, O. J., Ousdal, O. T., and Hammar, A. (2021). Short and long-term effects of single and multiple sessions of electroconvulsive therapy on brain gray matter volumes. *Brain Stimul.* 14, 1330–1339. doi: 10.1016/j.brs.2021.08.018

Bremner, J. D. (2006). Traumatic stress: Effects on the brain. *Dial. Clin. Neurosci.* 8, 445–461. doi: 10.31887/DCNS.2006.8.4/jbremner

Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., and Afzal, N. (2005). Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol. Med.* 35, 791–806. doi: 10.1017/s0033291704003290

Butler, O., Willmund, G., Gleich, T., Gallinat, J., Kuhn, S., and Zimmermann, P. (2018). Hippocampal gray matter increases following multimodal psychological treatment for combat-related post-traumatic stress disorder. *Brain Behav.* 8:e00956. doi: 10.1002/brb3.956

Buysse, D. J., Reynolds, C. F. III, Monk, T. H., Berman, S. R., and Kupfer, D. J. (1989). The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* 28, 193–213.

Cajochen, C., Krauchi, K., and Wirz-Justice, A. (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. *J. Neuroendocrinol.* 15, 432–437. doi: 10.1046/j.1365-2826.2003.00989.x

Del Casale, A., Ferracuti, S., Barbetti, A. S., Bargagna, P., Zega, P., Iannuccelli, A., et al. (2022). Grey Matter Volume Reductions of the Left Hippocampus and Amygdala in PTSD: A Coordinate-Based Meta-Analysis of Magnetic Resonance Imaging Studies. *Neuropsychobiology* 81, 257–264. doi: 10.1159/000522003

Ditye, T., Kanai, R., Bahrami, B., Muggleton, N. G., Rees, G., and Walsh, V. (2013). Rapid changes in brain structure predict improvements induced by perceptual learning. *Neuroimage* 81, 205–212. doi: 10.1016/j.neuroimage.2013.05.058

Figueiro, M. G., Plitnick, B. A., Lok, A., Jones, G. E., Higgins, P., Hornick, T. R., et al. (2014). Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities. *Clin. Interv. Aging* 9, 1527–1537. doi: 10.2147/CIA.S68557

First, M. B. (2015). "Structured clinical interview for the DSM (SCID)," in *The encyclopedia of clinical psychology*, eds R. L. Cautin and S. O. Lilienfeld (Hoboken, NJ: Wiley).

Franz, C. E., Hatton, S. N., Hauger, R. L., Kredlow, M. A., Dale, A. M., Eyler, L., et al. (2020). Posttraumatic stress symptom persistence across 24 years: Association with brain structures. *Brain Imaging Behav.* 14, 1208–1220. doi: 10.1007/s11682-019-00059-x

Geerdink, M., Walbeek, T. J., Beersma, D. G., Hommes, V., and Gordijn, M. C. (2016). Short Blue Light Pulses (30 Min) in the Morning Support a Sleep-Advancing Protocol in a Home Setting. *J. Biol. Rhythms* 31, 483–497. doi: 10.1177/0748730416657462

Gehrman, P., Seelig, A. D., Jacobson, I. G., Boyko, E. J., Hooper, T. I., Gackstetter, G. D., et al. (2013). Predeployment Sleep Duration and Insomnia Symptoms as Risk Factors for New-Onset Mental Health Disorders Following Military Deployment. *Sleep* 36, 1009–1018. doi: 10.5665/sleep.2798

Gilbert, K. S., Kark, S. M., Gehrman, P., and Bogdanova, Y. (2015). Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clin. Psychol. Rev.* 40, 195–212. doi: 10.1016/j.cpr.2015.05.008

Goldstein, A. N., and Walker, M. P. (2014). The role of sleep in emotional brain function. *Annu. Rev. Clin. Psychol.* 10, 679–708. doi: 10.1146/annurev-clinpsy-032813-153716

Hermes, E. D. A., Sernyak, M., and Rosenheck, R. (2013). Use of Second-Generation Antipsychotic Agents for Sleep and Sedation: A Provider Survey. *Sleep* 36, 597–600. doi: 10.5665/sleep.2554

Hoge, C. W., Castro, C. A., Messer, S. C., Mcgurk, D., Cotting, D. I., and Koffman, R. L. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N. Engl. J. Med.* 351, 13–22. doi: 10.1056/NEJMoa040603

Husain, F. T., Zimmerman, B., Tai, Y., Finnegan, M. K., Kay, E., Khan, F., et al. (2019). Assessing mindfulness-based cognitive therapy intervention for tinnitus using behavioural measures and structural MRI: A pilot study. *Int. J. Audiol.* 58, 889–901. doi: 10.1080/14992027.2019.1629655

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., and Killgore, W. D. S. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med.* 8, 215–221. doi: 10.1016/j.sleep.2006.08.007

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., and Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. General Psychiatry* 62, 593–602. doi: 10.1001/archpsyc.62.6.593

Killgore, W. D. S., Alkozei, A., Vanuk, J. R., Reign, D., Grandner, M. A., and Dailey, N. S. (2022). Blue light exposure increases functional connectivity between dorsolateral prefrontal cortex and multiple cortical regions. *Neuroreport* 33, 236–241. doi: 10.1097/WNR.0000000000001774

Killgore, W. D. S., Kahn-Greene, E. T., Lipizzi, E. L., Newman, R. A., Kamimori, G. H., and Balkin, T. J. (2008). Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Med.* 9, 517–526. doi: 10.1016/j.sleep.2007.07.003

Killgore, W. D. S., Vanuk, J. R., Shane, B. R., Weber, M., and Bajaj, S. (2020). A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. *Neurobiol. Dis.* 134:104679. doi: 10.1016/j.nbd.2019.104679

Krakow, B., Schrader, R., Tandberg, D., Hollifield, M., Koss, M. P., Yau, C. L., et al. (2002). Nightmare frequency in sexual assault survivors with PTSD. *J. Anxiety Disord.* 16, 175–190.

Laugharne, J., Kullack, C., Lee, C. W., Mcguire, T., Brockman, S., Drummond, P. D., et al. (2016). Amygdala Volumetric Change Following Psychotherapy for Posttraumatic Stress Disorder. *J. Neuropsychiatry Clin. Neurosci.* 28, 312–318. doi: 10.1176/appi.neuropsych.16010006

Lavie, P. (2001). Sleep-wake as a biological rhythm. *Annu. Rev. Psychol.* 52, 277–303. doi: 10.1146/annurev.psych.52.1.277

Liberzon, I., and Martis, B. (2006). Neuroimaging studies of emotional responses in PTSD. *Ann. New York Acad. Sci.* 1071, 87–109. doi: 10.1196/annals.1364.009

Liberzon, I., Taylor, S. F., Amdur, R., Jung, T. D., Chamberlain, K. R., Minoshima, S., et al. (1999). Brain activation in PTSD in response to trauma-related stimuli. *Biol. Psychiatry* 45, 817–826. doi: 10.1016/S0006-3223(98)00246-7

Logue, M. W., Van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., et al. (2018). Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. *Biol. Psychiatry* 83, 244–253. doi: 10.1016/j.biopsych.2017.09.006

Mancke, F., Schmitt, R., Winter, D., Niedtfeld, I., Herpertz, S. C., and Schmahl, C. (2018). Assessing the marks of change: How psychotherapy alters the brain structure in women with borderline personality disorder. *J. Psychiatry Neurosci.* 43, 171–181. doi: 10.1503/jpn.170132

Mcglashan, E. M., Poudel, G. R., Jamadar, S. D., Phillips, A. J. K., and Cain, S. W. (2021). Afraid of the dark: Light acutely suppresses activity in the human amygdala. *PLoS One* 16:e0252350. doi: 10.1371/journal.pone.0252350

Mellman, T. A., Bustamante, V., Fins, A. I., Pigeon, W. R., and Nolan, B. (2002). REM sleep and the early development of posttraumatic stress disorder. *Am. J. Psychiatry* 159, 1696–1701. doi: 10.1176/appi.ajp.159.10.1696

Miller, K. E., Brownlow, J. A., and Gehrman, P. R. (2019). Sleep in PTSD: Treatment approaches and outcomes. *Curr. Opin. Psychol.* 34, 12–17.

Morey, R. A., Gold, A. L., Labar, K. S., Beall, S. K., Brown, V. M., Haswell, C. C., et al. (2012). Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Arch. Gen. Psychiatry* 69, 1169–1178. doi: 10.1001/archgenpsychiatry.2012.50

Neylan, T. C., Marmar, C. R., Metzler, T. J., Weiss, D. S., Zatzick, D. F., Delucchi, K. L., et al. (1998). Sleep disturbances in the Vietnam generation: Findings from a nationally representative sample of male Vietnam veterans. *Am. J. Psychiatry* 155, 929–933. doi: 10.1176/ajp.155.7.929

Ohayon, M. M., and Shapiro, C. M. (2000). Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr. Psychiatry* 41, 469–478. doi: 10.1053/comp.2000.16568

Oldfield, R. C. (1971). The assessment of handedness: The Edinburgh inventory. *Neuropsychologia* 9, 97–111. doi: 10.1016/0028-3932(71)90067-4

Ousdal, O. T., Milde, A. M., Hafstad, G. S., Hodneland, E., Dyb, G., Craven, A. R., et al. (2020). The association of PTSD symptom severity with amygdala nuclei volumes in traumatized youths. *Transl. Psychiatry* 10:288. doi: 10.1038/s41398-020-00974-4

Panda, S., Nayak, S. K., Campo, B., Walker, J. R., Hogenesch, J. B., and Jegla, T. (2005). Illumination of the melanopsin signaling pathway. *Science* 307, 600–604. doi: 10.1126/science.1105121

Perini, G. I., Toffanin, T., Pigato, G., Ferri, G., Follador, H., Zonta, F., et al. (2017). Hippocampal Gray Volumes Increase in Treatment-Resistant Depression Responding to Vagus Nerve Stimulation. *J. ECT* 33, 160–166. doi: 10.1097/YCT.0000000000000424

Provencio, I., Rodriguez, I. R., Jiang, G., Hayes, W. P., Moreira, E. F., and Rollag, M. D. (2000). A novel human opsin in the inner retina. *J. Neurosci.* 20, 600–605. doi: 10.1523/JNEUROSCI.20-02-00600.2000

Qiu, X., Kumbalasiri, T., Carlson, S. M., Wong, K. Y., Krishna, V., Provencio, I., et al. (2005). Induction of photosensitivity by heterologous expression of melanopsin. *Nature* 433, 745–749. doi: 10.1038/nature03345

Raikes, A. C., Dailey, N. S., Forbeck, B., Alkozei, A., and Killgore, W. D. S. (2021). Daily Morning Blue Light Therapy for Post-mTBI Sleep Disruption: Effects on Brain Structure and Function. *Front. Neurol.* 12:625431. doi: 10.3389/fneur.2021.625431

Raikes, A. C., Dailey, N. S., Shane, B. R., Forbeck, B., Alkozei, A., and Killgore, W. D. S. (2020). Daily Morning Blue Light Therapy Improves Daytime Sleepiness, Sleep Quality, and Quality of Life Following a Mild Traumatic Brain Injury. *J. Head. Trauma Rehabil.* 35:E405–E421. doi: 10.1097/HTR.0000000000000579

Raikes, A. C., and Killgore, W. D. (2018). Potential for the development of light therapies in mild traumatic brain injury. *Concussion* 3:CNC57. doi: 10.2217/cnc-2018-0006

Rauch, S. L., Van Der Kolk, B. A., Fisler, R. E., Alpert, N. M., Orr, S. P., Savage, C. R., et al. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch. Gen. Psychiatry* 53, 380–387. doi: 10.1001/archpsyc.1996.01830050014003

Rauch, S. L., Whalen, P. J., Shin, L. M., Mcinerney, S. C., Macklin, M. L., Lasko, N. B., et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. *Biol. Psychiatry* 47, 769–776. doi: 10.1016/s0006-3223(00)00828-3

Richardson, C., Cain, N., Bartel, K., Micic, G., Maddock, B., and Gradisar, M. (2018). A randomised controlled trial of bright light therapy and morning activity for adolescents and young adults with Delayed Sleep-Wake Phase Disorder. *Sleep Med.* 45, 114–123. doi: 10.1016/j.sleep.2018.02.001

Rogers, M. A., Yamasue, H., Abe, O., Yamada, H., Ohtani, T., Iwanami, A., et al. (2009). Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. *Psychiatry Res.* 174, 210–216. doi: 10.1016/j.pscychresns.2009.06.001

Saxvig, I. W., Wilhelmsen-Langeland, A., Pallesen, S., Vedaa, O., Nordhus, I. H., and Bjorvatn, B. (2014). A randomized controlled trial with bright light and melatonin for delayed sleep phase disorder: Effects on subjective and objective sleep. *Chronobiol. Int.* 31, 72–86. doi: 10.3109/07420528.2013.823200

Schading, S., Pohl, H., Gantenbein, A., Luechinger, R., Sandor, P., Riederer, F., et al. (2021). Tracking tDCS induced grey matter changes in episodic migraine: A randomized controlled trial. *J. Headache Pain* 22:139. doi: 10.1186/s10194-021-01347-y

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., et al. (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch. Gen. Psychiatry* 61, 168–176.

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., Mcmullin, K., Martis, B., et al. (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch. Gen. Psychiatry* 62, 273–281. doi: 10.1001/archpsyc.62.3.273

Soshi, T., Andersson, M., Kawagoe, T., Nishiguchi, S., Yamada, M., Otsuka, Y., et al. (2021). Prefrontal Plasticity after a 3-Month Exercise Intervention in Older Adults Relates to Enhanced Cognitive Performance. *Cereb. Cortex* 31, 4501–4517. doi: 10.1093/cercor/bhab102

Starcevic, A., Postic, S., Radojicic, Z., Starcevic, B., Milovanovic, S., Ilankovic, A., et al. (2014). Volumetric analysis of amygdala, hippocampus, and prefrontal cortex in therapy-naive PTSD participants. *Biomed. Res. Int.* 2014:968495. doi: 10.1155/2014/968495

Sun, J., Chen, Q., Zhang, Q., Li, Y., Li, H., Wei, D., et al. (2016). Training your brain to be more creative: Brain functional and structural changes induced by divergent thinking training. *Hum. Brain Mapp.* 37, 3375–3387. doi: 10.1002/hbm.23246

Talbot, L. S., Maguen, S., Metzler, T. J., Schmitz, M., Mccaslin, S. E., Richards, A., et al. (2014). Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: A randomized controlled trial. *Sleep* 37, 327–341. doi: 10.5665/sleep.3408

Tanielian, T., and Jaycox, L. (eds) (2008). *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Concequences, and Services to Assist Recovery*. Santa Monica, CA: RAND Corporation. doi: 10.1037/e527612010-001

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289.

Ueno, T., Oishi, N., and Murai, T. (2018). Sex-specific regional grey matter volume correlates of daily activities. *Sci. Rep.* 8:9935. doi: 10.1038/s41598-018-28252-w

Van Liempt, S. (2012). Sleep disturbances and PTSD: A perpetual circle? *Eur. J. Psychotraumatol.* 3:19142. doi: 10.3402/ejpt.v3i0.19142

Walker, M. P., and Van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135, 731–748.

Wang, J., Tang, Y., Curtin, A., Xia, M., Tang, X., Zhao, Y., et al. (2019). ECT-induced brain plasticity correlates with positive symptom improvement in schizophrenia by voxel-based morphometry analysis of grey matter. *Brain Stimul.* 12, 319–328. doi: 10.1016/j.brs.2018.11.006

Weber, F. C., and Wetter, T. C. (2021). The Many Faces of Sleep Disorders in Post-Traumatic Stress Disorder: An Update on Clinical Features and Treatment. *Neuropsychobiology* 81, 85–97.

Wenger, E., Brozzoli, C., Lindenberger, U., and Lovden, M. (2017). Expansion and Renormalization of Human Brain Structure During Skill Acquisition. *Trends Cogn. Sci.* 21, 930–939.

Wenger, E., Papadaki, E., Werner, A., Kuhn, S., and Lindenberger, U. (2021). Observing Plasticity of the Auditory System: Volumetric Decreases Along with Increased Functional Connectivity in Aspiring Professional Musicians. *Cereb. Cortex Commun.* 2:tgab008. doi: 10.1093/texcom/tgab008

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., et al. (2018). The clinician-administered PTSD scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychol. Assess.* 30, 383–395.

Woo, C. W., Krishnan, A., and Wager, T. D. (2014). Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. *Neuroimage* 91, 412–419. doi: 10.1016/j.neuroimage.2013.12.058

Wu, L. M., Amidi, A., Valdimarsdottir, H., Ancoli-Israel, S., Liu, L., Winkel, G., et al. (2018). The Effect of Systematic Light Exposure on Sleep in a Mixed Group of Fatigued Cancer Survivors. *J. Clin. Sleep Med.* 14, 31–39. doi: 10.5664/jcsm.6874

Yang, J., Hellerstein, D. J., Chen, Y., Mcgrath, P. J., Stewart, J. W., Liu, Z., et al. (2021). Gray matter reorganization underpinnings of antidepressant treatment of persistent depressive disorder. *Eur. Neuropsychopharmacol.* 43, 129–138. doi: 10.1016/j.euroneuro.2020.12.009

Yoo, S. S., Gujar, N., Hu, P., Jolesz, F. A., and Walker, M. P. (2007). The human emotional brain without sleep–a prefrontal amygdala disconnect. *Curr. Biol.* 17:R877–R878. doi: 10.1016/j.cub.2007.08.007

Youngstedt, S. D., Kline, C. E., Reynolds, A. M., Crowley, S. K., Burch, J. B., Khan, N., et al. (2021). Bright Light Treatment of Combat-related PTSD: A Randomized Controlled Trial. *Mil Med.* 187:e435–e444. doi: 10.1093/milmed/usab014

Zalta, A. K., Bravo, K., Valdespino-Hayden, Z., Pollack, M. H., and Burgess, H. J. (2019). A placebo-controlled pilot study of a wearable morning bright light treatment for probable PTSD. *Depress Anxiety* 36, 617–624. doi: 10.1002/da.22897

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Morning blue light treatment improves sleep complaints, symptom severity, and retention of fear extinction memory in post-traumatic stress disorder

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Disrupted sleep is a major feature in numerous clinical disorders and is related to decrements in affective memory processing. The prevalence of sleep disruption in post-traumatic stress disorder (PTSD) is suggested to be a key feature that exacerbates the impaired ability to recall extinction memories during experimental fear conditioning. We hypothesized that an intervention employing blue-wavelength light therapy (BLT) to regulate sleep and stabilize circadian rhythms in patients with PTSD (i.e., via regulated morning exposure) would be associated with PTSD symptom improvement, decreased sleep-related complaints, as well as improved consolidation and retention of extinction memories relative to a fear conditioning/extinction paradigm. Eighty-two individuals with PTSD underwent a well-validated fear conditioning/extinction protocol with subsequent assignment to receive morning BLUE (BLT) or placebo AMBER (ALT) light therapy daily for 30-min over 6-weeks. Participants returned after the intervention for post-treatment extinction recall, comprised of exposure to the previously conditioned stimuli, with the difference in skin conductance response between the "extinguished" and the "never-extinguished" stimuli at follow-up. Participants also viewed previously conditioned stimuli in a novel context during a functional magnetic resonance imaging (fMRI) scan. BLUE light therapy was associated with improvements relative to correlated decreases between PTSD symptoms and sleep-related complaints. Participants receiving BLT also sustained retention of the extinction memory, while those in the placebo amber light treatment group showed impairment, characterized by the restoration of the extinguished fear response after 6-weeks. Participants in the ALT also demonstrated greater reactivity in the left insula when viewing the previously extinguished fear-conditioned stimuli in a novel context. Daily BLUE-wavelength morning light exposure was associated with greater retention of extinction learning in patients with PTSD when compared to ALT, as supported by both autonomic and neurobiological reactivity. We speculate that improved sleep facilitated by a stabilized circadian rhythm,

after fear-learning, led to greater consolidation of the fear extinction memory, decreased PTSD symptom presentation, and associated decreases in sleep-related complaints. Prominent exposure treatments for PTSD incorporate principles of fear extinction, and our findings suggest that blue light treatment may facilitate treatment gains by promoting the consolidation of extinction memories via improved sleep.

KEYWORDS

blue light therapy, post traumatic stress disorder, sleep, fear conditioning, fear extinction memory, autonomic reactivity, neurobiological reactivity, fMRI

Introduction

Adversity is inherent to life, yet individuals have remarkably different affective experiences and behavioral outcomes under conditions potentially assessed as "adverse." Individuals experience different types/levels of exposure to stressful life events and demonstrate varying capacities for resilience or vulnerability to those adverse circumstances (Masten et al., 1999). The inter-individual capacity for resilience ranges in contexts from the biological, such as fending off an attacking virus, to behavioral, such as the ability to sustain attention during prolonged periods of sleep deprivation, to emotional, such as the ability to recover rapidly from emotionally challenging setbacks or traumatic experiences. Emotional resilience draws upon diverse cognitive and emotional competencies and differs widely across individuals. Affective responses to the same contextual environment/situation are heterogeneous and dependent on an individual's appraisal of their impending context (Lazarus, 1999). These appraisals rely on the degree that an individual perceives the setting as a challenge or a threat, in conjunction with their ability to cope with the demands specific to the context (Oken et al., 2015). As such, individuals can have vastly different emotional and behavioral outcomes following the experience of objectively similar adverse/traumatic life events.

In recent decades, there has been an increasing awareness concerning the psychological and physical impact that trauma-based experiences can have on an individual. Rates of exposure to a single traumatic event over the life course are estimated as high as 70%, with approximately 30% of individuals experiencing four or more traumatic events during their life (Roberts et al., 2011). A critical factor to highlight, however, is that not all individuals who experience trauma develop the sustained maladaptive psychological and behavioral responses that manifest as clinically significant posttraumatic stress disorder (PTSD). As such, PTSD can be thought of as a disorder related to recovery rather than initial reactivity to a trauma experience. The inter-individual variability in resiliency and potential to successfully engage in empirically based treatments with sustained improvements remains unclear, likely due to the multitude of factors contributing to these capacities (Van Minnen et al., 2002).

Accumulating evidence suggests that the development and maintenance of PTSD is highly dependent on the functioning of the fear neurocircuitry within the brain. Early work suggested that PTSD was associated with a deficit in the ability of the regulatory regions of the brain (i.e., ventromedial prefrontal cortex) to effectively modulate fear responses within the more primitive limbic structures (i.e., amygdala; Rauch et al., 2006; Shin et al., 2006). Functional connectivity between the medial prefrontal cortex (mPFC) and amygdala is critical to decreasing the negative affective salience of memories and is contingent on proper sleep architecture (van der Helm and Walker, 2010; Pace-Schott et al., 2015b). These brain regions also play a crucial role in cardiac vagal control and emotion regulation capacities (Sakaki et al., 2016). The neurovisceral integration model provides further insight into the brain-body relationship by describing the relationship between mPFC function and autonomic control and implications on emotion and health outcomes related to these biological processes (Thayer and Lane, 2000). The insular cortex is another key area in the brain involved in emotional regulation of learning and memory and is particularly important for the interoceptive experience of anxiety (Liberzon and Martis, 2006; Chellappa and Aeschbach, 2021). While not directly associated with the hypothalamic-pituitary-adrenal axis, insula responses are suggested to play a key role in its activity (Fornari et al., 2012; Linnman et al., 2012). Maladaptive HPA function can interrupt critical diurnal cycles, such as the sleep-wake pattern, impacting emotional health and wellbeing (Killgore et al., 2008; Nader et al., 2010). Notably, a growing body of work demonstrates sleep disturbance as one of the most common complaints by individuals suffering from affective disorders and postulated to be a core dimension in the persistence of both depression and post-traumatic stress

disorder (PTSD; van der Helm and Walker, 2010; Germain, 2013; Richards et al., 2020).

Exposure to chronic or severe stress primes the neuroendocrine system to prepare the body and brain for survival. The anterior cingulate cortex (ACC), insula, and amygdala are brain regions that functionally adapt to these types of experiences and can become hyper-responsive to any context assessed as a potential threat (Milad and Quirk, 2012; Pace-Schott et al., 2015b; Alexandra Kredlow et al., 2022). Specifically, exaggerated responses by the amygdala during adverse experiences enhance the encoding of emotionally salient memories (Sharot and Yonelinas, 2008). The affective content of these types of memories can lead to subsequent maladaptive changes in behavior such as physiological hyperarousal, intrusive memories, and persistent nightmares that can continue long after the acute effects of their trauma experience have subsided and have pronounced implications on their daily function and, when severe enough, can manifest as post-traumatic stress disorder (PTSD; Yehuda et al., 2015; Shalev et al., 2017; Ressler et al., 2022). Sleep problems are the most prevalent complaint in individuals with PTSD, with self-report rates as high as 90%, and are postulated to be a driving factor in both the persistence and severity of symptom presentations related to the disorder (van der Helm and Walker, 2010; Germain, 2013; Richards et al., 2020). The sleep problems often observed may be attributable to the occurrence of reduced slow-wave sleep, prolonged time spent in stage 1 sleep, as well as a higher density of rapid-eye movements during sleep cycles (Kobayashi et al., 2007). The severity of sleep disturbance is also associated with PTSD symptom severity, and evidence suggests that sleep problems play a mediating role between exposure to stressors and the manifestation of symptoms contributing to PTSD (Gehrman et al., 2013; Wang et al., 2019; Neylan et al., 2021). Restorative sleep offers one of the most potent non-pharmacologic mechanisms for influencing behavior and affect. A critical insight from research using fear conditioning is that fear extinction learning may not generalize to unextinguished but similar stimuli without post-learning sleep (Pace-Schott et al., 2009). Without proper sleep during a critical post-learning temporal window, an individual's chance for recovery is significantly decreased, making sleep a viable intervention target for PTSD symptom severity (Pace-Schott et al., 2015a).

From a learning theory perspective, PTSD can be characterized by hyper-responsive reactions to stimuli to which an individual has a conditioned fear response (i.e., stimuli related to the traumatic event). Neuroimaging studies suggest that exposure to fear-based stimuli often results in a dampening of activity in the mPFC in conjunction with amygdalar activation that leads to an emotionally salient memory and subsequent conditioned fear response to that memory (Milad and Quirk, 2012; Shalev et al., 2017; Ressler et al., 2022). Fear extinction learning and memory are proposed to be critical mechanisms linking risk factors such as hormones, genotype, cognition, and sleep disturbance with PTSD symptoms and severity (Zuj et al., 2016). Cognitive therapy treatments targeting PTSD, such as prolonged exposure (PE) therapy, leverage continued exposure to fear-based memories in a safe environment to create new memories that compete with and eventually inhibit the trauma memories (Foa et al., 2007). Of interest, studies in both animals and humans demonstrate a positive association between the quality of sleep after a safety-learning experience and the extinction of conditioned fear responses (Fu et al., 2007; Pace-Schott et al., 2015a). Specifically, research demonstrates learning may not generalize to unextinguished but similar stimuli without post-learning sleep (Pace-Schott et al., 2015a). This is a critical insight relative to applications for cognitive-behavioral treatments. Reductions in fear responses fostered through exposure in the therapy room may sustain in that singular environment but these extinction memories are less likely to transfer and generalize to the broader real world environment if adequate restorative sleep is not obtained following treatment (Pace-Schott et al., 2012; Straus et al., 2017). This lack of safety learning generalizability can result in a "vicious cycle" where patients become trapped in the cyclic nature of worsening sleep exacerbating symptom presentation, while those same symptoms contribute to sleep disruption (Walker and van Der Helm, 2009; Goldstein and Walker, 2014; Pace-Schott et al., 2015b; Colvonen et al., 2019).

Because sleep is so critical for retention of extinction memories, it is vital that sleep interventions be incorporated into treatment for PTSD. While there are a number of pharmacologic treatments for sleep issues, there continues to be a need for non-pharmacologic approaches. Continuous positive airway pressure (CPAP) has been shown to significantly enhance improvements in the inhibition and extinguishing of fear based memory for patients with obstructive sleep apnea (OSA), and suggested as an integral consideration in treatment algorithms for patients with co-morbid PTSD and OSA (Reist et al., 2021). Targeted light exposure is an emerging non-pharmacological method of modulating the sleep-wake cycle. While bright light can be effective, recent research suggests that the blue wavelengths of light (446–477 nm) appear to be the active ingredient that is most effective at producing circadian shifts (Lockley et al., 2006). The observed effects are attributable to the presence of photosensitive retinal ganglion cells, which respond to blue light specifically and have a direct connection to a critical brain region involved in melatonin secretion and circadian rhythms: the suprachiasmatic nucleus of the hypothalamus (Lack et al., 2007; Hankins et al., 2008). Blue light exposure has differential effects on the sleep and wake cycle based on the timing of exposure (Terman, 2007). Interestingly, the impact of light exposure is contingent on core body temperature, with an exposure that occurs after the nadir in body temperature

at night resulting in a phase advance of the sleep-wake cycle (earlier to rise, earlier to sleep), while exposure before the nadir has an opposite effect and induces a phase delay on the sleep cycle (Bjorvatn and Pallesen, 2009). Short-wavelength light has also been demonstrated to have acute effects on physiology and behavior, such as decreasing HRV, increasing prefrontal brain activation, along with improving alertness and memory (Münch et al., 2012; Sahin and Figueiro, 2013; Alkozei et al., 2016a; Lazzerini Ospri et al., 2017; Fernandez et al., 2018). Our group has demonstrated the combined effects of blue light therapy (BLT) on circadian timing, neurocognitive performance and neural mechanisms in patients recovering from mTBI, which are characterized by sleep related problems post injury (Alkozei et al., 2017a; Raikes et al., 2020; Bajaj et al., 2021; Killgore et al., 2022). The potent influence of sleep disruption on PTSD symptom severity is well established. Multiple studies have investigated sleep-specific interventions within this population, and recent preliminary findings from two small pilot trials suggested that a light treatment in the green wavelengths (∼500 nm; Zalta et al., 2019) and another using broad-spectrum white light showed promise for improving PTSD symptoms (Youngstedt et al., 2021). However, the full utility of morning BLT for improving sleep and reducing symptom severity in PTSD has yet to be formally investigated. Intervening at the biological level may be critical to treatment, as some work demonstrates that improvements in autonomic function measured by HRV were associated with a reduction in PTSD symptoms for individuals who completed biofeedback treatments in conjunction with cognitive therapy, as compared to individuals who only engaged in cognitive therapy (Tan et al., 2011). These results suggest that improvements in symptom severity in PTSD may be facilitated by appropriately timed BLT.

Here, we conducted a comprehensive assessment of the neurobiological, autonomic, and behavioral outcome changes produced by a 6-week intervention of daily morning blue-wavelength light exposure in individuals with clinically significant levels of PTSD. In a randomized, double-blind, placebo-controlled trial, adults with a verified diagnosis of PTSD and concurrent symptom presentation used an LED lightbox each morning for 30-min within the first 2 h after awakening. Each device was fitted with either BLUE (active treatment) or AMBER (control treatment) LEDs. Sleep/wake activity was monitored via online sleep diaries for 1 week before treatment, and throughout the 6-week intervention period. Participants also completed a cognitive assessment battery, resting HRV monitoring, a fear conditioning paradigm, and functional and structural magnetic resonance imaging (MRI) scans on the day before the treatment period and again upon completion of the intervention. We hypothesized that the blue light intervention would lead to improved sleep via circadian phase advancement, a decrease in the severity of PTSD symptoms, increased vagal control of HRV, and sustained fear extinction learning relative to amber placebo light. Further, we hypothesized that these changes would correspond to decreased amygdala, insular, and ACC activity during a post-treatment fear extinction recall task.

Materials and methods

Study procedures were evaluated and approved by the Institutional Review Board of the University of Arizona College of Medicine and the U.S. Army's Human Research Protections Office. All participants provided written informed consent prior to participation.

Participants

Individuals that experienced an index trauma event consistent with a Diagnostic and Statistical Manual - V (DSM-V) diagnosis of PTSD and were currently experiencing symptoms consistent with such a diagnosis were recruited for the present study. Individuals were recruited via advertisements placed within the local Tucson and surrounding metropolitan areas, including posted flyers, radio advertisements, and various internet ad campaigns. Interested participants contacted the investigators and underwent a thorough telephone screening interview. Potentially eligible participants were then invited to attend an in-person visit to determine full eligibility (Visit 1). Eligible participants were between the ages of 18 and 50 years old, right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), primary English speakers (i.e., those who began speaking English as their primary language in the home by 3 years of age), and received a diagnosis consistent with PTSD based on the Structured Clinical Interview for DSM-V (SCID-V) during Visit 1 were included. Potential volunteers were excluded for any history of head injury with loss of consciousness for greater than 30 min, or post-traumatic amnesia for > 24 h, major neurological illness (e.g., epilepsy, multiple sclerosis); chronic medical condition (e.g., heart conditions, cystic fibrosis, diabetes, cancer, HIV/AIDS, HEP C, thyroid problems, high blood sugar) or psychiatric condition (e.g., bipolar disorder/manic or hypomanic episodes, personality disorders, schizophrenia/other psychotic disorders, severe OCD or ADHD), an index trauma occurring before the age of 18, an index trauma occurring 10 years or longer prior to participation in the study, ongoing trauma (e.g., currently being in an abusive relationship) or non-qualifying trauma (e.g., index trauma emotional/verbal abuse, children being taken away by the CPS, divorce, natural deaths by age or illness) that would confound interpretation of results. Other exclusionary criteria included abnormal visual acuity that was not correctable by contact lenses (necessary to see stimuli in the magnetic environment of the scanner), IQ

estimate less than 70, metal within the body, pregnancy, or other contraindication for MRI procedures, previous formal treatment with light therapy, history of light-induced migraine or epilepsy, medical complications that could elevate the risk of discomfort associated with light-therapy, use of medications that could affect functional neuroimaging results (e.g., beta-blockers, mood stabilizers, atypical antipsychotics, benzodiazepines, hypertension medication, chemotherapy, photosensitive medications etc.), current suicidal intent based on an assessment conducted by a licensed clinical psychologist, currently taking or anticipating the need to take sleep-inducing medications (e.g., zolpidem) or supplements that have known effects on sleep (e.g., melatonin) during the course of the study, reading test score indicative of less than a 6th grade level of reading comprehension, or drug use (marijuana use was not exclusionary). Past drug dependence (other than marijuana) was not exclusionary if individuals had sustained remission (no drug use in the past 12 months).

Prior to undergoing the clinical assessment, all interested individuals were briefed on the study and provided written informed consent. Participants were then evaluated for PTSD severity using the Structured Clinical Interview for DSM-V (SCID) and were required to meet DSM-V criteria for PTSD at a clinical to subclinical severity. A total of 90 participants were enrolled, however, eight participants failed to complete the study, resulting in a final sample of N = 82 (blue light treatment—BLT: n = 43; amber light treatment—ALT: n = 39). Six of these eight participants were removed due to lack of compliance with study procedures based on data collected through the online portal (e.g., daily use of the light device and completion of the online questionnaire) and two of these participants were completing their participation at the outset of the COVID-19 pandemic, so it was not possible to collect all in-person data from those individuals due to institutional COVID mitigation measures in place at that time. Out of the 82 participants who completed the study, 77 met clinically significant criteria for PTSD on the SCID-V, while 5 were just below the threshold and were listed as "sub-clinical" (BLT n = 2; ALT n = 3). The proportion of clinical to sub-clinical participants between BLT and ALT groups did not differ significantly ($\chi^2 = 0.08$, $p = 0.77$).

Basic demographic characteristics for the groups **(BLT: *n* = 43; ALT *n* = 39)** are reported in Table 1. The ratio of males to females between the groups did not differ significantly (χ^2 = 0.01, p = 0.94). In addition, groups did not differ significantly on basic demographic variables including age (t = –1.1, p = 0.27), years of education (t = –0.27, p = 0.79), or full-scale IQ as measured by the Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-II) (t = 1.26, p = 0.21). Similarly, the groups did not differ for age at index trauma (t = –0.74, p = 0.46) or for years since the index trauma (t = –0.79, p = 0.43).

General procedure

Over a 7 week period, participants completed three laboratory visits, including two full-day neurocognitive assessments plus neuroimaging scans, and were randomly assigned to complete a 6-week at-home light treatment regimen with either daily BLUE (BLT) or AMBER (ALT) light therapy for 30-min each morning (see Figure 1).

Visit 1: Intake

During the first visit, eligible participants completed the informed consent process followed by an evaluation of PTSD severity and other psychopathology using the Structured Clinical Interview for DSM-V (SCID; First et al., 2015). Each eligible participant was shown how to log onto a secure web-based sleep diary to complete daily questions about sleep and activity. Participants were instructed to return to the lab for a baseline neurocognitive assessment and MRI scan 1 week later.

Visit 2: Baseline neurocognitive assessment/magnetic resonance imaging scan

After 1 week participants returned for a baseline neurocognitive and neuroimaging assessment, as well as engaged in the initial phase of a fear conditioning paradigm. Participants arrived at the lab and completed a resting electrocardiogram (ECG) assessment, followed by the initial phases of the fear conditioning paradigm (habituation, conditioning, extinction), as well as pre-scan procedures, including a pregnancy test for females. Beginning at 9:00 a.m., participants underwent a neuroimaging scan that included a standard structural T1 magnetization prepared gradient echo (MPRAGE) MRI scan. On a strict, time-controlled schedule throughout the day, participants then completed in-lab sleep, neurocognitive, and psychological assessments. After testing, the participant was provided with a light therapy device with a full demonstration of its use, as well as a printed instruction brochure that provided detailed information about the use of the device.

Six-week light therapy

A computer-generated randomization scheme assigned participants to receive either a BLUE or AMBER light device (described in greater detail below) in a double-blind manner (i.e., participants were not informed that there were different colors of lights and all study staff with direct participant contact were blind to the color of the light device assigned). Participants were instructed to use the light device every morning continuously for 30 min, within 2 h of awakening, no later than 11:00 a.m. Participants were instructed to place the lightbox at approximately arm's length (20–30 in. from their face) and a slight angle (20–40°), so that both sides of the face would be exposed to the light, as well as were encouraged to avoid looking directly at the light diodes to

TABLE 1 Baseline demographic characteristics.

Baseline Demographics	Blue (active) $n = 43$		Amber (placebo) $n = 39$		
	M	*SD*	*M*	*SD*	*p*-value
Age	31.76	8.80	30.26	8.73	0.27
Education Category	4.91	1.61	4.82	1.50	0.79
Full Scale IQ	100.86	11.08	103.31	13.49	0.21
Age at Index Trauma	28.10	8.46	27.14	8.25	0.46
Years since Index Trauma	3.30	2.27	3.03	2.19	0.43
Male/Female (n)	14/29	–	12/27	–	0.94

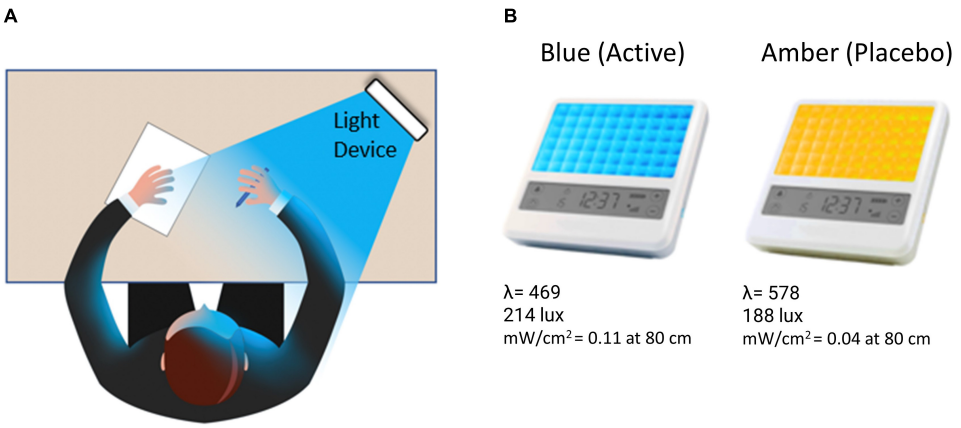

FIGURE 1
(A) The participant was instructed to bathe their face with the light for 30-min each morning by placing the light device at arm's length on a table at an approximately 45-degree angle. **(B)** Participants received either a blue (active condition) or amber (placebo condition) lightbox fitted with light-emitting diodes.

avoid visual discomfort. The device was programmed to turn off automatically after 30 min of continuous use. Participants were also instructed to complete a sleep and light use diary each morning via a secure online portal after finishing light exposure, and also wore wrist actigraphs for the duration of the study (Actiwatch Spectrum Pro®, Philips).

Visit 3 post-treatment assessment/fear conditioning/magnetic resonance imaging scan

Upon completion of the 6-weeks of daily morning light exposure, participants returned to the lab for a final assessment session, which was virtually identical in timing and procedures to the baseline session except for an additional Fear Extinction memory component during their MRI scan. At the end of the day, participants returned all equipment and were released from the study (see Figure 2).

Assessment measures

The following assessment measures and devices were used:

Light exposure devices

Participants were provided with either a BLUE or AMBER light therapy device based on randomized assignment (see Figure 1). The devices were manufactured by Philips Electronics (Stamford, CT, United States). All units were identical in design, with the exception of the color wavelength of the LEDs. Each device consisted of a 13.5 × 14 cm plastic-encased table-mounted device with a 10 × 6 array of light emitting diodes (LEDs). For the active BLUE condition, participants were provided with a commercially available Philips goLITE BLU® Energy Light device (Model HF3321/60). The goLITE BLU Energy Light has a narrow bandwidth (peaking at $\lambda = 469$ nm, at 214 Lux, and single panel irradiance (mW/cm^2) = 0.11 at 80 cm). The AMBER devices were designed to be identical to the goLITE BLU devices, with the exception that the LEDs emitted amber light [peaking at $\lambda = 578$ nm, at 188 Lux, and panel irradiance (mW/cm^2) = 0.04 at 80 cm].

Post-traumatic stress disorder symptoms

Participants were administered the Structured Clinical Interview for DSM-V (SCID; First et al., 2015) to ensure

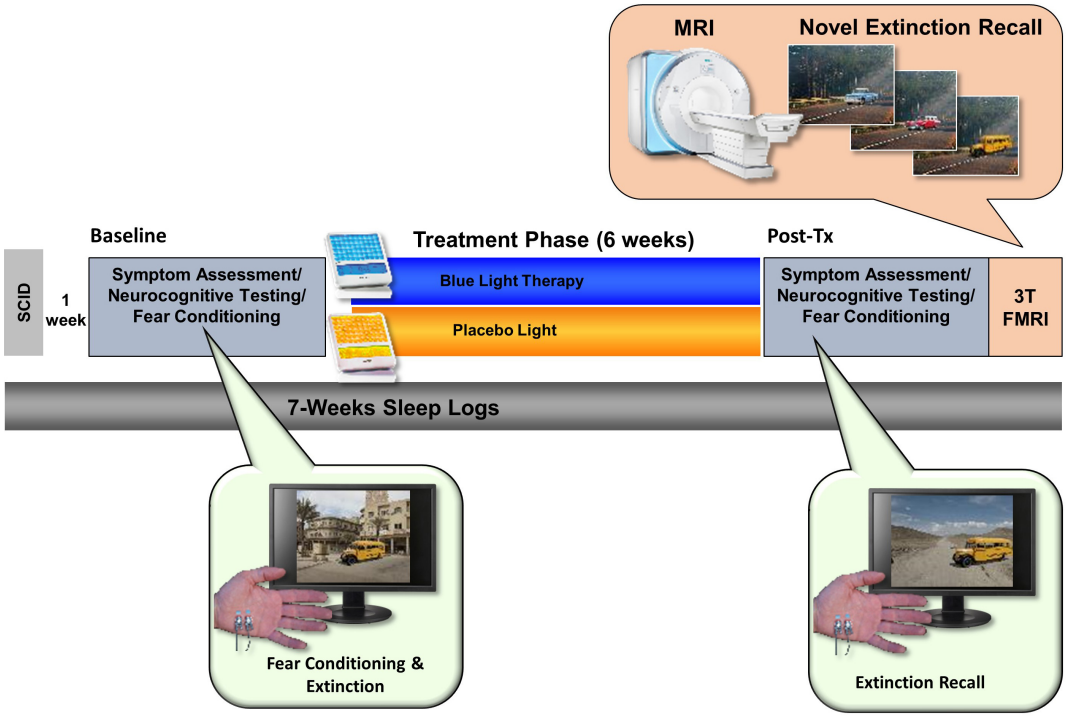

FIGURE 2
The total study lasted 7 weeks and comprised an initial visit for a structured clinical interview. After 1 week, participants returned for a Baseline assessment day that included neurocognitive testing (including a fear conditioning and extinction protocol). Participants were then randomly assigned to either the Blue Light Treatment (BLT) or placebo Amber Light Treatment (ALT). During treatment, participants used a lightbox (blue or amber) each morning for 30 min over the 6-week period. Participants returned to complete the same assessment battery at the end of the study as well as a 3T fMRI scan while engaging in a novel context extinction recall task.

individuals met diagnostic criteria for a current PTSD diagnosis, as well as the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018), and Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5; Blevins et al., 2015), in order to assess PTSD symptom severity at visits two and three.

Sleep dysfunction and subjective sleep need assessment

Participants completed the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness (Johns, 1991); the Pittsburg Sleep Quality Index (PSQI), a measure of sleep habits and sleep quality in the past month (Buysse et al., 1991), the Functional Outcomes of Sleep Questionnaire (FOSQ), a measure of the impact of daytime sleepiness on function (Chasens et al., 2009), the Insomnia Severity Index, a measure of both nighttime and daytime insomnia components (Bastien et al., 2001), and the Disturbing Dreams and Nightmares Severity Index (DDNSI), a measure of the frequency and severity of nightmares (Krakow et al., 2002).

Fear conditioning

During the baseline visit, participants underwent a modified version of a well-validated fear conditioning protocol (Milad et al., 2007; Pace-Schott et al., 2009; Marin et al., 2017). While the original version of the task utilized photographs of colored lamps on a desk (Milad et al., 2005), the current version was modified to be more appropriate to military PTSD settings. Specifically, the participant was first conditioned to fear two particular stimuli (e.g., a blue or red or yellow vehicle) in a specific context (e.g., city street in Baghdad Iraq), by providing a mild electric shock when the conditioned stimuli were shown, as shown in **Figure 3A**. A third stimulus (e.g., yellow bus) was never paired with the electric shock and served as a "non-reinforced CS" or CS–. Participants were randomized across 8 different stimulus/context conditions, counterbalancing vehicle color and conditions across CS conditions and presentation contexts, as well. Our participants showed a rapid acquisition of the conditioned fear response for the conditioned stimuli (e.g., red and blue vehicles), as evidenced by increased skin conductance and/or self-report indicating they expected a shock by the last two stimulus presentations during conditioning for the CS + S. Next, as shown in **Figure 3B**, the goal was to extinguish one conditioned stimulus (i.e., blue truck) by repeatedly showing the stimuli in a novel context (e.g., a dirt road in Afghanistan), but without any electric shock administered. After 16 trials where the stimuli were shown without any further shock, the skin conductance response (SCR) to the blue truck is expected to return to normal.

Thus, at this phase of the task, the fear response to the blue truck has been successfully "extinguished" by the creation of a new "safety memory." However, the red vehicle, which was previously paired with the electric shock, is never shown again in this new context, so it retains the saliency of the initial conditioned fear response. In this example, the yellow bus was never paired with a shock, so it is expected to continue to evoke very little SCR. After 6-weeks of light exposure therapy (BLUE or AMBER), participants returned to the lab and were shown the same stimuli again but without any new shock stimuli. Skin conductance was monitored throughout to assess the degree to which the safety memory was consolidated and retained subsequent to extinguishing (see **Figure 3C**).

Psychophysiological monitoring

Skin conductance

During the fear conditioning paradigm, skin conductance was continuously monitored at 37.5 Hz using disposable, MRI-safe 11-mm, Ag/AgCl sensors filled with isotonic paste attached 14 mm apart on the hypothenar surface of the left hand and recorded using the MP150 system with *Acqknowledge* acquisition software (BIOPAC Systems, Inc., Goleta, CA, United States). SCR was calculated for each trial as the mean skin conductance level in microSiemens (μS) during the last 2 s of context presentation, subtracted from the maximum skin conductance level during the 6 s of CS presentation. SCRs were square-root transformed; if the untransformed SCR was negative, the negative sign was retained after calculating the square root of the SCR's absolute value (Orr et al., 2000). "Non-conditioners" were defined as those who exhibited less than 2 non-square-root transformed SCR responses to a CS + that equal to or exceeding 0.05 μS during the Fear Conditioning phase. Non-conditioners (8 Blue and 6 Amber) were excluded from analyses.

Outcome variables included SCR and Differential SCR (SCRd) equal to SCR to a CS + minus SCR to its ordinally corresponding CS-. Summary variables for the Fear Conditioning phase included a measure of differential "Conditionability" that was defined as the mean SCRd to all CS + s (excluding the first to each CS +). For the Extinction Learning phase, an Extinction Learning Index (EXTidx) was defined. EXTidx was calculated by subtracting mean SCR to the last four CS + E presentations from mean SCR to the first four CS + E presentations, dividing this value by the Maximum Conditioning CR, and multiplying by 100. The degree of extinction recall was represented by the Extinction Recall Index (ERI) calculated from the differential SCRs during the first two trials of the CS + E minus the first two trials of the CS + U during the extinction memory recall test. Difference scores greater than zero indicate greater responding to the CS + E, while difference scores equal to zero reflect no difference in responding between the CS + E and CS + U, and negative values reflect greater responding to the CS + U (Rabinak et al., 2013). The magnitude of extinction recall (ERM) was also quantified by subtracting the mean SCR of the first four CS + from the mean SCR for the first four CS + E during extinction recall and is representative of the same contrast used in the main neuroimaging analysis (CS + E > CS + ; Shvil et al., 2014).

Electrocardiogram

Participants also had ECG monitored for a 5-min resting period prior to fear conditioning, during which participants were instructed to sit quietly without talking or moving while focusing on a fixation cross positioned in front of them. ECG was acquired using a Zephyr Biopatch[1] sampling at 1000 Hz. Off-line analysis was performed by extracting the interbeat interval (IBI) series from the raw digitized ECG signal using QRSTool Software (Allen et al., 2007). The extracted IBI series was then hand-corrected for artifacts such as ectopic, erroneous, and missed beats.

Data were processed using Matlab with parameters modeled on CMetX Cardiac Metric Software and using a "moving window" (Allen et al., 2007). The moving window comprised 16-s chunks that shift by 4 s at a time. The IBI series was converted to a time series sampled at 10 Hz with linear interpolation in order to estimate total heart-rate variability (Cook and Miller, 1992). The root mean square of successive differences (RMSSD), a time-domain measure proposed to quantify parasympathetic mediated autonomic control was also derived for use in subsequent analyses (Berntson et al., 2005; Kromenacker et al., 2018).

Neuroimaging

Fear conditioning extinction recall task

Figure 3D, shows that the final phase of the fear conditioning paradigm was to examine brain activation patterns to the same stimuli during functional magnetic resonance imaging (fMRI). An important consideration is that prior to the fMRI scan, the CS + U image (e.g., red vehicle) was also "extinguished" by presenting the CS + E and CS + U in the extinction context eight more times, as part of the standard fear conditioning protocol to ensure no latent adverse experiment effects related to a sustained conditioned fear response. Following the final extinguishing phase, participants reported not expecting a shock to any stimuli/context presentation administered. As shown in **Figure 3D**, while undergoing a later fMRI, participants were shown a new set of images that included the three previously seen target stimuli (i.e., blue truck, red car, yellow school bus), without any new shocks but in a completely novel situation. Prior studies have demonstrated adequate sleep is critical to context generalization following safety learning, in that the fear-conditioned response can return when the previous

1 https://www.zephyranywhere.com/media/download/zephyr-performance-biopatchhp-brochure.pdf

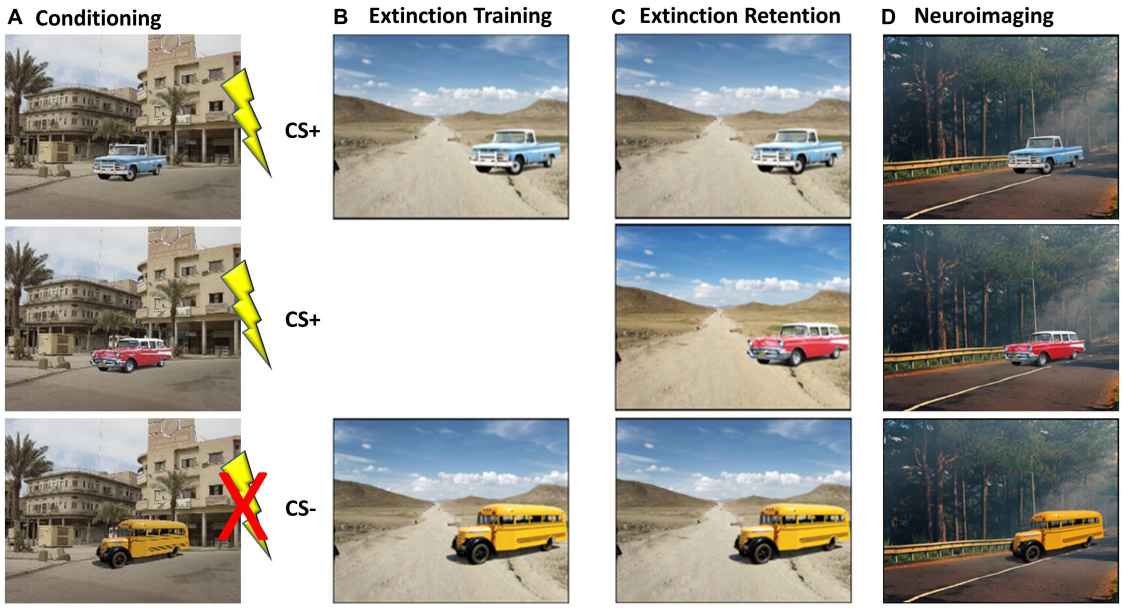

FIGURE 3
Overview of the modified fear-conditioning/fear-extinction protocol. **(A)** At baseline, participants were conditioned to fear two of three stimuli (i.e., blue truck and red car) by a mild but not painful electric shock (Pace-Schott et al., 2009), and skin conductance was measured. **(B)** On the same day, participants underwent extinction of the blue truck, but not the red car. Extinction was demonstrated by a reduction in skin conductance. **(C)** After 6 weeks of morning light treatment (blue or amber), participants returned to the lab and were shown the same stimuli again and skin conductance was measured. **(D)** Participants were shown the same stimuli, in a different visual context, while undergoing functional magnetic resonance imaging (fMRI).

CS + stimuli are shown in a novel visual context (e.g., forest road). The stimuli were shown in a new visual context. Scanning occurred on a 3T Siemens Skyra MRI scanner. Contrasts were created that directly compared brain activation patterns from the previously extinguished stimuli (CS + E; blue truck) versus the never extinguished stimuli (CS + ; red car) and non-conditioned stimuli (CS–, yellow bus). These contrast maps were then compared at post-treatment between the BLUE and AMBER conditions.

Neuroimaging parameters

Neuroimaging data were collected using a 3T Siemens MAGNETOM Skyra using a 32-channel head coil. Head movement was restricted using foam cushions during image acquisition. We collected a high-resolution anatomical T1-weighted (T1w) MPRAGE (TR/TE/flip angle = 2100 msec., 2.33 ms, 12°) that consisted of 176 slices (256 × 256 matrix) with a slice thickness of 1 mm and voxel size of 1 mm × 1 mm × 1 mm. Functional images were acquired using a gradient echo T2*-weighted sequence (TR/TE/flip angle = 2000 ms, 25 ms, 90°). Before each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium. The T1 and T2 images were collected in the same plane (whole brain acquisition; axial slices angled perpendicular to the AC-PC line). During the 9-min functional task, participants monitored a screen and were presented with the same CSs from the initial fear conditioning paradigm in a novel environmental context. Images were collected with the same slice thickness (3.125 mm, skip 1 mm; voxel size 3.125 × 3.125 × 3.125 mm) across 34 interleaved slices using head to foot phase encoding for a T2*-weighted BOLD EPI sequence (TR/TE/flip angle = 2.5 s/35 ms/90°).

Statistical analysis

Hypotheses for repeated measures were tested, relative to main treatment effects, using 2 (BL, PL) × 2 (baseline, post-treatment) linear mixed models (estimated using REML and nloptwrap optimizer) for psychological outcome variables; to investigate interactions between treatment group, study phase, and potentially meaningful outcome measures. Sex and age were also included as covariates to account for theorized differences in symptomology. Dependent measures were log-transformed as necessary to improve normality and meet model assumptions (verified via AIC-criteria model comparison), and participants were included in the model as a random effect. Standardized parameters were obtained by fitting the model on a standardized version of the dataset, with 95% Confidence Intervals (CIs) and *p*-values computed using the Wald approximation. Results include Nakagawa's Pseudo-R^2 for marginal (only variances of the fixed components), as well as conditional (variance

considered for both fixed and random effects). Analyses targeting interactions were performed using R (v4.1.0) with the lme4 package, and the report and sjtools packages were employed for model summarization. See Appendix 1 for full summaries of model coefficients reported below.

Fear conditioning statistical analysis

Skin conductance response data during Fear Conditioning, Extinction Learning, and Extinction Recall were analyzed using mixed Analysis of Variance (ANOVA). Included in all ANOVAs was the between-subjects factor for "Group" (Amber, Blue) and the within-subject factor CS Type (CS + and CS–) and Trial (number varied with phase and analysis, see section "Results"). For Fear Conditioning, a second within-subject variable, "Order" (CS + 1 and CS + 2), was added to the model. For Extinction Learning, Trial was replaced with "Trial Pair," which averaged Extinction Learning trials in a pair-wise manner (Trial 1 and 2, 3 and 4. . . 15 and 16). During Extinction Recall, an additional within-subject variable, "CS + Type" (CS + E and CS + U) variable was added to the model. All pair-wise comparisons within the ANOVA model were made using means comparisons. Potential confounding effects of discrete (sex) or continuous variables PTSD severity (PCL-5 total, CAPS-5 severity), age, and maximum SCR to a CS + during Conditioning were tested by adding them to total models. Significance was set at $p < 0.05$ and the Greenhouse–Geisser correction was applied to all within-subject main effects and their interactions. Simple regression analyzed relationships between psychophysiological and subjective summary outcome measures, subjective and objective sleep variables, and psychometric measures. Two-sample *t*-tests compared BLT and ALT groups for each of the unitary indices (CondIdx, ExtIdx, ERI).

Image processing and statistical analysis

Image processing and statistical analysis were undertaken in SPM12 (Wellcome Department of Cognitive Neurology, London, United Kingdom[2]) following a standard pipeline that involved image realignment, unwarping, co-registration, normalization to Montreal Neurological Institute (MNI) coordinate space, spatial smoothing (6 mm full-width at half maximum), and reslicing to 2 × 2 × 2 mm voxels. A high pass filter (128 s cut-off period) was implemented to remove low frequency confounds, and the Artifact Detection Tool[3] was used to remove motion artifacts and outlier scans that exceeded 3 SD in mean global intensity. At the individual level, a general linear model (GLM) was specified for contrasts that directly compared brain activation patterns from the previously extinguished stimuli (CS + E; e.g., blue truck) versus the never extinguished stimuli (CS + ; e.g., red car) and non-conditioned stimuli (CS-; e.g., yellow bus). These contrast maps were then compared at post-treatment between the BLUE and AMBER conditions. Based on prior research investigating functional brain activation during fear conditioning (Linnman et al., 2012), our analyses included regions of interest comprising a model of the fear neurocircuitry that included the following: the anterior cingulate cortex (ACC; a region associated with the expression of fear memories), the amygdala (a region associated with threat responding), and the insula (a region associated with the mediation of context threat). As the sample was underpowered relative to the targeted size identified in our power analysis, we employed a more liberal height threshold ($p < 0.005$, uncorrected), and utilized family wise error extent threshold correction (FWE cluster correction, $p < 0.05$, which resulted in $k = 103$ voxels, as indicated by SPM12). The first eigenvariate (a standard SPM output vector reflecting the signal intensity for each participant for that cluster) was extracted for secondary analyses.

2 http://www.fil.ion.ucl.ac.uk/spm

3 http://www.nitrc.org/projects/artifact_detect/

Results

Structured clinical interview for DSM-V and clinician administered post-traumatic stress disorder scale for DSM-V

Participants showed a decline in PTSD symptoms and severity between baseline and post-treatment assessments. There was a strong effect of time on both PTSD severity, *beta = –0.62, 95% CI [–0.80, –0.44], t(154) = –6.67, p < 0.001,* as assessed by the Clinician-Administered PTSD Scale (CAPS-5). There was also a decrease in PTSD symptoms, as assessed by the PTSD checklist (PCL-5), *beta = –0.38, 95% CI [–0.52, –0.24], t(155) = –5.24, p < 0.001*. However, the effect of time was not qualified by a significant group x time interaction, *p*s > 0.290, suggesting that both groups improved in PTSD symptoms and severity.

Sleep

Results showed that subjective sleep tended to improve between baseline and post-treatment. However, this improvement was not qualified by significant interaction effects and both groups tended to show similar improvements. Individuals in both the ALT and BLT reported improved sleep as measured by lower PSQI scores (indicating fewer symptoms of disrupted sleep), *beta = –0.23, 95% CI [–0.37, –0.09], [t(151) = –3.21, p = 0.001*] and higher FOSQ scores *beta = 0.07, 95% CI [0.00, 0.14], t(154) = 2.16, p = 0.031*. Both groups also reported lower levels of insomnia severity as measured by the ISI *{beta = –0.38, 95% CI [–0.54, –0.21], t(157) = –4.47, p < 0.001}* and nightmares as measured by the DDNSI *{beta = –0.16, 95% CI [–0.30, 0.03], t(142) = –2.32, p = 0.020}*. Changes in daytime sleepiness as measured by the ESS were not significant *{beta = –0.13, 95% CI [–0.29, 0.04], t(155) = –1.52, p = 0.128}*

and none of the group x time interactions were significant, all *p*s > 0.130. Outcomes based on actigraphy data are discussed elsewhere, see Killgore et al. (2022) in review.

Fear conditioning and extinction learning

Because there was a main effect on SCR of being a conditioner vs. non-conditioner [*F(1,74) = 6.11, p = 0.0158,* η_p^2 = 0.0762], the 8 BLT- and 6 ALT-Group non-conditioners were excluded from further analyses. This left a total sample size of 68 with 34 each in the ALT and BLT groups and 23 males and 45 females. Lack of baseline differences in SCR between Groups during Fear Conditioning was confirmed by there being no main effect of Group or interaction of Group with Order, CS Type or Trial or higher order interactions of Group with these factors (all *p*'s > 0.22). Similarly, at Extinction Learning there was no main effect of Group or interactions of Group with CS Type, Trial or higher-order interactions (all *p*'s > 0.26). SCR measurements confirmed that differential conditioning was acquired and extinguished. For Fear Conditioning there was a significant Order × CS Type X Trial interaction *[F(6,342) = 2.76, p = 0.0172,* η_p^2 *= 0.0462]*. Similarly, at Early Extinction there was a significant CS Type x Trial interaction *[F(7,462) = 2.98, p = 0.0082,* η_p^2 *= 0.0432]*. Among unitary indices, ALT and BLT groups did not differ in maximum SCR to a CS + (at Conditioning) or in CondIDx and ExtIdx at baseline (*p*'s > 0.42). However, significant group effects were observed in ERI at the end of treatment *{F(1, 60) = 5.08, p = 0.028;* η_p^2 *= 0.08, 90% CI [4.69e-03, 0.20]}* (see **Figure 4**); as well as ERM *{F(1, 60) = 4.33, p = 0.042;* η_p^2 *= 0.07, 90% CI [1.40e-03, 0.19]}*. In addition, none of these indices correlated with PCL-5 total or CAPS-5 severity scores (all *p*'s > 0.23) with the exception of a positive correlation between CAPS-5 severity and maximum SCR to a CS + at Conditioning (*R* = 0.252, *p* = 0.045).

At Extinction Recall, a main effect of CS_Type (CS + vs. CS–) indicated retention of differential conditioning. However, lack of a main effect of CS + Type (CS + E vs. CS + U) indicated that the distinction between the extinguished and unextinguished CS + was not retained across all subjects. At Extinction Recall, there was no main effect of Group, nor were there interactions of Group with CS_Type, CS + Type, or Trial (all *p*'s > 0.13) or 3- or 4-way interactions with these within-subject factors with the exception of a Group × CS + Type × Trial interaction *[F(3,186) = 3.48, p = 0.026,* η_p^2 *= 0.0531]*. Therefore the 2 Groups were examined individually. In the BLT Group, there were no significant main effects or interactions. However, CS + -Type, CS_Type and Trial main effects appeared as trends (*p* = 0.089, 0.089, and 0.068 respectively) with absolute value of SCR for CS + > CS- and CS + U > CS + E. In the ALT Group, there was no main effect of CS + Type, but significant main

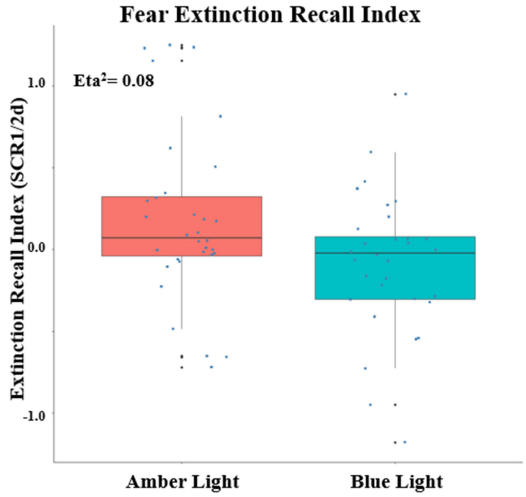

FIGURE 4
Fear Extinction Index (ERI) calculated from the differential SCRs during the first two trials of the CS + E minus the first two trials of the CS + U during the extinction memory recall test, Positive values indicate greater recall as measured by Skin Conductance Response (SCR) at post-treatment. The upper and lower "hinges" correspond to the first and third quartiles (the 25th and 75th percentiles) and lines correspond the median value. SCR1/2d: differential SCR.

effects for CS_Type *[F(1,31) = 11.86, p = 0.0017,* η_p^2 *= 0.277]* and Trial *[F(3,93) = 6.30, p = 0.0025,* η_p^2 *= 0.169]*. There was, in addition, a CS + x Trial interaction *[F(3,93) = 4.05, p = 0.0184,* η_p^2 *= 0.116]*. This interaction resulted from a significantly greater SCR in the first trial to the CS + E than to the CS + U [*p* = 0.0025), but not in Trials 2–4 (all *p*'s > 0.38). In contrast, in the BLT group, despite lack of an overall interaction (*p* = 0.666), there was a greater SCR in the first trial to the CS + U than to the CS + E (*p* = 0.0464) while in all other trials the CS + Type did not significantly differ (all *p*'s > 0.15). In each trial the absolute value of CS + U was greater than CS + E, resulting in the above-noted a trend for main effect of CS + Type (CS + U > CS + E) (see **Figure 5**).

When added ANOVA models, the continuous variables that included PTSD severity (PCL-5 total, CAPS-5 severity), age, and maximum SCR to a CS + during Conditioning, showed no main effects and only a few interactions with Group. Age showed a three-way interaction with Group and CS_Type *[F*(1,60) = 5.73, *p* = 0.0198, η_p^2 = 0.087*]* and the Group × CS_Type trended [*F*(1,60) = 3.84, *p* = 0.055, η_p^2 = 0.06]. Similarly, when maximum SCR to a CS + during Conditioning was added, it showed a three-way interaction with Group and CS_Type *[F(1,57) = 8.80, p = 0.004,* η_p^2 *= 0.087]* and the Group × CS_Type interaction was significant *[F(1,57) = 4.34, p = 0.0418,* η_p^2 *= 0.134]*. In both cases, the difference between the (combined) CS + s and the CS- was greater in ALT. However, when Sex was added to the model, there was a significant Group x Sex

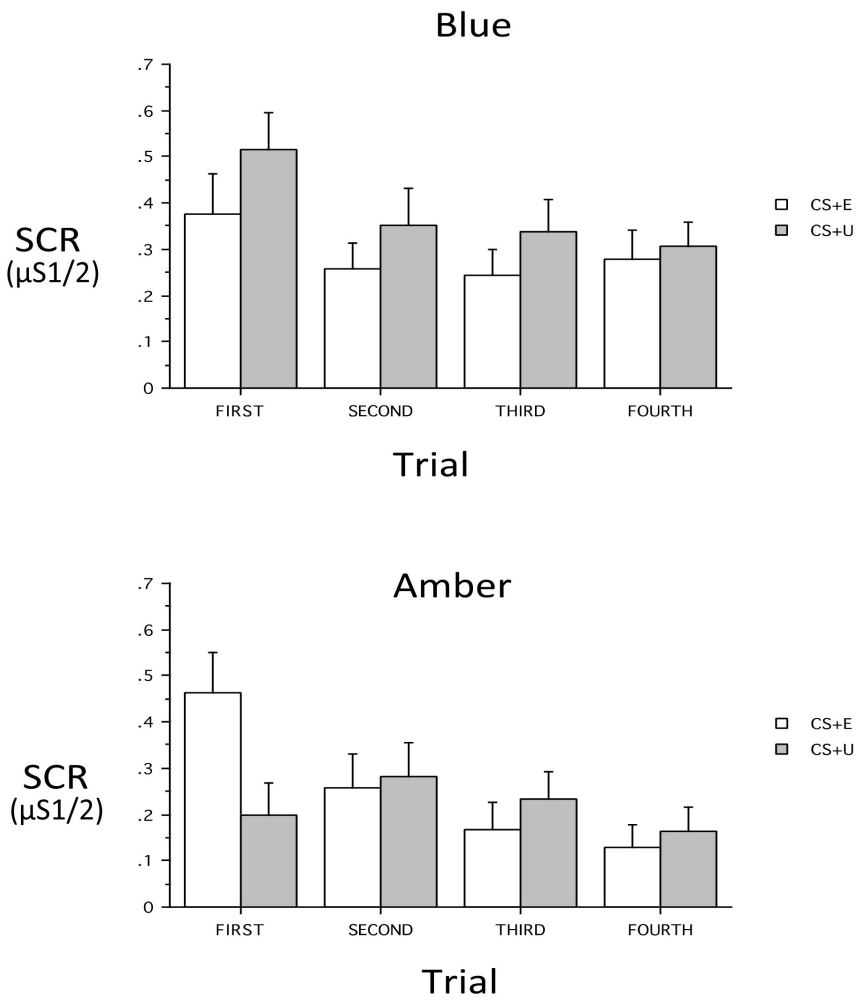

FIGURE 5
Skin conductance responses (SCR) across trials for the blue light treatment-BLT **(top)** and amber light placebo treatment-ALT **(bottom)** for the extinguished (CS + E) versus unextinguished (CS + U). The BLT condition led to reduced SCR to extinguished relative to unextinguished stimuli (especially on the first trial), while the opposite was true for the amber placebo condition. μS, microSiemens. Error bars represent standard error of the mean.

interaction *[F(1,60) = 5.10, p = 0.027,* η_p^2 *= 0.079]* as well as Group × CS + Type *[F(1,60) = 4.32, p = 0.0420,* η_p^2 *= 0.067]* and Group × CS_Type × Sex interaction *[F(1,60) = 4.03, p = 0.0493,* η_p^2 *= 0.063]*. The Group × CS + Type × Trial interaction was a trend *[F(2,180) = 2.85, p = 0.053,* η_p^2 *= 0.045]* (see Figure 6). When the 23 males were examined separately, there was a significant Group main effect *[F(1,18) = 8.12, p = 0.0107,* η_p^2 *= 0.311*, BLT larger] and the Group × CS + Type Interaction demonstrated a trend *[F(1,18) = 4.31, p = 0.0525,* η_p^2 *= 0.193]*. The Group × CS + Type × Trial interaction observed in the total sample was absent (p = 0.30). Among males there was no CS + Type × Trial interaction in either the 10 ALT or the 13 BLT males (p = 0.26 and 0.51 respectively). The 45 females were examined separately among 24 ALT and 21 BLT, and there was a Group × CS_Type interaction *[F(1,42) = 4.15, p = 0.048,* η_p^2 *= 0.09]* and the Group × CS + Type × Trial was a trend *[F(3,126) = 2.68, p = 0.07,* η_p^2 *= 0.06]*. Among ALT females there was a CS + Type × Trial interaction trend *[F(3,66) = 2.83, p = 0.06,* η_p^2 *= 0.114; CS + E larger]* whereas no associated interaction was found in BLT females (p = 0.66).

Root mean square of successive differences results

In total, 14 subjects had unusable ECG recordings due to noise or data corruption, while another 11 participants had to be excluded due to the presence of ectopic heartbeats. This yielded 57 cases with complete pre- and post-treatment ECG recordings. No significant time or group x time interactions were observed for RMSSD, *beta = 0.03, 95% CI [–0.29, 0.34], t(112) = 0.17, p* = 0.863.

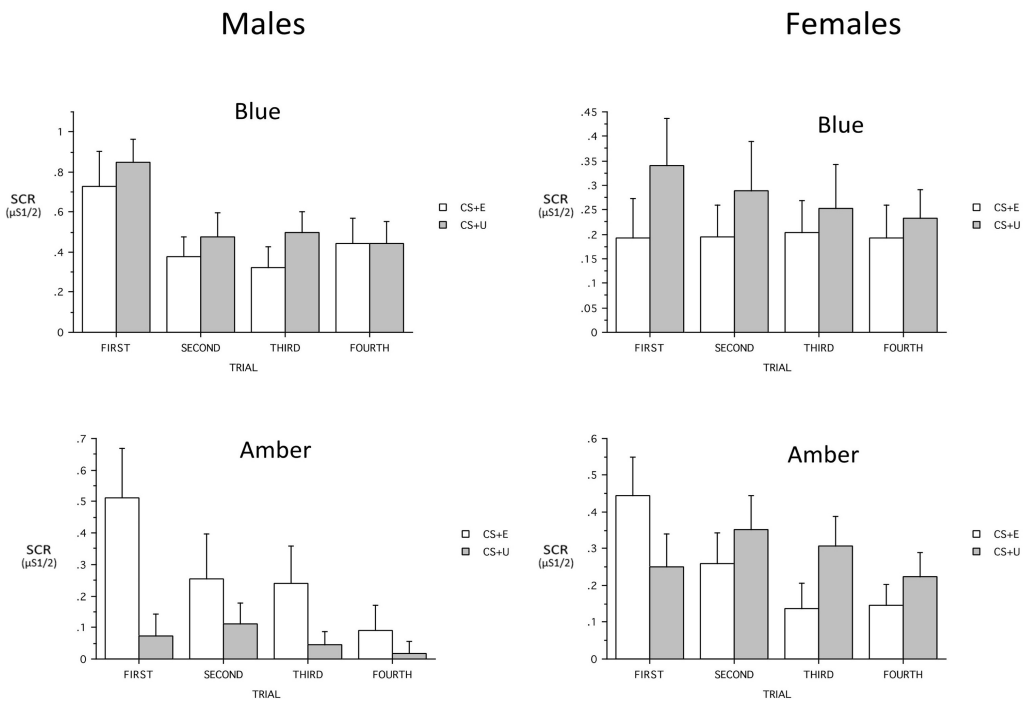

FIGURE 6
Sex × light color interactions on skin conductance responses (SCR) across trials for the blue light treatment-BLT (top) and amber light placebo treatment-ALT (bottom) for the extinguished (CS + E) versus unextinguished (CS + U). μS, microSiemens. Error bars represent standard error of the mean. Error bars represent standard error of the mean and Y-axis scales are heterogeneous.

Neuroimaging

In total, 1 participant did not demonstrate fear-based learning, 9 participants had unusable scans, and an additional 18 participants were excluded due to excessive movements during the post-treatment scan. This yielded 48 cases with complete post-treatment scans. Table 2 shows that BLT was associated with significant differences in responses to previously extinguished stimuli relative to ALT. Moreover, as seen in Figure 7, BLT resulted in a significant decrease in activation responses within the left insular cortex relative to ALT, which was significant after cluster correction for multiple comparisons. Overall, this suggests that when viewing previously feared and then extinguished stimuli, ALT participants responded with increased activation of somato-visceral brain regions involved in anxiety, while BLT participants showed a reduction of responses in this area.

Full sample zero-order correlations

Bivariate correlations assessing relationships among BLT (see Figure 8) and ALT (see Figure 9) for residual change scores of PTSD severity, sleep outcomes, RMSSD, as well as fear responding across either treatment group. For BLT, decreased PTSD symptoms and symptom severity were associated with improvements in sleep quality, daytime sleepiness, functional outcomes, nightmares, as well as insomnia; while associations for ALT were only observed relative to decreased symptoms and two metrics of daytime sleepiness and insomnia. Relative to autonomic and neural outcomes, individuals in the ALT demonstrated an association between decreased RMSSD across the treatment period and activation in the insula. No associations between autonomic and neural outcomes with behavioral metrics for BLT were observed (see Figure 8). However, observed associations did not remain significant after Bonferroni correction for multiple comparisons for either group.

Discussion

In this study, we investigated the hypothesis that exposure to blue-wavelength light for 30-min each morning for 6-weeks would enhance sleep and the retention of fear extinction memory during a classical fear conditioning paradigm. Based on prior findings, we hypothesized that BLT would be associated with improvements in sleep, PTSD symptomology, and related neurobiological outcomes. Overall, we found support for this hypothesis, although with some qualifications. We discuss these findings and their implications in detail below.

TABLE 2 Fear conditioning recall activation clusters.

Region of Interest	Cluster	Peak	MNI	Peak Region
	Size (voxels)	equiv Z	*x y z*	
Insula	49	3.53	38 4 14	Right Insula
	108	3.43	−38 6 8	Left Insula*
	32	3.4	44 4 −10	Right Insula
	4	2.89	32 28 −4	Right Insula
Cingulate Cortex				
	41	3.74	16 −24 42	Right MCC
	15	3.39	10 46 26	Right ACC
	8	2.8	0 40 20	ACC
Amygdala				
	4	2.82	22 0 −18	Right Amygdala

All voxels significant at $p < 0.005$ (uncorrected); *Indicates cluster survived cluster-based Family Wise Error Correction FWEc. MNI, Montreal Neurologic Institute coordinates.

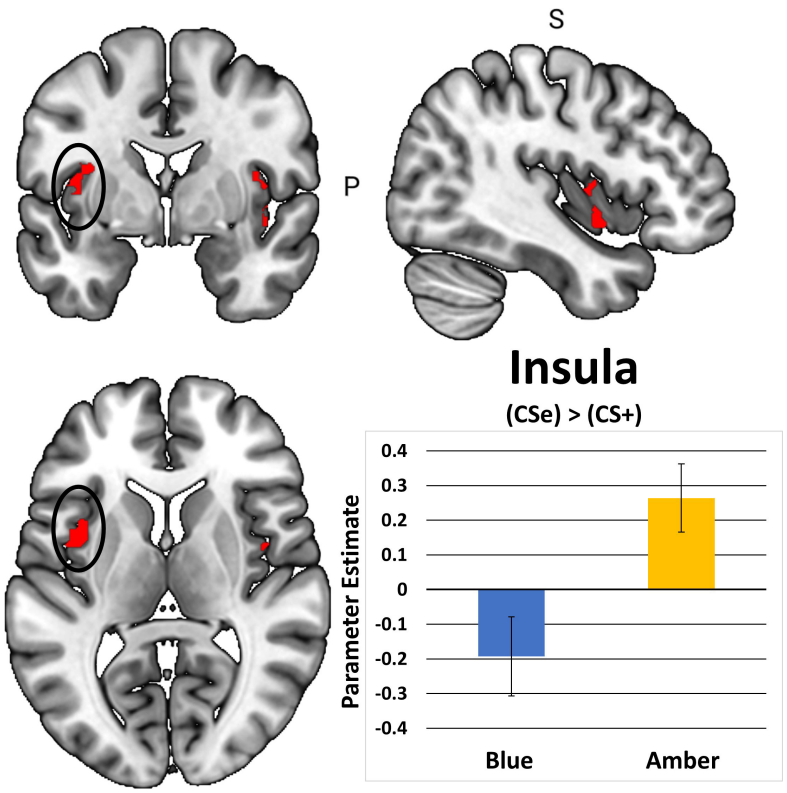

FIGURE 7
The contrast between extinguished (CS + E) versus unextinguished (CS +) was compared between the BLUE and AMBER conditions at post-treatment. Participants in the amber light condition showed a significant increase of activation in the bilateral insula areas, with the left insula activation (circle) surviving FWE correction. Error bars represent standard error of the mean.

Primary hypotheses

First, we hypothesized that daily morning blue-wavelength light exposure would lead to associated improvements in self-reported sleep and reduced PTSD symptom severity relative to amber placebo treatment. This hypothesis was supported, as individuals receiving BLT demonstrated significant improvements in the severity of their PTSD symptoms, which were associated with improvements across the indices measuring components of sleep and dysfunction. Contradictory to expectations, individuals in the ALT group also demonstrated significant decreases in PTSD symptom

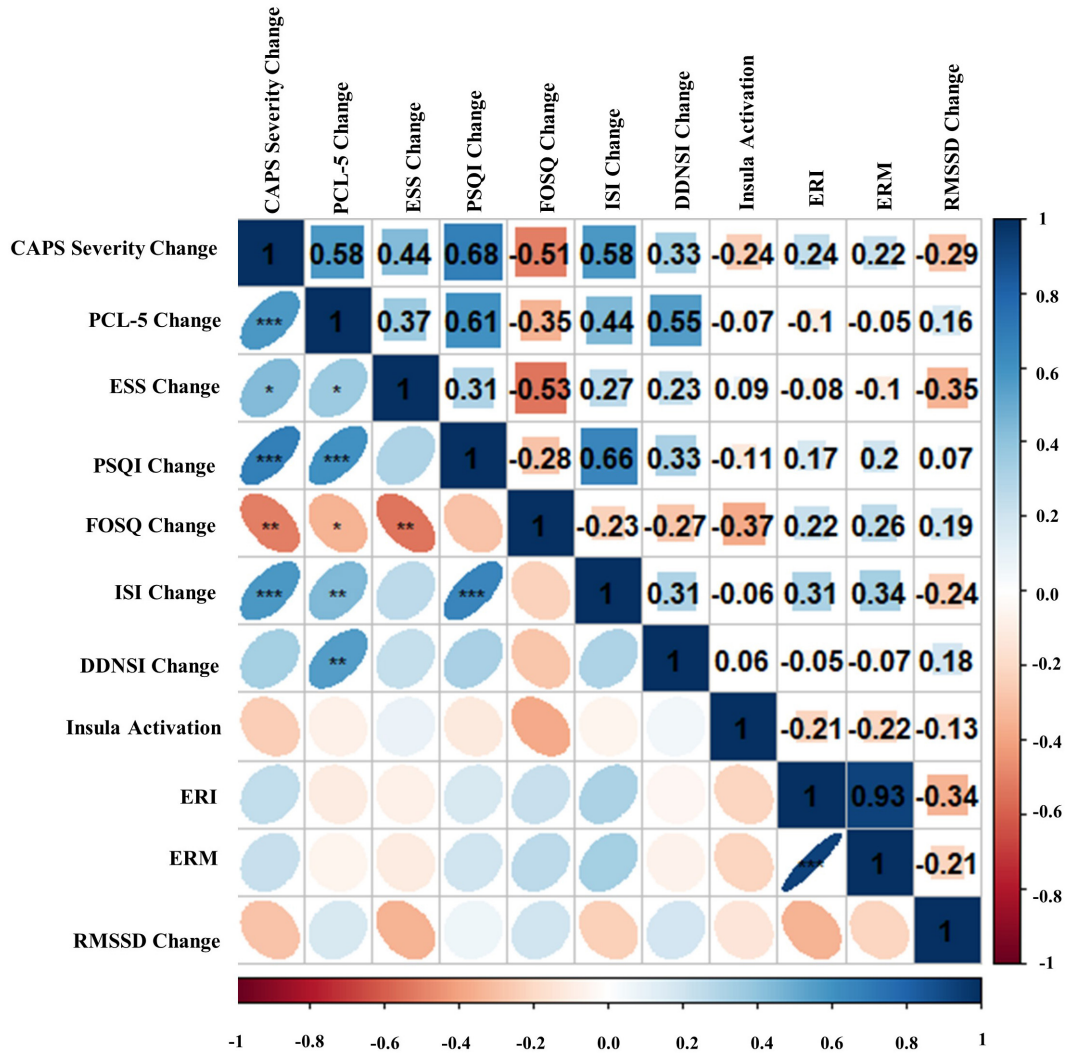

FIGURE 8
Bivariate Pearson correlations were performed across Blue Light Treatment (BLT) subjects with correlation coefficients in the upper portion of the matrix and significant correlations identified in the lower portion of the matrix. Change represents residualized change scores. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), PTSD Checklist for DSM-5 (PCL-5), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), Disturbing Dreams and Nightmares Severity Index (DDNSI), Extinction Recall Index (ERI), Extinction Recall Magnitude (ERM), Root Mean Square of Successive Differences (RMSSD).

severity; however, these changes were not associated with improvements in subjective sleep outcomes. This may be because the behavioral component of the intervention, requiring participants to wake up before 11 a.m. every day and engage in a specific task (light exposure for 30-min), may have served to stabilize their circadian rhythm relative to pretreatment for both groups. However, changes in PTSD severity for individuals receiving ALT were independent of functional outcomes related to sleep, suggesting that BLT directly influences the reciprocal nature of sleep dysfunction and PTSD (see **Figure 8**), as opposed to the two domains independently.

Second, we hypothesized that individuals receiving daily morning blue-wavelength light exposure would demonstrate enhanced retention of extinction learning in patients with PTSD, as evidenced by changes in autonomic and neural responses. We found that relative to BLT, individuals in the ALT demonstrated increased responding, as measured by SCR, for stimuli they had demonstrated a previous safety learning response after initial fear conditioning. The chief difference between the BLT and ALT groups at Extinction Recall was that, in the BLT group, absolute values of the SCR to conditioned and un-extinguished stimuli (CS + U) were consistently higher than the conditioned and extinguished stimuli (CS + E) as would

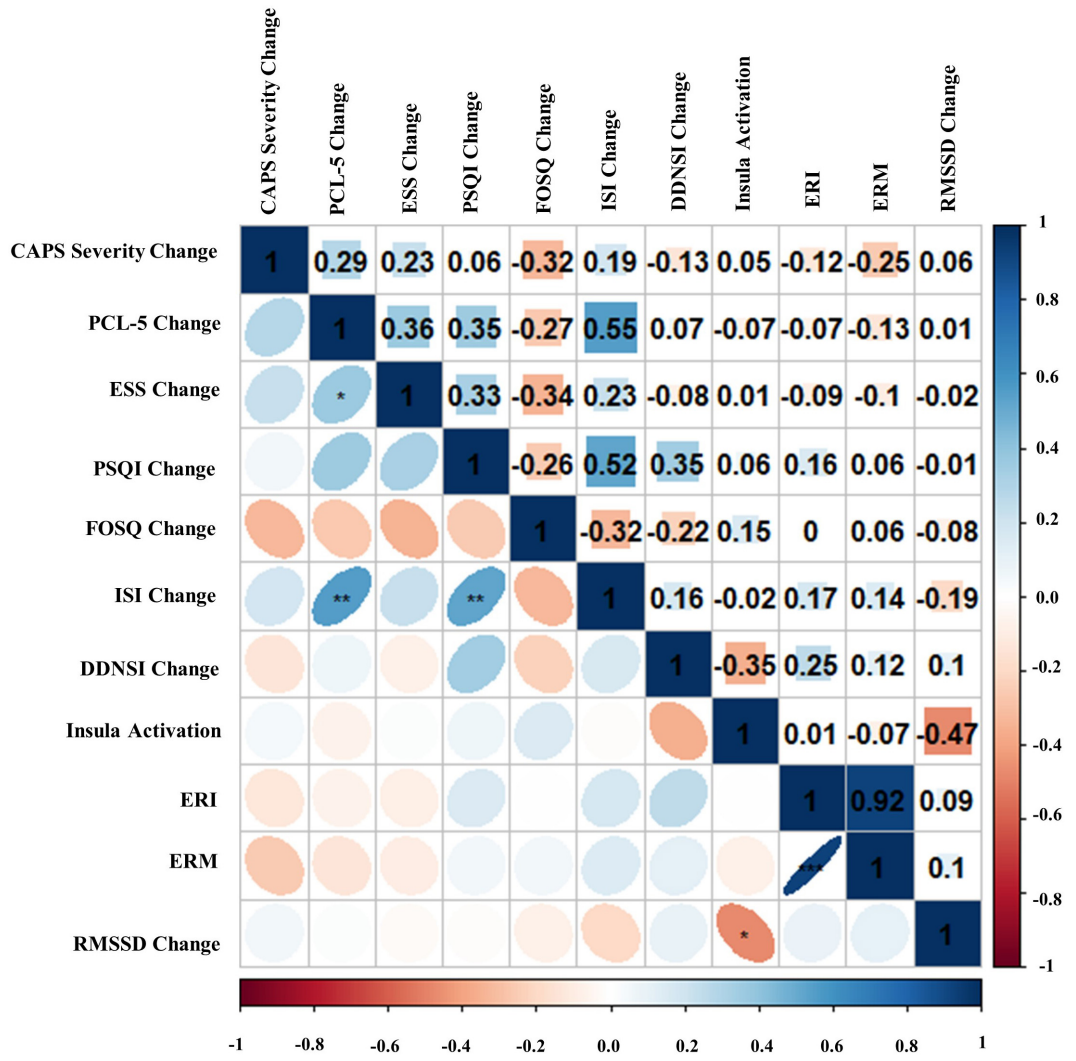

FIGURE 9
Bivariate Pearson correlations were performed across Amber Light Treatment (ALT) subjects with correlation coefficients in the upper portion of the matrix and significant correlations identified in the lower portion of the matrix. Change represents residualized change scores. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), PTSD Checklist for DSM-5 (PCL-5), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), Disturbing Dreams and Nightmares Severity Index (DDNSI), Extinction Recall Index (ERI), Extinction Recall Magnitude (ERM), Root Mean Square of Successive Differences (RMSSD).

be expected from retained extinction memory (see Figure 5). In contrast, in the ALT group, the opposite was the case (see Figure 5). Whereas this interaction (Group × CS + Type) did not reach trend or significance levels across all 4 trials, in the first trial, SCR to the CS + E significantly exceeded that to the CS + U in the ALT group whereas SCR to the CS + U significantly exceeded that to the CS + E in the BLT group. If one assumes new (re)extinction immediately begins to take place during Extinction Recall, then this first trial takes on special significance as purely reflecting extinction recalled rather a combination of prior extinction memory and new extinction being learned. As there was a significant Group × Sex interaction and the Group × CS + Type × Trial interaction demonstrated a trend, the two groups within each of the two sexes were examined individually. Although the CS + Type × Trial interaction did not reach significance in either sex alone, a similar Group difference (i.e., SCR to CS + U > CS + E in BLT, CS + E > CS + U in ALT) appeared in each sex individually especially in the first trial (see Figure 6). Although one might expect the CS + Type × Trial interaction to be present in ALT Males (see Figure 6), the low sample size of this subgroup ($N = 10$) likely prevented this. Thus, the ALT group reacted to the previously extinguished stimulus not only as if was unextinguished, but to a greater degree than the

unextinguished stimulus. The BLT group, however, reacted to previously extinguished stimuli as expected (i.e., diminished fear response). This suggests that, although differential conditioning was retained across all subjects (CS + > CS–), retention of stimulus-specific extinction memory occurred only in the BLT group. This was further evidenced by increased activation in the insular region of the brain for individuals that received ALT when they were shown the previously feared stimuli in a novel context following a second safety learning period. We also found that for individuals in the ALT group, this increased insular responding was associated with diminished autonomic regulation at rest, as measured by RMSSD, while no such association was observed for individuals in the BLT group.

Considerations

No known studies have examined the neurobiological or autonomic correlates of symptom improvement in patients with PTSD following blue light exposure therapy. Prior work has demonstrated BLT as an effective treatment for sleep disruption following mild traumatic brain injury (Raikes et al., 2020; Killgore et al., 2022), however, the use of this type of treatment as a means of improving PTSD symptoms is novel. Recent pilot studies have examined the potential to use light-based treatments to facilitate recovery from PTSD and have shown promising results in preliminary trials. For instance, Zalta et al. (2019) used a commercial head-mounted device that presented green wavelength light and found that the bright light exposure condition was better than the dim light control condition at improving symptoms of PTSD and depression. Similarly, Youngstedt et al. (2021) used a bright white light device compared to an inert control condition (i.e., an ion generator) and found that 4-weeks of daily light exposure for 30-min was effective at improving symptoms of PTSD and general clinical impression ratings. Those samples were small to modest in size and included significantly fewer controls than in the present study. Here, we find that under more tightly controlled conditions, with a similar bright light control condition, we were able to find significant improvements in clinical outcomes, fear conditioning, and neuroimaging activation patterns. Sleep-focused interventions have also been proposed as a means of augmenting current TBI and PTSD treatment protocols (Gilbert et al., 2015). As the two disorders often co-occur and also present with co-morbidities, such as depression (Tanev et al., 2014), BLT may serve to meet future needs as an effective treatment that positively influences factors predictive of treatment success. The present study provides clear evidence that both functional and neurobiological changes are associated with changes in sleep, fear extinction memory consolidation, and PTSD symptoms from pre- to post-treatment for individuals receiving BLT.

A growing body of work demonstrates daily BLT can be used as a potent non-pharmacological intervention to improve sleep and mood symptoms. Depressive symptoms associated with seasonal affective disorder have often been a target for BLT interventions, with multiple studies demonstrating its efficacy for inducing clinically significant changes in symptom presentation (Glickman et al., 2006; Strong et al., 2009; Chang et al., 2018). Furthermore, PTSD and depression, while distinct, have numerous overlapping distress components (Post et al., 2011). Here we demonstrate that the well-established use of BLT for decreasing mood symptoms relating to depression can be extended to individuals suffering from PTSD. This may be, in part, due to the underlying neurobiological relationship between sleep and emotional wellbeing (Goldstein and Walker, 2014). Light therapy as a treatment for mood disorders is becoming increasingly accepted, and the current study is consistent with calls for standard approaches and rigorous study designs relative to its utility (Golden et al., 2005). However, more work is necessary to identify individual features that contribute to mood-related outcomes in BLT, as well as, how best to optimize a standardized intervention approach for delivering light therapy.

A key finding is that participants receiving ALT showed a return of learned fear responses, while BLT led to a retention of learned extinction. A resurgence of fear-based responding is a hallmark symptom in PTSD and findings suggest that increased sleep quality and decreased PTSD symptom severity via BLT during the intervening weeks led to greater consolidation of the fear extinction memory. Prior work demonstrates acute exposure to blue light augments memory consolidation and working memory (Alkozei et al., 2016b, 2017b), however, those studies also demonstrated differences in memory effects relative to sex, and the present study revealed significant sex differences in extinction recall. Females in the ALT group demonstrated increased responding to the previously extinguished stimuli at the first trial relative to the unextinguished stimuli, while subsequent trials demonstrated the expected relationship in SCR (CS + U > CS + E). However, males in the ALT group demonstrated greater SCR to the CS + E stimuli compared to the CS + U stimuli across all four initial trials during fear recall. The current observations are consistent with prior work that has demonstrated sex differences in fear conditioning and recall (Baran et al., 2009; Velasco et al., 2019). Of interest, females with PTSD demonstrate greater acquisition of conditioned fear relative to men, and findings regarding sex differences in this patient population are not entirely clear (Inslicht et al., 2013), with other work demonstrating associations between pre-acquisition stress and increased fear learning in men and mixed findings in females (Peyrot et al., 2020). While the sex-based differences in fear recall observed in the current study are consistent with previous findings, future work is necessary to identify how sex influences BLT treatment outcomes for individuals with PTSD.

The finding of decreased insular responses to previously extinguished stimuli in the BLT group is particularly

enlightening. Prior work has found that insula reactivity is related to fear conditioning and greater SCR (Critchley et al., 2000; Linnman et al., 2012; Fullana et al., 2016; Seo et al., 2022), which is consistent with findings we report here. Insula reactivity has been demonstrated to increase relative to uncertainty-related expectations, which may have been facilitated by presenting the fear-conditioned stimuli in a novel context during the neuroimaging task (Sarinopoulos et al., 2010). Furthermore, REM sleep dysfunction is associated with a lack of generalization relative to safety learning, and eliciting this deficit in safety learning was the main consideration relative to the novel task-based neuroimaging design (Pace-Schott et al., 2015b). It is also important to note that extinction learning was facilitated for all stimuli prior to neuroimaging, as both the CS + E and CS + U are extinguished during extinction recall as part of the established fear conditioning protocol after which our procedures were modeled, which may be why observable differences were not observed in the ACC or amygdala areas of the cortex. Prior studies demonstrate that autonomic dysfunction is associated with PTSD and that emotional reactivity and regulation become decoupled relative to HRV and insular activity (Thome et al., 2017; Schneider and Schwerdtfeger, 2020). This may be a driving factor in the association between diminished RMSSD across the intervention period for ALT relative to increased insular reactivity to previously feared stimuli.

Overall, these findings suggest that BLT was effective at sustaining fear extinction memory relative to ALT. This is critical to recovery from PTSD, as several prominent exposure treatments for this disorder are based extensively on principles of fear extinction (Paredes and Morilak, 2019). As fear conditioning is often cited as a key pathogenic mechanism in PTSD (Rauch et al., 2006), anything that augments fear extinction consolidation, such as BLT, would logically decrease the likelihood of PTSD subsequent to a traumatic event/intervention (Linnman et al., 2012). The current results suggest that BLT may potentially facilitate treatment gains from exposure-based therapies through non-circadian effects of blue light and melanopsin, as well as by stabilizing the circadian clock and improving sleep in a manner that promotes consolidation of extinction-based memories (Lazzerini Ospri et al., 2017). These initial findings are encouraging and suggest the need for further research to delineate the factors that contribute to positive outcomes. Future work would benefit by identifying the genetic, psychophysiological, and other individual difference factors that could allow greater precision in treatment application. Studies utilizing polysomnographic monitoring to better assess specific changes across multiple sleep parameters will also be particularly important in future investigations. Additional work will also be necessary to determine the specific timing, duration, and wavelengths that are most effective in producing changes in circadian timing and clinical outcomes.

Limitations

Several limitations should be considered when interpreting the results of this study. The study sample was relatively small and multiple confounds (attrition, lack of fear learning, data corruption) led to many of the presented analyses being underpowered. Further work will be necessary to replicate and build on the current findings and observations relative to the effects of 6 weeks of morning BLT. It should be noted that these correlations do not indicate causal relationships between sleep and symptom improvement. As sleep and clinical symptomology are tightly intertwined, it is possible that improvements to PTSD, anxiety, and depression symptoms may have led to improvements to sleep, or that there were bidirectional effects. However, regardless of the precise directional relationship involved, the present results highlight the importance of sleep in the continuation of psychopathology and/or symptomatic improvements.

Upon the conclusion of the study, participants were asked whether they thought they had been assigned to the active or placebo treatment, and to indicate their confidence in their guess. The majority of participants believed that they had been assigned to the active condition, but this was also equally distributed between actual treatment assignments. The participants assigned to the BLT and ALT were also similarly confident in their guess, $t(78) = 0.56$, $p = 0.576$, $d = 0.13$, with both BLT ($M = 3.63$, $SD = 1.05$) and ALT ($M = 3.48$, $SD = 1.38$) groups being between 50 and 75% confident in their assessments. This suggests that participants did not have insight as to whether they were receiving the active or placebo treatment.

It is important to highlight that our placebo treatment, ALT, showed evidence of active effects. Amber light has previously been used as a placebo therapy (Raikes et al., 2020; Killgore et al., 2022), but further work will need to be done on whether it also significantly impacts sleep. Future research should consider adding an inactive no light condition to fully separate the effects of different light exposures on sleep and improvements to mental health. Another possible explanation for the consistent improvements is that the interventions may have been associated with better sleep and mental health for reasons other than the effects of active light components on sleep or brain function. For example, the act of using the lightbox, regardless of wavelength, may have aided in the development of a daily routine, which could provide patients with PTSD with a sense of control and purpose, as well as establish a more consistent daily rhythm through other zeitgebers (e.g., eating; social contact). Similarly, filling out sleep diaries every day may have helped participants become more aware of their sleep, mood, and day-to-day factors that influence sleep. Future research will be necessary to further investigate these possibilities, and to identify the specific parameters of light

exposure (e.g., length of the treatment phase, light exposure duration) that will optimize treatment gains.

Conclusion

The present study examined the association between 6 weeks of daily morning blue-wavelength light relative to amber-wavelength light placebo treatment. Overall, we found support for the hypothesis that improvements in sleep would be linearly correlated with improvements in PTSD symptom severity. Furthermore, the findings from the fear extinction task support the global hypothesis that BLT improves autonomic reactivity and brain function in a manner that aids in fear extinction/safety memory, even across longer durations of time than this type of paradigm is typically employed. This is especially important, as safety learning is critical to recovery and several prominent evidence-based treatments for PTSD are based extensively on principles of fear extinction. These results suggest that BLT is a promising non-pharmacological intervention that may potentially facilitate the retention of treatment gains from exposure-based therapies by resetting the circadian clock and improving sleep in a manner that promotes consolidation of extinction memory. Future work will need to identify the clinical significance of these outcomes as well as their temporal effect, but these results suggest that BLT may be useful for improving sleep and consolidating safety learning outcomes in a manner that promotes the reduction of sleep-related complaints and PTSD symptoms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Institutional Review Board of the University of Arizona College of Medicine, The U.S. Army's Human Research Protections Office. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WK: study conception and design. WK, JV, AB, ND, and SE: data collection. WK, JV, and EP-S: analysis and interpretation of results. JV, WK, EP-S, AB, ND, and SE: draft manuscript preparation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2022.886816/full#supplementary-material

References

Alexandra Kredlow, M., Fenster, R. J., Laurent, E. S., Ressler, K. J., and Phelps, E. A. (2022). Prefrontal cortex, amygdala, and threat processing: Implications for PTSD. *Neuropsychopharmacology* 47, 247–259.

Alkozei, A., Killgore, W. D. S., Smith, R., Dailey, N. S., Bajaj, S., and Haack, M. (2017a). Chronic sleep restriction increases negative implicit attitudes toward Arab Muslims. *Sci. Rep.* 7:4285. doi: 10.1038/s41598-017-04585-w

Alkozei, A., Smith, R., Dailey, N. S., Bajaj, S., and Killgore, W. D. S. (2017b). Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLoS One* 12:e0184884. doi: 10.1371/journal.pone.0184884

Alkozei, A., Smith, R., and Killgore, W. D. (2016a). Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to "uncertain"

versus "certain" anticipation of positive stimuli. *Neurosci. Lett.* 616, 5–10. doi: 10.1016/j.neulet.2016.01.034

Alkozei, A., Smith, R., Pisner, D. A., Vanuk, J. R., Berryhill, S. M., Fridman, A., et al. (2016b). Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* 39, 1671–1680. doi: 10.5665/sleep.6090

Allen, J. J., Chambers, A. S., and Towers, D. N. (2007). The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics. *Biol. Psychol.* 74, 243–262. doi: 10.1016/j.biopsycho.2006.08.005

Bajaj, S., Raikes, A. C., Razi, A., Miller, M. A., and Killgore, W. D. S. (2021). Blue-light therapy strengthens resting-state effective connectivity within default-mode network after mild TBI. *J. Cent. Nerv. Syst. Dis.* 13:11795735211015076. doi: 10.1177/11795735211015076

Baran, S. E., Armstrong, C. E., Niren, D. C., Hanna, J. J., and Conrad, C. D. (2009). Chronic stress and sex differences on the recall of fear conditioning and extinction. *Neurobiol. Learn. Mem.* 91, 323–332.

Bastien, C. H., Vallières, A., and Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2, 297–307.

Berntson, G. G., Lozano, D. L., and Chen, Y. (2005). Filter properties of root mean square successive difference (RMSSD) for heart rate. *Psychophysiology* 42, 246–252. doi: 10.1111/j.1469-8986.2005.00277.x

Bjorvatn, B., and Pallesen, S. (2009). A practical approach to circadian rhythm sleep disorders. *Sleep Med. Rev.* 13, 47–60.

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., and Domino, J. L. (2015). The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *J. Trauma. Stress* 28, 489–498.

Buysse, D. J., Reynolds, C. F. III, Monk, T. H., Hoch, C. C., Yeager, A. L., and Kupfer, D. J. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep* 14, 331–338.

Chang, C.-H., Liu, C.-Y., Chen, S.-J., and Tsai, H.-C. (2018). Efficacy of light therapy on nonseasonal depression among elderly adults: A systematic review and meta-analysis. *Neuropsychiatr. Dis. Treat.* 14:3091.

Chasens, E. R., Ratcliffe, S. J., and Weaver, T. E. (2009). Development of the FOSQ-10: A short version of the Functional Outcomes of Sleep Questionnaire. *Sleep* 32, 915–919. doi: 10.1093/sleep/32.7.915

Chellappa, S. L., and Aeschbach, D. (2021). Sleep and anxiety: From mechanisms to interventions. *Sleep Med. Rev.* 61:101583.

Colvonen, P. J., Straus, L. D., Acheson, D., and Gehrman, P. (2019). A review of the relationship between emotional learning and memory, sleep, and PTSD. *Curr. Psychiatry Rep.* 21, 1–11.

Cook, E. W., and Miller, G. A. (1992). Digital filtering: Background and tutorial for psychophysiologists. *Psychophysiology* 29, 350–362. doi: 10.1111/j.1469-8986.1992.tb01709.x

Critchley, H. D., Elliott, R., Mathias, C. J., and Dolan, R. J. (2000). Neural activity relating to generation and representation of galvanic skin conductance responses: A functional magnetic resonance imaging study. *J. Neurosci.* 20, 3033–3040. doi: 10.1523/JNEUROSCI.20-08-03033.2000

Fernandez, D. C., Fogerson, P. M., Ospri, L. L., Thomsen, M. B., Layne, R. M., Severin, D., et al. (2018). Light affects mood and learning through distinct retina-brain pathways. *Cell* 175, 71–84. doi: 10.1016/j.cell.2018.08.004

First, M. B., Williams, J. B. W., Karg, R. S., and Spitzer, R. L. (2015). *Structured clinical interview for DSM-5—Research version (SCID-5 for DSM-5, research version; SCID-5-RV)*. Arlington, VA: American Psychiatric Association, 1–94.

Foa, E., Hembree, E., and Rothbaum, B. O. (2007). *Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences therapist guide*. Oxford: Oxford University Press.

Fornari, R., Wichmann, R., Atucha, E., Desprez, T., Eggens-Meijer, E., and Roozendaal, B. (2012). Involvement of the insular cortex in regulating glucocorticoid effects on memory consolidation of inhibitory avoidance training. *Front. Behav. Neurosci.* 6:10. doi: 10.3389/fnbeh.2012.00010

Fu, J., Li, P., Ouyang, X., Gu, C., Song, Z., Gao, J., et al. (2007). Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats. *Neuroscience* 144, 1186–1192. doi: 10.1016/j.neuroscience.2006.10.050

Fullana, M. A., Harrison, B. J., Soriano-Mas, C., Vervliet, B., Cardoner, N., Àvila-Parcet, A., et al. (2016). Neural signatures of human fear conditioning: An updated and extended meta-analysis of fMRI studies. *Mol. Psychiatry* 21, 500–508. doi: 10.1038/mp.2015.88

Gehrman, P., Seelig, A. D., Jacobson, I. G., Boyko, E. J., Hooper, T. I., Gackstetter, G. D., et al. (2013). Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. *Sleep* 36, 1009–1018. doi: 10.5665/sleep.2798

Germain, A. (2013). Sleep disturbances as the hallmark of PTSD: Where are we now? *Am. J. Psychiatry* 170, 372–382. doi: 10.1176/appi.ajp.2012.12040432

Gilbert, K. S., Kark, S. M., Gehrman, P., and Bogdanova, Y. (2015). Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clin. Psychol. Rev.* 40, 195–212. doi: 10.1016/j.cpr.2015.05.008

Glickman, G., Byrne, B., Pineda, C., Hauck, W. W., and Brainard, G. C. (2006). Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). *Biol. Psychiatry* 59, 502–507. doi: 10.1016/j.biopsych.2005.07.006

Golden, R. N., Gaynes, B. N., Ekstrom, R. D., Hamer, R. M., Jacobsen, F. M., Suppes, T., et al. (2005). The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. *Am J Psychiatry* 162, 656–662. doi: 10.1176/appi.ajp.162.4.656

Goldstein, A. N., and Walker, M. P. (2014). The Role of Sleep in Emotional Brain Function. *Annu. Rev. Clin. Psychol.* 10, 679–708. doi: 10.1146/annurev-clinpsy-032813-153716

Hankins, M. W., Peirson, S. N., and Foster, R. G. (2008). Melanopsin: An exciting photopigment. *Trends Neurosci.* 31, 27–36.

Inslicht, S. S., Metzler, T. J., Garcia, N. M., Pineles, S. L., Milad, M. R., Orr, S. P., et al. (2013). Sex differences in fear conditioning in posttraumatic stress disorder. *J. Psychiatr. Res.* 47, 64–71.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 14, 540–545.

Killgore, W. D. S., Kahn-Greene, E. T., Lipizzi, E. L., Newman, R. A., Kamimori, G. H., and Balkin, T. J. (2008). Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Med.* 9, 517–526. doi: 10.1016/j.sleep.2007.07.003

Killgore, W. D. S., Vanuk, J. R., and Dailey, N. S. (2022) Treatment with morning blue light increases left amygdala volume and sleep duration among individuals with posttraumatic stress disorder. *Front. Behav. Neurosci.* 16:910239. doi: 10.3389/fnbeh.2022.910239

Kobayashi, I., Boarts, J. M., and Delahanty, D. L. (2007). Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. *Psychophysiology* 44, 660–669. doi: 10.1111/j.1469-8986.2007.537.x

Krakow, B., Schrader, R., Tandberg, D., Hollifield, M., Koss, M. P., Yau, C. L., et al. (2002). Nightmare frequency in sexual assault survivors with PTSD. *J. Anxiety Disord.* 16, 175–190.

Kromenacker, B. W., Sanova, A. A., Marcus, F. I., Allen, J. J. B., and Lane, R. D. (2018). Vagal mediation of low-frequency heart rate variability during slow yogic breathing. *Psychosom. Med.* 80, 581–587. doi: 10.1097/PSY.0000000000000603

Lack, L., Wright, H., and Paynter, D. (2007). The treatment of sleep onset insomnia with bright morning light. *Sleep Biol. Rhythms* 5, 173–179. doi: 10.1016/j.jpsychores.2004.02.005

Lazarus, R. S. (1999). Hope: An emotion and a vital coping resource against despair. *Soc. Res.* 66, 653–678.

Lazzerini Ospri, L., Prusky, G., and Hattar, S. (2017). Mood, the circadian system, and melanopsin retinal ganglion cells. *Annu. Rev. Neurosci.* 40:539.

Liberzon, I., and Martis, B. (2006). Neuroimaging studies of emotional responses in PTSD. *Ann. N. Y. Acad. Sci.* 1071, 87–109.

Linnman, C., Zeidan, M. A., Pitman, R. K., and Milad, M. R. (2012). Resting cerebral metabolism correlates with skin conductance and functional brain activation during fear conditioning. *Biol. Psychol.* 89, 450–459.

Lockley, S. W., Evans, E. E., Scheer, F., Brainard, G. C., Czeisler, C. A., and Aeschbach, D. (2006). Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep N. Y. Westchester* 29:161.

Marin, M.-F., Zsido, R. G., Song, H., Lasko, N. B., Killgore, W. D. S., Rauch, S. L., et al. (2017). Skin conductance responses and neural activations during fear conditioning and extinction recall across anxiety disorders. *JAMA Psychiatry* 74, 622–631.

Masten, A. S., Hubbard, J. J., Gest, S. D., Tellegen, A., Garmezy, N., and Ramirez, M. (1999). Competence in the context of adversity: Pathways to resilience and maladaptation from childhood to late adolescence. *Dev. Psychopathol.* 11, 143–169. doi: 10.1017/s0954579499001996

Milad, M. R., and Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annu. Rev. Psychol.* 63:129. doi: 10.1146/annurev.psych.121208.131631

Milad, M. R., Orr, S. P., Pitman, R. K., and Rauch, S. L. (2005). Context modulation of memory for fear extinction in humans. *Psychophysiology* 42, 456–464.

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., and Rauch, S. L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol. Psychiatry* 62, 446–454. doi: 10.1016/j.biopsych.2006.10.011

Münch, M., Linhart, F., Borisuit, A., Jaeggi, S. M., and Scartezzini, J.-L. (2012). Effects of prior light exposure on early evening performance, subjective sleepiness, and hormonal secretion. *Behav. Neurosci.* 126:196. doi: 10.1037/a0026702

Nader, N., Chrousos, G. P., and Kino, T. (2010). Interactions of the circadian CLOCK system and the HPA axis. *Trends Endocrinol. Metab.* 21, 277–286.

Neylan, T. C., Kessler, R. C., Ressler, K. J., Clifford, G., Beaudoin, F. L., An, X., et al. (2021). Prior sleep problems and adverse post-traumatic neuropsychiatric sequelae of motor vehicle collision in the AURORA study. *Sleep* 44:zsaa200. doi: 10.1093/sleep/zsaa200

Oken, B. S., Chamine, I., and Wakeland, W. (2015). A systems approach to stress, stressors and resilience in humans. *Behav. Brain Res.* 282, 144–154.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9, 97–113.

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., and Pitman, R. K. (2000). De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *J. Abnorm. Psychol.* 109:290.

Pace-Schott, E. F., Germain, A., and Milad, M. R. (2015a). Effects of sleep on memory for conditioned fear and fear extinction. *Psychol. Bull.* 141, 835–857. doi: 10.1037/bul0000014

Pace-Schott, E. F., Germain, A., and Milad, M. R. (2015b). Sleep and REM sleep disturbance in the pathophysiology of PTSD: The role of extinction memory. *Biol. Mood Anxiety Disord.* 5, 1–19.

Pace-Schott, E. F., Milad, M. R., Orr, S. P., Rauch, S. L., Stickgold, R., and Pitman, R. K. (2009). Sleep promotes generalization of extinction of conditioned fear. *Sleep* 32, 19–26. doi: 10.5665/sleep/32.1.19

Pace-Schott, E. F., Verga, P. W., Bennett, T. S., and Spencer, R. M. C. (2012). Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. *J. Psychiatr. Res.* 46, 1036–1044. doi: 10.1016/j.jpsychires.2012.04.015

Paredes, D., and Morilak, D. A. (2019). A rodent model of exposure therapy: The use of fear extinction as a therapeutic intervention for PTSD. *Front. Behav. Neurosci.* 13:46. doi: 10.3389/fnbeh.2019.00046

Peyrot, C., Brouillard, A., Morand-Beaulieu, S., and Marin, M.-F. (2020). A review on how stress modulates fear conditioning: Let's not forget the role of sex and sex hormones. *Behav. Res. Ther.* 129:103615. doi: 10.1016/j.brat.2020.103615

Post, L. M., Zoellner, L. A., Youngstrom, E., and Feeny, N. C. (2011). Understanding the relationship between co-occurring PTSD and MDD: Symptom severity and affect. *J. Anxiety Disord.* 25, 1123–1130. doi: 10.1016/j.janxdis.2011.08.003

Rabinak, C. A., Angstadt, M., Sripada, C. S., Abelson, J. L., Liberzon, I., Milad, M. R., et al. (2013). Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology* 64, 396–402.

Raikes, A. C., Dailey, N. S., Shane, B. R., Forbeck, B., Alkozei, A., and Killgore, W. D. S. (2020). Daily morning blue light therapy improves daytime sleepiness, sleep quality, and quality of life following a mild traumatic brain injury. *J. Head Trauma Rehabil.* 35, E405–E421. doi: 10.1097/HTR.0000000000000579

Rauch, S. L., Shin, L. M., and Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future. *Biol. Psychiatry* 60, 376–382. doi: 10.1016/j.biopsych.2006.06.004

Reist, C., Jovanovic, T., Kantarovich, D., Weingast, L., Hollifield, M., Novin, M., et al. (2021). An analysis of fear inhibition and fear extinction in a sample of veterans with obstructive sleep apnea (OSA): Implications for co-morbidity with post-traumatic stress disorder (PTSD). *Behav. Brain Res.* 404:113172. doi: 10.1016/j.bbr.2021.113172

Ressler, K., Berretta, S., Bolshakov, V. Y., Rosso, I. M., Meloni, E. G., Rauch, S. L., et al. (2022). Post-traumatic stress disorder: Clinical and translational neuroscience from cells to circuits. *Nat. Rev. Neurol.* 18, 273–288. doi: 10.1038/s41582-022-00635-8

Richards, A., Kanady, J. C., and Neylan, T. C. (2020). Sleep disturbance in PTSD and other anxiety-related disorders: An updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. *Neuropsychopharmacology* 45, 55–73.

Roberts, A. L., Gilman, S. E., Breslau, J., Breslau, N., and Koenen, K. C. (2011). Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. *Psychol. Med.* 41:71. doi: 10.1017/S0033291710000401

Sahin, L., and Figueiro, M. G. (2013). Alerting effects of short-wavelength (blue) and long-wavelength (red) lights in the afternoon. *Physiol. Behav.* 11, 1–7. doi: 10.1016/j.physbeh.2013.03.014

Sakaki, M., Yoo, H. J., Nga, L., Lee, T.-H., Thayer, J. F., and Mather, M. (2016). Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *Neuroimage* 139, 44–52. doi: 10.1016/j.neuroimage.2016.05.076

Sarinopoulos, I., Grupe, D. W., Mackiewicz, K. L., Herrington, J. D., Lor, M., Steege, E. E., et al. (2010). Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. *Cereb. cortex* 20, 929–940.

Schneider, M., and Schwerdtfeger, A. (2020). Autonomic dysfunction in posttraumatic stress disorder indexed by heart rate variability: A meta-analysis. *Psychol. Med.* 50, 1937–1948. doi: 10.1017/S003329172000207X

Seo, J., Oliver, K. I., Daffre, C., Moore, K. N., Gazecki, S., Lasko, N. B., et al. (2022). Associations of sleep measures with neural activations accompanying fear conditioning and extinction learning and memory in trauma-exposed individuals. *Sleep* 45:zsab261. doi: 10.1093/sleep/zsab261

Shalev, A., Liberzon, I., and Marmar, C. (2017). Post-traumatic stress disorder. *N. Engl. J. Med.* 376, 2459–2469.

Sharot, T., and Yonelinas, A. P. (2008). Differential time-dependent effects of emotion on recollective experience and memory for contextual information. *Cognition* 106, 538–547. doi: 10.1016/j.cognition.2007.03.002

Shin, L. M., Rauch, S. L., and Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann. N. Y. Acad. Sci.* 1071, 67–79.

Shvil, E., Sullivan, G. M., Schafer, S., Markowitz, J. C., Campeas, M., Wager, T. D., et al. (2014). Sex differences in extinction recall in posttraumatic stress disorder: A pilot fMRI study. *Neurobiol. Learn. Mem.* 113, 101–108. doi: 10.1016/j.nlm.2014.02.003

Straus, L. D., Drummond, S., Risbrough, V. B., and Norman, S. B. (2017). "Sleep disruption, safety learning, and fear extinction in humans: Implications for posttraumatic stress disorder," in *Behavioral Neurobiology of PTSD*, eds E. Vermetten, D. G. Baker, and V. B. Risbrough (Berlin: Springer), 193–205. doi: 10.1007/7854_2017_31

Strong, R. E., Marchant, B. K., Reimherr, F. W., Williams, E., Soni, P., and Mestas, R. (2009). Narrow-band blue-light treatment of seasonal affective disorder in adults and the influence of additional nonseasonal symptoms. *Depress. Anxiety* 26, 273–278. doi: 10.1002/da.20538

Tan, G., Dao, T. K., Farmer, L., Sutherland, R. J., and Gevirtz, R. (2011). Heart rate variability (HRV) and posttraumatic stress disorder (PTSD): A pilot study. *Appl. Psychophysiol. Biofeedback* 36, 27–35.

Tanev, K. S., Pentel, K. Z., Kredlow, M. A., and Charney, M. E. (2014). PTSD and TBI co-morbidity: Scope, clinical presentation and treatment options. *Brain Inj.* 28, 261–270. doi: 10.3109/02699052.2013.873821

Terman, M. (2007). Evolving applications of light therapy. *Sleep Med. Rev.* 11, 497–507.

Thayer, J. F., and Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *J. Affect. Disord.* 61, 201–216. doi: 10.1016/s0165-0327(00)00338-4

Thome, J., Densmore, M., Frewen, P. A., McKinnon, M. C., Théberge, J., Nicholson, A. A., et al. (2017). Desynchronization of autonomic response and central autonomic network connectivity in posttraumatic stress disorder. *Hum. Brain Mapp.* 38, 27–40. doi: 10.1002/hbm.23340

van der Helm, E., and Walker, M. P. (2010). Overnight therapy? The role of sleep in emotional. *Psychol. Bull.* 135, 731–748. doi: 10.1037/a0016570.Overnight

Van Minnen, A., Arntz, A., and Keijsers, G. P. J. (2002). Prolonged exposure in patients with chronic PTSD: Predictors of treatment outcome and dropout. *Behav. Res. Ther.* 40, 439–457.

Velasco, E. R., Florido, A., Milad, M. R., and Andero, R. (2019). Sex differences in fear extinction. *Neurosci. Biobehav. Rev.* 103, 81–108.

Walker, M. P., and van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135:731.

Wang, H. E., Campbell-Sills, L., Kessler, R. C., Sun, X., Heeringa, S. G., Nock, M. K., et al. (2019). Pre-deployment insomnia is associated with post-deployment post-traumatic stress disorder and suicidal ideation in US Army soldiers. *Sleep* 42:zsy229. doi: 10.1093/sleep/zsy229

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., et al. (2018). The clinician-administered PTSD scale for DSM–5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychol. Assess.* 30:383. doi: 10.1037/pas0000486

Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., et al. (2015). Post-traumatic stress disorder. *Nat. Rev. Dis. Prim.* 1, 1–22.

Youngstedt, S. D., Kline, C. E., Reynolds, A. M., Crowley, S. K., Burch, J. B., Khan, N., et al. (2021). Bright light treatment of combat-related PTSD: A randomized controlled trial. *Mil. Med.* 187, e435–e444. doi: 10.1093/milmed/usab014

Zalta, A. K., Bravo, K., Valdespino-Hayden, Z., Pollack, M. H., and Burgess, H. J. (2019). A placebo-controlled pilot study of a wearable morning bright light treatment for probable PTSD. *Depress. Anxiety* 36, 617–624. doi: 10.1002/da.22897

Zuj, D. V., Palmer, M. A., Lommen, M. J. J., and Felmingham, K. L. (2016). The centrality of fear extinction in linking risk factors to PTSD: A narrative review. *Neurosci. Biobehav. Rev.* 69, 15–35. doi: 10.1016/j.neubiorev.2016.07.014

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Dreamers' evaluation of the emotional valence of their day-to-day dreams is indicative of some mood regulation function

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Dreams may contribute to psychological adaptation by aiding in mood regulation. One way it could be achieved is through a desensitization process whereby negative events are replayed within the dream under lower conditions of negative emotionality. Evidence of this theory is supported by the tendency of dreamers to evaluate their emotions felt in their dreams more positively compared to an independent judge (i.e., positivity bias). Additionally, it has been observed that while dream emotions are typically more negative than pre-sleep emotions, morning emotions are more positive, suggesting that emotional regulation occurs overnight and may help improve mood in the morning. The present study aimed to examine the relationships between pre-sleep, dream, and morning mood and the potential desensitization function of remembered dreams as indicated by their effects on morning mood and stress.

Methodology: Participants (N = 188; Mean age = 19.2, SD = 3.0) recorded their dreams (N = 345 dreams) and self-reported their stress and mood at bedtime, during their dream retrospectively, and upon waking. A judge also evaluated the subjects' dream moods. Subjects' positivity bias was defined as the difference between the subjects and the judge's evaluation of the positive emotions in the dream.

Results: A MANOVA revealed that subjects perceived a higher level of positive emotions in their dreams compared to a judge. Multi-group path analysis revealed that some relationships between pre-sleep, dream, and morning emotions and stress differed in positive and negative dream nights. In both groups, the strongest predictors of morning mood and stress were pre-sleep mood and stress, respectively. The second strongest predictor of positive morning mood was the subjects' dream positivity bias.

Conclusion: Results provide some support for the association of dreaming in mood regulation attributable to REM sleep. They also highlight that pathways implicated in mood regulation may be distinct from stress regulation.

KEYWORDS

function of dreams, dream mood regulation, desensitization in dreams, dream emotions, rating of dream emotional valence

Introduction

The extensive research on dream formation has shown empirical support for the presence of some continuity between waking life and dream content. It has been postulated that dreams tend to reflect waking life experiences. It has also been suggested that the incorporation of waking-life events in dreams could have implications on an individual's psychological adaptation to these experiences. These notions have become key postulates of the continuity hypothesis of dreams (CH), which is now an umbrella theory first described in detail by Hall and Nordby (1972). Regarding the CH, the term continuity is very general and has thus encompassed several hypotheses and, at times, conflicting interpretations regarding the formation and function of dreams. Some researchers have postulated that the continuity was in the dreamer's cognitive activity, such as their perceptions and concerns (Domhoff, 2018). Schredl and Hofmann (2003) argued that waking-life experiences and events influenced dream content more generally, suggesting that dreamers' specific concerns and preoccupations were not uniquely represented in dreams. Modern research tends to show that all of these elements (i.e., thoughts, perceptions, preoccupations) and daily activities can be found in dream content since these concepts are often difficult to dissociate (Schredl, 2019). Research has shown that various aspects of waking life are incorporated into the content of dreams. Examples include social roles (Lortie-Lussier et al., 1985), gender (Dale et al., 2016), physical health (King and DeCicco, 2007), mental health (Schredl and Montasser, 1999) personality and psychotherapy process (Koulack et al., 1976; Busby and De Koninck, 1980; Hartmann et al., 1991; Samson-Daoust et al., 2019), remote past experiences (Grenier et al., 2005) and cognitive capacity (Fogel et al., 2018). Other studies have observed that certain chronobiological determinants, such as hormonal fluctuations (Wiebe et al., 2007), and certain major life changes, such as pregnancy (Sabourin et al., 2018), can influence dream content and result in dream modulations (e.g., affective changes, element incorporations). One important common denominator is that dream incorporations of waking life are typically distorted, such that independent observers are unable to detect a clear resemblance between participants' daily events descriptions and manifest dream content reports (Roussy et al., 2000). This is unsurprising since some types of day activities, typically cognitive activities, such as reading, writing, and counting, are seldomly reported in dreams (Hartmann, 1998) and there is essentially no episodic memory in the manifest content of dreams. Finally, new experiences, such as learning a second language, can take several days or weeks to be incorporated into dreams; therefore, there is also a temporal aspect to consider when examining the degree of continuity between waking life and dreams (De Koninck et al., 1990).

De Koninck (2012) has proposed a hierarchy, in terms of importance, of the contributions of the different factors and components that shape the construction of dreams. Consistent with this layered approach is the increasing evidence that, once the proper physiological substrate and cognitive capacity are in place, dream construction prioritizes emotional waking-life experiences and concerns with a negative bias (Malinowski and Horton, 2014; Domhoff, 2019). It is thus not surprising that traumatic events and major life changes have also been found to have a significant impact on dream content. Events, such as divorce (Cartwright, 1991), sexual and physical abuse (Belicki and Cuddy, 1991), and torture and war (Lavie and Kaminer, 1991; Valli et al., 2006) have been shown to have a significant impact on emotions in the content dreams of individuals who have experienced these events. Results from more recent studies examining the impacts of COVID-19 on dreams demonstrate that individuals who were more strongly affected by the pandemic physically, socially, or psychologically had more negatively toned dreams (Schredl and Bulkeley, 2020). Finally, anticipatory stressful events, for example, an academic examination, et al., has been found to be incorporated into a recent dream, such that many students dreamt of forgetting answers or being late for the exam the night before (Arnulf et al., 2014). Furthermore, students who dreamt of the exam the night before performed better on the exam (Arnulf et al., 2014), demonstrating that episodic simulation during dreaming has an adaptive value and that there is a degree of continuity between anticipatory feelings during waking and in dreams as suggested by Lemyre et al. (2022).

While it is thus well documented that waking life can shape dream formation and that the most significant relation resides in the emotional dimension with its accompanying mood, a more challenging dimension of the CH is whether there is a relationship between dreams and subsequent waking life. This notion has led to dream function theories in relation to the impact of dreams on waking life (Kuiken and Sikora, 1993) and their potential adaptive role. It is well established that nightmares have a negative impact on waking life (Nixon et al., 2017); however, less is known on how dreams could contribute to psychological adaptation in average waking life, such as daily mood or stress. Studies starting in the 1960s and 1970s have explored the dreams of individuals who had been exposed to naturally or experimentally induced stress (Breger et al., 1971; Cohen and Cox, 1975; De Koninck and Koulack, 1975) in order to test dream function theories that ranged from mastery to compensation (Dallett, 1973). For example, Breger (1967) proposed that dreams "serve to integrate affectively aroused material into structures within the memory system that have previously proved satisfactory in dealing with similar material and serve a unique function in the assimilation and mastery of arousal material into the "solutions" embodied in existing memory systems." Some studies supported the mastery hypothesis (Cohen and Cox, 1975), while others did not (De Koninck and Koulack, 1975; Koulack et al., 1985). The alternative hypothesis was that dreams serve an adaptive function through a compensating mechanism of needs arising from the presleep experience (PE). For example, Foulkes et al. (1967) reported that following the presentation of a baseball film, the dreams of young males were more aggressive than the dreams following a Western film, suggesting compensation for the hostility dimension. Wright and Koulack (1987) proposed a disruption-avoidance model combining these approaches. Despite their divergence on the interpretation of dream function, these two approaches share the postulate that dreams can act as a "safe space" and help individuals to explore and resolve emotional problems (Hartmann, 1998). Aligned with this notion, Cartwright (2001) reported that newly divorced individuals who dreamt about their spouse better adapted to their new situation. Other researchers have explored the potential mood regulation function of dreaming given that emotions play an important role in dream formation.

While in the early 70s most theories were focused on dream content itself as an agent of adaptation, studies conducted by Kramer and colleagues demonstrated that successive REM dreams during the night progressively improved mood and thus served an adaptive role (Kramer and Roth, 1972; Kramer et al., 1974). This is achieved through the content of the dream. These observations lead to his mood regulation theory elaborated in future works (Kramer, 1993, 2007). He proposed that "the physiological and psychological activities during sleep appear to be corrective like a thermostat operating to move the mood level toward a central and lower point" (Kramer, 2007, p. 183). Perlis and Nielsen (1993) more specifically suggested that a process of desensitization was taking place during REM dreams, notably with the reduction of muscle tone. In agreement with Kramer (1993, 2007), they generalized the function of REM sleep to the function of dreaming. It also did not limit the adaption process to rely on the specific type of content, such as mastery or compensation, but on a more encompassing process. Therefore, it is proposed plausible that dreams may be responsible for sensory and affective integration and the process of desensitization as indicated by the increased subjective perception in the pleasantness of emotionally intense dreams would be enabled by specific processes that occur during REM sleep such as muscle relaxation and or positive emotions.

This notion is consistent with the consensus that REM sleep plays a pivotal role in the processing of emotional waking-life experiences by contributing to emotional memory consolidation (Breger, 1967). Not surprisingly, Kramer (2007) suggests uninterrupted REM sleep is more conducive to better morning mood regulation than when there are awakenings from REM sleep with dream recall (for example, Koulack et al., 1985). To some extent, neuroimaging studies have found some overlap in the neural substrates that regulate dreaming and their emotional salience and those involved in emotion regulation during waking (Scarpelli et al., 2019). EEG studies also found that theta activity patterns during REM sleep in individuals who had incorporations of memories in their dream experience were similar to patterns observed when memory processing is occurring during wakefulness, suggestive of a continuation of emotional processing of waking-life events in sleep cycles where dreaming is most likely to occur (De Gennaro et al., 2012; Scarpelli et al., 2015). Levin and Nielsen (2009) refined this model, which is currently known as the Neurocognitive Model of Nightmares (NMN) and propose that dreams regulate fear-infused emotions by a recombination of fearful memories with non-fearful mnesic elements. More recently, a study by Malinowski and Horton (2014) further explored the potential emotion regulation function of dreams. They found that elements of waking life that were consistently incorporated in dreams were significantly more emotional, but not necessarily more stressful. Malinowski and Horton (2014) also suggested that the preferential incorporation of emotional experiences into dreams may contribute to psychological adaptation in various ways. For instance, it could aid in problem-solving and help individuals derive a sense of mastery over affectively arousing dreams. Regarding emotion regulation, in particular, this incorporation process could help ameliorate emotions attached to arousing waking-life experiences, which, in turn, may reduce arousal to this event in waking-life. The benefits of emotional processing occurring during dreaming have been demonstrated in those who suppressed their unpleasant thoughts: they were more likely to experience dream rebound compared to those who suppressed pleasant thoughts, which

in turn, had a therapeutic effect by providing a more pleasant perspective on unpleasant thoughts (Malinowski et al., 2019). Furthermore, Vallat et al. (2018) also observed that dreams contribute to emotion regulation, such that subjects whose dreams reflected their waking-life experiences perceived their dreams more positively than the actual event. This finding is further corroborated by our recent study that demonstrated that subjects who had experienced a recent troubling life event had a higher level of negative emotions but similar levels of positive emotions in their dreams compared to those who did not have a recent troubling experience (Barbeau et al., 2022). Both of these studies support the notion that dreams can contribute to psychological adaption by aiding in the integration and consolidation of emotions through a process of desensitization, which may have the potential to positively affect subsequent waking-life. However, it remains unknown how this positive dream affectivity present even during negatively toned dreams influences subsequent waking states, such as morning mood and stress. An interesting observation that may be indicative of the desensitization process during dreaming are studies reporting that dreamers tend to self-evaluate their emotions in dreams more positively than independent judges who read their dream narrative (Schredl and Doll, 1998; Sikka et al., 2014, 2017, 2018, 2021). Studies assessing this phenomenon have found that the discrepancy can be affected by the personality of the dreamer, the length of the dream report, and potentially the instructions given to the external raters (Röver and Schredl, 2017). For instance, Röver and Schredl (2017) observed that judges underestimate the intensity of dream emotions, specifically positive ones, and the word length of the dream report was inversely associated with the discrepancy between the subjects' and evaluators' ratings of negative dream emotions only. This finding was interpreted as a potential artifact elicited by either methodological design (i.e., dream recall instructions not specifying for subjects to focus on reporting their emotions felt while dreaming; Sikka et al., 2017) or subjects' tendency to underreport positive emotions in their dream reports, particularly when their reports are shorter in length (Röver and Schredl, 2017). Nonetheless, these observations have been interpreted by others as an illustration of a positive bias within the dream experience, which recently has been found in waking mind wandering (Sikka et al., 2021). Essentially, the literal objective content is in contrast with the subjective emotional experience of dreams, which would contribute to its adaptive value. In a similar fashion outlined by Scarpelli et al. (2019), Sikka et al. (2021) proposed a neural basis of affective experience and the role of the default-mode network (DMN) and the prefrontal cortex (PFC) in the management of subjective experiences. Finally, what gives credence to the notion of subjects' positive bias is the very well-documented presence of negative components in dreams beyond emotions. Indeed, the first normative study of dream content by Hall and Van De Castle (1966), which has been replicated in a normative Canadian population (Dale et al., 2016), confirms the predominance of aggression over friendliness, failures over success and misfortune over fortune in dreams. However, the interpretation of these events may differ depending on the evaluator [i.e., self (subject) vs. external evaluator] and thus the evaluation of emotions felt during these dreams may also consequently differ. Of interest to the present study, the extent of this positive bias could then serve as a tool to assess the impact that desensitized dream experiences have on morning emotional states, such as improved mood (e.g., more positive morning emotions) and/or lowered stress.

Hypothesis and predictions

The objective of the present study was to continue to assess the relationships between the dreamer's mood and stress prior to sleep and the emotional experience during the dream, while also examining the relationship between these pre-sleep and remembered dream states on waking mood and stress.

When testing dream function theories, it is essential to evaluate the post-sleep experience and go beyond extrapolating from dream content in relation to the preceding waking experience. Early studies seeking to examine the relationship between dreaming and subsequent morning waking states attempted to experimentally manipulate dreams by exposing subjects to external stimulation during REM sleep episodes (De Koninck and Koulack, 1975) or exposing them to pre-sleep stimulations followed by REM dream report collections (Cohen and Cox, 1975). These studies have yielded inconclusive results due to eliciting sleep disruptions and the effect of these disruptions on dream recall and morning mood. For example, Koulack et al. (1985) observed that morning mood was significantly more positive following uninterrupted sleep compared to a REM dream collected during the night regardless of dream valence. For the present study, it was decided to use a correlational model applied used in previous studies (Schredl and Reinhard, 2010; Nixon et al., 2017) to elaborate on the relationship between pre-sleep, dream, and morning emotions. This allowed us to determine which is the best predictor of subsequent morning mood and stress using a protocol of normal dream diaries without manipulation and without taking into account dream content. We also attempted to examine the notion of the adaptive function of dreaming on emotion and stress regulation through desensitization as assessed by dreamers' positive bias of their recalled dreams. In a stepwise approach, we attempted to replicate previous findings that found a discrepancy between dreamers and independent judge's ratings of positive emotions in subjects' recalled dreams (i.e., positivity bias) while taking into consideration artifacts identified in previous studies, such as dream length and mood rating methods, notably by establishing the reliability of external judges. Thus, we assessed whether this bias is a useful indicator of the desensitizing

power of the dream as indicated by its association with positive morning emotions and lower morning negative emotions and stress.

According to mood regulation theories of dreams we predicted that dreamers would evaluate the content of their dreams more positively than independent judges. More specifically, there should be a significant discrepancy between the emotions present in the dreamer's dream narrative as assessed by independent judge and the emotions that the dreamer reported feeling.

According to the CH, there is a certain degree of continuity between waking-life states and dream states; therefore, we hypothesized that pre-sleep emotions and stress would be associated with dream emotions. We further extended the postulates of the CH to morning states and hypothesized that pre-sleep emotions and stress and dream emotions would be associated with morning emotions and stress.

Dreaming should facilitate the desensitization to negative waking-life events through simulations in recalled dreams, which aids psychological adaptation in waking-life. Therefore, we predicted that there would be stronger positive associations between positive dream emotions and positive morning emotions compared to positive pre-sleep emotions and positive morning emotions. Furthermore, the process of desensitization and its adaptive value were gauged by examining the predictive power of dreamers' positivity bias on morning mood and stress. We predicted that dreamers' positivity bias would be the strongest predictor of positive morning emotions and would contribute to lower morning stress as indicated by a negative association. Considering that much of the research examining the emotion regulation function of dreams has been conducted in individuals who experienced traumatic or adverse events, who in turn typically have more negative dreams compared to normative populations, we predicted that the desensitization process, an indicated through dreamer's positivity bias, may have different impacts on dreamers waking mood and stress depending on whether they have a positive or negative dream night.

Method

Participants

One hundred eighty-eight participants were selected from a pool of participants that was previously collected in a larger study examining normative dreams among Canadians between 2004 and 2017 (Dale et al., 2016), which was before the COVID-19 pandemic. Male (n = 90; 48%) and female participants (52%) were between the ages of 12–24 years old (Mean = 19.2, SD = 3.0). Most reported on two dreams (n = 157; 84%). Participants were recruited through advertisements (e.g., at a university and on social media), word of mouth (e.g., personal contacts at school boards, at public presentations and conferences), and through retiree associations. Participants were unaware of the purposes of the study and provided written consent. The study was approved by the Research Ethics Board (REB) at the University of Ottawa.

After obtaining participants' consent, they were instructed to complete a dream questionnaire using pen and paper at home until they reported at least one dream for a maximum period of 10 days. The dream questionnaire (DQ), which was developed for the Normative Study on the dreams of Canadians (Dale et al., 2015, 2016, 2017), comprised several sections. Of particular interest to this study, were the data from the sections related to participants' emotions and stress experienced in the evening before sleeping and upon waking in the morning, and sections related to aspects of their (recalled) dreams, such as the narrative of their dream and the emotions in their dream. Further descriptions of these subsections of the DQ used in the current study are described below.

Measures

Sociodemographic questionnaire

The DQ included a sociodemographic questionnaire. Participants self-reported their age, gender, marital status, profession, and education.

Pre-sleep stress and morning stress

A section of the DQ measuring aspects of waking life included questions related to levels of stress experienced in the evening at bedtime. On a Likert scale ranging from 0 (*none*) to 4 (*very high*), participants rated their current level of stress. Participants also reported their level of stress upon waking using the same scale. In the current study, participants' scores on pre-sleep stress and morning stress represent their level of stress at bedtime and upon waking on nights when they had dreams.

Pre-sleep emotions and morning emotions

The section of the DQ measuring aspects of waking life and stress before bedtime also contained a mood checklist developed by Folkman and Lazarus (1985) measuring the subject's current levels of 15 positive and negative emotions. On a Likert scale ranging from 0 (*not at all*) to 3 (*a lot*), subjects rated the degree to which the following emotions were experienced before bedtime: worried, fearful, anxious, angry, sad, guilty, disappointed, disgusted, exhilarated, happy, pleased, relieved, confident, hopeful, and eager. Subjects completed the mood checklist again upon waking to measure participants' positive

and negative morning emotions. Subject's positive and negative pre-sleep and morning emotions scores were transformed from a 0 to 3 to a 1 to 4 scale (i.e., a 0 became a 1, a 1 became a 2, a 2 became a 3, and a 3 became a 4) to be on the same scale as our other questionnaires, such as our measures of stress and dream emotions. After re-scaling, the subject's pre-sleep positive emotions score was created by averaging their ratings on exhilarated, happy, pleased, relieved, confident, hopeful, and eager before bedtime. Subject's pre-sleep negative emotions score was created by averaging their ratings on worried, fearful, anxious, angry, sad, guilty, disappointed, and disgusted before bedtime. Similarly, the subject's morning negative emotions score was created by averaging their ratings on worried, fearful, anxious, angry, sad, guilty, disappointed, and disgusted upon waking. Subject's morning positive emotions score was created by averaging their ratings on exhilarated, happy, pleased, relieved, confident, hopeful, and eager upon waking. Cronbach's alpha for the pre-sleep negative emotions and positive emotions scores were 0.79 and 0.82, respectively. Cronbach's alpha for the morning negative emotions and positive emotions scores were 0.83 and 0.81, respectively.

Dream reports and dream emotions

Following the section of the DQ related to waking life experiences and pre-sleep emotions and stress, participants completed the morning section of the DQ. This section comprised the description of the narrative of their dream immediately upon waking followed by assessing their emotions experienced in their dream. Using a four-point Likert scale (1 = *not at all*, 2 = *a little*, 3 = *moderate*, 4 = *a lot*) was used to assess the five emotions found in the scale developed by Hall and Van De Castle (1966) with the added anxiety dimension. More specifically, participants rated the degree to which they experienced joy, happiness, apprehension, anger, sadness, fear, and anxiety in their dream. Subjects' evaluations of the positive emotions in their dream were created by averaging their ratings on joy and happiness. Subjects' evaluations of the negative emotions in their dream were achieved by averaging their ratings on apprehension, anger, sadness, fear, and anxiety. Cronbach's alpha was 0.94 for the subject's mean score of positive dream emotions and 0.62 for the subject's mean score of negative dream emotions.

Considering that we were interested in examining the potential discrepancy between a subject's and a judge's rating of oneiric emotions, an independent judge also evaluated the degree of positive and negative emotions in subjects' dream narratives. After being trained in scoring emotions in dream narratives, the independent judge scored the degree of positive and negative emotions present in subjects' dream narratives using the same Likert scale that was used by the subjects. The independent judge was one of several whose reliability of scoring was assessed against another judge. Due to the high level of agreement between the two judge's ratings (i.e., each positive and negative dream emotion level rating), only one judge's evaluations were used in the current study. The independent judge was blind to the subjects' evaluations of positive or negative emotions experienced in their dream to ensure that their evaluation remained unbiased. The judge's evaluation of positive emotions in the dream was created by averaging their ratings on joy and happiness. The judge's evaluation of negative emotions in the dream was created by averaging their ratings on apprehension, anger, sadness, fear, and anxiety. Cronbach's alpha was 0.95 for the judge's mean score of positive dream emotions and 0.70 for the judge's mean score of negative dream emotions.

To assess whether subjects display a positivity bias when recalling their dream emotions, a score was created to represent the discrepancy between the subject's and judge's ratings of the level of positive emotions in the dream. This score was computed by subtracting the subject's mean positive dream emotions score from the judge's mean positive dream emotions score. If this computation resulted in a negative score, denoting that the subject's mean positive dream score was lower than the judge's mean positive dream score, the subjects' positivity bias score was then transformed to a 0 to represent the absence of a positivity bias (n = 132 dreams originally had no presence of a positivity bias; n = 53 additional scores were transformed to a 0 due to a negative score).

Since we conducted our analyses on positive and negative dreams separately, we decided to use an objective categorization of emotional valence. Thus, we used the difference between the judge's positive and negative emotions scores to dichotomize the dreams according to their global emotional valence. A negative score suggested that the subject had a more negative dream, a positive score suggested that the subject had a more positive dream, and a score of 0 suggested that the subjects had a dream with equal levels of positive and negative emotions.

Data analytical plan

To examine whether subjects possess a positivity bias when perceiving their emotions in their dreams, a between subjects MANOVA was conducted to examine if there were differences in the subjects' and judge's ratings of the positive and negative emotions in the dreams. An *a priori* power analysis using G*Power (Faul et al., 2007) recommended a sample size of 158 participants for detecting a medium effect size with power of 0.80 and an alpha of 0.05. To reduce Type 1 error from conducting multiple comparisons, a Bonferroni adjustment was applied to each *post hoc* comparison (0.05/2 = 0.025). Due to previous studies finding an association between word length of the dream report and magnitude of the discrepancy between a subject's and judge's evaluations of positive dream emotions, we randomly selected 50 subjects who had a more negative

dream and 50 subjects who had a more positive dream and assessed whether word length was associated with subjects' positivity bias score by conducting a Pearson's Correlation. To examine the associations between pre-sleep stress and emotions, dream emotions, including subjects' positivity bias, and morning stress and emotions, a path analysis using Mplus Version 7 was conducted. For this analysis, we used the judge's ratings of the positive and negative emotions in the dreams because they were considered more objective, while also examining the contribution of the subject's positivity bias (i.e., a score representing the discrepancy between the subject and judge's ratings of the positive emotions in the dream) on morning emotions. Furthermore, we sought to examine whether these associations were similar across nights where subjects had more positive or negative dreams. Thus, we tested the tenability of our path model and the invariance (equivalency) between the correlations observed in these paths (parameters) across these two groups using a multigroup approach in Mplus.

To test the invariance in parameters across positive and negative dream nights in the multigroup path analysis, a constrained model was tested against an unconstrained model. In the constrained model, parameters were constrained to be equivalent across groups (i.e., across dream nights), whereas in the unconstrained model, parameters were free to vary. The constrained and unconstrained models were then compared using a chi-square difference (χ^2diff) test to determine whether global dream valence played a moderating role on the path model. A significant chi-square difference would support the notion that dream valence plays a moderating role on the path model and that the parameters are not equivalent across dream nights. In the event of this result, follow-up analyses testing each parameter separately for invariance by unconstraining the relationship between variables would be conducted; the χ^2diff resulting from this would be compared to the constrained model whereby $p < 0.05$ suggests invariance across the groups (i.e., dream nights).

For all models generated in the study (e.g., constrained, unconstrained, final accepted model), model fit was considered good if the χ^2 value was nonsignificant (Barbeau et al., 2019), the comparative fit index (CFI) and Tucker-Lewis index were $\geq$0.90 (Forza and Filippini, 1998; Hair et al., 2010), (b) the root mean square error of approximation (RMSEA) was $\leq$0.06 (Barbeau et al., 2019), and the standardized root mean square residual (SRMR) index was $\leq$0.08 (Hu and Bentler, 1999).

Results

Univariate outliers were winsorized. The assumption of multivariate normality, which was assessed by examining scatterplots, equality of covariances MANOVA (Box's M, $p < 0.001$), and multivariate outliers were violated. The multivariate outlier was retained because the presence and absence of the outlier had no effect on the MANOVA results. Furthermore, MANOVA is robust to departures of normality and equality of covariances; therefore, this analysis was still pursued. Regarding the assumptions of the multi-group path analysis, $n = 11$ participants were considered multivariate outliers according to their group membership (i.e., dream valence) and were removed from the analysis.

Overall ($N = 334$ dreams), $n = 205$ subjects' dreams were considered more negative, $n = 117$ subject's dreams were considered more positive, and $n = 12$ subject's dreams were considered to be equally mixed based on the judge's score of positive and negative dream emotions. Additionally, of those included in the path analysis model ($N = 322$), 137 subjects exhibited a positivity bias ($n = 81$ subjects who had a more negative dream and $n = 56$ subjects who had a more positive dream). For the multi-path analysis, the invariance model was tested between those who were considered to have more positive or more negative dream nights only. Means, standard deviations, and correlations among the variables in the model in the positive and negative dream night group appear in **Tables 1**, **2**, respectively.

Main analyses

The discrepancy between subject and judge's evaluations of positive and negative emotions in dreams

The between-subjects MANOVA ($N = 334$) demonstrated that there were differences in the mean positive and mean negative emotional rating of the dream, $F_{(2,665)} = 14.21$, $p < 0.001$, $\eta_p^2 = 0.041$. This effect was driven by differences in subjects and judge's mean scores in positive dream emotions only, $F_{(1,666)} = 22.73$, $p < 0.001$, $\eta_p^2 = 0.033$. As illustrated in **Figure 1**, Bonferroni corrected pairwise comparisons revealed that the subject's positive dream emotion scores were higher than the judge's positive dream emotion scores, $p < 0.001$. This suggests that subjects have a bias toward perceiving their dreams more positively than a judge, supporting the idea of a positivity bias. Furthermore, a Pearson's correlation analysis demonstrated that the word length of the subject's dream report was not significantly associated with their positivity bias score ($N = 100$; $r = -0.16$, $p = 0.112$).

Multi-group path analysis

A model examining the associations between pre-sleep emotions and stress, dream emotions, and morning emotions and stress was examined ($N = 322$; $n = 205$ positive dreams, $n = 117$ negative dreams). The first model, in which the structural parameters were constrained to be equal across

TABLE 1 Means, standard deviations, and correlations among the variables in those who had positive dream nights.

Variable	Mean	SD	2	3	4	5	6	7	8	9
1. Pre-sleep positive emotions	2.3	(0.7)	−0.31*	−0.30*	−0.02	−0.10	0.01	0.37*	0.07	0.15
2. Pre-sleep negative emotions	1.5	(0.4)	-	0.54*	0.08	0.14	0.04	−0.09	0.44*	0.18
3. Pre-sleep stress	1.1	(1.0)	-	-	−0.10	0.14	0.01	−0.18	0.20*	0.32*
4. Positive dream emotions	2.6	(0.7)	-	-	-	−0.29*	−0.38*	0.13	−0.10	−0.10
5. Negative dream emotions	1.4	(0.4)	-	-	-	-	0.06	−0.27*	0.15	0.03
6. Subject's positivity bias	0.5	(0.6)	-	-	-	-	-	0.16	0.02	−0.04
7. Morning positive emotions	2.1	(0.7)	-	-	-	-	-	-	−0.16	−0.03
8. Morning negative emotions	1.3	(0.4)	-	-	-	-	-	-	-	0.31*
9. Morning stress	0.9	(0.9)	-	-	-	-	-	-	-	-

$N = 117$ dreams, $^*p < 0.05$.

TABLE 2 Means, standard deviations, and correlations among the variables in those who had negative dream nights.

Variable	Mean	SD	2	3	4	5	6	7	8	9
1. Pre-sleep positive emotions	2.2	(0.7)	−0.34*	−0.27*	0.02	−0.16*	0.06	0.54*	−0.14*	−0.02
2. Pre-sleep negative emotions	1.5	(0.5)	-	0.68*	0.05	0.21*	−0.08	−0.24*	0.56*	0.42*
3. Pre-sleep stress	1.1	(1.0)	-	-	−0.04	0.16*	−0.10	−0.17*	0.47*	0.44*
4. Positive dream emotions	1.1	(0.3)	-	-	-	0.06	0.09	0.07	−0.04	−0.03
5. Negative dream emotions	2.3	(0.5)	-	-	-	-	0.03	−0.14	0.16*	0.17*
6. Subject's positivity bias	0.5	(0.8)	-	-	-	-	-	0.28*	−0.11	−0.03
7. Morning positive emotions	1.8	(0.7)	-	-	-	-	-	-	−0.23*	−0.10
8. Morning negative emotions	1.5	(0.6)	-	-	-	-	-	-	-	0.49*
9. Morning stress	1.2	(1.0)	-	-	-	-	-	-	-	-

$N = 205$ dreams, $^*p < 0.05$.

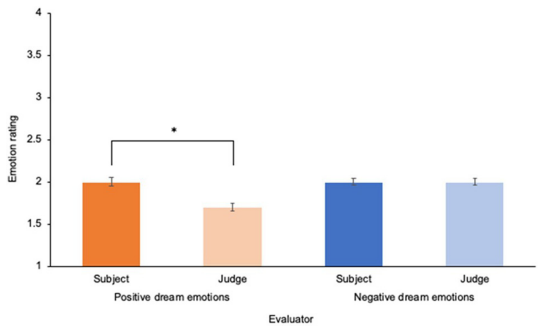

FIGURE 1
Mean differences in subject's and a judge's evaluations of positive and negative emotions in dreams. $N = 345$ dreams, $^*p < 0.05$. Error bars represent standard error of the mean.

positive and negative dream nights, did not fit the data well ($\chi^2_{(46)} = 94.22$, $p < 0.001$, CFI = 0.87, TLI = 0.81, RMSEA = 0.08, SRMR = 0.09), rejecting the null hypothesis that the paths are equal across positive and negative dream nights. The χ^2 diff test between the constrained and unconstrained model further suggested that some paths were different, $p = 0.001$. By unconstraining each path independently and conducting a χ^2diff test, paths were different in the following relationships in those who had positive vs. negative dream nights: between pre-sleep stress and morning negative emotions ($p = 0.020$; pre-sleep stress was positively significantly associated with negative morning emotions in the negative dream nights only), between positive and negative dream emotions ($p < 0.001$; judge's ratings of positive and negative dream emotions were negatively associated in positive dream nights only), and between positive dream emotions and subjects' positivity bias ($p < 0.001$; judge's ratings of positive dream emotions and subjects' positivity bias was negatively associated in positive dream nights only). The final model with the aforementioned relationships unconstrained, allowing variability in the paths based on dream valence, is displayed in Figure 2. This model fit the data well and thus was retained, $\chi^2_{(42)} = 56.89$, $p = 0.062$, CFI = 0.96, TLI = 0.93, RMSEA = 0.05 (CI = 0.000–0.076), SRMR = 0.07. In those who had positive dreams, the following amount of variance was explained per construct: 0% in positive dream emotions, 5% in negative dream emotions, 0% in subject's positivity bias, 26% in positive morning emotions, 23% in negative morning emotions, and 19% in morning stress. In those who had negative dreams, the following amount of variance was explained per construct: 0% in positive dream emotions, 3% in negative dream emotions, 0% in subject's positivity bias, 34% in positive morning emotions, 30% in negative morning emotions, and 17% in morning stress.

As displayed in Figure 2, across both positive and negative dream nights, positive pre-sleep emotions were not associated with positive dream emotions or subjects' dream positivity bias; however, positive pre-sleep emotions were significantly positively associated with positive morning emotions. Across negative and positive dream nights, pre-sleep negative emotions were significantly positively associated with negative dream emotions, morning stress, and negative morning emotions.

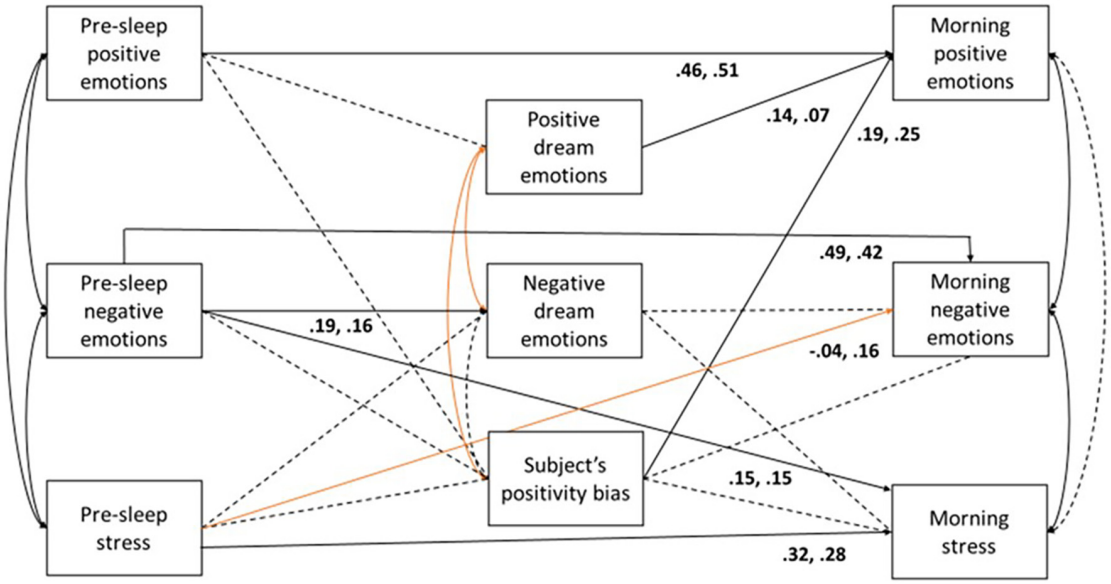

FIGURE 2
Multi-group path analysis model. Solid lines represent $p < 0.05$; dotted lines represent $p > 0.05$. Curved lines represent correlations; arrows represent regressed relationships. Orange lines represent paths that significantly differed between positive and negative dream nights. Coefficients are standardized and are presented in the following order: positive dream nights (n = 117 dreams) and negative dream nights (n = 205 dreams).

There was no significant association between pre-sleep negative emotions and subjects' dream positivity bias. Across negative and positive dream nights, pre-sleep stress was significantly positively associated with morning stress; however, pre-sleep stress was not associated with negative dream emotions or subjects' dream positivity bias. In those who had negative dream nights, there was a positive association between pre-sleep stress and negative morning emotions, which was not present in those who had positive dream nights.

Regarding the associations between dream emotions and morning emotions, in those who had positive and negative dream nights, both positive dream emotions and subjects' positivity bias were significantly positively associated with positive morning emotions. However, negative dream emotions and subjects' positivity bias were not associated with negative morning emotions or morning stress. By examining the strength of the associations, irrespective of dream valence, the strongest predictor of positive morning emotions was pre-sleep positive emotions followed by subjects' positivity bias. The strongest predictor of negative morning emotions was pre-sleep negative emotions. Finally, the strongest predictor of morning stress was pre-sleep stress followed by pre-sleep negative emotions.

Discussion

This study sought to examine the relationships between bedtime mood and stress, dream mood, and waking mood and stress. We also sought to explore how an indicator of desensitization occurring in dreams (i.e., dreamer's positivity bias) was associated with morning mood and stress. As observed in other research, dreamers perceived higher levels of positive emotions in their dreams compared to a judge even though most dreamers had more negative dream nights (Schredl and Doll, 1998; Sikka et al., 2014, 2018); however, there were no differences in the appraisal of negative emotions in the dream. Our results also suggest that mood and stress before sleep is the best predictor of mood and stress in the morning, respectively. However, the subject's positivity bias is the second strongest predictor of positive morning emotions, suggestive of some evidence of mood regulation provided by desensitization during dreaming.

Congruent with our first prediction and with the observation of others (Schredl and Doll, 1998; Sikka et al., 2014, 2018), dreamers possess a bias that leads to the perception of a higher level of positive emotions in their dream compared to an objective evaluator (i.e., judge), which we refer to as a *positivity bias*. However, dreamer's do not perceive a reduced level of negative emotions in their dream compared to a judge. This is consistent with previous works by others that demonstrate that subjects perceive a higher level of positive emotions in their dreams even when their dreams are objectively evaluated (by an independent judge) as negative (Schredl and Doll, 1998; Samson-Daoust et al., 2019). This finding is intriguing and suggests several phenomena at play. First, as seen in previous research, this difference could suggest that judges have

more difficulty evaluating the positive emotions experienced by the dreamer in their dream narrative (Sikka et al., 2017; Lemyre et al., 2022). Interestingly, we did not find a correlation between the word length of the dream report and the degree of the subject's positivity bias, potentially suggesting that the positivity bias is not created by methodological artifact but rather may represent an adaptive psychological response. For instance, it is plausible that this bias represents a mechanism that occurs during the dream experience as a result of the desensitization process. A similar adaptive response has also been found to be present in daytime mind wandering (Sikka et al., 2021).

In partial support of our third prediction, we observed that the discrepancy between the evaluation of positive emotions in the dream between the subject and the judge, termed as subjects' positivity bias, played a positive role in morning emotions, supporting the emotion regulation function theories of dreams (Perlis and Nielsen, 1993; Malinowski et al., 2019). The positive relationship observed between the subject's dream positivity bias and positive morning emotions may also be attributed to the feeling priming effect postulated by the Feeling Priming Theory (FPT; Lemyre et al., 2022) of dreams. According to FPT, feelings felt in dreams may be associated with feelings felt in waking due to the continued activation of dream feelings, in this case, heightened subjective perception of positive emotions, in memory during the postsleep period (Lemyre et al., 2022). In the multi-group path analysis model, we observed that subject's positivity bias was the second strongest predictor of positive morning emotions; however, we did not observe any associations between the subject's positivity bias and negative morning emotions or stress, which was incongruent with our predictions (Lemyre et al., 2022). Although the statistical significance of the path between the subject's positivity bias and positive morning emotions was not significantly different between those who had more negative or positive dream nights, this association was still indeed stronger in those who had more negatively toned dreams, which partially supports our fourth prediction. This finding may suggest that emotion regulation processes are occurring in those who have more positive or negative dreams; however, this mechanism may be strengthened, perhaps through desensitization, as the dream increases in negative affectivity. As can be viewed in **Tables 1**, **2**, the bivariate correlations between subject's positivity bias and morning mood are stronger in those who had more negative dreams: there was a larger negative correlation between subject's positivity bias and negative morning emotions and a larger positive correlation between subject's positivity bias and positive morning emotions. Furthermore, our null findings of the relative role of the subject's positivity bias and morning stress may suggest that the mechanism underlying emotion regulation is distinct from the regulation of perceived stress. Further research is required to confirm this speculation. Taken together, these findings may be suggestive of a stronger mood regulation effect upon waking as a result of desensitization captured through the subject's positivity bias when dreams increase in negative emotionality.

In relation to our predictions aligned with the CH, our findings partially support the notion of continuity between bedtime mood and stress, dream emotions, and waking mood and stress. Bedtime emotions and stress were the strongest predictors of waking emotions and stress irrespective of dream valence, suggestive of a certain degree of continuity between waking-life states after sleeping. We also observed that stress before sleep was positively associated with waking negative emotions but only in those who have negative dream nights. Furthermore, emotions and stress before sleep were not associated with dream emotions with the exception of negative bedtime emotions. This finding is relatively consistent with studies that suggest that salient emotions associated with everyday events are preferentially incorporated into dreams (De Koninck, 2012) and the presence of negative emotions at bedtime can be reflected in dreams (Malinowski and Horton, 2014). Furthermore, recent studies have shown that the best waking-life predictor of dream emotions is trait anxiety. Samson-Daoust et al. (2019) found that trait anxiety was the only factor that predicted the emotional tone of the dream through its interaction with other waking life factors, such as mood in the evening and stress during the day. This provides a nuanced understanding of the pattern of results we observed between pre-sleep and dream emotions such that there was a stronger degree of continuity between waking and dream affect when emotions were more negatively toned. Finally, dream emotions, with the exception of the dreamer's positivity bias, were not associated with morning emotions or stress, which was partially incongruent with our predictions posited by the CH. It is plausible that these null findings were the result of our data analytical approach, such that we used the judge's evaluations of the emotion levels in the dream as predictors, while also examining the variance explained by the subject's positivity bias in morning mood and stress. From these results, it is clear that the subject's evaluations of the emotions in their dream is a stronger predictor of their morning mood, especially when trying to predict positive morning emotions. Overall, our results offer some support for the CH, such that negative bedtime emotions can manifest into dreams, and that subject's positivity bias, in addition to the subject's bedtime mood and stress, is predictive of their waking mood and stress, respectively. The next step would be to link the positive bias to the actual content of dreams, most notably dream content characteristics identified in normative studies, such as aggression, failures, or misfortunes in addition to balance between positive and negative events in the dream (Dale et al., 2016) while using the same study design to examine whether the positivity bias is present and aids morning mood regulation through the desensitization to threats simulated in dreams.

Limitations and future directions

Although the results of the present study provide some insight into theories of dream function, such as mood regulation, as well as insight into the relationships between waking-life and dream experience, they must be considered in light of certain limitations. First, the present study relied upon self-report measures for bedtime mood and stress, in the dream, and upon waking, and using a retrospective dream recall method. It is plausible that some subjects could have biases during their dream recall, which could impact the subjective evaluation of their emotions present in the dream and which dreams were reported. For instance, dream recall frequency and intensity of dream emotions are shown to enhance the feeling priming effect on waking states (Schredl, 2009). We consider this limitation to be somewhat unavoidable in dream studies, but it is nonetheless important to mention. Second, we did not use the same scales to evaluate emotions across all three time-points (bedtime, in the dream, and in the morning), which may have impacted the strength of the associations between them. For instance, we used the same scale for assessing emotions at bedtime and upon waking (i.e., emotion checklist) and a different scale to assess dream emotions (i.e., Hall and Van De Castle, 1966 rating system), which could have resulted in stronger associations between bedtime mood and morning mood and weaker associations between dream mood and morning mood. Due to this, we examined the strength and directionality of the correlations between the positive and negative emotions that were present in each scale and were measured across all three time-points (e.g., happiness, anxiety, anger, sadness, fear). We observed the same pattern of correlations present in **Tables 1**, **2** when we examined the correlation of matched emotions over time (e.g., happiness at pre-sleep, evaluated in the dream, and at post-sleep), suggesting that our results are not due to a lack of systematic measurement of emotions across pre- and post-sleep and dreams. Furthermore, another factor that could have led to these patterns of results is the source of scoring for dream emotions. For instance, it is plausible that there would be stronger associations between subjects' pre- and post-sleep emotions and dream emotions if we used subjects' dream emotion scores in our model. However, due to the overlapping variance explained in positive morning emotions by subjects' positive dream emotions score and their positivity bias score, this analytical technique was not pursued. Future studies should strive to replicate our findings using the same emotion checklists across time. Third, our sample consisted of individuals between the ages of 12 and 24, making our results difficult to generalize to the rest of the normative dream study sample. Future studies should strive to replicate our findings across all ages to understand the impacts of age on the degree of the subject's positivity bias and its ability to contribute to mood regulation. Despite previous research suggesting that positive emotions reported by dreamers do not differ by developmental stages (Barbeau et al., 2022), it is still plausible that the subject's may differ in their degree of positivity bias depending on their age. Finally, our results are correlational in nature; therefore, we cannot infer that the relationships that we observed are causal. Studies where the content of dreams is manipulated (De Koninck and Koulack, 1975; Koulack et al., 1985), would, when combined with the current methodology and data analytical technique, allow us to directly assess the adaptive role of the subject's positivity bias on waking mood regulation. More importantly, from a theoretical perspective, our results reflect the impact of remembered dreams while most dreams in day-to-day life are not recalled. Most theories, including the most recent formulations (Lemyre et al., 2022; Wamsley, 2022) do not address this important matter; however, it is interesting to note that Freud postulated that dreams were the "Guardians of Sleep" and that dreams that are remembered have failed their function. A similar point is made by Kramer (2007) who also suggested that mood regulation is best achieved during undisrupted sleep with the normal REM sleep components. Despite this notion, the desensitizing mechanism that is thought to be attributed to muscle relaxation during REM (Perlis and Nielsen, 1993) or its neuronal basis (Scarpelli et al., 2019; Sikka et al., 2021) is thought to still apply to non-remembered REM dreams (De Koninck, 2012). It is thus possible that the observed desensitization observed here in dream mood reflects the more important desensitization attributable to REM sleep itself. Future research is required to understand potential mechanistic differences, including differential impacts on affect regulation, in the desensitization process in remembered and non-remembered dreams.

Conclusion and practical implications

Our results lend partial support to emotion regulation theories of dream function and to the CH. We observed that subjects possess a positivity bias as indicated by a discrepancy between dreamers and a judge's evaluations of positive emotions in the dream. In turn, this bias was positively associated with positive morning emotions; stronger associations between these constructs were found in those who had more negatively toned dreams. These findings support the adaptive role of the subject's positivity bias in recalled dreams on their waking emotions. They also shed light on the potential mechanism by which desensitization, as indicated by this bias, supports emotion regulation. These findings are particularly relevant in understanding the importance and function of the dream experience in dampening the emotional tone of traumatic memories in individuals who may have compromised emotion regulation and fear extinction mechanisms during wakefulness due to their exposure to an

adverse event in waking-life (Scarpelli et al., 2019). Future research should examine whether these individuals demonstrate a dream positivity bias and its respective implications on their subsequent waking mood. Furthermore, our results may also have neurodevelopmental implications given that the participants in our sample were adolescents and young adults. Previous work demonstrates that adolescents and young adults have more nightmares compared to older adults (Salvio et al., 1992; Schredl and Doll, 1998; Nielsen et al., 2006); however, we observed that despite our sample having more negatively toned dreams, many demonstrated a dream positivity bias. It is plausible that the presence of this bias or its magnitude is attributed to a compensatory mechanism that aids psychological adaptation during developmental periods where fear conditioning and extinction are still developing, such as in adolescence (Shechner et al., 2014). Therefore, the positivity bias may be indicative of an adaptive associative learning mechanism that is reflected in the dream experience, which pairs higher levels of positivity affectivity with simulations of feared waking events to help downregulate neuronal fear responses to these events during wakefulness during a developmental period characterized by overactive fear responding and weak functional connectivity between brain regions involved in the fear response (i.e., amygdala) and emotion regulation (i.e., pre-frontal regions; Somerville et al., 2010).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Board of the University of Ottawa. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JD, KB, CT, and AL: all contributed to the conception and design of the study. CT, AL, and EC: contributed to the data gathering and dream scoring. CT: collated the data in preparation of the statistical analyses, wrote an Honours Thesis in French based on part of this study. KB and CT: carried out the statistical analyses of the dreams, carried out the statistical analyses. KB, CT, JD, and AL: prepared the final manuscript. JD: obtained the funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Arnulf, I., Grosliere, L., Le Corvec, T., Golmard, J.-L., Lascols, O., Duguet, A., et al. (2014). Will students pass a competitive exam that they failed in their dreams? *Conscious. Cogn.* 29, 36–47. doi: 10.1016/j.concog.2014.06.010

Barbeau, K., Boileau, K., Sarr, F., and Smith, K. (2019). Path analysis in mplus: a tutorial using a conceptual model of psychological and behavioral antecedents of bulimic symptoms in young adults. *Quant. Methods Psychol.* 15, 38–53. doi: 10.20982/tqmp.15.1.p038

Barbeau, K., Lafrenière, A., Ben Massaoud, H., Campbell, E., and De Koninck, J. (2022). Dissociated effects of age and recent troubling experiences on nightmares, threats and negative emotions in dreams. *Front. Psychiatry* 13:770380. doi: 10.3389/fpsyt.2022.770380

Belicki, K., and Cuddy, M. A. (1991). "Nightmares: facts, fictions and future directions," in *Dream Images: A Call to Mental Arms*, eds J. Gackenbach, and A. A. Sheikh (Amityville, NY: Baywood), 99–115.

Breger, L. (1967). Function of dreams. *J. Abnorm. Psychol.* 72, 1–28.

Breger, L., Hunter, I., and Lane, R. W. (1971). The effect of stress on dreams. *Psychol. Issues* 7, 1–213.

Busby, K., and De Koninck, J. (1980). Short-term effects of strategies for self-regulation on personality dimensions and dream content. *Percept. Motil. Skills* 50, 751–765.

Cartwright, R. (1991). Dreams that work: the relation of dream incorporation to adaptation to stressful events. *Dreaming* 1, 3–9. doi: 10.1037/h0094312

Cartwright, R. (2001). Dream incorporation of a sentinel life event and its relation to waking adaptation. *Sleep Hypn.* 3, 25–32.

Cohen, D. B., and Cox, C. (1975). Neuroticism in the sleep laboratory: implications for representational and adaptive properties of dreaming. *J. Abnorm. Psychol.* 84, 91–108. doi: 10.1037/h0076938

Dale, A., Lafrenière, A., and Koninck, J. D. (2017). Dream content of Canadian males from adolescence to old age: an exploration of ontogenetic patterns. *Conscious. Cogn.* 49, 145–156. doi: 10.1016/j.concog.2017.01.008

Dale, A., Lortie-Lussier, M., and Koninck, J. D. (2015). Ontogenetic patterns in the dreams of women across the lifespan. *Conscious. Cogn.* 37, 214–224. doi: 10.1016/j.concog.2015.09.008

Dale, A., Lortie-Lussier, M., Wong, C., and De Koninck, J. (2016). Dreams of Canadian students: norms, gender differences and comparison with American norms. *J. Cross Cult. Psychol.* 47, 941–955. doi: 10.1177/0022022116655788

Dallett, J. (1973). Theories of dream function. *Psychol. Bull.* 6, 408–416.

De Gennaro, L., Marzano, C., Cipolli, C., and Ferrara, M. (2012). How we remember the stuff that dreams are made of: neurobiological approaches to the brain mechanisms of dream recall. *Behav. Brain Res.* 226, 592–596. doi: 10.1016/j.bbr.2011.10.017

De Koninck, J. (2012). "Sleep, dreams and dreaming," in *The Oxford Handbook of Sleep and Sleep Disorders*, eds C. A. Espie, and C. M. Morin (New York, NY: Oxford), 150–171.

De Koninck, J., Christ, G., Hébert, G., and Rinfret, N. (1990). Language learning efficiency, dreams and REM sleep. *Psychiatr J. Univ. Ott.* 15, 91–92.

De Koninck, J. M., and Koulack, D. (1975). Dream content and adaptation to a stressful situation. *J. Abnorm. Psychol.* 84, 250–260. doi: 10.1037/h0076648

Domhoff, G. W. (2018). *The Emergence of Dreaming: Mind-Wandering, Embodied Simulation and the Default Network*. New York, NY: Oxford University Press.

Domhoff, W. (2019). "The neurocognitive theory of dreaming," in *Dreams: Understanding Biology, Psychology and Culture*, eds K. Valli, and R. Hoss (Santa Barbara, CA: ABC-CLIO), 95–99.

Faul, F., Erdfelder, E., Lang, A.-G., and Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral and biomedical sciences. *Behav. Res. Methods* 39, 175–191. doi: 10.3758/bf03193146

Fogel, S., Ray, L., Sergeeva, V., De Koninck, J., and Owen, A. M. (2018). A novel approach to dream content analysis reveals links between learning-related dream incorporation and cognitive abilities. *Front. Psychol.* 9:1398. doi: 10.3389/fpsyg.2018.01398

Folkman, S., and Lazarus, R. S. (1985). If it changes it must be a process: study of emotion and coping during three stages of a college examination. *J. Pers. Soc. Psychol.* 48, 150–170. doi: 10.1037//0022-3514.48.1.150

Forza, C., and Filippini, R. (1998). TQM impact on quality conformance and customer satisfaction: a causal model. *Int. J. Prod. Econ.* 55, 1–20. doi: 10.1016/S0925-5273(98)00007-3

Foulkes, D., Pivik, T., Steadman, H. S., Spear, P. S., and Symonds, J. D. (1967). Dreams of the male child: an EEG study. *J. Abnorm. Psychol.* 72, 457–467. doi: 10.1037/h0025183

Grenier, J., Cappeliez, P., St-Onge, M., Vachon, J., Vinette, S., Roussy, F., et al. (2005). Temporal references in dreams and autobiographical memory. *Mem. Cogn.* 33, 280–288. doi: 10.3758/bf03195317

Hair, J. F., Black, W. C., Babin, B. J., and Anderson, R. E. (2010). *Multivariate Data Analysis*. Uppersaddle River, NJ: Prentice Hall.

Hall, C. S., and Nordby, V. J. (1972). *The Individual and his Dreams*. New York: New American Library.

Hall, C. S., and Van De Castle, R. L. (1966). *The Content Analysis of Dreams*. New York: Appleton-Century-Crofts.

Hartmann, E. (1998). *Dreams and Nightmares: The New Theory on the Origin and Meaning of Dreams*. New York: Plenum Trade.

Hartmann, E., Elkin, R., and Garg, M. (1991). Personality and dreaming: the dreams of people with very thick or very thin boundaries. *Dreaming* 1, 311–324. doi: 10.1037/h0094342

Hu, L., and Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct. Equ. Modeling* 6, 1–55. doi: 10.1080/10705519909540118

King, D. B., and DeCicco, T. L. (2007). The relationships between dream content and physical health, mood and self-construal. *Dreaming* 17, 127–139. doi: 10.1037/1053-0797.17.3.127

Koulack, D., Lebow, M. D., and Church, M. (1976). The effect of desensitization on the sleep and dreams of a phobic subject. *Can. J. Behav. Sci.* 8, 418–421. doi: 10.1037/h0081968

Koulack, D., Prevost, F., and De Koninck, J. (1985). Sleep, dreaming and adaptation to a stressful intellectual activity. *Sleep* 8, 244–253. doi: 10.1093/sleep/8.3.244

Kramer, M. (1993). "The selective mood regulatory function of dreaming: an update and revision," in *The Functions of Dreaming*, eds A. Moffitt, M. Kramer, and R. Hoffmann (New York, NY: University of New York Press), 139–195.

Kramer, M. (2007). *The Dream Experience: A Systematic Exploration*. New York: Routledge, Taylor and Francis Group.

Kramer, M., Czaya, J., Arand, D., and Roth, T. (1974). The development of psychological content across the REM period. *Sleep Res.* 3:121.

Kramer, M., and Roth, T. (1972). "The mood regulating function of sleep," in *Physiology, Biochemistry, Psychology, Pharmacology, Clinical Implications*, eds W. P. Koella, and P. Levin (Basel: 1st European Congress on Sleep Research), 563–571.

Kuiken, D., and Sikora, S. (1993). "The impact of dreams on waking thoughts and feelings," in *The Functions of Dreaming*, eds A. Moffitt, M. Kramer, and R. Hoffman (Albany, NY: State University of New York Press), 419–476.

Lavie, P., and Kaminer, H. (1991). Dreams that poison sleep: dreaming in Holocaust survivors. *Dreaming* 1, 11–21. doi: 10.1037/h0094313

Lemyre, A., Bastien, C., and Vallieres, A. (2022). The Feeling Priming Theory (FPT) of dreaming. *Dreaming* doi: 10.1037/drm0000202

Levin, R., and Nielsen, T. (2009). Nightmares, bad dreams and emotion dysregulation: a review and new neurocognitive model of dreaming. *Curr. Dir. Psychol. Sci.* 18, 84–88. doi: 10.1111/j.1467-8721.2009.01614.x

Lortie-Lussier, M., Schwab, C., and De Koninck, J. (1985). Working mothers versus homemakers: do dreams reflect the changing roles of women? *Sex Roles* 12, 1009–1021. doi: 10.1007/BF00288101

Malinowski, J., Carr, M., Edwards, C. L., Ingarfill, A., and Pinto, A. (2019). The effects of dream rebound: evidence for emotion-processing theories of dreaming. *J. Sleep Res.* 28:e12827. doi: 10.1111/jsr.12827

Malinowski, J., and Horton, C. L. (2014). Evidence for the preferential incorporation of emotional waking-life experiences into dreams. *Dreaming* 24, 18–31. doi: 10.1037/a0036017

Nielsen, T. A., Stenstrom, P., and Levin, R. (2006). Nightmare frequency as a function of age, gender and September 11, 2001: findings from an internet questionnaire. *Dreaming* 16, 145–158. doi: 10.1037/1053-0797.16.3.145

Nixon, A., Robidoux, R., Dale, A., and De Koninck, J. (2017). Pre-sleep and post-sleep mood as a complementary evaluation of emotionally impactful dreams. *Int. J. Dream Res.* 10, 141–150. doi: 10.11588/ijodr.2017.2.35411

Perlis, M. L., and Nielsen, T. A. (1993). Mood regulation, dreaming and nightmares: evaluation of a desensitization function for REM sleep. *Dreaming* 3, 243–257.

Röver, S. A., and Schredl, M. (2017). Measuring emotions in dreams: effects of dream length and personality. *Int. J. Dream Res.* 10, 65–68. doi: 10.11588/ijodr.2017.1.34565

Roussy, F., Brunette, M., Mercier, P., Gonthier, I., Grenier, J., Sirois-Berliss, M., et al (2000). Daily events and dream content: unsuccessful matching attempts. *Dreaming* 10, 77–83. doi: 10.1023/A:1009496604922

Sabourin, C., Robidoux, R., Pérusse, A., and De Koninck, J. (2018). Dream content in pregnancy and post-partum: refined exploration of continuity between waking and dreaming. *Dreaming* 28, 122–139. doi: 10.1037/drm0000070

Salvio, M., Wood, J. M., Eichling, P. S., and Schwartz, J. (1992). Nightmare prevalence in the healthy elderly. *Psychol. Aging* 7, 324–3255. doi: 10.1037//0882-7974.7.2.324

Samson-Daoust, E., Julien, S. H., Beaulieu-Prévost, D., and Zadra, A. (2019). Predicting the affective tone of everyday dreams: a prospective study of state and trait variables. *Sci. Rep.* 9:14780. doi: 10.1038/s41598-019-50859-w

Scarpelli, S., Bartolacci, C., D'Atri, A., Gorgoni, M., and De Gennaro, L. (2019). The functional role of dreaming in emotional processes. *Front. Psychol.* 10:459. doi: 10.3389/fpsyg.2019.00459

Scarpelli, S., D'Atri, A., Gorgoni, M., Ferrara, M., and De Gennaro, L. (2015). EEG oscillations during sleep and dream recall: state- or trait-like individual differences? *Front. Psychol.* 6:605. doi: 10.3389/fpsyg.2015.00605

Schredl, M. (2009). Effect of dreams on daytime mood: the effects of gender and personality. *Sleep Hypn.* 11, 51–57. doi: 10.5665/sleep.3646

Schredl, M. (2019). "Continuity hypothesis of dreaming," in *Dreams: Understanding Biology, Psychology and Culture*, eds K. Valli, and R. Hoss (Santa Barbara, CA: ABC-CLIO.), 88–94.

Schredl, M., and Bulkeley, K. (2020). Dreaming and the COVID-19 pandemic: a survey in a US sample. *Dreaming* 30, 189–198. doi: 10.1037/drm0000146

Schredl, M., and Doll, E. (1998). Emotions in diary dreams. *Conscious. Cogn* 7, 634–646. doi: 10.1006/ccog.1998.0356

Schredl, M., and Hofmann, F. (2003). Continuity between waking activities and dream activities. *Conscious. Cogn* 12, 298–308. doi: 10.1016/s1053-8100(02)00072-7

Schredl, M., and Montasser, A. (1999). Dreaming and eating disorders. *Sleep Hypn.* 1, 225–231.

Schredl, M., and Reinhard, I. (2010). The continuity between waking mood and dream emotions: direct and second-order effects. *Imagination Cogn. Pers.* 29, 271–282. doi: 10.2190/IC.29.3.f

Shechner, T., Hong, M., Britton, J. C., Pine, D. S., and Fox, N. A. (2014). Fear conditioning and extinction across development: evidence from human studies and animal models. *Biol. Psychol.* 100, 1–12. doi: 10.1016/j.biopsycho.2014.04.001

Sikka, P., Feilhauer, D., Valli, K., and Revonsuo, A. (2017). How you measure is what you get: differences in self- and external ratings of emotional experiences in home dreams. *Am. J. Psychol.* 130, 367–384. doi: 10.5406/amerjpsyc.130.3.0367

Sikka, P., Revonsuo, A., Sandman, N., Tuominen, J., and Valli, K. (2018). Dream emotions: a comparison of home dream reports with laboratory early and late REM dream reports. *J. Sleep Res.* 27, 206–214. doi: 10.1111/jsr.12555

Sikka, P., Valli, K., Revonsuo, A., and Tuominen, J. (2021). The dynamics of affect across the wake-sleep cycle: from waking mind-wandering to night-time dreaming. *Conscious. Cogn.* 94:103189. doi: 10.1016/j.concog.2021.103189

Sikka, P., Valli, K., Virta, T., and Revonsuo, A. (2014). I know how you felt last night, or do I? Self- and external ratings of emotions in REM sleep dreams. *Conscious. Cogn.* 25, 51–66. doi: 10.1016/j.concog.2014.01.011

Somerville, L. H., Jones, R. M., and Casey, B. (2010). A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain Cogn.* 72, 124–133. doi: 10.1016/j.bandc.2009.07.003

Vallat, R., Eskinazi, M., Nicolas, A., and Ruby, P. (2018). Sleep and dream habits in a sample of French college students who report no sleep disorders. *J. Sleep Res.* 27:e12659. doi: 10.1111/jsr.12659

Valli, K., Revonsuo, A., Pälkäs, O., and Punamäki, R. L. (2006). The effect of trauma on dream content: a field study of Palestinian children. *Dreaming* 16, 63–87. doi: 10.1037/1053-0797.16.2.63

Wamsley, E. J. (2022). Constructive episodic simulation in dreams. *PLoS One* 17:e0264574. doi: 10.1371/journal.pone.0264574

Wiebe, S., Lamarche, L., Sabourin, C., Lortie-Lussier, M., and De Koninck, J. (2007). The dreams of women with severe emotional/behavioral premenstrual symptoms. *Dreaming* 17, 199–207. doi: 10.1037/1053-0797.17.4.199

Wright, J., and Koulack, D. (1987). Dreams and contemporary stress: a disruption-avoidance model. *Sleep* 10, 172–179. doi: 10.1093/sleep/10.2.172

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Acute sleep deprivation disrupts emotion, cognition, inflammation, and cortisol in young healthy adults

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Chronic sleep deprivation has been demonstrated to diminish cognitive performance, alter mood states, and concomitantly dysregulate inflammation and stress hormones. At present, however, there is little understanding of how an acute sleep deprivation may collectively affect these factors and alter functioning. The present study aimed to determine the extent to which 24-h of sleep deprivation influences inflammatory cytokines, stress hormones, cognitive processing across domains, and emotion states. To that end, 23 participants (mean age = 20.78 years, SD = 2.87) filled out clinical health questionnaires measured by the Pittsburgh Sleep Quality Index, Morningness Eveningness Questionnaire, and Center for Epidemiological Studies Depression Scale. Actigraph was worn for seven days across testing to record sleep duration. At each session participants underwent a series of measures, including saliva and blood samples for quantification of leptin, ghrelin, IL-1β, IL-6, CRP, and cortisol levels, they completed a cognitive battery using an iPad, and an emotion battery. We found that an acute sleep deprivation, limited to a 24 h period, increases negative emotion states such as anxiety, fatigue, confusion, and depression. In conjunction, sleep deprivation results in increased inflammation and decreased cortisol levels in the morning, that are accompanied by deficits in vigilance and impulsivity. Combined, these results suggest that individuals who undergo 24 h sleep deprivation will induce systemic alterations to inflammation and endocrine functioning, while concomitantly increasing negative emotions.

KEYWORDS

sleep deprivation, inflammation, emotion, cognition, cortisol, neurobehavioral functioning

Introduction

Sleep serves a critical role to human health and is commonly viewed as a restorative process. Previous work has emphasized sleep's involvement in maintaining immune functioning, metabolic conservation, psychological well being, and cognitive functioning. Despite the important role good sleep hygiene plays in health and well

being, the deleterious effects of sleep loss are commonly overlooked. Unfortunately, poor sleep health has become a normalized experience and characteristic feature of modern society. Sleep loss is characterized as insufficient sleep time, often ≤7 h of sleep per 24-h period (Altevogt and Colten, 2006). There is growing evidence to suggest that sleep disturbance and deprivation is a health concern and threat to society in the United States (Schoenborn and Adams, 2010). This is particularly prevalent among medical professionals, shift workers, flight personnel, graduate students, not to mention older adults who have sleep disturbances that go untreated. Many professional settings, however, require adequate functioning to execute complex tasks which involve but are not limited to attention, executive functioning, and the ability to regulate emotion. Studies using human and non-human animal samples have established that acute and chronic sleep deprivation leads to deleterious changes in neurobehavioral functioning, such as induced anxiety states and deficits in attention and memory, warranting further understanding of the systemic consequences sleep deprivation ensues (Tononi and Cirelli, 2006; Chee and Chuah, 2007; Kahn-Greene et al., 2007; Yang et al., 2014; Mishra et al., 2016; Kaur et al., 2017; Manchanda et al., 2018; Tomaso et al., 2021).

It has been shown that sleep deprivation can influence neurobehavioral outcomes through altering the inflammatory response and neuroendocrine stress system (Haack et al., 2007; Irwin et al., 2008; Vgontzas et al., 2013), thereby inducing symptoms such as anxiety and aggravating cognitive performance (Chee and Chuah, 2007; Kahn-Greene et al., 2007; Kahn et al., 2013). With respect to inflammation, pro-inflammatory cytokines are typically investigated, and findings suggests widespread immune changes following poor sleep. For instance, in an animal study using male Wistar rats, chronic sleep deprivation induced elevated inflammatory levels of Tumor Necrosis Factor alpha (TNF- α) and interleukin (IL)-1β, which led to anxiety-like behavior and cognitive deficits (Manchanda et al., 2018). Similarly, another study using a rat model indicated that acute sleep deprivation was linked to a global decrease of the following pro-inflammatory markers: IL-6, TNF- α, IL-1β, and Monocyte Chemoattractant Protein-1 (MCP-1) (Bajaj and Kaur, 2022). Humans comparably exhibit alterations in inflammatory markers under poor sleep conditions. There is a trend for elevations in inflammatory markers that is more readily apparent in humans relative to non-human animals. Following acute sleep deprivation in a human sample of healthy subjects, studies have shown a significant increase in proinflammatory markers such as IL-6 and IL-1β (Frey et al., 2007; Haack et al., 2007; Vgontzas et al., 2007; Sauvet et al., 2010; Abedelmalek et al., 2013). Of note, IL-6 is implicated in acute immune responses and the secretion of C-reactive protein (CRP), which also has pro-inflammatory activity and are both frequently altered following sleep deprivation.

As a testament to the consistent findings implicating IL-6 and CRP changes after sleep deprivation, a systematic review exploring the relationship between sleep deprivation and inflammatory markers in humans, solely focused on these two markers. The study yielded similar results found in non-human animal studies following chronic sleep deprivation which showed an increase in IL-6 and CRP (Irwin et al., 2016). Interestingly, these findings on acute sleep deprivation showed no effects on inflammation markers; accordingly, the author suggested that acute sleep deprivation may not influence the inflammatory signaling pathway. Nevertheless, other studies have shown elevated inflammation markers following an acute sleep deprivation (Kato et al., 2000; Shearer et al., 2001; Meier-Ewert et al., 2004; Dimitrov et al., 2006; Irwin et al., 2006, 2008; Bajaj and Kaur, 2022). Compared to IL-6, IL-1β has remained an understudied variable, with respect to sleep deprivation, despite evidence suggesting an intimate relationship between the two. In fact, Jewett and Krueger (2012) asserted that IL-1β promotes non-rapid eye movement (NREM) sleep, and therefore can induce sleepiness and fatigue, alongside decreased cognition, in both humans and non-human animals. Hence, studies have found altered levels of IL-1β in the face of sleep deprivation. In the absence of sleep deprivation, IL-1β, like IL-6, follows a diurnal pattern with lower levels throughout the day and peak levels at night. Given this, in an experimental study, one night of sleep deprivation resulted in the absence of the IL-1β nocturnal rise (Covelli et al., 1992), conversely a more recent study by Tartar et al. (2015) demonstrated elevated levels in a chronic sleep restricted group. In agreement with these results were the findings by Frey et al. (2007), suggesting that 40 h of an acute sleep deprivation induced a significant increase in IL-1β. Nevertheless, it is worth noting, there are still inconsistent results within the literature. For example, studies such as Sauvet et al. (2010) found low levels of IL-1 β after sleep deprivation. Changes in IL-1β with sleep loss is commonly studied in rat models which generally find IL-1β elevations with chronic sleep deprivation and decreased levels after total sleep deprivation (Manchanda et al., 2018; Bajaj and Kaur, 2022). Combined, elevated levels in inflammation markers would plausibly account for mood changes observed following acute sleep deprivation (Benson et al., 2017), as neuroimaging supports the finding that peripheral inflammation contributes to behavioral changes (Felger, 2018). Furthermore, the inflammatory pathway has been implicated in influencing cognitive functioning in healthy young adults and most notably, older adults. For example, CRP and IL-6 were shown to associate with reduced cognitive performance (Frydecka et al., 2015; Tegeler et al., 2016; Vintimilla et al., 2019). These changes in immune functioning in turn, are likely related to a dysregulation in cortisol release that occurs with sleep loss (Spiegel et al., 1999).

Regarding neuroendocrine functioning, rats in the aforementioned acute sleep deprivation condition exhibited a reduction in cortisol levels and an increase in both leptin and

insulin (Bajaj and Kaur, 2022). With that said, pro-inflammatory markers are known to have endocrine and metabolic effects (Agorastos et al., 2014). Once the stress system is activated, inflammatory cytokines and cortisol levels are altered, creating a chain effect once one system experiences dysregulation (Yeager et al., 2011; Jones and Gwenin, 2021). Cortisol is a primary stress biomarker that is controlled by the hypothalamic–pituitary adrenal (HPA) axis. Along with changes in inflammation, sleep and circadian rhythmicity are crucial in the regulation of the HPA axis (Guyon et al., 2014). Accordingly, sleep deprivation has been shown to have an effect on cortisol levels as the end product of HPA axis activity (Vgontzas et al., 2004; Omisade et al., 2010; Thorsley et al., 2012; Song et al., 2015; Wright et al., 2015). Whereas, experimental evidence in humans indicates that cortisol levels elevate in response to acute sleep deprivation (Balbo et al., 2010; Omisade et al., 2010), a range of studies have found that cortisol levels decrease (Weibel et al., 1995; Gronfier et al., 1997, 1998; Leproult et al., 1997; Spiegel et al., 1999, 2004a; Omisade et al., 2010; Guyon et al., 2014), which is more consistent with controlled findings in animal models (Bajaj and Kaur, 2022). To that point, endocrine hormones, ghrelin and leptin are also implicated in the stress response ensued by sleep deprivation and have regulatory effects on the HPA axis secretion of cortisol (Omisade et al., 2010). A systematic review of studies in humans concluded that leptin levels decrease following an acute stressor such as sleep deprivation (Bouillon-Minois et al., 2021), while ghrelin levels increase (Spiegel et al., 2004b; Bali and Singh Jaggi, 2016). Ostensibly, the combination of these changes explains the weight gain that occurs with poor sleep hygiene, as leptin is a hormone released from an adipocyte tissue that signals satiety (i.e., an appetite suppressing hormone) and ghrelin signals hunger to the brain (i.e., an appetite stimulating hormone). Although studies have supported the notion that sleep has an effect on neuroendocrine functioning, the results are ambiguous in the direction of these effects on cortisol, thereby limiting our general understanding of the effect on the neuroendocrine system. In other words, the research has been limited to examining one variable of the system, rather than an integrative analysis.

Despite the consequences of sleep deprivation being well-documented, the overall effects are not well-understood under varying sleep conditions, namely an acute sleep deprivation. Taken together, between non-human animal and human studies, there is widespread inconsistency regarding the impact of endocrine and immune functioning on biological markers, including the well-studied markers, IL-6 and cortisol. Furthermore, as it stands, IL-1β remains understudied in the context of acute sleep deprivation, despite evidence showing its possible implication. One of the complications in understanding the effects of poor sleep health is that the HPA axis, appetite system, and immune system are part of a complex extended endocrine-immune network where each system can modify one another. As such, there is considerable inconsistency in the literature regarding acute sleep deprivation. Consequently, additional research is needed to understand the systemic effects on health and well being. The current study examined the effects of 24 h of sleep deprivation on markers of inflammation, stress hormones, cognition, and emotion in healthy young adults with no prior history of sleep disturbance. Our goal was to provide a comprehensive multi-methodological approach that goes beyond a single marker approach and explain how disruption of the inflammatory and hormonal pathway has neurobehavioral effects. This provides the opportunity to see how the isolated effect of one night of an acute deprivation can affect multiple systems.

Materials and methods

Participants

This study was carried out according to a protocol approved by the Nova Southeastern University (NSU) Institutional Review Board. Twenty-three participants were recruited ($n = 23$; 9 females, 14 males, μ age=20.78, SD =2.87), of which all read and signed a written informed consent. Following consent, all participants completed the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Test (PSQI), Morningness Eveningness Questionnaire (MEQ), and Center for Epidemiological Studies Depression Scale (CESD) as a pre-screening tool. Exclusionary criteria included scores indicative of sleep disorder, sleep disturbance, or depression. The cutoff scores were as follows: ESS $\geq$10 (Johns, 1991), PSQI >7(Carpenter and Andrykowski, 1998; Beck et al., 2004), CESD $\geq$16 (Lewinsohn et al., 1997). Mental health status was assessed using a pre-screening questionnaire for history and current diagnosis. No participants were excluded based on these criterions. Instructions were verbally provided to refrain from caffeine intake at least 24 h before testing. Compensation of $100 Visa gift card was provided for participant's time.

Procedure

Sleep monitoring and sleep deprivation

Testing occurred between 7:00 and 9:00 a.m. and included one baseline testing session and one sleep deprivation testing session seven days later (see Figure 1). Total sleep time was calculated through the use of Actiwatch wrist monitors and Actiware software (Phillips Respironics, New Jersey). Actiwatch data were also used to verify that participants were awake during the day of sleep deprivation before they arrived to the laboratory. During the sleep deprivation session, the participants came to the laboratory at 9:00 p.m. for overnight total sleep deprivation. The participants were constantly monitored by 2–4 researchers throughout the evening. In addition, all participants wore actigraphy monitors throughout the sleep deprivation period.

During sleep deprivation, the participants were permitted to engage in non-stressful activities (e.g., talking, board games etc.,). Only water was permitted during the sleep deprivation period (no other beverages or food was permitted).

At each testing session, the participants provided saliva samples for cortisol quantification. Saliva was also collected from each participant by unstimulated passive drool for salivary cortisol analysis (participants drooled directly into a 1.5 mL microcentrifuge tube through a small sterile cylinder). Following this, 3 mLs of blood was taken through venipuncture. Blood was collected into EDTA coated tubes. Immediately after collection, the tubes were centrifuged for 10 min at 1,500 x g at 4°C. The plasma was then apportioned into 0.5 ml aliquots and stored at −20°C until analyses were conducted.

Biomarker quantification

Cortisol, CRP, Il-6, and Il-1β

Saliva tubes were placed in a freezer following participant testing and stored at −20°C. Saliva samples were run in duplicate and quantified *via* human enzyme immunoassay kits per the manufacturer's instructions (Salimetrics LLC, USA: Cat# 1-3102, RRID:AB_2801306). The samples were immediately read in a BioTek ELx800 plate reader (BioTek Instruments, Inc, USA) at 450 nm with a correction at 630 nm. All samples were within the detection ranges indicated in the immunoassay kits. The variation of sample readings was within the expected limits. Final concentrations for the biomarkers were generated by interpolation from the standard curve in μg/dL for cortisol and pg/mL for CRP, IL-6, and IL-1β.

Leptin and ghrelin

Aliquoted plasma samples were placed in a freezer following participant testing and stored at −20°C. Saliva samples were run in duplicate and quantified *via* human enzyme immunoassay kits per the manufacturer's instructions for leptin (R&D systems, Inc. USA, Cat# DLP00, RRID:AB_2783014) and ghrelin (Thermo Fisher Scientific Inc., USA, Cat# BMS2192, RRID:AB_2575470). The samples were immediately read in a BioTek ELx800 plate reader (BioTek Instruments, Inc, USA) at 450 nm. All samples were within the detection ranges indicated in the immunoassay kits. The variation of sample readings was within the expected limits. Final concentrations for the biomarkers were generated by interpolation from the standard curve in pg/mL for ghrelin and ng/mL for leptin.

Cognitive measures

Cognition testing was conducted using the automated "Cognition" test battery from Joggle Research (Joggle Research, Seattle WA). The Joggle Cognition battery consists of eight cognitive measures administered on a standard electronic tablet (Apple IPad). Total testing time is ∼20 min, which prevents participant fatigue. The cognition test battery consists of eight tasks covering a diverse set of cognitive domains (e.g., executive function, episodic memory, complex cognition, and sensorimotor speed) and are based on tests known to activate specific brain systems (Basner et al., 2015). The tests include a Psychomotor Vigilance Test (PVT), the Balloon Analog Risk Task (BART). the Digital Symbol Substitution Task (DSST), the Line Orientation Task (LOT), an Abstract Matching (AM) test, the number back (NBACK) task, a Visual Object Learning Task (VOLT), a Motor Praxis Task (MPT).

Emotion measures

State-Trait anxiety inventory (STAI-Y)

State and Trait anxiety were measured using the STAI-Y (Spielberger et al., 1983). Each scale is composed of 20 questions that tap stable aspects of an individual's general pre-disposition to experience anxiety symptoms and 20 items that focus on transitory emotional/anxious arousal. Items are rated on a four-point Likert scale. The instrument shows adequate reliability and validity (Spielberger et al., 1983).

Profile of Mood States (POMS)

The POMS is a psychometrically sound instrument that measures acute mood ("How do you feel right now") and ongoing mood ("How have you been feeling during the past week, including today") (McNair et al., 1971). The measure consists of 65 adjectives rated by participants on a five-point likert scale that asked participants about their mood in the past week. The 65 items yield six subscales: anger–hostility, confusion–bewilderment, depression–dejection, fatigue–inertia, tension–anxiety, and vigour–activity. A Total Mood Disturbance (TMD) score is also calculated based on the scores of each subscale. The range for each scale is as follows: Anger (0–48), Confusion (0–28), Depression (0–60), Fatigue (0–28), Tension (0–36), Vigour (0–32), and TMD (−32–100).

Baseline clinical health questionnaires

Depression, sleep quality, and chronotype were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), Pittsburgh Sleep Quality Index (PSQI), and the Morningness–Eveningness Questionnaire (MEQ), respectively. The CES-D is a short self-report measure shown to be reliable and valid across a variety of demographic characteristics in the general population (Radloff, 1977). This measure consists of 20 items asking questions about the frequency of symptoms associated with depression in the past week, with items rated on a four-point Likert scale. A score of 16 or greater is indicative of possible depression. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), a self-report instrument comprised of 19 items evaluating seven components of sleep over the past month: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency,

sleep disturbances, daytime dysfunction, and use of sleep medications. The seven components can be summed to yield a global score that ranges from 0 to 21. Generally, higher scores indicate poorer sleep quality, and a global score >5 is suggestive of poor sleep quality. The instrument exhibits adequate psychometric properties (Buysse et al., 1989). The Morningness–Eveningness Questionnaire (MEQ) is a widely administered self-report measure composed of 19 items used to determine if one's peak sleepiness and alertness is in the morning or in the evening (Horne and Östberg, 1976).

Statistical analyses

The effect of sleep deprivation on each of our continuous variables were individually analyzed using paired samples *t*-tests at baseline and post for participants' performance of neurocognitive measures, mood states, stress hormones, and inflammation. All reported *p*-values are two-tailed with an a priori significance level of $p < 0.05$. Effect size are reported using Cohen's d and interpreted small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) according to the recommendations set forth by Cohen (1988). Before conducting the statistical analyses, preliminary checks on statistical assumptions were verified. Using the Schapiro-Wilk test, the assumption of normal distribution was met for most, but not all variables, warranting the inclusion of non-parametric, Wilcoxon signed ranked tests in these instances. All data were analyzed using SPSS statistical package version 25 (IBM, NY, USA, RRID:SCR_016479).

Follow up correlation analyses

Given that baseline average sleep duration was moderately lower than expected (see results), this prompted us to carry out a follow-up analysis on self-report and actigraphy sleep measures in order determine if the low average sleep duration (prior to SD) had any bearing on our outcome measures. To that end, we conducted a correlation analysis to estimate the relation between total sleep time and all outcome measures. Correlation analyses were also conducted using the subjective measure of the PSQI and all outcome measures. Due to the number of correlations calculated, a Bonferroni correction was implemented. One-way ANOVAs were also conducted to determine the effect of MEQ (morning, intermediate, and evening chronotypes) on all outcome measures.

Results

Actigraphy

Although participants were instructed to sleep 8 h each night prior to sleep deprivation, sleep behavior was still objectively verified the week prior to sleep deprivation through actigraphy monitoring to ensure that the participants were not experiencing sleep loss the week prior to experimental sleep deprivation. Actigraphy recording showed that the total sleep time was only 6 h and 51 min (SD = 1.24), falling slightly below the 8 h instruction. Although, the total sleep time was in line with typical habitual sleep (Belenky et al., 2003; Rupp et al., 2009; Broussard et al., 2015) for this age group's patterns. Participants averaged an awake time of 7:32 a.m., with times ranging from 4:58 to 7:45 a.m.

Biomarkers of inflammation and hormonal function

Paired samples *t*-tests revealed that relative to baseline (mean = 66.78, SD = 37.86), IL-6 levels were significantly increased following one night of sleep deprivation (mean = 140.95, SD = 125.48), $t_{(22)} = -3.031$, $p < 0.01$, $d = 0.63$. Following sleep deprivation, CRP levels (mean = 16148.84, SD = 10423.49) were also significantly increased relative to baseline (mean = 11080.38, SD = 9848.60), $t_{(22)} = -3.412$, $p < 0.01$, $d = 0.71$. There was no effect of sleep deprivation on IL-1β, $t_{(22)} = 0.414$, $p = 0.683$, although IL-1β levels at baseline (mean = 266.51, SD = 395.41) were relatively lower to the night of deprivation (mean = 290.89, SD = 225.49). Significant differences emerged when examining morning cortisol levels at baseline *versus* post-sleep deprivation showing a reduction, some of which has been previously reported in Trivedi et al. (2017), $t_{(22)} = 5.196$, $p < 0.01$, $d = 1.083$. There were no significant changes in leptin relative to baseline $t_{(22)} = 1.149$, $p = 0.263$, nor were changes observed in ghrelin $t_{(22)} = -0.362$, $p = 0.721$. Figure 2 shows the means and SEs for the biomarkers. Assumptions of normality were violated when examining leptin and IL-1β, however non-parametric tests yielded results consistent with the paired samples *t*-test, leptin $p = 0.054$, and IL-1β $p = 0.346$.

Cognitive functioning

Table 1 shows means and standard deviations for cognition measures.

Psychomotor Vigilance Task (PVT)

Upon conducting a paired sample *t*-tests to examine performance post-sleep deprivation (mean = 316.09, SD = 74.54), it was revealed that the mean reaction time were significantly increased relative to baseline (mean = 285.98, SD = 27.79), $t_{(22)} = -2.142$, $p = 0.044$, $d = 0.447$. There were no significant differences in lapses [$t_{(22)} = 1.28$, $p = 0.214$] and false starts [$t_{(22)} = 0.058$, $p = 0.954$]. Assumptions of normality were

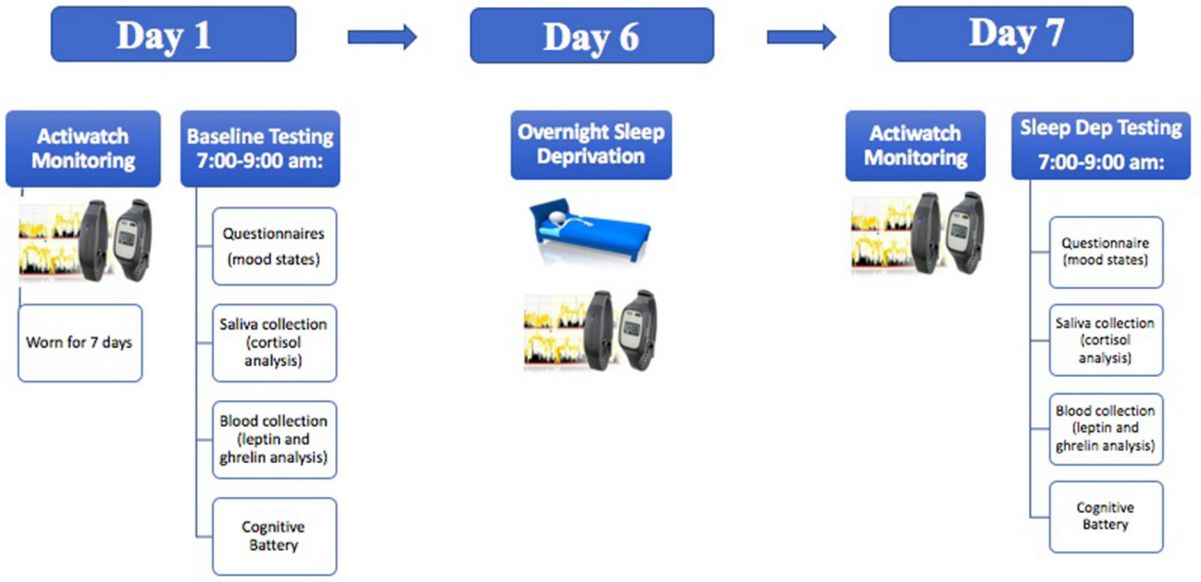

FIGURE 1
A schematic illustration demonstrating the experimental timeline.

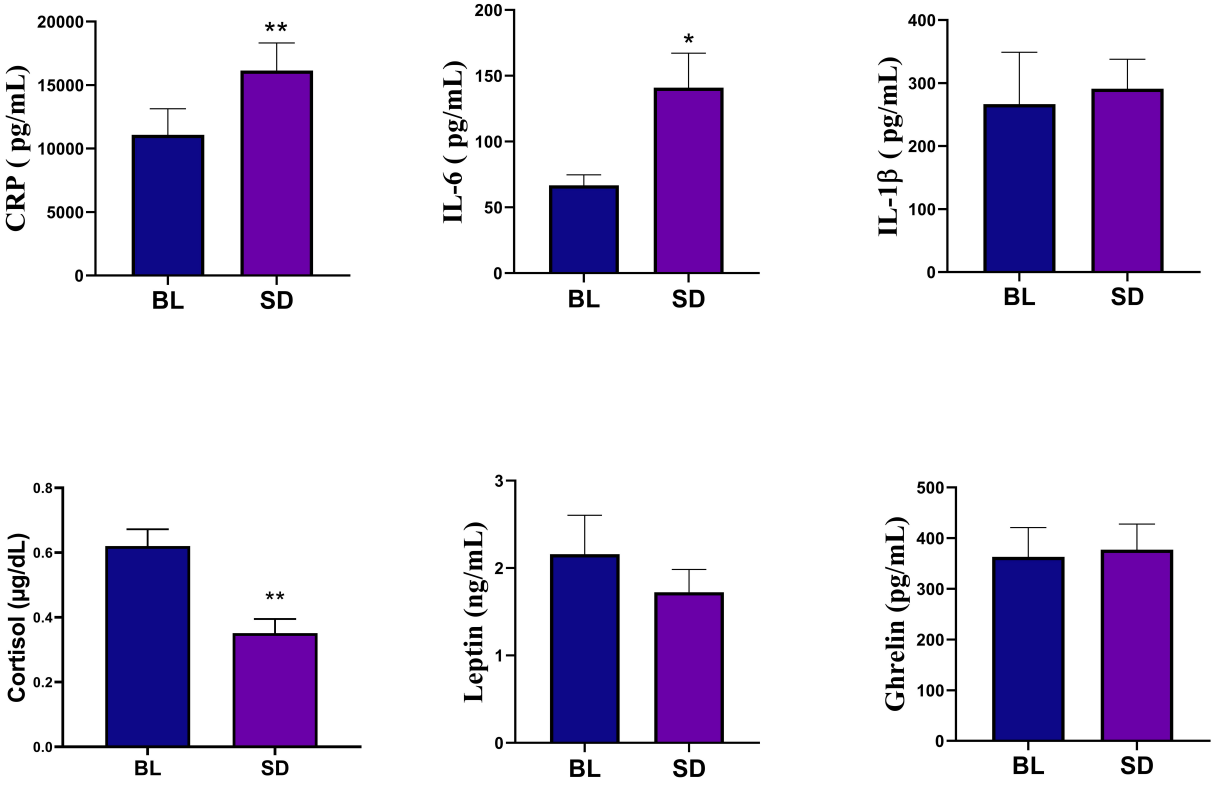

FIGURE 2
Biomarker analyses showed that compared to baseline (BL), the sleep deprivation (SD) condition significantly increased in C-Reactive Protein (CRP) and IL-6. There was also a significant decrease in cortisol levels. Errors bars represent SEM and asterisks indicate $p < 0.01$.

TABLE 1 Cognitive functioning.

		Baseline Mean ± SD	Sleep deprivation Mean ± SD	*T*-value	*P*-value	Cohen's d
PVT	RT	285.98 ± 27.79	316.09 ± 74.54	−2.142	p =0.044	0.447
	Lapses	2.83 ± 2.55	2.74 ± 3.29	1.28	$p = 0.214$	0.024
	FS	2.69 ± 2.63	2.65 ± 3.31	0.058	$p = 0.954$	0.012
BART	RT	737.76 ± 900.03	367.19 ± 327.08	2.868	$p = 0.009$	0.598
	Total pumped	136.65 ± 19.64	133.69 ± 27.70	0.640	$p \geq 0.05$	0.113
	Total ballpop	12.73 ± 2.13	12.21 ± 3.074	0.972	$p > 0.05$	0.203
DSST	RT	925.23 ± 115.21	951.99 ± 140.13	−1.44	$p > 0.05$	0.301
	CR	86.04 ± 9.71	84.47 ± 12.33	0.983	$p > 0.05$	0.205
LOT	RT	7169.69 ± 3099.28	6300.22 ± 3340	2.36	$p = 0.028$	0.491
	CR	12.43 ± 3.96	11.91 ± 4.15	0.619	$p = 0.542$	
	EC	3.41 ± 1.86	2.94 ± 2.39	0.090	$p = 0.180$	0.289
VOLT	RT	2184.93 ± 824.35	1785.52 ± 500.06	3.005	$p = 0.007$	0.627
	CR	16.08 ± 1.59	16.73 ± 1.76	−1.845	$p = 0.079$	0.385
MPT	RT	494.79 ± 78.96	459.82 ± 52.51	2.37	$p = 0.027$	0.494
NBACK	RT	615.88 ± 91.22	603.53 ± 87.38	0.471	$p > 0.05$	0.098
	CR	47.83 ± 8.25	49.91 ± 6.71	−1.44	$p >0.05$	0.302
AM	RT	2125.97 ± 1006.95	1683.74 ± 501.38	2.85	$p = 0.009$	0.594
	CR	16.96 ± 2.74	17.21 ± 3.32	−0.371	$p = 0.714$	0.077

This table demonstrates the means, standard deviations, p-values, and effects sizes for pre- and post-tests on cognitive measures using the computerized Joggle tests.
RT, Reaction time; CR, Correct responses; FS, False starts; Total pumped, Total ballons pumped; Total ballpop, Total balloons popped; and EC, excess clicks.

violated when examining mean reaction time and false start, however non-parametric tests yielded results consistent with the paired samples *t*-test, mean reaction time $p = 0.024$, and false start $p = 0.774$.

Balloon Analog Risk Task (BART)

Upon conducting a paired sample *t*-tests to examine performance on the Balloon Analog Risk Task (BART) post-sleep deprivation (mean = 367.19, SD = 327.08), it was revealed that the mean reaction time were significantly decreased relative to baseline (mean = 737.76, SD = 900.03), $t_{(22)} = 2.868$, $p = 0.009$, $d = 0.598$. There were no significant differences in total balloons pumped and popped. Assumptions of normality were violated when examining mean reaction time, however non-parametric tests yielded results consistent with the paired samples *t*-test, mean reaction time $p < 0.001$.

Digital Symbol Substitution Task (DSST)

Performance on the Digital Symbol Substitution Task was examined post-sleep deprivation using a paired samples *t*-test. Results yielded no significant difference in number of correct responses or reaction time. Assumptions of normality were violated when examining correct responses, however non-parametric tests yielded results consistent with the paired samples *t*-test, correct responses $p = 0.425$.

Line Orientation Task

Performance on the Line Orientation Task (LOT) was examined post-sleep deprivation using a paired samples *t*-test. Results revealed that mean reaction time was significantly decreased following one night of sleep deprivation (mean = 6300.22, SD = 3340) relative to baseline (mean = 7169.69, SD = 3099.28), $t_{(22)} = 2.36$, $p = 0.028$, $d = 0.491$. There were no significant changes in number of correct responses, $t_{(22)} = 0.619$, $p = 0.542$ and mean excess clicks, $t_{(22)} = 0.090$, $p = 0.180$. Assumptions of normality were violated when examining mean reaction time, however non-parametric tests yielded results consistent with the paired samples *t*-test, mean reaction time $p = 0.008$.

Visual Object Learning Task

Upon conducting a paired sample *t*-tests to examine performance on the Visual Objet Learning Task (VOLT) post-sleep deprivation (mean = 1785.52.19, SD = 500.06), it was revealed that the mean reaction time were significantly decreased relative to baseline (mean = 2184.93, SD = 824.35), $t_{(22)} = 3.005$, $p = 0.007$, $d = 0.627$. There was no significant difference in the number of correct responses $t_{(22)} = -1.845$, $p = 0.079$. Assumptions of normality were violated when examining mean reaction time, however non-parametric tests yielded results consistent with the paired samples *t*-test, mean reaction time $p = 0.003$.

Motor Praxis Task

Performance on the Motor Praxis Task (MPT) was examined post-sleep deprivation using a paired samples t-test. Results yielded a significant reduction in mean reaction time $t_{(22)} = 2.37$, $p = 0.027$, $d = 0.494$.

NBACK

There were no significant differences on the NBack (all p's > 0.05).

Abstract Matching (AM)

Upon conducting a paired sample t-tests to examine performance on Abstract Matching (AM) post-sleep deprivation (mean = 1683.74, SD = 501.38), it was revealed that the mean reaction time were significantly decreased relative to baseline (mean = 2125.97, SD = 1006.95), $t_{(22)} = 2.85$, $p = 0.009$, $d = 0.594$. There was no significant difference in the number of correct responses $t_{(22)} = -0.371$, $p = 0.714$.

Emotion measures

The results of the Profile of Mood States (POMS) data are shown in Figure 3. POMS measures showed that compared to baseline, there was a significant increase in tension [$t_{(22)} = -4.09$, $p < 0.001$, $d = 0.854$], depression [$t_{(22)} = -2.355$, $p = 0.028$, $d = 0.491$], anger [$t_{(22)} = -3.99$, $p < 0.001$, $d = 0.831$], fatigue [$t_{(21)} = -5.86$, $p < 0.001$, $d = 1.25$], confusion [$t_{(22)} = -4.24$, $p < 0.001$, $d = 0.89$], and TMD [$t_{(20)} = -5.49$, $p < 0.001$, $d = 1.20$]. There was a significant decrease in vigor, [$t_{(22)} = 4.81$, $p < 0.001$, $d = 0.99$]. Compared to baseline (mean = 32.35, SD = 7.91), there was a significant increase in state anxiety (see Figure 4) following sleep deprivation (mean = 42.78, SD = 8.90), $t_{(22)} = -5.012$, $p < 0.001$, $d = 1.045$.

Associations between sleep and outcome measures

Pearson correlation analysis revealed no significant correlation between self-reported or actigraphy-measured sleep and the outcome measures. This indicates that prior sleep behavior, whether normal (TST 7–9 h) or dysfunctional, did not have any bearing on the biochemical measures taken at baseline or after sleep deprivation. A one-way ANOVA revealed no effect of MEQ (morning, intermediate, and evening chronotypes) on outcome measures.

Discussion

The current findings demonstrate that one night of acute sleep deprivation altered circulating markers of systemic inflammation, cortisol, emotion, and cognitive performance. Specifically, we identified a significant decrease in cortisol levels, accompanied by an increase in inflammatory markers, CRP and IL-6, which is consistent with prior findings suggesting sleep modulates immune and endocrine functioning (Leproult et al., 1997; Spiegel et al., 1999, 2004a; Omisade et al., 2010; Guyon et al., 2014; Minkel et al., 2014; Wright et al., 2015; Atrooz and Salim, 2020). Although there were no significant changes in either ghrelin or leptin, there was a trend for leptin to decrease following sleep deprivation, while ghrelin trended towards an increase. In general, changes to leptin and ghrelin are related to increased metabolic demands of sleep deprivation. We also found an increase in negative mood ratings and impulsivity, whereas vigilance and sensorimotor speed were decreased. We did not find any effects of sleep deprivation on executive functioning, spatial learning/memory, spatial orientation, abstraction, complex scanning, or concept formation.

While cognitive deficits have been well-documented as a consequence of sleep deprivation (Kahn et al., 2013; Short and Louca, 2015), the present results support the argument that there is a threshold of sleep loss that needs to be reached before higher order cognitive domains are affected (e.g., executive functioning). This also explains why executive functioning is typically impaired with chronic sleep loss but not always with acute sleep loss (Binks et al., 1999; Quigley et al., 2000; Sagaspe et al., 2003, 2006; Drummond et al., 2006; Tucker et al., 2010). Nevertheless, there are mixed findings on the effects of acute sleep deprivation on cognitive performance (Nilsson et al., 2005; Lim and Dinges, 2010; Killgore and Weber, 2014; Chua et al., 2017; Kusztor et al., 2019), and specific cognitive domains are still disputed. An alternative explanation for the cognitive results is that any decreases induced by sleep deprivation may have been masked by practice effects. Often reaction time on computerized neurocognitive tasks have shown to be increased on post measures, due to familiarity with the task and learning effects (Calamia et al., 2012). Practice effects would elucidate the observable patterns of reduced reaction time across higher order cognitive tasks in our study, such as LOT, AM, NBACK, and VOLT, while not being prone to increased error. Seen through this light, impulsivity, vigilance, and sensorimotor speed may be less susceptible to practice effects under acute sleep deprivation. Hence, studies have suggested that practice effects are minimally related to cognitive domains such as attention (Duff et al., 2012) and that tests within cognitive domains may be less or more resistant to practice (Bartels et al., 2010).

Despite studies suggesting that acute sleep deprivation is not sufficient to initiate inflammatory signaling that can be translated into increased systemic inflammation (Irwin et al., 2016), studies such as ours and others have yielded contrasting results (Kato et al., 2000; Shearer et al., 2001; Meier-Ewert et al., 2004; Dimitrov et al., 2006; Irwin et al., 2006, 2008). Of note, the effect size for CRP was moderately strong and slightly better than those found for Il-6, as seen in Figure 2. These results may suggest that an acute sleep deprivation of one night can

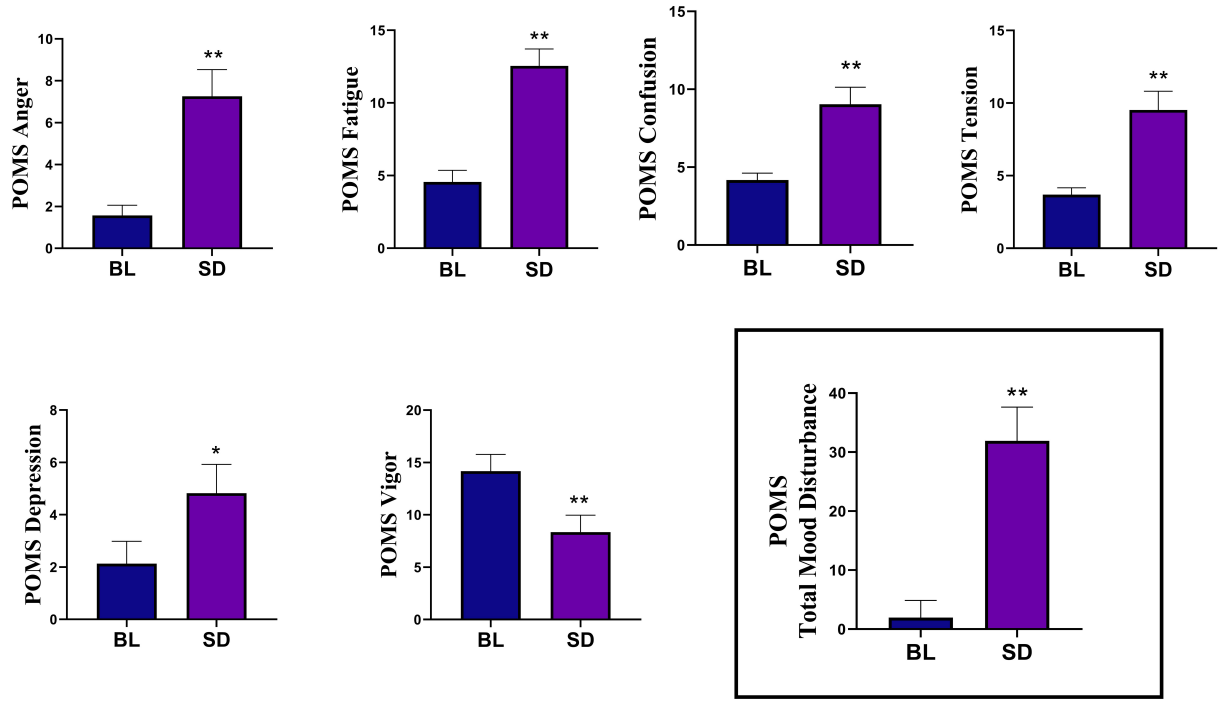

FIGURE 3
The results of the Profile of Mood States (POMS) measures showed that compared to baseline (BL), sleep deprivation (SD) significantly increased in tension, depression, anger, fatigue, and confusion. There was a significant decrease in vigor. The Total Mood Disturbance composite score was also significantly increased. Errors bars represent SEM, asterisks indicates $p < 0.05$, and double asterisks indicate $p < 0.01$.

induce an increase in toll-like receptor (TLR)−4 production of inflammatory cytokines (Irwin et al., 2006), through activation of the control pathway in the inflammatory signaling cascade, nuclear factor kappa B (NF-κB) (Irwin et al., 2008). It is worth noting, activation of NF-κB leads to subsequent upregulation of inflammatory response genes, as well as the master circadian clock regulator which has an interrelated regulatory network with the HPA axis, modulating glucocorticoid release (Kalsbeek et al., 2006; Oster et al., 2006).

To this end, the reduced cortisol levels following acute sleep deprivation reflect the altered state of the HPA axis, as the morning cortisol peak was not apparent. Few studies have shown similar outcomes in dampened or reduced morning cortisol awakening response (Leproult et al., 1997; Spiegel et al., 1999, 2004a; Omisade et al., 2010; Guyon et al., 2014). Interestingly, symptoms of anxiety associate with blunted cortisol levels in healthy adults across age and sex (Brooks and Robles, 2009; de Rooij et al., 2010; Crișan et al., 2016). This supports the idea that disrupted HPA regulation in response to an acute stress can contribute to altered behavioral and mental health outcomes (Kinlein et al., 2015; Fiksdal et al., 2019). HPA axis dysregulation presented a state effect in response to the physiological stress of sleep deprivation, as evidenced by an increase on the STAI. Considering we did not evaluate cortisol at different time points following deprivation, we were

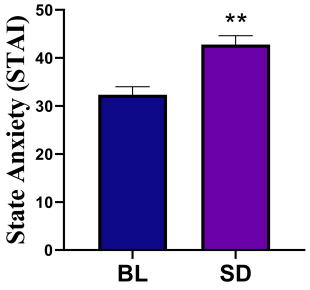

FIGURE 4
Compared to baseline (BL) there was a significant increase in state anxiety following sleep deprivation. Errors bars represent SEM and double asterisks indicate $p < 0.01$.

unable to determine if the circadian modulation would have resulted in an elevation in cortisol during the evening as seen in other studies as a demonstration of HPA axis recovery (Leproult et al., 1997; Spiegel et al., 2004a; Omisade et al., 2010). Nevertheless, our findings are critical in showing that sleep deprivation decreases the HPA axis activity. This can result in dysregulation of the circadian rhythm in the peripheral CLOCK through the subsequent release of glucocorticoids. Herein, the HPA pathway is forced to reconfigure its responsiveness under

stress due to a possible increase in the negative feedback regulation (Redwine et al., 2000). The effects on peripheral CLOCKS are known to influence the expression of clock related genes which regulates emotions and inflammatory reactions such as the Per2. In both interactions between the CLOCK system and inflammation, as well as the HPA axis, physiologic concentrations of glucocorticoids are necessary for adequate functioning. Yet, one night of sleep deprivation, although not persistent, can induce stress that disrupts the circadian fluctuation produced by the CLOCK system, thereby altering many systemic factors.

The deleterious effects of sleep deprivation lend themselves to widespread altered immune functioning, along with dysregulated cortisol levels which can impact mood (Benson et al., 2017; Bollen et al., 2017; Felger, 2018) and cognition (Frydecka et al., 2015; Tegeler et al., 2016; Vintimilla et al., 2019). Decreased cortisol awakening response (CAR) has been related to the vulnerability of depression (Kuehner et al., 2007). In agreement, the current study found increased depressive symptomatology as well as decreased morning cortisol levels after sleep deprivation. Specifically, participants demonstrated negative mood changes in vigor, tension, depression, anxiety, anger, confusion, and fatigue, which parallels previous findings. Endeavors to overcome the negative effects induced by sleep deprivation during neurocognitive testing becomes arduous, like engaging in daily life activities when sleep deprived. Among the cognitive domains reported to have deficits from sleep deprivation, vigilant attention remains the most prominent which was corroborated in our study by the PVT (Dinges et al., 1997; Doran et al., 2001; Sagaspe et al., 2003; Lim and Dinges, 2008) signifying significantly slower speed. In line with these results, were slower sensorimotor speed in MPT performance. Yet interestingly, lapses and false starts on the PVT were similar between baseline and post-sleep deprivation. In agreement with previous work (Saksvik-Lehouillier et al., 2020), we also found reduced reaction time on the BART which reflects deficits in impulsivity after sleep deprivation. Although, there was no difference on the total balloons pumped or popped suggesting risk decision making remained intact, which contradicts the literature. Reduced reaction time was observed across all other cognitive measures (except PVT). As previously mentioned, these results may have altered due to practice effects or reflective of impulsivity as it has been previously observed following sleep deprivation, due to a speed-accuracy tradeoff (Saksvik-Lehouillier et al., 2020).

The current study provides a unique multi-methodological approach to investigating a 24-h acute sleep deprivation and presents an integrative systems perspective. Nevertheless, there are limitations to this study that are worth mentioning as they provide uncertainty to the results. Caffeine has pro- and anti-inflammatory effects, as well as effects on cognition and mood. Therefore, studies on sleep deprivation should instruct subjects to avoid caffeine. However, despite our initial instructions, there were no objective data collected to ensure participants adhered to this request. Furthermore, caffeine withdrawal could alter the results for subjects that are accustomed to their daily caffeine intake. Caffeine withdrawal symptoms can appear very early after stopped use and last for 2–9 days (Juliano and Griffiths, 2004). These symptoms include, but are not limited to, fatigue, decreased energy, decreased alertness, depressed mood, difficulty concentrating, and irritability. The emotion measures utilized also pose a limitation in identifying whether changes in negative affect are clinically meaningful. Currently, the literature on the POMS lacks anchor-based approaches to identify clinically relevant changes on the scales; therefore, mean improvement scores are generally relied upon (Dworkin et al., 2008). With respect to cortisol measurement, participants individual morning peak were not accounted for when collecting samples, which stems caution in interpreting these results. Future studies would benefit by tailoring the collection time to the individuals usual wake time, to ensure obtaining the morning cortisol peak. Lastly, given the small sample size and expected trends seen in leptin and ghrelin, it is plausible that the study did not yield sufficient power to show these effects. On the otherhand, IL-1β may require sustained levels of deprivation as results did not reveal any pattern. To further derive at a consensus in the literature, it is recommended that these findings are validated in a larger cohort. Moreover, the current study should motivate further investigation into the effects of sleep deprivation using incremental variances of sleep deprivation, ranging from 24 to 48 h., to determine if there are critical limits within sleep deprivation with marked deficits. Future studies may also use incremental measures of cortisol following sleep deprivation to better understand the potential HPA axis recovery period following sleep deprivation.

Combined, these findings advance the understanding of the deleterious effects of an acute sleep deprivation by demonstrating system-wide changes in humans. Given the association between these systemic alterations and age-related pathology, these findings are particularly relevant for understanding the potential health costs of those in careers that commonly involve sleep deprivation, as well as those with untreated or undetected sleep disturbances. To combat these issues, treatments are able to target sleep behaviors which may modify outcomes such as inflammation and improve overall health (Irwin et al., 2014).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Nova Southeastern University Institutional

Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JT and AF designed the study. JT, ML, and LH carried out experimental procedures and participant testing. MC and KT carried out data analyses. KT drafted the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abedelmalek, S., Chtourou, H., Aloui, A., Aouichaoui, C., Souissi, N., and Tabka, Z. (2013). Effect of time of day and partial sleep deprivation on plasma concentrations of IL-6 during a short-term maximal performance. *Eur. J. Appl. Physiol.* 113, 241–248. doi: 10.1007/s00421-012-2432-7

Agorastos, A., Hauger, R. L., Barkauskas, D. A., Moeller-Bertram, T., Clopton, P. L., Haji, U., et al. (2014). Circadian rhythmicity, variability and correlation of interleukin-6 levels in plasma and cerebrospinal fluid of healthy men. *Psychoneuroendocrinology* 44, 71–82. doi: 10.1016/j.psyneuen.2014.02.020

Altevogt, B. M., and Colten, H. R. (2006). *Sleep Disorders and Sleep Deprivation: an Unmet Public Health Problem*. Washington, DC: National Academies Press.

Atrooz, F., and Salim, S. (2020). Sleep deprivation, oxidative stress and inflammation. *Adv. Protein Chem. Struct. Biol.* 119, 309–336. doi: 10.1016/bs.apcsb.2019.03.001

Bajaj, P., and Kaur, G. (2022). Acute sleep deprivation-induced anxiety and disruption of hypothalamic cell survival and plasticity: a mechanistic study of protection by butanol extract of *Tinospora cordifolia*. *Neurochem. Res.* 47, 1692–1706. doi: 10.1007/s11064-022-03562-8

Balbo, M., Leproult, R., and Van Cauter, E. (2010). Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. *Int. J. Endocrinol.* 2010:759234. doi: 10.1155/2010/759234

Bali, A., and Singh Jaggi, A. (2016). An integrative review on role and mechanisms of ghrelin in stress, anxiety and depression. *Curr. Drug Targets* 17, 495–507. doi: 10.2174/1389450116666150518095650

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., and Ehrenreich, H. (2010). Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC Neurosci.* 11, 1–12. doi: 10.1186/1471-2202-11-118

Basner, M., Savitt, A., Moore, T. M., Port, A. M., McGuire, S., Ecker, A. J., et al. (2015). Development and validation of the cognition test battery for spaceflight. *Aerosp. Med. Hum. Perform.* 86, 942–952. doi: 10.3357/AMHP.4343.2015

Beck, S. L., Schwartz, A. L., Towsley, G., Dudley, W., and Barsevick, A. (2004). Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. *J. Pain Symptom Manage.* 27, 140–148. doi: 10.1016/j.jpainsymman.2003.12.002

Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., et al. (2003). Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J. Sleep Res.* 12, 1–12. doi: 10.1046/j.1365-2869.2003.00337.x

Benson, S., Brinkhoff, A., Lueg, L., Roderigo, T., Kribben, A., Wilde, B., et al. (2017). Effects of acute systemic inflammation on the interplay between sad mood and affective cognition. *Transl. Psychiatry* 7, 1–10. doi: 10.1038/s41398-017-0043-0

Binks, P. G., Waters, W. F., and Hurry, M. (1999). Short-term total sleep deprivations does not selectively impair higher cortical functioning. *Sleep* 22, 328–334. doi: 10.1093/sleep/22.3.328

Bollen, J., Trick, L., Llewellyn, D., and Dickens, C. (2017). The effects of acute inflammation on cognitive functioning and emotional processing in humans: a systematic review of experimental studies. *J. Psychosom. Res.* 94, 47–55. doi: 10.1016/j.jpsychores.2017.01.002

Bouillon-Minois, J.-B., Trousselard, M., Thivel, D., Benson, A. C., Schmidt, J., Moustafa, F., et al. (2021). Leptin as a biomarker of stress: a systematic review and meta-analysis. *Nutrients* 13:3350. doi: 10.3390/nu13103350

Brooks, K. P., and Robles, T. F. (2009). Recent depressive and anxious symptoms predict cortisol responses to stress in men. *Psychoneuroendocrinology* 34, 1041–1049. doi: 10.1016/j.psyneuen.2009.02.005

Broussard, J. L., Chapotot, F., Abraham, V., Day, A., Delebecque, F., Whitmore, H. R., et al. (2015). Sleep restriction increases free fatty acids in healthy men. *Diabetologia* 58, 791–798. doi: 10.1007/s00125-015-3500-4

Buysse, D. J., Reynolds, I. I. I., C. F., Monk, T. H., Berman, S. R., and Kupfer, D. J. (1989). The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28, 193–213. doi: 10.1016/0165-1781(89)90047-4

Calamia, M., Markon, K., and Tranel, D. (2012). Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. *Clin. Neuropsychol.* 26, 543–570. doi: 10.1080/13854046.2012.680913

Carpenter, J. S., and Andrykowski, M. A. (1998). Psychometric evaluation of the Pittsburgh sleep quality index. *J. Psychosom. Res.* 45, 5–13. doi: 10.1016/S0022-3999(97)00298-5

Chee, M. W., and Chuah, Y. L. (2007). Functional neuroimaging and behavioral correlates of capacity decline in visual short-term memory after sleep deprivation. *Proc. Natl. Acad. Sci. U. S. A.* 104, 9487–9492. doi: 10.1073/pnas.0610712104

Chua, E. C.-P., Fang, E., and Gooley, J. J. (2017). Effects of total sleep deprivation on divided attention performance. *PLoS ONE* 12:e0187098. doi: 10.1371/journal.pone.0187098

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Earlbaum Associates.

Covelli, V., Massari, F., Fallacara, C., Munno, I., Jirillo, E., Savastano, S., et al. (1992). Interleukin-ibeta and beta-endorphin orcadian rhythms are inversely related in normal and stress-altered sleep. *Int. J. Neurosci.* 63, 299–305. doi: 10.3109/00207459208987204

Crișan, L. G., Vulturar, R., Miclea, M., and Miu, A. C. (2016). Reactivity to social stress in subclinical social anxiety: emotional experience, cognitive appraisals, behavior, and physiology. *Front. Psychiatry* 7:5. doi: 10.3389/fpsyt.2016.00005

de Rooij, S. R., Schene, A. H., Phillips, D. I., and Roseboom, T. J. (2010). Depression and anxiety: associations with biological and perceived stress reactivity to a psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology* 35, 866–877. doi: 10.1016/j.psyneuen.2009.11.011

Dimitrov, S., Lange, T., Benedict, C., Nowell, M. A., Jones, S. A., Scheller, J., et al. (2006). Sleep enhances IL-6 trans-signaling in humans. *FASEB J.* 20, 2174–2176. doi: 10.1096/fj.06-5754fje

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep* 20, 267–277.

Doran, S. M., Van Dongen, H. P., and Dinges, D. F. (2001). Sustained attention performance during sleep deprivation: evidence of state instability. *Arch. Ital. Biol.* 139, 253–267. doi: 10.4449/aib.v139i3.503

Drummond, S. P., Paulus, M. P., and Tapert, S. F. (2006). Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. *J. Sleep Res.* 15, 261–265. doi: 10.1111/j.1365-2869.2006.00535.x

Duff, K., Callister, C., Dennett, K., and Tometich, D. (2012). Practice effects: a unique cognitive variable. *Clin. Neuropsychol.* 26, 1117–1127. doi: 10.1080/13854046.2012.722685

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., et al. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J. Pain* 9, 105–121. doi: 10.1016/j.jpain.2007.09.005

Felger, J. C. (2018). Imaging the role of inflammation in mood and anxiety-related disorders. *Curr. Neuropharmacol.* 16, 533–558. doi: 10.2174/1570159X15666171123201142

Fiksdal, A., Hanlin, L., Kuras, Y., Gianferante, D., Chen, X., Thoma, M. V., et al. (2019). Associations between symptoms of depression and anxiety and cortisol responses to and recovery from acute stress. *Psychoneuroendocrinology* 102, 44–52. doi: 10.1016/j.psyneuen.2018.11.035

Frey, D. J., Fleshner, M., and Wright, Jr, K. P. (2007). The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. *Brain Behav. Immun.* 21, 1050–1057. doi: 10.1016/j.bbi.2007.04.003

Frydecka, D., Misiak, B., Pawlak-Adamska, E., Karabon, L., Tomkiewicz, A., Sedlaczek, P., et al. (2015). Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. *Eur. Arch. Psychiatry Clin. Neurosci.* 265, 449–459. doi: 10.1007/s00406-014-0533-5

Gronfier, C., Chapotot, F., Weibel, L., Jouny, C., Piquard, F., and Brandenberger, G. (1998). Pulsatile cortisol secretion and EEG delta waves are controlled by two independent but synchronized generators. *Am. J. Physiol. Endocrinol. Metab.* 275, E94–E100. doi: 10.1152/ajpendo.1998.275.1.E94

Gronfier, C., Luthringer, R., Follenius, M., Schaltenbrand, N., Macher, J., Muzet, A., et al. (1997). Temporal relationships between pulsatile cortisol secretion and electroencephalographic activity during sleep in man. *Electroencephalogr. Clin. Neurophysiol.* 103, 405–408. doi: 10.1016/S0013-4694(97)00013-1

Guyon, A., Balbo, M., Morselli, L., Tasali, E., Leproult, R., L'hermite-Balériaux, M., et al. (2014). Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. *J. Clin. Endocrinol. Metab.* 99, 2861–2868. doi: 10.1210/jc.2013-4254

Haack, M., Sanchez, E., and Mullington, J. M. (2007). Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 30, 1145–1152. doi: 10.1093/sleep/30.9.1145

Horne, J. A., and Östberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int. J. Chronobiol.* 4, 97–110.

Irwin, M. R., Olmstead, R., Carrillo, C., Sadeghi, N., Breen, E. C., Witarama, T., et al. (2014). Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. *Sleep* 37, 1543–1552. doi: 10.5665/sleep.4008

Irwin, M. R., Olmstead, R., and Carroll, J. E. (2016). Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol. Psychiatry* 80, 40–52. doi: 10.1016/j.biopsych.2015.05.014

Irwin, M. R., Wang, M., Campomayor, C. O., Collado-Hidalgo, A., and Cole, S. (2006). Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch. Intern. Med.* 166, 1756–1762. doi: 10.1001/archinte.166.16.1756

Irwin, M. R., Wang, M., Ribeiro, D., Cho, H. J., Olmstead, R., Breen, E. C., et al. (2008). Sleep loss activates cellular inflammatory signaling. *Biol. Psychiatry* 64, 538–540. doi: 10.1016/j.biopsych.2008.05.004

Jewett, K. A., and Krueger, J. M. (2012). Humoral sleep regulation; interleukin-1 and tumor necrosis factor. *Vitam. Horm.* 89, 241–257. doi: 10.1016/B978-0-12-394623-2.00013-5

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14, 540–545. doi: 10.1093/sleep/14.6.540

Jones, C., and Gwenin, C. (2021). Cortisol level dysregulation and its prevalence—is it nature's alarm clock? *Physiol. Rep.* 8:e14644. doi: 10.14814/phy2.14644

Juliano, L. M., and Griffiths, R. R. (2004). A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology* 176, 1–29. doi: 10.1007/s00213-004-2000-x

Kahn, M., Sheppes, G., and Sadeh, A. (2013). Sleep and emotions: bidirectional links and underlying mechanisms. *Int. J. Psychophysiol.* 89, 218–228. doi: 10.1016/j.ijpsycho.2013.05.010

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., and Killgore, W. D. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med.* 8, 215–221. doi: 10.1016/j.sleep.2006.08.007

Kalsbeek, A., Palm, I., La Fleur, S., Scheer, F., Perreau-Lenz, S., Ruiter, M., et al. (2006). SCN outputs and the hypothalamic balance of life. *J. Biol. Rhythms* 21, 458–469. doi: 10.1177/0748730406293854

Kato, M., Phillips, B. G., Sigurdsson, G., Narkiewicz, K., Pesek, C. A., and Somers, V. K. (2000). Effects of sleep deprivation on neural circulatory control. *Hypertension* 35, 1173–1175. doi: 10.1161/01.HYP.35.5.1173

Kaur, T., Singh, H., Mishra, R., Manchanda, S., Gupta, M., Saini, V., et al. (2017). Withania somnifera as a potential anxiolytic and immunomodulatory agent in acute sleep deprived female Wistar rats. *Mol. Cell. Biochem.* 427, 91–101. doi: 10.1007/s11010-016-2900-1

Killgore, W. D., and Weber, M. (2014). "Sleep deprivation and cognitive performance," in *Sleep Deprivation and Disease,* ed M. T. Bianchi (NewYork, NY: Springer), 209–229. doi: 10.1007/978-1-4614-9087-6_16

Kinlein, S. A., Wilson, C. D., and Karatsoreos, I. N. (2015). Dysregulated hypothalamic–pituitary–adrenal axis function contributes to altered endocrine and neurobehavioral responses to acute stress. *Front. Psychiatry* 6:31. doi: 10.3389/fpsyt.2015.00031

Kuehner, C., Holzhauer, S., and Huffziger, S. (2007). Decreased cortisol response to awakening is associated with cognitive vulnerability to depression in a nonclinical sample of young adults. *Psychoneuroendocrinology* 32, 199–209. doi: 10.1016/j.psyneuen.2006.12.007

Kusztor, A., Raud, L., Juel, B. E., Nilsen, A. S., Storm, J. F., and Huster, R. J. (2019). Sleep deprivation differentially affects subcomponents of cognitive control. *Sleep* 42:zsz016. doi: 10.1093/sleep/zsz016

Leproult, R., Copinschi, G., Buxton, O., and Van Cauter, E. (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 20, 865–870.

Lewinsohn, P. M., Seeley, J. R., Roberts, R. E., and Allen, N. B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol. Aging* 12:277. doi: 10.1037/0882-7974.12.2.277

Lim, J., and Dinges, D. F. (2008). Sleep deprivation and vigilant attention. *Ann. N. Y. Acad. Sci.* 1129, 305–322. doi: 10.1196/annals.1417.002

Lim, J., and Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136, 375–389. doi: 10.1037/a0018883

Manchanda, S., Singh, H., Kaur, T., and Kaur, G. (2018). Low-grade neuroinflammation due to chronic sleep deprivation results in anxiety and learning and memory impairments. *Mol. Cell. Biochem.* 449, 63–72. doi: 10.1007/s11010-018-3343-7

McNair, D. M., Lorr, M., and Droppleman, L. F. (1971). *Manual Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service.

Meier-Ewert, H. K., Ridker, P. M., Rifai, N., Regan, M. M., Price, N. J., Dinges, D. F., et al. (2004). Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J. Am. Coll. Cardiol.* 43, 678–683. doi: 10.1016/j.jacc.2003.07.050

Minkel, J., Moreta, M., Muto, J., Htaik, O., Jones, C., Basner, M., et al. (2014). Sleep deprivation potentiates HPA axis stress reactivity in healthy adults. *Health Psychol.* 33, 1430–1434. doi: 10.1037/a0034219

Mishra, R., Manchanda, S., Gupta, M., Kaur, T., Saini, V., Sharma, A., et al. (2016). Tinospora cordifolia ameliorates anxiety-like behavior and improves cognitive functions in acute sleep deprived rats. *Sci. Rep.* 6, 1–15. doi: 10.1038/srep25564

Nilsson, J. P., Söderström, M., Karlsson, A. U., Lekander, M., Åkerstedt, T., Lindroth, N. E., et al. (2005). Less effective executive functioning after one night's sleep deprivation. *J. Sleep Res.* 14, 1–6. doi: 10.1111/j.1365-2869.2005.00442.x

Omisade, A., Buxton, O. M., and Rusak, B. (2010). Impact of acute sleep restriction on cortisol and leptin levels in young women. *Physiol. Behav.* 99, 651–656. doi: 10.1016/j.physbeh.2010.01.028

Oster, H., Damerow, S., Kiessling, S., Jakubcakova, V., Abraham, D., Tian, J., et al. (2006). The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. *Cell Metab.* 4, 163–173. doi: 10.1016/j.cmet.2006.07.002

Quigley, N., Green, J., Morgan, D., Idzikowski, C., and King, D. (2000). The effect of sleep deprivation on memory and psychomotor function in healthy volunteers. *Hum. Psychopharmacol. Clin. Exp.* 15, 171–177. doi: 10.1002/(SICI)1099-1077(200004)15:3<171::AID-HUP155>3.0.CO;2-D

Radloff, L. S. (1977). The CES-D scale: a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1, 385–401. doi: 10.1177/014662167700100306

Redwine, L., Hauger, R. L., Gillin, J. C., and Irwin, M. (2000). Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *J. Clin. Endocrinol. Metab.* 85, 3597–3603. doi: 10.1210/jc.85.10.3597

Rupp, T. L., Wesensten, N. J., Bliese, P. D., and Balkin, T. J. (2009). Banking sleep: realization of benefits during subsequent sleep restriction and recovery. *Sleep* 32, 311–321. doi: 10.1093/sleep/32.3.311

Sagaspe, P., Charles, A., Taillard, J., Bioulac, B., and Philip, P. (2003). Inhibition et mémoire de travail: effet d'une privation aiguë de sommeil sur une tâche de génération aléatoire. *Can. J. Exp. Psychol. Rev. Can. Psychol. Exp.* 57, 265–273. doi: 10.1037/h0087430

Sagaspe, P., Sanchez-Ortuno, M., Charles, A., Taillard, J., Valtat, C., Bioulac, B., et al. (2006). Effects of sleep deprivation on color-word, emotional, and specific stroop interference and on self-reported anxiety. *Brain Cogn.* 60, 76–87. doi: 10.1016/j.bandc.2005.10.001

Saksvik-Lehouillier, I., Saksvik, S. B., Dahlberg, J., Tanum, T. K., Ringen, H., Karlsen, H. R., et al. (2020). Mild to moderate partial sleep deprivation is associated with increased impulsivity and decreased positive affect in young adults. *Sleep* 43:zsaa078. doi: 10.1093/sleep/zsaa078

Sauvet, F., Leftheriotis, G., Gomez-Merino, D., Langrume, C., Drogou, C., Van Beers, P., et al. (2010). Effect of acute sleep deprivation on vascular function in healthy subjects. *J. Appl. Physiol.* 108, 68–75. doi: 10.1152/japplphysiol.00851.2009

Schoenborn, C. A., and Adams, P. E. (2010). Health behaviors of adults: United States, 2005–2007. *Vital Health Stat.* 10, 1–132.

Shearer, W. T., Reuben, J. M., Mullington, J. M., Price, N. J., Lee, B.-N., Smith, E. B., et al. (2001). Soluble TNF-α receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J. Allergy Clin. Immunol.* 107, 165–170. doi: 10.1067/mai.2001.112270

Short, M. A., and Louca, M. (2015). Sleep deprivation leads to mood deficits in healthy adolescents. *Sleep Med.* 16, 987–993. doi: 10.1016/j.sleep.2015.03.007

Song, H.-T., Sun, X.-Y., Yang, T.-S., Zhang, L.-Y., Yang, J.-L., and Bai, J. (2015). Effects of sleep deprivation on serum cortisol level and mental health in servicemen. *Int. J. Psychophysiol.* 96, 169–175. doi: 10.1016/j.ijpsycho.2015.04.008

Spiegel, K., Leproult, R., L'hermite-Balériaux, M., Copinschi, G., Penev, P. D., and Van Cauter, E. (2004a). Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J. Clin. Endocrinol. Metab.* 89, 5762–5771. doi: 10.1210/jc.2004-1003

Spiegel, K., Leproult, R., and Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet* 354, 1435–1439. doi: 10.1016/S0140-6736(99)01376-8

Spiegel, K., Tasali, E., Penev, P., and Cauter, E. V. (2004b). Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann. Intern. Med.* 141, 846–850. doi: 10.7326/0003-4819-141-11-200412070-00008

Spielberger, C., Gorsuch, R., Lushene, R., Vagg, P., and Jacobs, G. (1983). *Manual for the State-Trait Anxiety Scale.* Palo Alto, CA: Consulting Psychologists Press.

Tartar, J. L., Fins, A. I., Lopez, A., Sierra, L. A., Silverman, S. A., Thomas, S. V., et al. (2015). Sleep restriction and delayed sleep associate with psychological health and biomarkers of stress and inflammation in women. *Sleep Health.* 1, 249–256. doi: 10.1016/j.sleh.2015.09.007

Tegeler, C., O'sullivan, J. L., Bucholtz, N., Goldeck, D., Pawelec, G., Steinhagen-Thiessen, E., et al. (2016). The inflammatory markers CRP, IL-6, and IL-10 are associated with cognitive function—data from the Berlin Aging Study II. *Neurobiol. Aging* 38, 112–117. doi: 10.1016/j.neurobiolaging.2015.10.039

Thorsley, D., Leproult, R., Spiegel, K., and Reifman, J. (2012). A phenomenological model for circadian and sleep allostatic modulation of plasma cortisol concentration. *Am. J. Physiol. Endocrinol. Metab.* 303, E1190–E1201. doi: 10.1152/ajpendo.00271.2012

Tomaso, C. C., Johnson, A. B., and Nelson, T. D. (2021). The effect of sleep deprivation and restriction on mood, emotion, and emotion regulation: three meta-analyses in one. *Sleep* 44:zsaa289. doi: 10.1093/sleep/zsaa289

Tononi, G., and Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med. Rev.* 10, 49–62. doi: 10.1016/j.smrv.2005.05.002

Trivedi, M. S., Holger, D., Bui, A. T., Craddock, T. J., and Tartar, J. L. (2017). Short-term sleep deprivation leads to decreased systemic redox metabolites and altered epigenetic status. *PLoS ONE* 12:e0181978. doi: 10.1371/journal.pone.0181978

Tucker, A. M., Whitney, P., Belenky, G., Hinson, J. M., and Van Dongen, H. P. (2010). Effects of sleep deprivation on dissociated components of executive functioning. *Sleep* 33, 47–57. doi: 10.1093/sleep/33.1.47

Vgontzas, A. N., Fernandez-Mendoza, J., Liao, D., and Bixler, E. O. (2013). Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med. Rev.* 17, 241–254. doi: 10.1016/j.smrv.2012.09.005

Vgontzas, A. N., Pejovic, S., Zoumakis, E., Lin, H.-M., Bixler, E. O., Basta, M., et al. (2007). Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *Am. J. Physiol. Endocrinol. Metab.* 292, E253–E261. doi: 10.1152/ajpendo.00651.2005

Vgontzas, A. N., Zoumakis, E., Bixler, E. O., Lin, H.-M., Follett, H., Kales, A., et al. (2004). Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J. Clin. Endocrinol. Metab.* 89, 2119–2126. doi: 10.1210/jc.2003-031562

Vintimilla, R., Hall, J., Johnson, L., and O'bryant, S. (2019). The relationship of CRP and cognition in cognitively normal older Mexican Americans: a cross-sectional study of the HABLE cohort. *Medicine* 98:e15605. doi: 10.1097/MD.0000000000015605

Weibel, L., Follenius, M., Spiegel, K., Ehrhart, J., and Brandenberger, G. (1995). Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. *Sleep* 18, 549–556.

Wright, Jr, K. P., Drake, A. L., Frey, D. J., Fleshner, M., Desouza, C. A., et al. (2015). Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. *Brain Behav. Immun.* 47, 24–34. doi: 10.1016/j.bbi.2015.01.004

Yang, G., Lai, C. S. W., Cichon, J., Ma, L., Li, W., and Gan, W.-B. (2014). Sleep promotes branch-specific formation of dendritic spines after learning. *Science* 344, 1173–1178. doi: 10.1126/science.1249098

Yeager, M. P., Pioli, P. A., and Guyre, P. M. (2011). Cortisol exerts bi-phasic regulation of inflammation in humans. *Dose-response,* 9, 332–347. doi: 10.2203/dose-response.10-013.Yeager

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Preferential consolidation of emotional reactivity during sleep: A systematic review and meta-analysis

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Many studies have investigated whether sleep affects cognitively unmodulated reactivity to emotional stimuli. These studies operationalize emotion regulation by using subjective and/or objective measures to compare pre- and post-sleep reactivity to the same emotional stimuli. Findings have been inconsistent: some show that sleep attenuates emotional reactivity, whereas others report enhanced or maintained reactivity. Across-study methodological differences may account for discrepant findings. To resolve the questions of whether sleep leads to the attenuation, enhancement, or maintenance of emotional reactivity, and under which experimental conditions particular effects are observed, we undertook a synthesized narrative and meta-analytic approach. We searched PubMed, PsycINFO, PsycARTICLES, Web of Science, and Cochrane Library databases for relevant articles, using search terms determined *a priori* and search limits of language = English, participants = human, and dates = January 2006–June 2021. Our final sample included 24 studies that investigated changes in emotional reactivity in response to negatively and/or positively valenced material compared to neutral material over a period of sleep compared to a matched period of waking. Primary analyses used random effects modeling to investigate whether sleep preferentially modulates reactivity in response to emotional stimuli; secondary analyses examined potential moderators of the effect. Results showed that sleep (or equivalent periods of wakefulness) did not significantly affect psychophysiological measures of reactivity to negative or neutral stimuli. However, self-reported arousal ratings of negative stimuli were significantly increased post-sleep but not post-waking. Subgroup analyses indicated that (a) sleep-deprived participants, compared to those who slept or who experienced daytime waking, reacted more strongly and negatively in response to positive stimuli; (b) nap-exposed participants, compared to those who remained awake or who slept a full night, rated negative pictures less negatively; and (c) participants who did not obtain substantial REM sleep, compared to those who did and

those exposed to waking conditions, had attenuated reactivity to neutral stimuli. We conclude that sleep may affect emotional reactivity, but that studies need more consistency in methodology, commitment to collecting both psychophysiological and self-report measures, and should report REM sleep parameters. Using these methodological principles would promote a better understanding of under which conditions particular effects are observed.

KEYWORDS

sleep, emotion, emotional reactivity, emotional regulation, meta-analysis, review, consolidation

Introduction

Numerous investigations have examined the role of sleep in emotion regulation (i.e., whether engaging in a period of sleep, be it across a full night, a partial night, or a daytime nap, can change emotional reactions to previously encountered events or stimuli). Among these investigations are studies of pre- to post-sleep changes in mood, in cognitively modulated emotion regulation (i.e., active control of responses to emotional stimuli), and in spontaneous reactivity to emotional stimuli (for a review, see Palmer and Alfano, 2017). These studies suggest that (a) mood is significantly negatively altered (i.e., people feel more depressed, anxious, angry, and/or confused) by periods of sleep loss; (b) these feelings are amplified as the sleep deprivation period increases; (c) participants with mood- and anxiety-related clinical symptoms who sleep poorly are less likely to use cognitive reappraisal strategies to modulate the negative impact of emotional experiences (see, e.g., Mauss et al., 2013; Baum et al., 2014; Short and Louca, 2015); and (d) participants who are sleep deprived, either experimentally or because of a sleep disorder (e.g., insomnia), do not extinguish reactivity to a previously conditioned stimulus after a period of sleep (Seo et al., 2018, 2022; Bottary et al., 2020). Regarding this latter point, although extinction is considered a form of emotional learning, successful extinction leads to an emotionally regulated state, where the individual is not likely to react inappropriately to unthreatening negative cues in the environment (Picó-Pérez et al., 2019; Frumento et al., 2021).

However, a larger group of studies within the sleep-emotion regulation literature has examined whether sleep affects spontaneous reactivity to emotional stimuli (i.e., reactivity that is not modulated through explicit or active use of emotion regulation strategies). The typical paradigm in this literature operationalizes emotional change by comparing pre- and post-sleep reactivity to the same set of emotional stimuli. This reactivity may be measured using either subjective or objective measures, with the latter including psychophysiological outcomes such as skin conductance levels and heart rate-associated variables (e.g., heart rate deceleration).

The outcome in these studies is the degree to which participants react differently to the same stimuli after a period of sleep as compared to an equivalent period of waking. An attenuated response (rather than an enhanced or maintained response) is considered more adaptive because in healthy individuals repeated exposure to emotional (and particularly negatively valenced) stimuli during waking hours and in an unthreatening environment is associated with increasingly attenuated responses to the material (Minkel et al., 2011; Baran et al., 2012). In this way, hyperactivation of fear networks that are associated with pathology (e.g., posttraumatic stress disorder) is avoided.

However, the exact mechanisms underlying modulation of emotional reactivity during sleep are not well understood. Neuroimaging studies show that regions involved in emotional processing, such as the anterior cingulate cortex, hippocampus, parahippocampus, amygdalar complex, pontine tegmentum, thalamus, and basal forebrain are active during sleep, and especially during rapid eye movement (REM) stages (Dang-Vu et al., 2010). Furthermore, a small number of studies show that after exposure to emotional material, brain regions associated with those stimuli (hippocampus and ventral tegmental area) are activated during sleep; notably, the magnitude of their activation is correlated with post-sleep task performance (Sterpenich et al., 2021; Legendre et al., 2022). These findings suggest that there is selective replay of emotional content during sleep, and that this replay aids in consolidation of emotional learning.

Limited understanding of mechanisms underlying the sleep-emotion regulation relations stands alongside inconsistent findings from studies investigating these relations. Whereas some studies show that sleep does attenuate reactivity to emotional stimuli (Gujar et al., 2011; Palmer and Alfano, 2017), others report enhanced (Wagner et al., 2002; Gilson et al., 2016; Jones et al., 2018) or maintained (Baran et al., 2012; Prehn-Kristensen et al., 2017) reactivity. For example, Cellini et al. (2016) found that a nap, compared to an equivalent period of waking, attenuated self-reported negative affect in response to negatively valenced (but not neutral) stimuli. However, Jones et al. (2018) found that, after a night of sleep in comparison to a day of wakefulness, participants tended to have elevated self-reported negative affect in response to negatively valenced (but not neutral) stimuli. Furthermore, Prehn-Kristensen et al. (2017) reported no significant differences in both post-sleep

and post-waking reactivity to all stimuli (emotionally valenced and neutral).

Differences in methodology may account for these across-study discrepancies in findings. These methodological differences include variations in the timing and duration of the sleep condition, whether participants obtained REM sleep (this stage of sleep appears to be central to the emotional regulatory benefits of sleep; Gujar et al., 2011; Palagini et al., 2013; Deliens et al., 2014; Altena et al., 2016), the type of waking control used, the kind of emotional stimuli presented, and the primary outcome measure used. However, because sleep can have clear benefits for emotion processing and because spontaneous and unmodulated emotional reactivity is an important influence on human behavior (Levenson, 1999; Gross et al., 2011; Becerra and Campitelli, 2013; Palmer and Alfano, 2017), it is important to determine whether a discernible pattern of sleep-dependent emotional regulation might emerge from this seemingly equivocal literature.

The current study

The existing literature in this field has not clearly answered the questions of (a) whether sleep leads to attenuation, enhancement, or maintenance of emotional reactivity, and (b) under which experimental conditions particular directions of results are observed. We conducted a systematic review with a narrative synthesis and meta-analysis, reviewing 24 studies that reported emotional reactivity for negatively and positively valenced material compared to neutral material over any period of sleep (whole night or nap) compared to a matched period of waking or sleep deprivation (i.e., wakefulness during either the day or the night). After a series of primary analyses assessing the general question of whether sleep preferentially modulates emotional reactivity in response to emotional stimuli, secondary analyses examined potential moderators of the effect.

Methods

Systematic review protocol

The study protocol was submitted and approved for registration on PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=271030.

Search strategy

Figure 1 is a PRISMA diagram providing details of the search process and of how we arrived at our final sample of articles for review.

Two authors (GL, JM) searched PubMed, PsycINFO, PsycARTICLES, Web of Science, and Cochrane Library databases using these terms: [(*sleep* AND *emotion* OR *affect*) NOT (*animal* OR *animals* OR *rat* OR *rats* OR *mouse* OR *mice* OR *survey* OR *surveys* OR *questionnaire* OR *questionnaires*)]. These terms were determined *a priori*, and the search was limited to articles published in English between January 1st 2006 and June 2nd 2021. The search process continued until July 2021. A total of 15,419 articles were retrieved.

GL and JM reviewed this dataset and removed duplicates, Cochrane protocols, and those not meeting the specified criteria. The term "affect" was excluded as it resulted in retrieval of articles that featured that word in the abstract, but which were unrelated to our research topic (e.g., how particular environments might affect animals' adaptive abilities). This initial scan of the dataset identified 45 review articles that might have been useful in alerting us to empirical articles of interest. Hence, author HA screened the full text of those review articles that were accessible ($n = 40$): a process which identified a further 112 articles.

At that point, a total of 4,181 articles remained for title and abstract screening. Three pairs of authors (JRM, KGFT; RL, DSB; GL, MH) each screened one-third of the papers, with each pair holding consensus meetings to finalize inclusion/exclusion decisions for each article. These decisions rested largely on whether the title/abstract made it clear that this was a study that (1) included healthy human participants and (2) described an experiment that compared a sleep condition to a waking control condition. As a result, 3,978 papers were excluded, leaving 203 articles for full-text screening. A further two papers were identified at an additional post-search check, resulting in a sample of 205 articles put forward for full-text screening.

The same author pairs then undertook detailed reviews of the full-text articles. They organized their examination of each paper so that they could make decisions around six specific eligibility criteria. These criteria were that the study must have:

1. used emotion-eliciting stimuli, and must have included at least a comparison of negatively valenced vs. neutral material;
2. elicited emotion spontaneously and not *via* modulated means (e.g., *via* cognitive appraisal);
3. been an experiment featuring at least one sleep condition (nap, whole night, or partial night) and at least one waking condition (sleep deprivation or daytime waking);
4. elicited emotion both before and after a period of sleep and a period of waking;
5. featured a sample of healthy individuals of any age and free from medications, neurological conditions, sleep difficulties, or psychological disorders;
6. reported outcome measures from before and after each interval period (sleep and waking).

Any article that did not meet any one of these six criteria was excluded from further consideration. We also excluded review articles and articles that did not present complete enough information for us to assess whether they should be included in

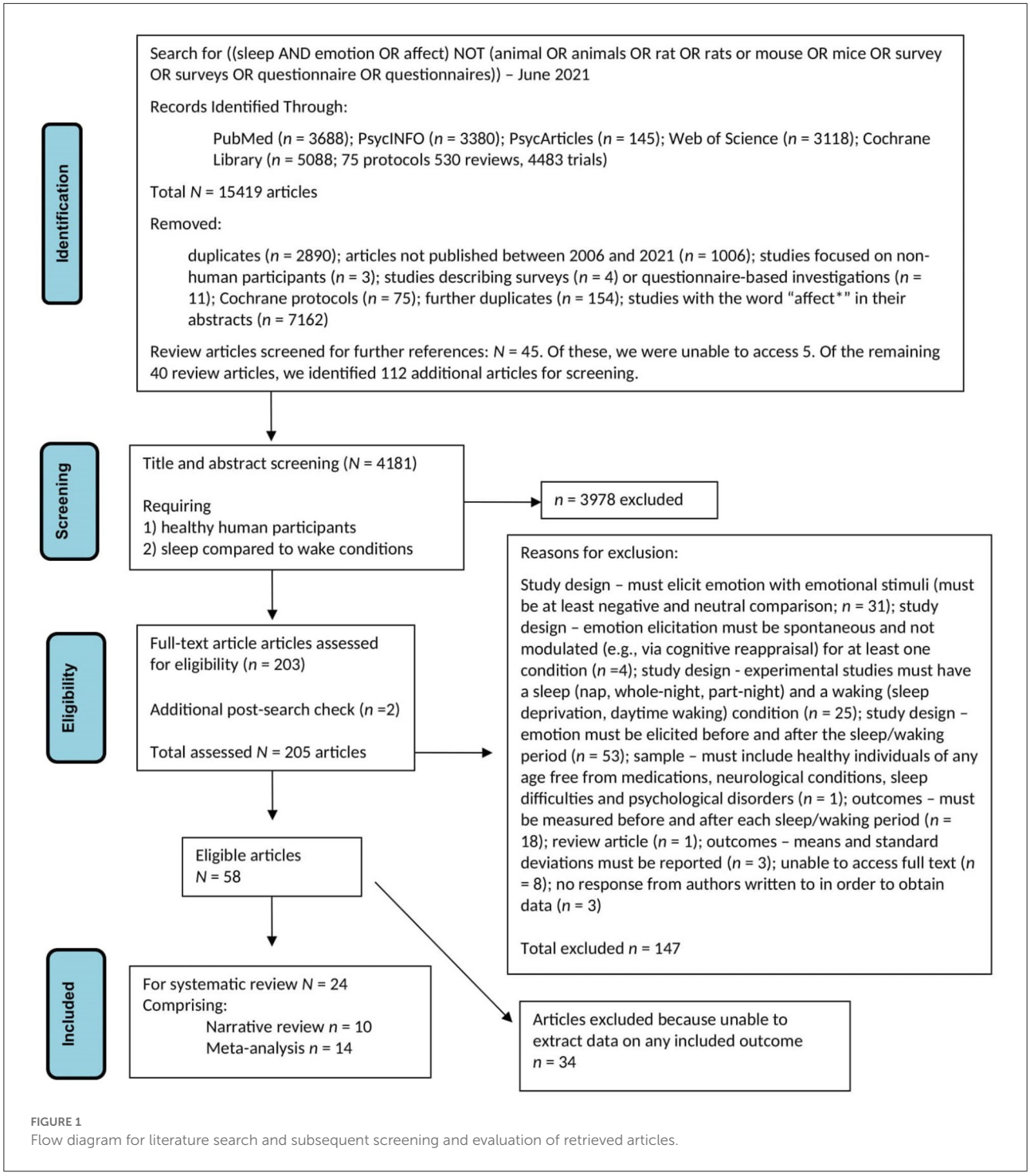

FIGURE 1
Flow diagram for literature search and subsequent screening and evaluation of retrieved articles.

the final sample. (In cases where articles did not provide such complete information, we contacted corresponding authors for further details and further evaluated the study only if further details were forthcoming.) Eventually, our author pairs achieved consensus for each article; if there was an initial disagreement this was discussed in a group meeting and consensus reached. A total of 147 articles were excluded at this stage.

A total of 58 articles remained eligible for inclusion in the review after full-text screening and consensus meetings were completed (i.e., 147 articles were excluded at this stage). However, on further review 34 of this pool of 58 were found to

TABLE 1 Datasets included in the meta-analysis: Study design, conditions, and sample characteristics ($N = 14$).

Study/Dataset	Sleep condition		Waking comparison condition		Sample characteristics	
	Type	*n*	Type	*n*	Age range (years)	Sex
1. Alfarra et al. (2015)	Full night	10	Full day	10	18–30	Mixed
2. Ashton et al. (2019)	Full night	34	Full day	27	NR	Mixed
3. Baran et al. (2012)	Full night	54	Full day	28	18–30	Mixed
4. Bolinger et al. (2018)	Full night (10)	16	Full day (10)	16	8–11	Mixed
5. Bolinger et al. (2019)	Full night (10)	16	Full day (10)	16	19–29	Mixed
6. Cellini et al. (2016)	90–120-min nap	30	90–120-min waking	16	20–30	Mixed
7. Gujar et al. (2011)	90-min nap	18	90-min waking	18	18–30	Mixed
8a. Jones et al. (2018)	Full night	20	Full day	20	18–30	Mixed
8b. Jones et al. (2018)	Full night	21	Full day	20	35–50	Mixed
9. Kuriyama et al. (2010)	Full night	14	Sleep deprivation	14	20–33	Mixed
10. Lipinska and Thomas (2019)	Full night	20	Full day	20	NR	All female
11. Pace-Schott et al. (2011)	120-min nap	22	120-min waking	21	18–27	Mixed
12. Prehn-Kristensen et al. (2017)	Full night	16	Full day	16	9–11	All male
13. Tempesta et al. (2010)	Full night	20	Sleep deprivation	20	20–36	All female
14. Tempesta et al. (2015)	Full night	52	Sleep deprivation	23	NR	Mixed

Most studies used a between-subjects design. Only these used a crossover design: Alfarra et al. (2015), Prehn-Kristensen et al. (2017), Bolinger et al. (2018), Lipinska and Thomas (2019). NR, not reported.

report only outcome measures that were not of interest to us (e.g., retention of memory for emotional vs. neutral material) or to include no extractable data for any reported outcome. A further 10 articles were only eligible for narrative systematic review of results. Of the remaining 14 articles, we were able to extract relevant statistical data directly from either text or tables in eight cases. In the other six articles, we used the WebPlotDigitizer software application (Version 4.5; Rohatgi, 2021) to extract relevant statistical data from figures.

Hence, our final sample for review was 24 studies, with 10 included only in the narrative review and 14 in meta-analysis (see Supplementary material for a brief description of each of these studies).

Data extraction and coding

We extracted the following sets of basic data from each of the 24 studies in our sample: study design (between-subjects or crossover); type of sleep condition (whole night or nap); type of comparison condition (wake or sleep deprivation); emotion elicitation technique [e.g., International Affective Picture System (IAPS), in-house pictures, Nencki Affective Picture System (NAPS), Ekman library of pictures, movie clips, emotional faces]; whether or not IAPS stimuli were used; total number of participants enrolled in the study; total number of participants who completed the protocol; sample age (*M*); and number of female participants (see Tables 1–4).

For the 14 studies included in the meta-analysis, we also extracted physiological and/or self-report emotion regulation outcome data (*M* and *SD* or *SEM*, as well as confidence intervals and *p*-values if those were available) for each stimulus category (negative, positive, and/or neutral), at each of the pre- and post-condition measurement points, for each of the sleep and comparison conditions. Physiological variables included heart rate deceleration (HRD), skin conductance response (SCR) or skin conductance level (SCL), pre-ejection period (PEP), and late positive potential (LPP) of the electroencephalogram. Self-report variables included valence and arousal ratings in response to the presented stimuli.

Finally, we coded each study's risk of bias as high, low, or unclear along the following dimensions: (a) clear definition of the study sample; (b) clear stipulation of study eligibility criteria and clear demonstration of how these were enforced; (c) clear definition of the sampling strategy/ies; (d) matching of groups/conditions on sociodemographic and/or other characteristics; (e) control of confounds (e.g., caffeine intake, daytime nap, adaptation night) for each sleep and comparison condition; (f) the quality and validity of outcome measures; (g) number of participants completing the study protocols >80%; (h) reporting on and accounting for missing data; (i) reporting of all study parameters; (j) use of WebPlotDigitizer to extract data; (k) statistical adjustment of results for confounders; and (1) other potential sources of bias.

All extracted data were entered into a Microsoft Excel spreadsheet, where they were cleaned and prepared for further analysis.

TABLE 2 Datasets included in the meta-analysis: Study stimulus characteristics and outcomes ($N = 14$).

Study/Dataset	Stimulus characteristics		Outcome measure(s)
	Type	Valence[1]	
1. Alfarra et al. (2015)	IAPS	–/+	Physiological: LPP/salivary cortisol
2. Ashton et al. (2019)	IAPS	–	Physiological: HRD/SCR
3. Baran et al. (2012)	IAPS	–	Self-report: Δ valence/Δ arousal
4. Bolinger et al. (2018)	IAPS	–	Physiological: LPP/HRD
5. Bolinger et al. (2019)	IAPS	–/+	Physiological: LPP/HRD
6. Cellini et al. (2016)	IAPS	–/+	Behavioral: *d'*
7. Gujar et al. (2011)	Facial expressions[2]	–/+	Behavioral: Δ emotional reactivity[3]
8a. Jones et al. (2018)	IAPS	–/+	Behavioral: *d'*
8b. Jones et al. (2018)	IAPS	–/+	Behavioral: *d'*
9. Kuriyama et al. (2010)	Movies[4]	–	Physiological and behavioral: SCR/recognition/fear rating
10. Lipinska and Thomas (2019)	IAPS	–	Physiological: HR/SCL
11. Pace-Schott et al. (2011)	IAPS	–	Physiological: SCR/HRD/EMG
12. Prehn-Kristensen et al. (2017)	Faces[5]	–/+[6]	Behavioral: *d'*/pupil reaction[7]
13. Tempesta et al. (2010)	IAPS	–/+	Self-report: Δ arousal[8]
14. Tempesta et al. (2015)	IAPS	–/+	Self-report: Δ valence/Δ arousal

IAPS, International Affective Picture System; LPP, late positive potential of the electroencephalogram (EEG); HRD, heart rate deceleration (emotional response to hits at recognition minus emotional response to same stimuli at encoding); SCR, skin conductance response; HR, heart rate; SCL, skin conductance level; EMG, electromyography.

d' (d prime) measures memory discrimination, and is calculated as z(Hit Rate) – z(False Alarm Rate).

[1]Studies presented the following variations of valence-based analyses: –na = negative and positive stimuli presented and analyzed separately; – = negative stimuli only presented and analyzed.

[2]Ekman pictures of facial affect (fearful, sad, angry, happy).

[3]Δ emotional reactivity = change from pre- to post-manipulation in the rating for each of the individual faces in a specified emotional category.

[4]14 movies, 7 of which showed safe driving and 7 of which showed a motor vehicle accident, accompanied by realistic sounds.

[5]320 black and white pictures of faces showing different kinds of emotional expressions (80 angry, 80 fearful, 80 happy, 80 neutral). Pictures were taken from the following databases: FACES (Ebner et al., 2010), Nim Stimset of Facial Expressions (Tottenham et al., 2009), 3D Facial Emotional Stimuli (Gur et al., 2002), Karolinska Directed Emotional Faces Systems (KDEF; Goeleven et al., 2008), and Productive Aging Laboratory Face Database (Minear and Park, 2004).

[6]Fearful (negative) and happy (positive) stimuli only; presented in separate blocks or trials.

[7]Binocular eye movements and pupil diameter - each event class (old/new by emotion) was averaged over the left and right eye.

[8]Valence data were collected but were not extractable.

Narrative synthesis

Because not all study characteristics and outcomes can be described adequately in accompanying tables, we include a narrative account of those articles whose study descriptions precluded incorporation of data into the meta-analysis ($n = 10$) as well as those that were included in the meta-analysis ($n = 14$).

Meta-analysis

Before analysis, we completed a rigorous process of coding outcome variables in each study to ensure consistent directionality for both psychophysiological and self-report data. For example, in the case of HRD more negative beats-per-minute values represent greater emotional reactivity. Hence, attenuation over the sleep or waking interval (post-interval minus pre-interval) is described by values that are larger and positive. In contrast, for SCR larger positive values represent greater emotional reactivity and, therefore, attenuation over the sleep or waking interval is described by values that are larger and negative. We completed a similar process of study-by-study evaluation for self-report data, which also varied depending on the stimulus used (e.g., IAPS pictures, film clips, or faces) and the subsequent method of emotion measurement related to that stimulus (e.g., self-assessment manikin, other rating scale).

Due to anticipated between-study heterogeneity, we pooled studies appropriate for meta-analysis using a generic inverse variance random effects model. Because different scales were reported across different studies, we report the meta-analysis of standardized mean differences, with associated 95% confidence intervals. The standardized mean difference can be interpreted in a similar manner to a Cohen's *d* standardized effect size.

Because the studies included in our review sample reported a mix of separate baseline and follow-up measures and collapsed change from baseline to follow-up scores, it was not possible to include all types of outcomes in a standardized mean differences meta-analysis. So, to maximize the data available for analysis, we used change scores only after (where necessary) converting separate baseline and follow-up values using procedures set out in the Cochrane Handbook (Section 6.5.2.8; Version 6.3; Higgins et al., 2022), with a conservative assumed correlation between measures of 0.5.

Because we sought to undertake the relatively complex tasks of exploring both valence and condition differences in the same meta-analysis, we undertook analyses in two stages. The first involved investigation of our primary question: i.e., is emotionally valenced material regulated more strongly than neutral material (e.g., is reactivity to emotional stimuli attenuated while reactivity to neutral material is not) over a period of sleep as compared to over a similar period of waking? Hence, at this stage we calculated the standardized mean change (SMC), in terms of emotional reactivity, for (a) valenced material over a period of sleep vs. over a comparison period

TABLE 3 Datasets included in the narrative analysis: Study design, conditions, and sample characteristics ($N = 10$).

Study/Dataset	Sleep condition		Waking comparison condition		Sample characteristics	
	Type	*n*	Type	*n*	Age range (years)	Sex
1. Cunningham et al. (2014)	Full night	18	Full day	21	NR	Mixed
2. Goldstein et al. (2013)	Full night	18	Other	18	NR	Mixed
3. Hot et al. (2016)[1]	Nap	30	No nap	30	NR	NR
4. Kuriyama et al. (2013)	Full night	31	Sleep deprivation	31	20–19	Mixed
5. Lau et al. (2020)	Nap	19/22	No nap	25	16–60	NR
6. Minkel et al. (2011)	Full night	8	Sleep deprivation	15	22–45	Mixed
7. Reddy et al. (2014)[1]	Full night	NR	Sleep deprivation	NR	13–17	NR
8. Reid et al. (2019)[1]	Full night	24	Forced awakenings	27	NR	Mixed
9a. Schoch et al. (2017)	Full night	29	Full day	28	18–35	Mixed
9b. Schoch et al. (2017)	Full night	28	Full day	27	18–35	Mixed
10. Wagner et al. (2002)	Full night	12	Full day	12	18–30	All male

All studies used a between-subjects design.
NR, not reported.
[1]Conference abstract – limited information available.

(i.e., daytime waking, sleep deprivation), and then (b) neutral material over a period of sleep vs. over a comparison period. We ran separate analyses for the psychophysiological (e.g., heart rate deceleration) outcomes and the self-report (valence, arousal) outcomes. In cases where it appeared there was indeed preferential regulation of emotionally valenced material, we then compared the SMC from the valenced condition(s) in the sleep-vs.-comparison analysis to the SMC from the neutral condition in the sleep-vs.-comparison analysis. The methods used for the calculations were as set out in Morris (2008) and Schäfer et al. (2020).

Funnel plots were produced to examine evidence of publication bias in all analytic comparisons that included 10 or more studies. Egger's test was carried out to test for small study effects.

We used the meta command in Stata version 17 for all analyses.

Results

Risk of bias

Most of the 24 studies in our review sample were rated as having low or unclear risk of bias on most rated dimensions (see Supplementary Figures 1, 2; Figures 2, 3). As the Figures show, only three studies (Reddy et al., 2014; Hot et al., 2016; Reid et al., 2019) were judged as having an unclear risk of bias across all domains. The descriptions of these studies, which were reported in conference abstracts, provided insufficient information to assess risk of bias. Several studies were judged as having an unclear risk of bias with regard to defining study samples, stipulating eligibility criteria, and reporting on levels of attrition—these studies did not provide adequate information regarding those aspects of their methods. Where studies were judged as having high risk of bias, it was most often a consequence of limited attempts to control for potential confounders, using non-standard measures that were not well described, significant participant attrition, and, in the case of studies included in the meta-analysis, data not being reported in text or tables and therefore needing to be extracted from figures, leading to approximations of *M* and *SD*/*SEM* values. The paragraphs below provide more detail regarding our risk-of-bias ratings.

Regarding *definition of the study sample*, we considered all studies to be of low or unclear risk of bias. Although all studies defined their samples adequately, those rated as unclear on this dimension provided few details regarding recruitment.

Regarding *stipulation of study eligibility criteria and demonstration of how these were enforced*, again we considered all studies to be of low or unclear risk of bias. Studies rated unclear on this dimension usually provided a list of exclusion criteria but gave little information on how participants were screened against these criteria or how their exclusion was ensured.

Regarding *definition of the sampling strategy*, again we considered all studies to be of low or unclear risk of bias. Studies rated unclear on this dimension were those that provided insufficient detail to allow clear judgment on how the sampling proceeded.

Regarding *matching of study groups/conditions on sociodemographic and/or other characteristics*, most studies provided a description of these matching processes and of an assessment of their success. Hence, they were rated as being at low risk of bias on this dimension. The remaining studies were rated as unclear.

TABLE 4 Datasets included in the narrative analysis: Study stimulus characteristics and outcomes ($N = 10$).

Study/Dataset	Stimulus characteristics		Outcome measure(s)
	Type	Valence[1]	
1. Cunningham et al. (2014)	Scenes[2]	–	HRD/SCR
2. Goldstein et al. (2013)	Emotion-anticipation task	–	fMRI
3. Hot et al. (2016)[3]	Movie scene	–	HRD
4. Kuriyama et al. (2013)	Movie clips[4]	–	*d*'/C/ΔSCR
5. Lau et al. (2020)	Emotional faces[5]	–/+	Intensity ratings of different emotions
6. Minkel et al. (2011)	Movie clips[6]		Facial expressiveness[7]
7. Reddy et al. (2014)[3]	IAPS Pictures	–/+	Affectivity
8. Reid et al. (2019)[3]	Words[8]	–	Attentional bias index[9]
9a. Schoch et al. (2017)	IAPS Pictures	–/+	Free recall
9b. Schoch et al. (2017)	IAPS Pictures	–/+	Free recall
10. Wagner et al. (2002)	IAPS Pictures	–	Valence/arousal

HRD, heart rate deceleration; SCR, skin conductance response; fMRI, neuronal activity as measured by functional magnetic resonance imaging. d' (d prime) measures memory discrimination, and is calculated as z(Hit Rate) - z(False Alarm Rate). C is a measure of recognition bias, calculated as 0.5 × z(Hit Rate) + 0.5× z(false alarm rate).

[1]Studies presented the following variations of valence-based analyses: –/+ = negative and positive stimuli presented and analyzed separately; – = negative stimuli only presented and analyzed.

[2]Participants viewed a set of 68 scenes that portrayed negatively arousing or neutral objects (34 of each valence) placed on plausible neutral backgrounds.

[3]Conference abstract – limited information available.

[4]Clips of motor vehicle accidents and of safe driving situations.

[5]Black-and-white pictures of faces of a Caucasian male and a Caucasian female expressing four emotions (happiness, sadness, fear, anger) were selected from the Karolinska Directed Emotional Faces (KDEF) set (Goeleven et al., 2008).

[6]Participants watched two film clips that were either sad or amusing. They were then randomized to either a night of sleep deprivation or a full night of sleep before watching another pair of sad and amusing clips.

[7]Videos were scored for global level of expressiveness based on the FACES scoring system (Kring and Sloan, 2007) by two raters.

[8]Threat-related versus neutral words.

[9]The extent to which participants showed preferential attentional allocation toward threat-related vs. neutral words.

Regarding *methodological attempts to control for potential confounding factors*, three studies were rated as being at high risk of bias. Ashton et al. (2019) (a study included in the meta-analysis) did not report including an adaptation night in their study protocol; Jones et al. (2018) (a study included in the meta-analysis) asked participants assigned to their waking comparison conditions not to nap and to limit caffeine between sessions but did not ask participants assigned to their sleep conditions to do similarly; and Kuriyama et al. (2013) did not report considering potential confounders of their outcome. One study included in the meta-analysis was rated as being unclear: Prehn-Kristensen et al. (2017) provided limited information on what instructions participants were given regarding factors such as diet or exercise. All other studies included in the meta-analysis were rated as being at low risk of bias on this dimension, while all other studies were rated as unclear.

Regarding *the quality and validity of outcome measures*, two studies were rated as being at high risk of bias. Jones et al. (2018) (a study included in the meta-analysis) used as stimuli pictures from an apparently unvalidated in-house set alongside IAPS images. In Minkel et al. (2011), it was unclear whether the film clip stimuli were of equivalent valence/arousal over the study period. All studies included in the meta-analysis (other than Jones et al., 2018) were rated as being at low risk of bias on this dimension, while all other studies were rated as being at low or unclear risk.

Regarding *participant attrition*, ratings were particularly difficult to make because most studies in the sample did not report any attrition statistics. (For instance, eight of the 14 studies included in the meta-analysis made no such report.) We decided to rate as unclear those studies that made no report, and as low risk those that made distinct statements indicating that more than 80% of enrolled participants had completed the study protocols. Ashton et al. (2019) (a study included in the meta-analysis) and Lau et al. (2020) were judged as being at high risk of bias on this dimension because it was clear from their study descriptions that fewer than 80% of enrolled participants completed the study.

Regarding *reporting on and accounting for missing data*, all studies were rated as being of low or unclear risk of bias.

Regarding *reporting of all study parameters*, two studies included in the meta-analysis were rated as being at high risk of bias: Alfarra et al. (2015) did not report on key characteristics of their sample, and Kuriyama et al. (2010) did not report fear ratings at baseline. All other studies (bar Gujar et al., 2011, which was rated as unclear) included in the meta-analysis were rated as being at low risk of bias on this dimension.

Regarding *the use of WebPlotDigitizer to extract data*, we had to do so for seven of the 14 studies included in the meta-analysis (Kuriyama et al., 2010; Tempesta et al., 2010, 2015; Gujar et al., 2011; Pace-Schott et al., 2011; Jones et al., 2018) because the data required for meta-analytic calculations were not available in text or tables. Data extracted in this way are an approximation, and so these studies were judged as being at high risk of bias on this dimension.

Regarding *statistical adjustment for confounders*, all studies either used a suitable method to perform such adjustment (and were therefore judged to be at low risk of bias; this includes all studies that formed part of the meta-analysis) or did not describe the methods used (and were therefore judged to have an unclear risk of bias).

Regarding *other potential sources of bias*, all studies either provided information on funding and potential conflicts of interest (and were therefore judged to be at low risk of bias; this includes all studies that formed part of the meta-analysis) or did not report this information (and were therefore judged to have an unclear risk of bias).

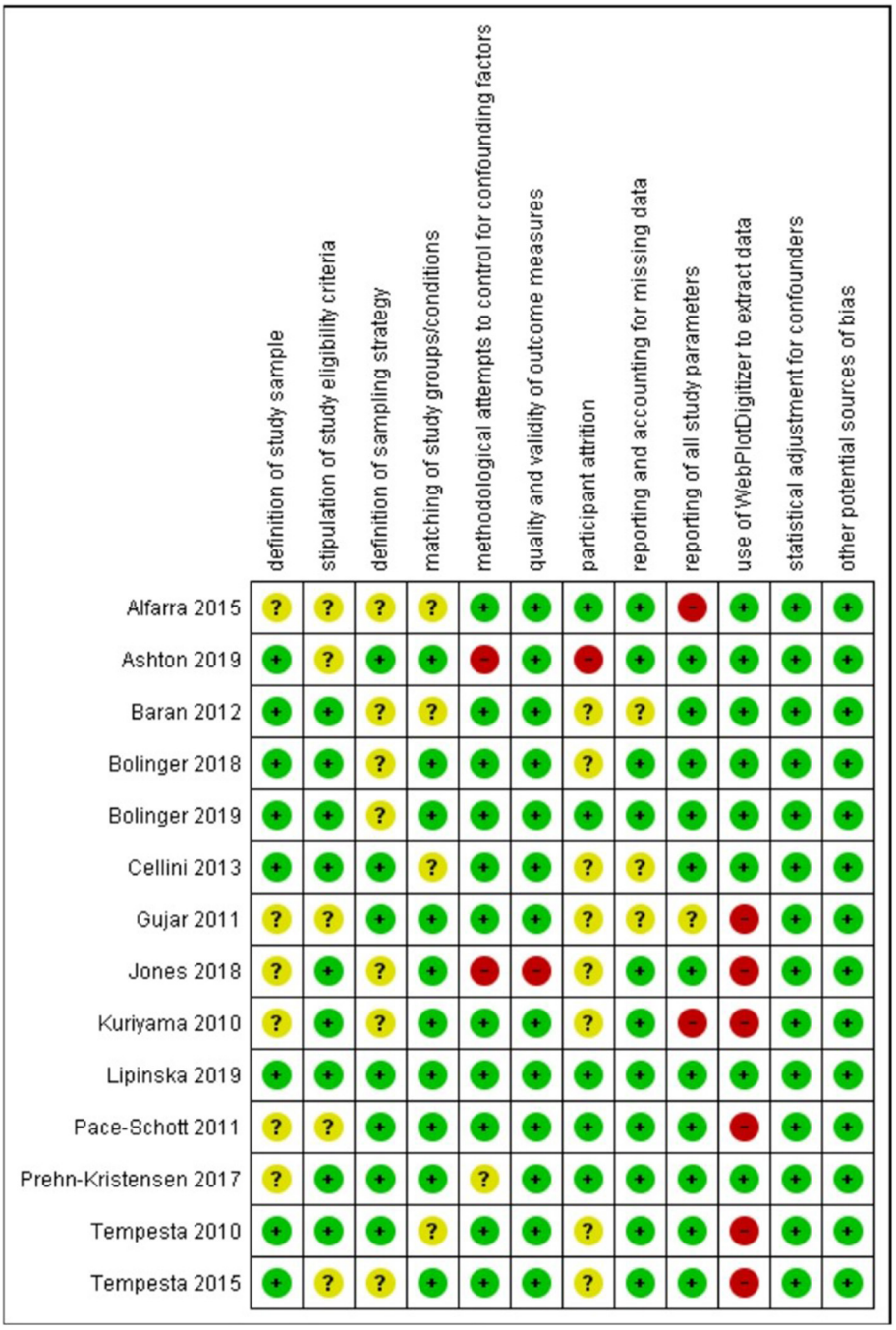

FIGURE 2
Risk of bias (low, unclear, or high) for each study included in meta-analysis on each rated methodological dimension ($N = 14$).

Narrative synthesis

Here, we provide a narrative account of all studies included in the review (i.e., the 10 articles whose study descriptions precluded incorporation of data into the meta-analysis, and the 14 that were included in the meta-analysis).

Studies reporting psychophysiological outcomes

Nine studies reported psychophysiological outcomes related to valenced material in comparison to neutral material after a period of sleep or waking. Two of those studies (Cunningham et al., 2014; Lipinska and Thomas, 2019)

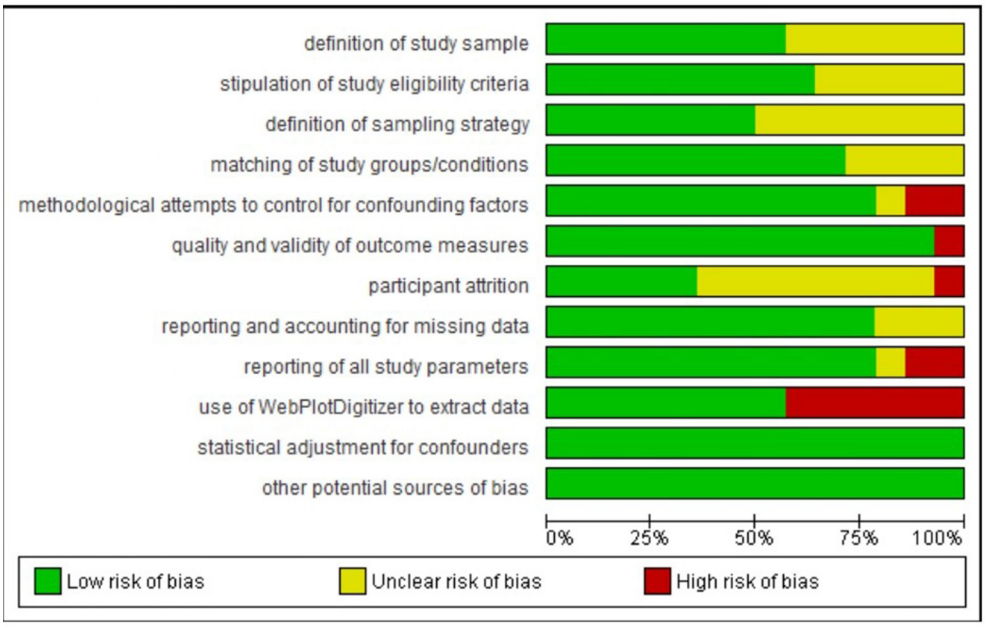

FIGURE 3
Percentage of studies in the metanalysis rated as being of low, unclear, and high risk of bias on each rated methodological dimension ($N = 14$).

showed that participants had attenuated HRD and PEP after a period of overnight sleep, in contrast to regular daytime waking activity, although this result was not specific to valenced material.

Five of the nine studies showed that, in response to both valenced and neutral material, there were no post-sleep HRD or SCL differences (Kuriyama et al., 2010, 2013; Hot et al., 2016; Bolinger et al., 2018, 2019). However, three of these studies showed that both HRD and SCL responses to the material were decreased after a period of either regular daytime waking activity or overnight sleep deprivation (Kuriyama et al., 2013; Bolinger et al., 2018, 2019). Bolinger et al. (2018) suggested that this effect was driven by a decrease in reactivity to negative stimuli. The other two studies showed no change in reactivity to all stimuli after a period of either regular daytime waking activity or overnight sleep deprivation (Kuriyama et al., 2010; Hot et al., 2016).

Two studies showed that HRD increased in response to negative stimuli after a period of sleep (either a full night or a 120-min nap) rather than waking (Pace-Schott et al., 2011; Ashton et al., 2019). However, Pace-Schott et al. (2011) indicated that this result was not specific to responses to negative stimuli: The same result was seen in response to neutral stimuli.

Overall, there is no discernible pattern in psychophysiological reactivity to valenced stimuli after a period of sleep rather than an equivalent period of waking.

Studies reporting valence ratings

Seventeen studies (incorporating 18 datasets) evaluated self-reported valence ratings in response to emotional and neutral stimuli. Only three of those studies showed less negative reactivity in response to negative rather than neutral stimuli after a period of either overnight sleep or a daytime nap (Gujar et al., 2011; Bolinger et al., 2018; Ashton et al., 2019). However, Ashton et al. (2019) found that this effect was not specific to sleep, as a similar tendency toward more positive ratings of negative stimuli was seen after an equivalent period of waking. In contrast, Schoch et al. (2017) found that participants rated stimuli as less negative after a period of continuous overnight sleep in contrast to continuity-disrupted sleep, but noted that this effect was not specific to valenced material (i.e., it was found with neutral material as well).

Most studies reporting data on valence ratings showed either maintained reactivity in post-sleep responses to emotional stimuli or no effect of either sleep or waking on reactivity. Two studies showed that while a period of overnight sleep maintained responses to negatively valenced material, an equivalent period of regular daytime waking activity resulted in more positive responses to the same stimuli (Jones et al., 2018; Bolinger et al., 2019). Two studies showed the opposite effect: While reactivity to valenced stimuli was maintained after sleep, normal waking (Lau et al., 2020) and sleep deprivation (Tempesta et al., 2015) resulted in more negative responses to negative and positive stimuli respectively. One study showed the same sleep effect,

but participants rated neutral stimuli as more negative after a period of sleep deprivation (Tempesta et al., 2010). Six studies showed no effect of sleep (either overnight or nap) or waking (either regular daytime activity or sleep deprivation) on both valenced and neutral material – reactivity was maintained in all conditions (Kuriyama et al., 2010; Minkel et al., 2011; Pace-Schott et al., 2011; Cellini et al., 2016; Prehn-Kristensen et al., 2017; Bolinger et al., 2018).

Only one study showed that after a period of sleep, but not waking, participants were more reactive to valenced stimuli in comparison to neutral stimuli (Wagner et al., 2002). This study showed that (a) after a period of REM-rich sleep, participants showed enhanced reactivity to negative stimuli, whereas (b) after a period of sleep rich in slow waves, their responses were enhanced for positive stimuli.

In summary, most studies showed either maintained reactivity to valenced material after a period of sleep, rather than waking, or no effect of sleep or waking on valenced or neutral material.

Studies reporting arousal ratings

Ten studies (incorporating 11 datasets) evaluated self-reported arousal ratings in response to emotional and neutral stimuli. Of these studies, two reported decreased arousal after a period of overnight sleep (Bolinger et al., 2018, 2019). However, in both cases this decrease was not specific to valenced material (i.e., it was also observed in response to neutral material), and in one case it was not specific to sleep (i.e., it was also observed after a period of regular daytime waking activity).

One study showed that a full night of sleep maintained arousal in response to all stimuli, but that total night-time sleep deprivation resulted in increased self-reported arousal to these stimuli (Tempesta et al., 2010). Four studies (incorporating five datasets) showed no effect of sleep (either overnight or nap) or waking (either regular daytime activity or sleep deprivation) on arousal responses to both emotional and neutral material (Tempesta et al., 2015; Cellini et al., 2016; Jones et al., 2018; Ashton et al., 2019).

Two studies showed increased arousal after a period of sleep. Baran et al. (2012) reported that this effect was specific to negatively valenced stimuli and that it was more pronounced after a full night of sleep in contrast with a full day of waking activity. However, Schoch et al. (2017), making an identical sleep-wake comparison, showed no effect of valence or of condition.

In summary, there is little consensus regarding attenuation, maintenance, or enhancement of arousal in response to valenced material after a period of sleep. Most studies in this group do, however, report no effect of valence and condition on self-reported arousal ratings.

Meta-analysis

Studies reporting psychophysiological outcomes

Five studies (Kuriyama et al., 2010; Pace-Schott et al., 2011; Bolinger et al., 2018; Ashton et al., 2019; Lipinska and Thomas, 2019; total $N = 96$) measured psychophysiological outcomes. Overall, this group of studies indicated that neither sleep nor equivalent periods of wakefulness had a statistically significant effect on emotional reactivity to either negatively valenced or neutral stimuli.

Regarding analyses of changes in reactivity to negatively valenced material over a period of sleep compared to changes over an equivalent comparison period, there was a standardized effect size of 0.02 (95% CI −0.44, 0.49) and no statistically significant difference ($p = 0.93$, $I^2 = 61\%$; see Figure 4). Because three of the five studies used the same outcome measure (HRD), we examined the collective results of these three studies (Pace-Schott et al., 2011; Bolinger et al., 2018; Ashton et al., 2019). These results were more consistent, with a small-to-moderate effect size of −0.30 (95% CI −0.66, 0.06). However, they still failed to meet the threshold for statistical significance ($p = 0.10$, $I^2 = 0\%$), perhaps due to the small sample size ($n = 62$; see Supplementary Figure 3).

Regarding analyses of changes in reactivity to neutral material over a period of sleep compared to changes over an equivalent comparison period, there was a standardized effect size of 0.19 (95% CI −0.22, 0.60) and no statistically significant difference ($p = 0.36$, $I^2 = 50\%$; see Figure 5). Analysis of the three studies reporting HRD measures only revealed a very small effect size of −0.05 (95% CI −0.42, 0.33) that was not statistically significant ($p = 0.80$, $I^2 = 9\%$; see Supplementary Figure 4).

Studies reporting valence ratings

The studies described in this subsection evaluated changes in reactivity (as indexed by self-reported valence ratings) to negative, neutral, or positive material over a period of sleep compared to changes over an equivalent comparison period. The three separate analyses (one for each stimulus type) all detected small-to-moderate effects sizes that were not statistically significant.

Twelve studies incorporating 13 datasets (Kuriyama et al., 2010; Tempesta et al., 2010, 2015; Gujar et al., 2011; Baran et al., 2012; Alfarra et al., 2015; Cellini et al., 2016; Prehn-Kristensen et al., 2017; Bolinger et al., 2018, 2019; Jones et al., 2018; Ashton et al., 2019; total $N = 297$) evaluated changes in reactivity to negatively valenced material over a period of sleep compared to changes over an equivalent comparison period. Analysis of those data detected a very small effect size of −0.07 (95% CI −0.52,

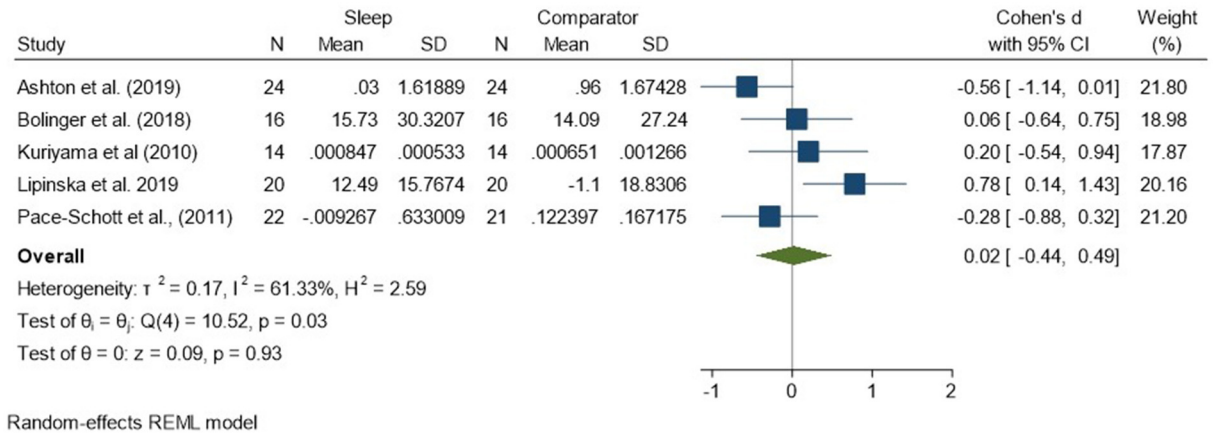

FIGURE 4
Meta-analysis I: Physiological outcomes in response to negative stimuli – changes across a period of sleep compared to across a period of waking ($K = 5$, $N = 155$).

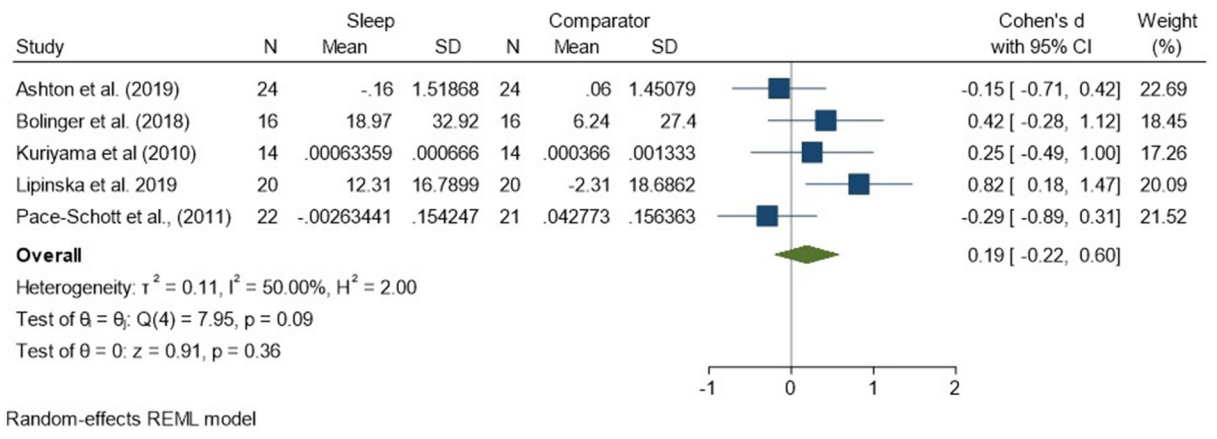

FIGURE 5
Meta-analysis II: Physiological outcomes in response to neutral stimuli – changes across a period of sleep compared to across a period of waking ($K = 5$, $N = 155$).

0.39) that was not statistically significant ($p = 0.76$; $I^2 = 84\%$; see Figure 6).

Ten studies incorporating 11 datasets (Kuriyama et al., 2010; Tempesta et al., 2010, 2015; Baran et al., 2012; Alfarra et al., 2015; Cellini et al., 2016; Prehn-Kristensen et al., 2017; Bolinger et al., 2018; Jones et al., 2018; Ashton et al., 2019; total $N = 240$) evaluated changes in reactivity to neutral material over a period of sleep compared to changes over an equivalent comparison period. Analysis of those data detected a moderate effect size of 0.44 (95% CI −0.04, 0.93) that was not statistically significant ($p = 0.07$, $I^2 = 83\%$; see Figure 7).

Six studies (Tempesta et al., 2010, 2015; Gujar et al., 2011; Alfarra et al., 2015; Cellini et al., 2016; Prehn-Kristensen et al., 2017; total $N = 97$) evaluated changes in reactivity to positively valenced material over a period of sleep compared to changes over an equivalent comparison period. Analyses of those data detected a small effect size of 0.11 (95% CI −0.51, 0.73) that was not statistically significant ($p = 0.73$, $I^2 = 77\%$; see Figure 8).

Studies reporting arousal ratings

The studies described in this sub-section evaluated changes (as indexed by self-reported arousal ratings) in reactivity to negative, neutral, or positive material over a period of sleep compared to changes over an equivalent comparison period. Only analyses of data comprising negative material detected a statistically significant effect; analyses of positive and neutral data detected small and non-significant effects.

Six studies incorporating 7 datasets (Kuriyama et al., 2010; Tempesta et al., 2010; Baran et al., 2012; Cellini et al., 2016;

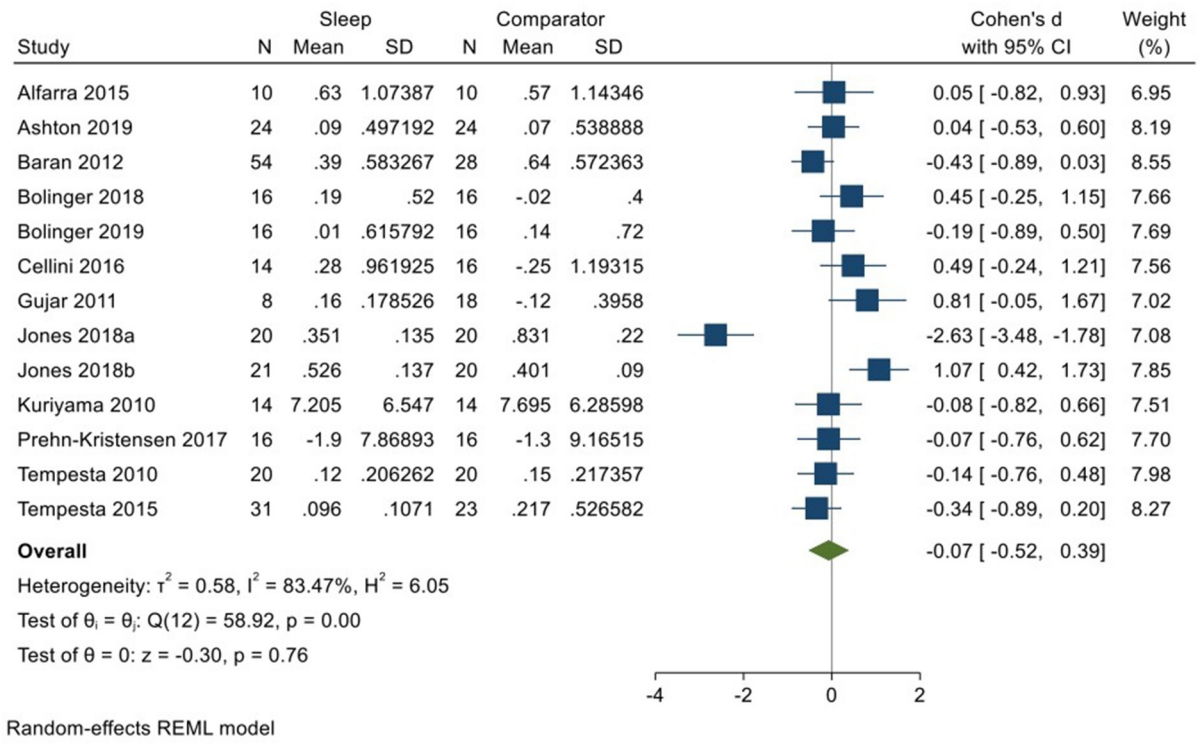

FIGURE 6
Meta-analysis III: Outcomes for self-reported valence ratings in response to negative stimuli – changes across a period of sleep compared to across a period of waking ($K = 13$, $N = 463$).

Jones et al., 2018; Ashton et al., 2019; Bolinger et al., 2019; total $N = 169$) evaluated changes in reactivity to negatively valenced material over a period of sleep compared to changes over an equivalent comparison period. Analysis of those data detected a modest effect size of −0.30 (95% CI −0.53, −0.07) that was statistically significant ($p = 0.01$, $I^2 = 0\%$; see Figure 9).

Five studies incorporating 6 datasets (Tempesta et al., 2010; Baran et al., 2012; Cellini et al., 2016; Jones et al., 2018; Ashton et al., 2019; total $N = 153$) evaluated changes in reactivity to neutral material over a period of sleep compared to changes over an equivalent comparison period. Analysis of those data detected a small effect size of −0.18 (95% CI −0.42, 0.06) that was not statistically significant ($p = 0.14$, $I^2 = 0\%$; see Figure 10).

Two studies (Tempesta et al., 2010; Cellini et al., 2016; total $N = 34$) evaluated changes in reactivity to positively valenced material over a period of sleep compared to changes over an equivalent comparison period. Analysis of those data detected a small effect size of −0.18 (95% CI −0.65, 0.29) that was not statistically significant ($p = 0.46$, $I^2 = 0\%$; see Figure 11).

There appears to be preferential regulation during sleep of self-reported arousal in response to negatively valenced material. We compared the SMC from the negative condition in the sleep-vs.-waking analysis to the SMC from the neutral condition in the sleep-vs.-waking analysis. Five studies comprising six datasets (Tempesta et al., 2010; Baran et al., 2012; Cellini et al., 2016; Jones et al., 2018; Ashton et al., 2019; total $N = 153$) contributed data to this analysis, which detected a moderate effect size of 0.65 (95% CI 0.30, 1.00) that was statistically significant ($p < 0.001$, $I^2 = 53\%$; see Figure 12).

Subgroup analyses

We examined whether age, gender, data extraction method (numerical or graphic), type of waking control (sleep deprivation vs. ordinary daytime waking), sleep duration (whole night vs. nap), kind of emotional stimuli (IAPS vs. other) and whether participants obtained REM sleep (either typical whole-night REM percentage or reported REM sleep in a nap paradigm) influenced self-reported valence and arousal outcomes.

Regarding psychophysiological outcomes, there was too little variation in these moderator variables between studies for us to conduct sub-group analyses. For example, Pace-Schott et al. (2011) was the only study in this group that required data extraction from figures. In four of the five studies, the research design featured a daytime waking control period; the only exception was Kuriyama et al. (2010), which used a period of sleep deprivation. Similarly, four of the

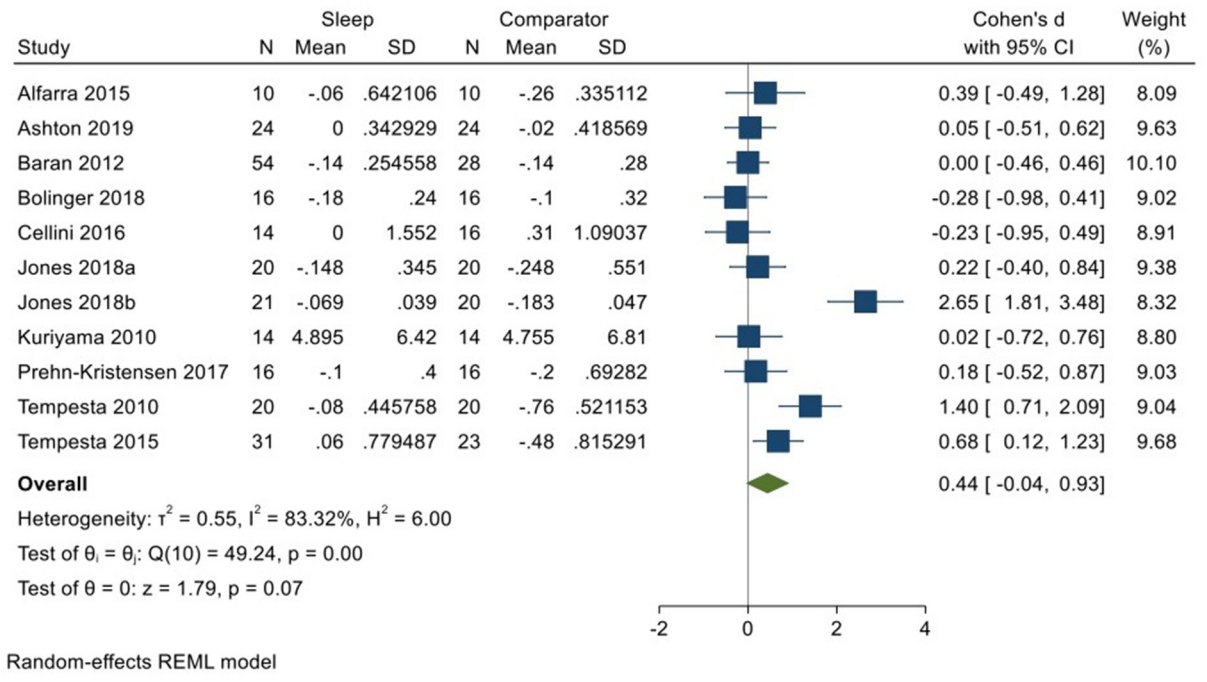

FIGURE 7
Meta-analysis IV: Outcomes for self-reported valence in response to neutral stimuli – changes across a period of sleep compared to across a period of waking ($K = 11$, $N = 405$).

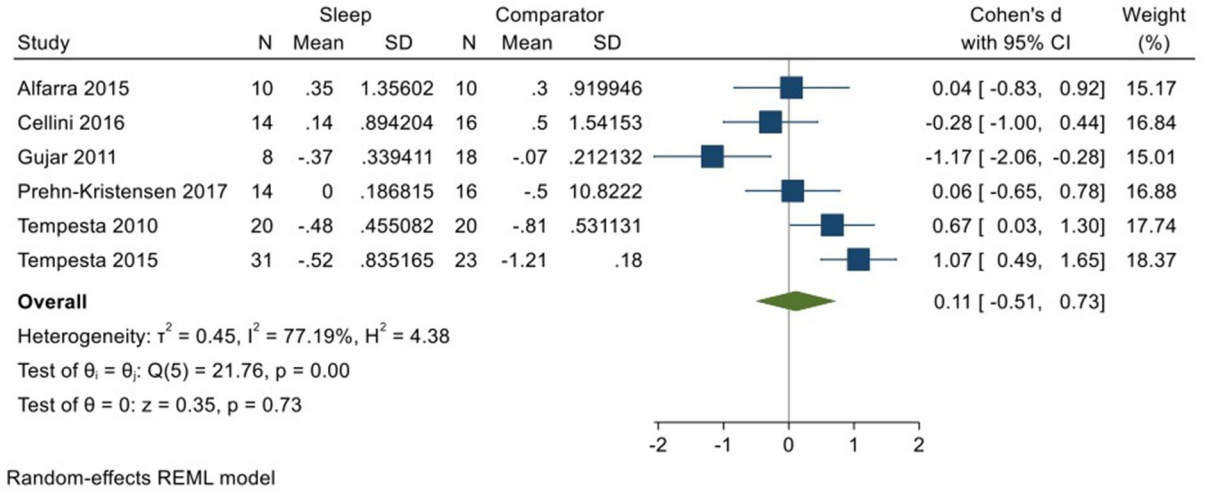

FIGURE 8
Meta-analysis V: Outcomes for self-reported valence ratings in response to positive stimuli – changes across a period of sleep compared to across a period of waking ($K = 6$, $N = 176$).

five study designs featured a whole-night sleep condition; the only exception was Pace-Schott et al. (2011), which used a nap condition. All five studies used IAPS stimuli. Finally, no study except Bolinger et al. (2018) presented REM data.

Regarding self-reported valence and arousal outcomes, analyses detected statistically significant subgroup effects for valence outcomes only. Three moderators had an influence on valence ratings: the kind of comparison condition used (daytime waking vs. sleep deprivation), the duration of sleep (whole night

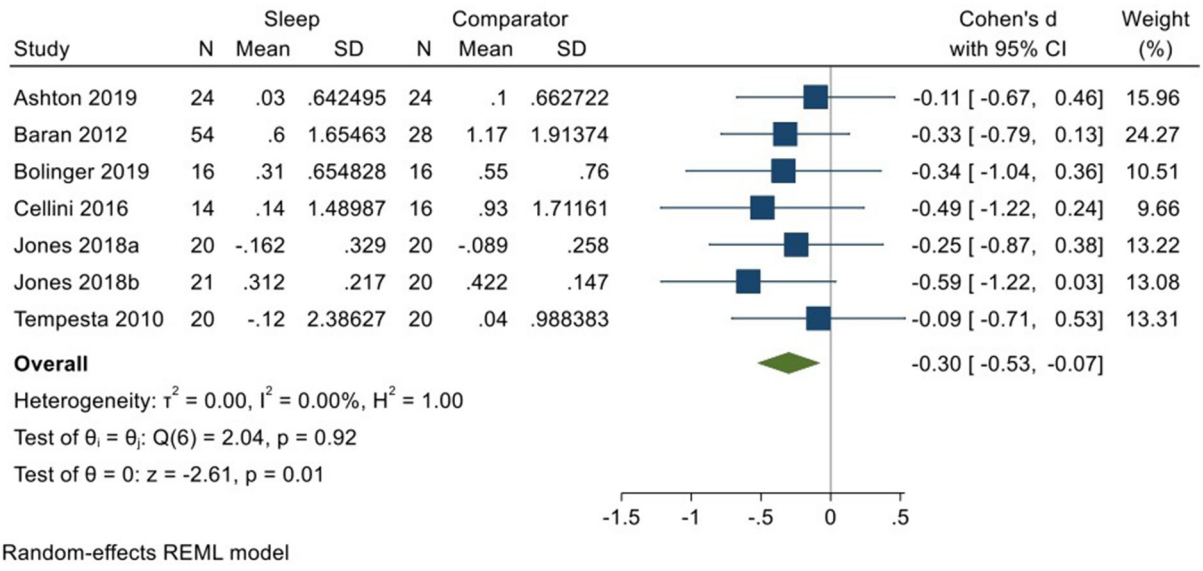

FIGURE 9
Meta-analysis VII: Outcomes for self-reported arousal ratings in response to negative stimuli – changes across a period of sleep compared to across a period of waking ($K = 7$, $N = 313$).

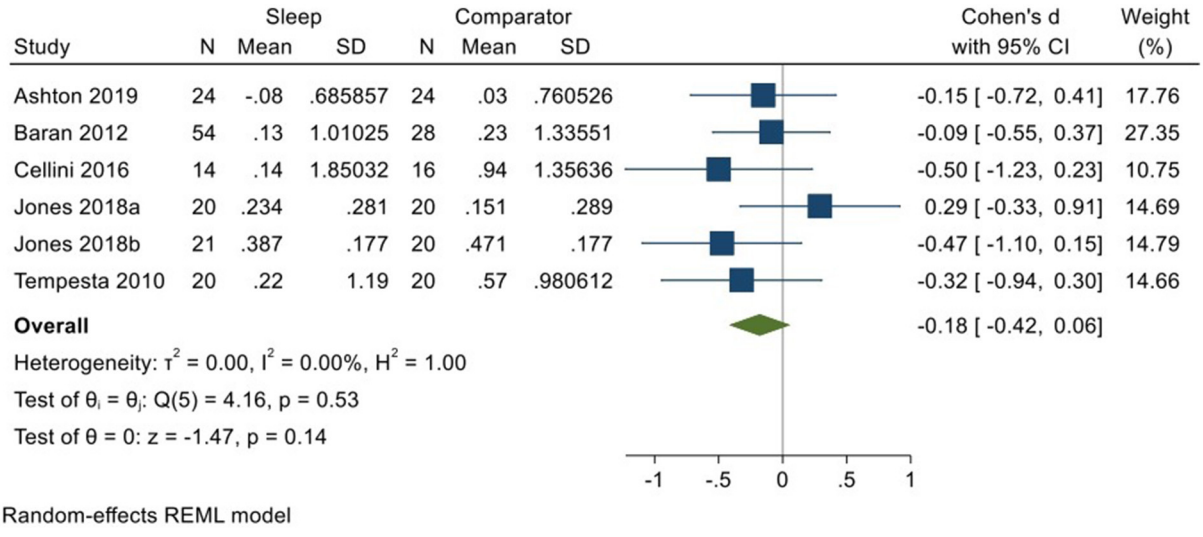

FIGURE 10
Meta-analysis VIII: Outcomes for self-reported arousal ratings in response to neutral stimuli – changes across a period of sleep compared to across a period of waking ($K = 6$, $N = 281$).

vs. nap), and whether participants experienced REM sleep or not (see Supplementary Figures 5–22 for details regarding all subgroup analyses).

Regarding the effect of the kind of waking comparison condition, the sub-group analysis showed that in response to positive stimuli (but not in response to negative or neutral stimuli, $p = 0.78$ and $p = 0.64$, respectively; see Supplementary Figures 5, 6), those who were sleep deprived tended to have significantly larger changes in reactivity than those who experienced a full night of sleep ($p = 0.01$; see Supplementary Figure 7). The study data showed that these enhanced responses were characterized by a more negative response to positive stimuli after sleep deprivation. However, when the comparison condition was daytime waking,

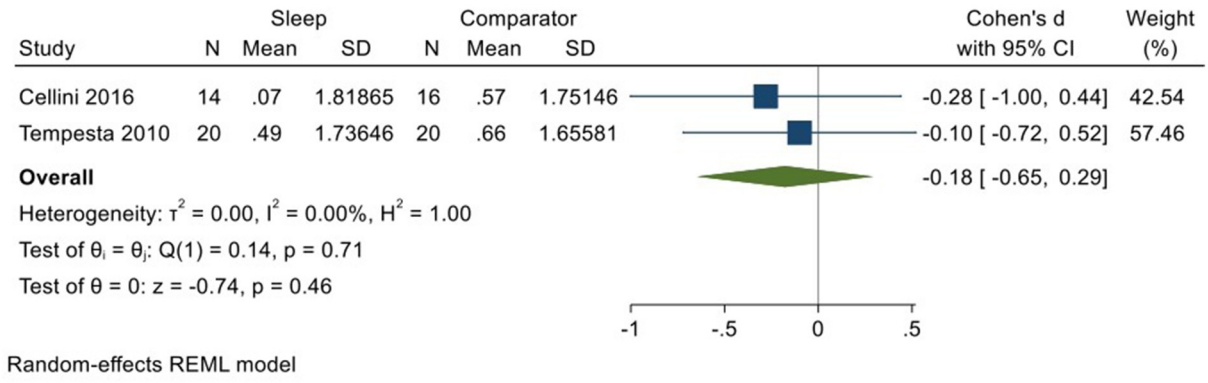

FIGURE 11
Meta-analysis IX: Outcomes for self-reported arousal ratings in response to positive stimuli – changes across a period of sleep compared to across a period of waking ($K = 2$, $N = 70$).

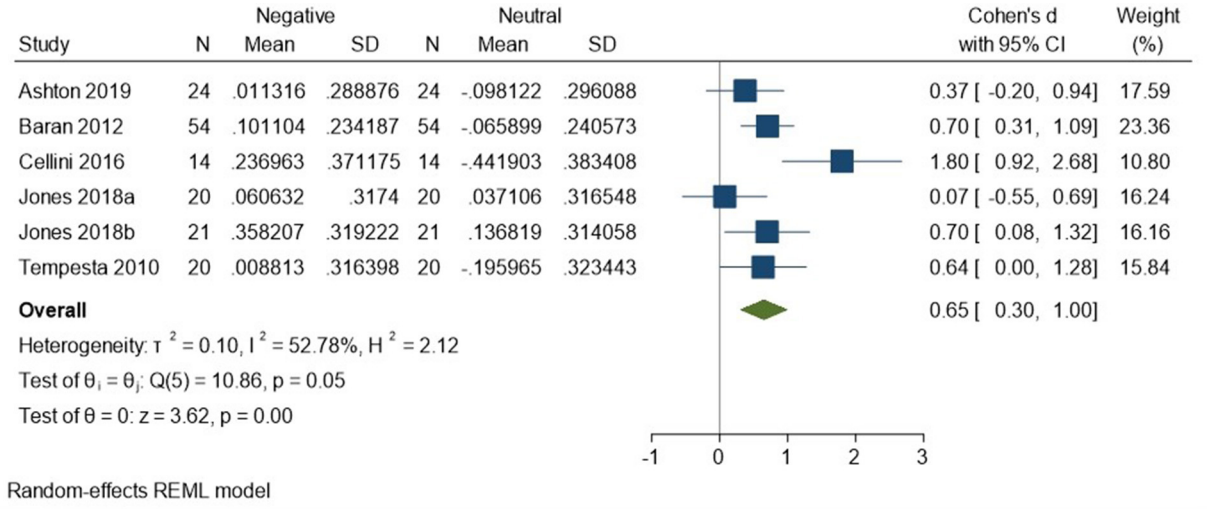

FIGURE 12
Meta-analysis X: a 2 (condition: sleep, waking) × 2 (valence: negative, neutral) comparison of self-reported arousal ratings ($K = 6$, $N = 281$).

participants tended to have increased reactivity, albeit somewhat unreliably, to positive stimuli after a period of sleep rather than waking.

Subgroup analyses examining the effect of sleep duration revealed that participants tended to have attenuated reactivity in response to negative stimuli after a nap, rather than an equivalent period of waking, and a slight but inconsistent increase in reactivity after a whole night of sleep ($p = 0.04$; see Supplementary Figure 8). However, the analyses showed an opposite effect for ratings in response to positive stimuli: Whereas participants responded more strongly to positive stimuli after a nap compared to a period of waking, after a whole night of sleep compared to a period of waking, they tended to have attenuated responses to these stimuli ($p = 0.02$; see Supplementary Figure 10). Notably, however, the differences observed in this analysis may be due to the effects of the comparator condition, given that all the studies using a nap paradigm had daytime waking as a control whereas almost all the studies using the whole night method used sleep deprivation as the comparison. There was no significant subgroup effect for valence ratings in response to neutral stimuli.

Finally, participants who obtained REM sleep, compared to those who did not spend any significant time in this sleep stage, did not react significantly differently to negative material in a sleep-vs.-waking analysis ($p = 0.76$; see Supplementary Figure 14). However, a similar analysis of data for reactivity to neutral material detected a significant subgroup effect ($p = 0.04$; see Supplementary Figure 15). This finding

suggests that participants who did not obtain a substantial amount of REM sleep (i.e., spent a larger proportion of their sleep time in non-REM stages) showed attenuated reactivity to neutral stimuli after a period of sleep but not after a period of ordinary daytime wakefulness or sleep deprivation. No such effect was observed for participants who obtained a substantial amount of REM sleep. Regarding reactivity in response to positive material, there was a significant difference between those that experienced REM sleep and those that were less likely to experience this stage of sleep, $p = 0.01$ (see Supplementary Figure 16). However, this effect overlaps almost entirely with the difference seen between studies that used a sleep deprivation versus daytime waking control condition, and as a result should not be interpreted as a REM-specific result.

Publication bias

Only the negative and neutral valence comparisons had a sufficient number of included studies to explore evidence for possible publication bias. The funnel plots (see Supplementary Figures 23, 24) suggested that although there were some outliers with large effect sizes, there was no systematic evidence of such bias. Results from Egger's test also suggested no evidence for small study effects in both the negative ($p = 0.79$) and neutral ($p = 0.21$) comparisons.

Discussion

Previously published studies investigating whether sleep regulates spontaneous emotional regulation have produced contradictory results: it is unclear whether a period of sleep experienced subsequent to encounters with emotionally valenced stimuli will, upon further exposure to those stimuli, attenuate, enhance, or simply maintain reactivity to them. Hence, we set out to systematically review and meta-analyze published work investigating whether sleep, without cognitive modulation, acts to regulate emotion. We reviewed studies that reported emotional reactivity for negatively and/or positively valenced material compared to neutral material over any period of sleep (whole night or nap) compared to a matched period of waking or sleep deprivation (i.e., wakefulness during either the day or the night). Given the broader literature indicating that sleep restriction impacts mood negatively, we hypothesized that our review would show that sleep preferentially down-regulates or ameliorates reactivity to emotional stimuli over neutral stimuli, and that this down-regulation or amelioration is greater than what is observed over equivalent periods of waking.

Broadly speaking, our results did not confirm this prediction. Sleep (or, indeed, equivalent periods of wakefulness) did not have a statistically significant effect on physiological measures of emotional reactivity to either negatively valenced or neutral stimuli. However, sleep did have a statistically significant effect on self-report measures of emotional reactivity, albeit not always in the predicted direction. Specifically, arousal ratings in response to negatively valenced stimuli (but not positively valenced or neutral stimuli) were significantly higher after a period of sleep but not after an equivalent period of waking.

Sub-group analyses of data regarding self-reported valence and arousal outcomes indicated that several important moderators influenced differences in emotional reactivity between sleep and waking conditions. First, participants who were sleep deprived in comparison to those who slept a full night rated positive stimuli more negatively, but no such between-condition difference was significant when the comparison condition was a period of daytime wakefulness. Second, participants in nap conditions in comparison to those who experienced an equivalent period of waking rated negative pictures less negatively. Participants showed a slight but inconsistent increase in reactivity after a whole night of sleep, in comparison with waking conditions. Third, participants who did not spend a significant amount of time in REM sleep tended to provide attenuated valence ratings in response to neutral stimuli after a period of sleep, rather than waking. This effect was not observed in those who did achieve REM sleep.

Studies reporting psychophysiological outcomes

Our finding that sleep did not have a statistically significant effect on changes in psychophysiological reactivity to negatively valenced or neutral stimuli is consistent with results reported previously in this literature. Several single empirical studies have shown that HRD or SCL responses to valenced and neutral material were not significantly different before and after a period of sleep (Kuriyama et al., 2010, 2013; Hot et al., 2016; Bolinger et al., 2018, 2019). However, three of these studies showed that HRD in response to such material decreased over a period of waking (Kuriyama et al., 2013; Bolinger et al., 2018, 2019). Furthermore, Bolinger et al. (2018) showed that this effect was driven by a decrease in reactivity to negative stimuli in particular.

Our meta-analysis detected a non-significant trend toward increased HRD in response to negatively valenced stimuli after a period of sleep relative to an equivalent period of waking. Some authors have found significantly enhanced HRD in response to negatively valenced material after sleep (Pace-Schott et al., 2011; Ashton et al., 2019), although the latter noted that this pattern of data was also observed for neutral stimuli.

In summary, the cumulative results from this group of studies suggest that psychophysiological measures of changes in emotional reactivity do not consistently detect any significant effects of sleep, and that when they

do detect these effects, they are not specific to valenced materials. Although one psychophysiological measure (HRD) does appear relatively more sensitive to sleep-associated changes in emotional reactivity, effects are not strong or consistent and it remains unclear whether they are specific to valenced material.

Studies reporting valence and arousal rating outcomes

Our finding of the trend toward post-sleep enhanced HRD in response to negative material is mirrored by our findings from the data regarding self-reported arousal ratings. Our analyses indicated that, for negative material to a significantly greater extent than neutral material, these ratings were also higher after a period of sleep compared to a period of waking. Overall, these results suggest that self-reported arousal is a sensitive measure of changes in emotional reactivity across periods of sleep.

This finding is consistent with some results reported previously in the literature. For example, Kuriyama et al. (2010) and Alfarra et al. (2015) found that emotionally valenced pictures were rated as having less emotional charge after a period of sleep deprivation.

This common trend across the psychophysiological and self-report data (i.e., distinct post-sleep increases in arousal responses to negatively valenced material) may reflect a type of environmental adaptation. In healthy adults, enhanced arousal after sleep may contribute to an emotional "next-day readiness" that allows the person an increased sensitivity to emotional stimuli in the environment. Future studies could examine sleep-dependent emotional processing in the context of the cortisol awakening response, which is a biological measure of next-day readiness (Xiong et al., 2021). It should be noted that none of the studies included in the meta-analysis investigated the impact of cortisol levels on emotion reactivity.

However, post-sleep enhancement of self-reported arousal to negative material is not found commonly in this literature. In fact, the opposite result is reported more frequently. For example, Gujar et al. (2011) showed that, in participants who had taken a 90-min nap and obtained REM sleep, post-vs. pre-sleep ratings of fearful expressions were lower (although ratings of angry expressions had not changed and ratings of happy expressions were higher). A different pattern of reactivity was observed in participants who had an afternoon of normal waking activity: They showed amplified reactivity to angry and fearful faces originally viewed earlier in the day.

The current finding of no significant effect of sleep on self-reported valence ratings for negative, positive, and neutral material is, unsurprisingly, consistent with the findings reported by most previous studies. Those studies tend to show either maintained reactivity to valenced material after a period of sleep compared to a period of waking, or no effect of either sleep or waking on both valenced and neutral material (e.g., Tempesta et al., 2015; Cellini et al., 2016; Prehn-Kristensen et al., 2017).

Our sub-group analyses of self-report outcomes suggested that the kind of waking comparison condition (daytime waking or nighttime waking, i.e., sleep deprivation), the duration of sleep (nap or whole night), and the presence/absence of REM sleep all had an impact on self-reported valence ratings.

Regarding the use of daytime waking or sleep deprivation as a comparison to the sleep condition, ideally we would have sought to examine the effects of each kind of comparison condition separately – sleep loss may have different effects on emotion regulation than the passage of ordinary wakefulness (Baran et al., 2012; Motomura et al., 2013). However, our sample did not include enough studies featuring each different comparison condition to examine these effects independently. Nonetheless, sub-group analyses revealed that the comparison between sleep and daytime waking differed from that between sleep and sleep deprivation with respect to self-reported valence ratings in response to positive stimuli. Whereas participants who were sleep deprived tended to respond significantly more negatively to positive stimuli in comparison to their sleep-condition counterparts, those who experienced daytime wakefulness tended to show a more neutral response to these stimuli than those who slept, who showed higher positive ratings. These findings are consistent with several studies indicating that there are specific decreases in positive emotion after sleep deprivation (McMakin et al., 2016; Finan et al., 2017). Furthermore, the finding that individuals may experience increased reactivity to positive stimuli after sleep in comparison with waking is consistent with our main finding of increased arousal (self-report and, to a lesser degree, psychophysiological) after sleep rather than waking.

Regarding sleep duration, we found that having a nap or experiencing a full night of sleep had differing effects on self-reported valence ratings in response to negative stimuli. Whereas a nap (in comparison with an equivalent period of daytime waking) tended to decrease valence ratings in response to these stimuli, a full night of sleep (in comparison to either daytime walking or night-time sleep deprivation) slightly increased valence ratings. These results suggest that responses to previously encountered negative stimuli are modulated differently by a daytime nap and a full night of sleep. One possible mechanism underlying this effect may be the differing proportions of NREM and REM sleep or spindle quality during napping and whole-night sleep (van Schalkwijk et al., 2019).

Finally, sub-group analyses indicated that the presence or absence of REM sleep moderated changes in emotional reactivity for neutral material. Participants who did not obtain substantial REM sleep during either a whole night of sleep or a daytime nap had attenuated reactivity to neutral stimuli, whereas the same effect was not found in those who either (a) did obtain substantial REM sleep, or (b) were exposed to sleep deprivation or ordinary wakefulness. This result may point to

differential effects of REM and NREM sleep stages on sleep-dependent emotional processing, with NREM sleep possibly more responsible for processing neutral information and down-regulating responses to such stimuli.

Limitations and directions for future research

Perhaps the most consequential limitation of the foundational literature, certainly in terms of its influence on our review, is the vast cross-study differences in methodology. These methodological variations include the timing and duration of the sleep condition, the type of waking control used, the kind of emotional stimulus presented, the primary outcome measured, and whether participants obtained REM sleep (a stage previously observed to be central to the emotional regulatory benefits of sleep; Palagini et al., 2013; Altena et al., 2016). The consequence of these variations is heterogeneity among reported results and limited power to draw conclusions from a meta-analysis.

A second potential limitation is that the relatively small sample sizes within each of our quantitative analyses meant we could not fully explore the bounds of our meta-analysis. For instance, when considering data from studies reporting psychophysiological outcomes, we could not conduct subgroup analyses investigating potential moderators of the effect of sleep on emotional reactivity. One potential moderator here is whether participants in the comparison condition experienced sleep deprivation (i.e., nighttime waking) or ordinary daytime waking, but because all the psychophysiological studies included in our sample used a waking control group we could not investigate further. Other potential moderators are sleep duration and whether participants in the sleep condition obtained REM sleep, but again only one psychophysiological study in our sample used a nap rather than a whole night condition and only one presented REM-specific data. Given this lack of sub-group analyses, we cannot comment fully on the question of under which specific experimental conditions particular effects might be observed.

A third potential limitation is that, in most studies included in our review sample (and, notably, in every psychophysiological study), participants viewed many IAPS pictures. Hence, after a certain point they may have become desensitized to the valenced material and might have begun to evince similar reactions to those images as to neutral images. This consequence of desensitization might explain why the analyses did not consistently detect differences in emotional reactivity to valenced vs. neutral material.

A fourth potential limitation is that not all studies in our sample controlled for time-of-day effects. These influence performance on a variety of cognitive tasks, including emotion regulation (Van Dongen and Dinges, 2003; Schmidt et al., 2007). Additionally, diurnal variations in emotional reactivity are associated with similar time-based changes in autonomic and sympathetic nervous system functioning, with some studies reporting increased reactivity to negative stimuli at "off peak" times of day (Hot et al., 2005; Tucker et al., 2012). Overall, there is a need for more research evaluating interactions between physiological states and emotion regulation to help discern the chronopsychophysiology of emotional processing.

Similarly, not all studies in our sample controlled for sleep history, sleepiness, and vigilance. Of the 14 studies included in the meta-analysis, only half reported methodological attempts to control for these potential confounders. Even the studies that did report implementing such controls took only between-group measures of sleepiness, psychomotor vigilance, and current subjective mood, and did so inconsistently. Furthermore, although most studies asked participants to maintain a regular sleep schedule prior to the starting the experimental procedures, not all measured whether this was achieved. Therefore, it is possible that circadian factors other than sleep had an influence on emotional reactivity. Future studies should strictly control for these factors.

Summary and conclusion

Overall, our systematic review and meta-analysis indicates that sleep (or, indeed, equivalent periods of wakefulness) does not have a statistically significant effect on psychophysiological measures of emotional reactivity, to either valenced or neutral stimuli. However, self-reported arousal ratings in response to negatively valenced stimuli (but not positively valenced or neutral stimuli) were significantly higher after a period of sleep but not after an equivalent period of waking. Sub-group analyses suggested that the kind of waking comparison condition (regular daytime waking or nighttime sleep deprivation), sleep duration (nap or whole night), and the presence/absence of REM sleep all had an impact on self-reported valence ratings.

Taken together, these results suggest that sleep may have a larger effect on subjective emotional experience than on objectively measured physiological experiences of emotion. In other words, sleep might impact more on responses that are subject to cognitive control than on those that are generated automatically. A caution here is that this speculation is influenced by the fact that a relatively small number of studies in this literature have taken psychophysiological measures.

More consistency in study methodology is needed before the field can gain a better understanding of how sleep impacts reactivity to emotionally valenced information. Future research studies should endeavor to collect both psychophysiological (with an emphasis on HRD) and self-report measures, to

report and collect REM sleep parameters, to report all different valence- and condition-specific data independently rather than in aggregate form and control for circadian and time-of-day effects.

A number of other important questions remain unanswered in the field. First, underlying mechanisms explaining sleep-dependent modulation of emotional reactivity remain poorly understood. These mechanisms may be numerous and anatomically widespread. For example, sleep-dependent memory consolidation is governed by reactivation, neocortical-thalamic- hippocampal dialogue, and synaptic downscaling (Diekelmann et al., 2009; Wilhelm et al., 2012; Goerke et al., 2017). Although there is some evidence of reactivation of emotional material during sleep (Cellini and Capuozzo, 2018; Hutchison et al., 2021), the neural patterns of activation and the specific electrophysiological frequencies that control autonomic and cognitive sleep-dependent emotion regulation remain unexplained (or, at best, are supported by conflicting strands of evidence). Second, in this review we focused on sleep-dependent modulation of emotional reactivity: however, many other forms of emotion-related processes may be modulated by sleep. These include extinction, habituation, mood, and intentional cognitive modulation of emotion. Future studies should state explicitly which kind of emotion-related process is being investigated; more broadly, the literature as a whole should seek to examine to what extent and in which ways each process is modulated by sleep.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

GL and JM conceived the project idea and conducted the initial literature search. GL, HA, RL, JM, KT, DB, and MH screened and evaluated article titles, abstracts, and texts for inclusion in the review. HA reviewed a set of review articles and searching for articles that might be included in the review. BS conducted the statistical analyses. GL contributed to interpretation of those analyses. HA and DB conducted the narrative analysis. GL, JM, and KT prepared the manuscript for submission. All authors discussed the results and contributed to writing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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References

Alfarra, R., Fins, A. I., Chayo, I., and Tartar, J. L. (2015). Changes in attention to an emotional task after sleep deprivation: neurophysiological and behavioral findings. *Biol. Psychol.* 104, 1–7. doi: 10.1016/j.biopsycho.2014.11.001

Altena, E., Micoulaud-Franchi, J.-A., Geoffroy, P.-A., Sanz-Arigita, E., Bioulac, S., et al. (2016). The bidirectional relation between emotional reactivity and sleep: from disruption to recovery. *Behav. Neurosci.* 130, 336–350. doi: 10.1037/bne0000128

Ashton, J. E., Harrington, M. O., Guttesen, A. Á. V., Smith, A. K., and Cairney, S. A. (2019). Sleep preserves physiological arousal in emotional memory. *Sci. Rep.* 9, 1–10. doi: 10.1038/s41598-019-42478-2

Baran, B., Pace-Schott, E. F., Ericson, C., and Spencer, R. M. C. (2012). Processing of emotional reactivity and emotional memory over sleep. *J. Neurosci.* 32, 1035–1042. doi: 10.1523/JNEUROSCI.2532-11.2012

Baum, K. T., Desai, A., Field, J., Miller, L. E., Rausch, J., and Beebe, D. W. (2014). Sleep restriction worsens mood and emotion regulation in adolescents. *J. Child. Psychol. Psychiatr.* 55, 180–190. doi: 10.1111/jcpp.12125

Becerra, R., and Campitelli, G. (2013). Emotional reactivity: critical analysis and proposal of a new scale. *Int. J. Appl. Psychol.* 3, 161–168. doi: 10.5923/j.ijap.20130306.03

Bolinger, E., Born, J., and Zinke, K. (2018). Sleep divergently affects cognitive and automatic emotional response in children. *Neuropsychologia* 117, 84–91. doi: 10.1016/j.neuropsychologia.2018.05.015

Bolinger, E., Cunningham, T. J., Payne, J. D., Bowman, M. A., Bulca, E., Born, J., et al. (2019). Sleep's benefits to emotional processing emerge in the long term. *Cortex* 120, 457–470. doi: 10.1016/j.cortex.2019.07.008

Bottary, R., Seo, J., Daffre, C., Gazecki, S., Moore, K. N., Kopotiyenko, K., et al. (2020). Fear extinction memory is negatively associated with REM sleep in insomnia disorder. *Sleep* 43, 1–12. doi: 10.1093/sleep/zsaa007

Cellini, N., and Capuozzo, A. (2018). Shaping memory consolidation via targeted memory reactivation during sleep. *Ann. N. Y. Acad. Sci.* 1426, 52–71. doi: 10.1111/nyas.13855

Cellini, N., Torre, J., Stegagno, L., and Sarlo, M. (2016). Sleep before and after learning promotes the consolidation of both neutral and emotional information regardless of REM presence. *Neurobiol. Learn. Mem.*133, 136–144. doi: 10.1016/j.nlm.2016.06.015

Cunningham, T. J., Crowell, C. R., Alger, S. E., Kensinger, E. A., Villano, M. A., Mattingly, S. M., et al. (2014). Psychophysiological arousal at encoding leads to reduced reactivity but enhanced emotional memory following sleep. *Neurobiol. Learn. Mem.*114, 155–164. doi: 10.1016/j.nlm.2014.06.002

Dang-Vu, T. T., Schabus, M., Desseilles, M., Sterpenich, V., Bonjean, M., and Maquet, P. (2010). Functional neuroimaging insights into the physiology of human sleep. *Sleep* 33, 1589–1603. doi: 10.1093/sleep/33.12.1589

Deliens, G., Gilson, M., and Peigneux, P. (2014). Sleep and the processing of emotions. *Exp. Brain Res.* 232, 1403–1414. doi: 10.1007/s00221-014-3832-1

Diekelmann, S., Wilhelm, I., and Born, J. (2009). The whats and whens of sleep-dependent memory consolidation. *Sleep Med. Rev.* 13, 309–321. doi: 10.1016/j.smrv.2008.08.002

Ebner, N. C., Riediger, M., and Lindenberger, U. (2010). FACES—a database of facial expressions in young, middle-aged, and older women and men: development and validation. *Behav. Res. Methods* 42, 351–362. doi: 10.3758/BRM.42.1.351

Finan, P. H., Quartana, P. J., Remeniuk, B., Garland, E. L., Rhudy, J. L., Hand, M., et al. (2017). Partial sleep deprivation attenuates the positive affective system: effects across multiple measurement modalities. *Sleep* 40, 1–9. doi: 10.1093/sleep/zsw017

Frumento, S., Menicucci, D., Hitchcott, P. K., and Zaccaro, A. (2021). Systematic review of studies on subliminal exposure to phobic stimuli: integrating therapeutic models for specific phobias. *Front. Neurosci.* 15, 654170. doi: 10.3389/fnins.2021.654170

Gilson, M., Deliens, G., Leproult, R., Bodart, A., Nonclercq, A., Ercek, R., et al. (2016). REM-enriched naps are associated with memory consolidation for sad stories and enhance mood-related reactivity. *Brain Sci.* 6, 1. doi: 10.3390/brainsci6010001

Goeleven, E., Raedt, D. E., Leyman, R. L., and Verschuere, B. (2008). The Karolinska directed emotional faces: a validation study. *Cogn. Emot.* 22, 1094–1118. doi: 10.1080/02699930701626582

Goerke, M., Müller, N. G., and Cohrs, S. (2017). Sleep-dependent memory consolidation and its implications for psychiatry. *J. Neural Transm.* 124, 163–178. doi: 10.1007/s00702-015-1476-3

Goldstein, A. N., Greer, S. M., Saletin, J. M., Harvey, A. G., Nitschke, J. B., and Walker, M. P. (2013). Tired and apprehensive: anxiety amplifies the impact of sleep loss on aversive brain anticipation. *J. Neurosci.* 33, 10607–10615. doi: 10.1523/JNEUROSCI.5578-12.2013

Gross, J. J., Sheppes, G., and Urry, H. L. (2011). Cognition and emotion lecture at the 2010 SPSP emotion preconference. *Cogn. Emot.* 25, 765–781. doi: 10.1080/02699931.2011.555753

Gujar, N., McDonald, S. A., Nishida, M., and Walker, M. P. (2011). A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. *Cereb. Cortex* 21, 115–123. doi: 10.1093/cercor/bhq064

Gur, R. C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., et al. (2002). A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *J. Neurosci. Methods* 115, 137–143. doi: 10.1016/S0165-0270(02)00006-7

Higgins, J. P. T., Li, T., and Deeks, J. J. (2022). "Choosing effect measures and computing estimates of effect: Section 6, 5.2.8," in *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.3 (updated February 2022)*, eds J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. Page, V.A. Welch. Available online at: www.training.cochrane.org/handbook (accessed April 01, 2022).

Hot, P., Leconte, P., and Sequeira, H. (2005). Diurnal autonomic variations and emotional reactivity. *Biol. Psychol.* 69, 261–270. doi: 10.1016/j.biopsycho.2004.08.005

Hot, P., Rutka, R., Belhandouz, J., Bazière, E., Madelon, C., Bachelin, P., et al. (2016). The role of slow wave sleep in emotion regulation. *Int. J. Psychophysiol.* 108, 146. doi: 10.1016/j.ijpsycho.2016.07.425

Hutchison, I. C., Pezzoli, S., Tsimpanouli, M. E., Abdellahi, M. E., Pobric, G., Hulleman, J., et al. (2021). Targeted memory reactivation in REM but not SWS selectively reduces arousal responses. *Commun. Biol.* 4, 1–6. doi: 10.1038/s42003-021-01854-3

Jones, B. J., Mackay, A., Mantua, J., Schultz, K. S., and Spencer, R. M. C. (2018). The role of sleep in emotional memory processing in middle age. *Neurobiol. Learn. Mem.* 155, 208–215. doi: 10.1016/j.nlm.2018.08.002

Kring, A. M., and Sloan, D. M. (2007). The Facial Expression Coding System (FACES): development, validation, and utility. *Psychol. Assess.*19, 210–224. doi: 10.1037/1040-3590.19.2.210

Kuriyama, K., Honma, M., Yoshiike, T., and Kim, Y. (2013). Memory suppression trades prolonged fear and sleep-dependent fear plasticity for the avoidance of current fear. *Sci.Rep.* 3, 2227. doi: 10.1038/srep02227

Kuriyama, K., Soshi, T., and Kim, Y. (2010). Sleep deprivation facilitates extinction of implicit fear generalization and physiological response to fear. *Biol. Psychiatry* 68, 991–998. doi: 10.1016/j.biopsych.2010.08.015

Lau, E. Y. Y., Lau, K. N. T., Chan, C. S., Tseng, C., Lam, Y. C., Tse, D. M., et al. (2020). Effects of REM sleep during a daytime nap on emotional perception in individuals with and without depression. *J.Affect.Disord.* 260, 687–694. doi: 10.1016/j.jad.2019.09.058

Legendre, G. Y. T., Bayer, L., Seeck, M., Spinelli, L., Schwartz, S., and Sterpenich, V. (2022). Reinstatement of emotional associations during human sleep: an intracranial EEG study. *bioRxiv*. doi: 10.1101/2022.06.24.497499

Levenson, R. W. (1999). The intrapersonal functions of emotion. *Cogn.Emot.*13, 481–504. doi: 10.1080/026999399379159

Lipinska, G., and Thomas, K. G. F. (2019). The interaction of REM fragmentation and night-time arousal modulates sleep-dependent emotional memory consolidation. *Front. Psychol.* 10, 1766. doi: 10.3389/fpsyg.2019.01766

Mauss, I. B., Troy, A. S., and LeBourgeois, M. K. (2013). Poorer sleep quality is associated with lower emotion-regulation ability in a laboratory paradigm. *Cogn. Emot.* 27, 567–576. doi: 10.1080/02699931.2012.727783

McMakin, D. L., Dahl, R. E., Buysse, D. J., Cousins, J. C., Forbes, E. E., Silk, J. S., et al. (2016). The impact of experimental sleep restriction on affective functioning in social and nonsocial contexts among adolescents. *J. Child Psychol. Psychiatry* 57, 1027–1037. doi: 10.1111/jcpp.12568

Minear, M., and Park, D. C. (2004). A lifespan database of adult facial stimuli. *Behav. Res. Meth. Instrum. Comput.* 36, 630–633. doi: 10.3758/BF03206543

Minkel, J., Htaik, O., Banks, S., and Dinges, D. (2011). Emotional expressiveness in sleep-deprived healthy adults. *Behav. Sleep Med.* 9, 5–14. doi: 10.1080/15402002.2011.533987

Morris, S. B. (2008). Estimating effect sizes from pretest-posttest-control group designs. *Organ. Res. Methods* 11, 364–386. doi: 10.1177/1094428106291059

Motomura, Y., Kitamura, S., Oba, K., Terasawa, Y., Enomoto, M., Katayose, Y., et al. (2013). Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PLoS ONE* 8, e56578. doi: 10.1371/annotation/5970fff3-0a1c-4056-9396-408d76165c4d

Pace-Schott, E. F., Shepherd, E., Spencer, R. M. C., Marcello, M., Tucker, M., Propper, R. E., et al. (2011). Napping promotes inter-session habituation to emotional stimuli. *Neurobiol. Learn. Mem.* 95, 24–36. doi: 10.1016/j.nlm.2010.10.006

Palagini, L., Baglioni, C., Ciapparelli, A., Gemignani, A., and Riemann, D. (2013). REM sleep dysregulation in depression: state of the art. *Sleep Med. Rev.* 17, 377–390. doi: 10.1016/j.smrv.2012.11.001

Palmer, C. A., and Alfano, C. A. (2017). Sleep and emotion regulation: an organizing, integrative review. *Sleep Med. Rev.* 31, 6–16. doi: 10.1016/j.smrv.2015.12.006

Picó-Pérez, M., Alemany-Navarro, M., Dunsmoor, J. E., Radua, J., Albajes-Eizagirre, A., Vervliet, B., et al. (2019). Common and distinct neural correlates of fear extinction and cognitive reappraisal: a meta-analysis of fMRI studies. *Neurosci. Biobehav. Rev.* 104, 102–115. doi: 10.1016/j.neubiorev.2019.06.029

Prehn-Kristensen, A., Molzow, I., Förster, A., Siebenhühner, N., Gesch, M., Wiesner, C. D., et al. (2017). Memory consolidation of socially relevant stimuli during sleep in healthy children and children with attention-deficit/hyperactivity disorder and oppositional defiant disorder: what you can see in their eyes. *Biol. Psychol.* 123, 196–204. doi: 10.1016/j.biopsycho.2016.12.017

Reddy, R., Jackson, C., Talavera, D., and Alfano, C. A. (2014). Changes in anxiety, affect, and emotion regulation among sleep-restricted healthy adolescents: an experimental investigation. *J. Sleep Res.* 23, 271.

Reid, M. J., Omlin, X., Notebaert, L., Espie, C., and Kyle, S. (2019). The effect of sleep continuity disruption on threat-related attentional bias: randomised controlled experiment in good sleepers. *Sleep* 42, A49–A50. doi: 10.1093/sleep/zsz067.118

Rohatgi, A. (2021). WebPlotDigitizer (Version 4.5). WebPlotDigitizer. Available online at: https://automeris.io/WebPlotDigitizer (accessed February 17, 2022).

Schäfer, S. K., Wirth, B. E., Staginnus, M., Becker, N., Michael, T., and Sopp, M. R. (2020). Sleep's impact on emotional recognition memory: a meta-analysis of whole-night, nap, and REM sleep effects. *Sleep Med. Rev* 51, 101280. doi: 10.1016/j.smrv.2020.101280

Schmidt, C., Collette, F., Cajochen, C., and Peigneux, P. (2007). A time to think: circadian rhythms in human cognition. *Cogn. Neuropsychol.* 24, 755–789. doi: 10.1080/02643290701754158

Schoch, S. F., Cordi, M. J., and Rasch, B. (2017). Modulating influences of memory strength and sensitivity of the retrieval test on the detectability of the sleep consolidation effect. *Neurobiol. Learn. Mem.* 145, 181–189. doi: 10.1016/j.nlm.2017.10.009

Seo, J., Moore, K. N., Gazecki, S., Bottary, R. M., Milad, M. R., Song, H., et al. (2018). Delayed fear extinction in individuals with insomnia disorder. *Sleep* 41, zsy095. doi: 10.1093/sleep/zsy095

Seo, J., Oliver, K. I., Daffre, C., Moore, K. N., Gazecki, S., Lasko, N. B., et al. (2022). Associations of sleep measures with neural activations accompanying fear conditioning and extinction learning and memory in trauma-exposed individuals. *Sleep*, 45, zsab261. doi: 10.1093/sleep/zsab261

Short, M. A., and Louca, M. (2015). Sleep deprivation leads to mood deficits in healthy adolescents. *J Sleep Med.* 16, 987–993. doi: 10.1016/j.sleep.2015.03.007

Sterpenich, V., van Schie, M. K., Catsiyannis, M., Ramyead, A., Perrig, S., Yang, H., et al. (2021). Reward biases spontaneous neural reactivation during sleep. *Nat. Commun.* 12, 1–11. doi: 10.1038/s41467-021-24357-5

Tempesta, D., Couyoumdjian, A., Curcio, G., Moroni, F., Marzano, C., Gennaro, D., et al. (2010). Lack of sleep affects the evaluation of emotional stimuli. *Brain Res. Bull.*, 82, 104–108. doi: 10.1016/j.brainresbull.2010.01.014

Tempesta, D., Gennaro, D. E., Natale, L. V., and Ferrara, M. (2015). Emotional memory processing is influenced by sleep quality. *J. Sleep. Med.* 16, 862–870. doi: 10.1016/j.sleep.2015.01.024

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., et al. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Res.* 168, 242–249. doi: 10.1016/j.psychres.2008.05.006

Tucker, A. M., Feuerstein, R., Mende-Siedlecki, P., Ochsner, K. N., and Stern, Y. (2012). Double dissociation: circadian off-peak times increase emotional reactivity; aging impairs emotion regulation via reappraisal. *Emotion* 12, 869. doi: 10.1037/a0028207

Van Dongen, H. P., and Dinges, D. F. (2003). Investigating the interaction between the homeostatic and circadian processes of sleep–wake regulation for the prediction of waking neurobehavioural performance. *J. Sleep Res.* 12, pp.181–187. doi: 10.1046/j.1365-2869.2003.00357.x

van Schalkwijk, F. J., Sauter, C., Hoedlmoser, K., Heib, D. P. J., Klösch, G., Moser, D., et al. (2019). The effect of daytime napping and full-night sleep on the consolidation of declarative and procedural information. *J. Sleep Res.* 28, e12649. doi: 10.1111/jsr.12649

Wagner, U., Fischer, S., and Born, J. (2002). Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. *Psychosom. Med.* 64, 627–634. doi: 10.1097/01.PSY.0000021940.35402.51

Wilhelm, I., Prehn-Kristensen, A., and Born, J. (2012). Sleep-dependent memory consolidation–what can be learnt from children? *Neurosci. Biobehav. Rev.* 36, 1718–1728. doi: 10.1016/j.neubiorev.2012.03.002

Xiong, B., Chen, C., Tian, Y., Zhang, S., Liu, C., Evans, T. M., et al. (2021). Brain preparedness: the proactive role of the cortisol awakening response in hippocampal-prefrontal functional interactions. *Prog. Neurobiol.* 205, 102127. doi: 10.1016/j.pneurobio.2021.102127

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Negative dream affect is associated with next-day affect level, but not with affect reactivity or affect regulation

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There is increasing evidence that sleep plays an important role in affective processing. However, it is unclear whether dreaming—the subjective experiences we have during sleep—also serves an affect regulation function. Here, we investigated the within-person relationship between negative affect experienced in dreams and next-day waking affect level, affect reactivity, and affect regulation. For 5 days, 40 participants reported their dreams and rated their dream affect and post-sleep waking affect level upon morning awakening. Thereafter, they performed an affect reactivity and regulation task which involved viewing neutral and negative pictures with the instruction either to simply view the pictures or to down-regulate the affect evoked by these pictures. Multilevel regression analyses showed that the more negative affect people experienced in their dreams at night, the more negative affect and the less positive affect they reported the next morning. However, negative dream affect was associated neither with affect reactivity to the pictures nor with the ability to down-regulate negative affect in response to these pictures. In fact, Bayesian analyses favored the null hypotheses. These findings fail to provide support for the affect regulation function of dreaming and, instead, speak for affective continuity between dreaming and post-sleep wakefulness.

KEYWORDS

emotion, emotion regulation, REM sleep, dreaming, continuity hypothesis

Introduction

Sleep, especially rapid eye movement (REM) sleep, plays an important role in affective processing. Poor sleep is a risk factor for a range of affective disorders, such as anxiety and depression (e.g., Alvaro et al., 2013). In non-clinical populations, sleep disturbances have been associated with next-day negative affect (Konjarski et al., 2018)

and enhanced reactivity to affective stimuli (Altena et al., 2016), although evidence remains mixed (ten Brink et al., 2022). It has been argued that this occurs because sleep plays an important role in affect regulation and poor sleep impairs this process (Walker and van der Helm, 2009; Palmer and Alfano, 2017; Tempesta et al., 2018). However, it remains unclear whether the subjective experiences we have during sleep—our dreams—also contribute to affect regulation.

According to the so-called emotion regulation theories of dreaming, the function of dreams is to (re)process and regulate affect (Cartwright, 1991, 2010; Kramer, 1991, 1993; Hartmann, 1996, 2011; Levin and Nielsen, 2007; Perogamvros and Schwartz, 2012; Malinowski and Horton, 2015). Despite some variation in the specifics of these theories, they all agree that dreams incorporate and reprocess the memories of affective experiences of the waking life, integrate them with existing memory elements, to ultimately downregulate their intensity and thus help us cope better with these experiences during wakefulness. Affect in dreams either reflects this process or is a necessary condition for regulation to take place (Malinowski and Horton, 2015). Most of these theories attribute a special role to negative affect: dreams specifically incorporate negative affect (e.g., fear) and the processing of this leads to more adaptive responses to negative (e.g., threatening) stimuli in wakefulness, akin to fear extinction (Scarpelli et al., 2019). This applies to so-called normal dreams and occasional bad dreams, because frequent nightmares reflect a failure of the affect regulation function (Levin and Nielsen, 2007). Dreaming is thus seen as an "emotional thermostat" (Kramer, 1991, 1993) or "overnight therapy" (Hartmann, 1996; Walker and van der Helm, 2009) that aids affective adaptation in wakefulness. Yet, it is not entirely clear from these theories how exactly the affect regulation function is meant to be reflected in waking affect. Some of the possible predictions derived from these theories are that negative dream affect may lead to (a) a less negative, and more positive, post-sleep *affect level* upon morning awakening; (b) lower *affect reactivity* to (negative) stimuli in wakefulness; and (c) improved *affect regulation* as such.

In contrast to emotion regulation theories, the so-called continuity theories of dreaming[1] assume that there is continuity between waking and dream experiences, that is, dream experiences do not serve any particular function but simply reflect waking events, experiences, and concerns (Schredl, 2003, 2018; Domhoff, 2017, 2018). Different types of continuity can be distinguished. For example, whereas thematic continuity refers to certain themes being continuous across wakefulness and dreaming (e.g., studying for exams in waking life and dreaming about exams), affective continuity refers to the affective tone of waking life events being continuous with dream affect, irrespective of the specific thematic content (e.g., watching a movie about zombies and having a nightmare about being late to the exam) (Schredl, 2018). According to affective continuity (the focus of this paper), pre-and post-sleep waking affect is continuous with dream affect, with the more affectively intense daytime events being more likely to be incorporated into dreams (Schredl and Hofmann, 2003; Schredl, 2018) and the affective nature of the dream, in turn, influencing affect experienced in subsequent waking life (Schredl and Reinhard, 2009–2010). Thus, negative dream affect reflects enhanced negativity in waking life (which could occur due to state and/or trait factors).

To date, most research has focused on the relationship between dream affect and (post-sleep) waking affect level. Whereas some earlier studies supported emotion regulation theories of dreaming, demonstrating that negatively valenced dreams are associated with more positively valenced post-sleep affect (e.g., Cohen and Cox, 1975) or better coping with adverse life experiences (e.g., Cartwright, 1991, 2010), more recent studies lend greater support for the continuity theories, reporting positive correlations between dream affect and post-sleep affect (e.g., Schredl and Doll, 1998; Yu, 2007; Mallett et al., 2021; Barbeau et al., 2022a). Importantly, studies directly testing the affect regulation function of dreaming have often failed to find evidence for the affect regulation function (e.g., De Koninck and Koulack, 1975; Tousignant et al., 2022).

Few studies have investigated the relationship between dream affect and affect reactivity in wakefulness. In one recent study, Sterpenich et al. (2019) found that individuals who tended to experience negative affect, especially fear, in their home dreams had decreased activity in affect-generative brain areas (i.e., amygdala, right insula) and increased activity in affect-regulatory brain areas (i.e., medial prefrontal cortex) in response to aversive stimuli in wakefulness. The authors concluded that experiencing negative affect in dreams (beyond sleep) is associated with more adaptive affect regulation in wakefulness. However, because the authors studied between-person variability of dream affect and its relationship to affect reactivity, it remains unknown how dream affect is linked to next-day affect reactivity and regulation within individuals. In another study, Lara-Carrasco et al. (2009) showed that participants who experienced less intense negative affect in laboratory REM sleep dreams displayed the highest evening-to-morning decreases in affect reactivity, as reflected in negativity ratings of pictures. These findings suggest that negative dream affect is not associated with decreased, but increased, affective reactivity in subsequent wakefulness and, therefore, provide support for the continuity theories of dreaming.

Thus, findings regarding the link between dream affect and post-sleep waking affect level and affect reactivity are mixed. Importantly, to date, no studies have directly examined the link between dream affect and waking affect regulation as such. In this study, we addressed this gap by investigating the within-person relationship between dream affect and

1 Varying conceptualizations of the Continuity Hypothesis exist (Domhoff, 1996, 2017; Schredl, 2003, 2017). For clarity, we refer to these here as continuity theories of dreaming.

next-day post-sleep waking affect level, affect reactivity, and affect regulation. Our focus on within- rather than between-person association was motivated by the goal of providing the most direct possible test of the emotion regulation vs. continuity theories of dreaming. We did so by directly opposing predictions derived from these theories (see also Revonsuo et al., 2016). Although both emotion regulation theories and continuity theories agree that pre-sleep waking affect influences dream affect in a corresponding manner, they differ in their predictions regarding the effect of dream affect on subsequent post-sleep affect. According to emotion regulation theories, after a night with high (vs. low) negative dream affect, participants should display less negative (and more positive) post-sleep affect level, lower affect reactivity, and improved affect regulation ability. In contrast, the continuity theories would predict the opposite: after a night with high (vs. low) negative dream affect, participants should display more negative (and less positive) post-sleep affect level, higher affect reactivity, and lower affect regulation ability. We focused specifically on negative (rather than positive) dream affect because the emotion regulation theories of dreaming attribute a special role to negative affect. Furthermore, since the emotion regulation theories argue that dreaming *per se*, beyond sleep, has an affect regulatory function, and due to the role of sleep in affective processing, we controlled for sleep quality in all the analyses.

Materials and methods

Participants

According to Arend and Schäfer (2019), two-level models that would yield sufficient power ($\geq$0.80) to detect at least medium level-1 effect sizes, require sample sizes 30/5 (i.e., 5 measurement occasions from 30 participants) or 40/3 (i.e., 3 measurement occasions from 40 participants). Thus, we aimed to recruit 40 participants with at least 3 measurement occasions. To account for possible dropouts, and for the possibility of some participants reporting no dreams (or no affect experienced in dreams), we aimed to collect data from at least 50 participants.

Fifty-one healthy Finnish adults (44 females, 1 "other," $M_{age} = 25.18$, $SD_{age} = 7.12$), who self-reported no neurological, psychiatric, or sleep disorders, and who were not on any medication affecting the central nervous system, participated in the study. Eleven participants were excluded during data preprocessing (see section "Data reduction"), leaving a final sample of 40 participants (33 females, 1 "other") with an age range of 19–55 ($M = 25.35$, $SD = 7.39$) to be included in statistical analyses.

Participants were recruited *via* the University of Turku psychology students' credit pool, mailing lists of Finnish universities, as well as *via* advertisements posted on social media. Participants did not receive any monetary compensation. However, psychology students at the University of Turku could receive course credits for their participation, and other participants had the opportunity to take part in a lottery (2 $\times$ 20 € gift cards) as compensation for their time.

Experimental design and procedure

Participants first completed an online well-being questionnaire (administered *via* Webropol 3.0 survey tool). It contained demographic questions as well as scales measuring different aspects of well-being and ill-being, trait affect regulation, and general sleep quality. Since these data were collected in the framework of another study, these results will not be discussed further in this paper.

After completing the online well-being questionnaire, participants kept an online home dream diary (*via* Webropol 3.0) until dream reports had been provided on five mornings (see **Figure 1**). Participants were instructed to fill in the diary each morning immediately upon awakening. The diary contained questions about bed-time the previous evening, awakening time for the morning of diary completion, sleep quality the previous night, and whether participants recalled having a dream last night. If a dream was remembered, participants were asked to report their dream(s) in as much detail as possible and to rate the affect they experienced in the dream (see section "Measures"). They were also asked to rate their momentary (i.e., post-sleep waking) affect using the same scale as for dream affect. On mornings when participants provided dream reports and ratings of dream affect, they were also instructed to carry out an affect reactivity and regulation task (see section "Measures") immediately upon filling in the dream diary.

The study was conducted in line with the Declaration of Helsinki and was approved by the Ethical Committee for Human Sciences at the University of Turku, Finland. Informed consent was obtained from all participants prior to participation.

Measures

Dream affect

Dream affect was measured using both dimensional and discrete rating scales. Using two unipolar dimensional scales, participants were asked to rate the extent to which they experienced positive affect (PA) and negative affect (NA) in the dream on a scale from 1 (not at all) to 5 (extremely).

For discrete affect, the modified Differential Emotions Scale (mDES; Fredrickson, 2013) was used. The scale has been shown to have good psychometric properties (Sikka et al., 2017; Conte et al., 2020) and the Finnish version of the scale has been used in previous studies investigating dream affect (Sikka et al., 2014,

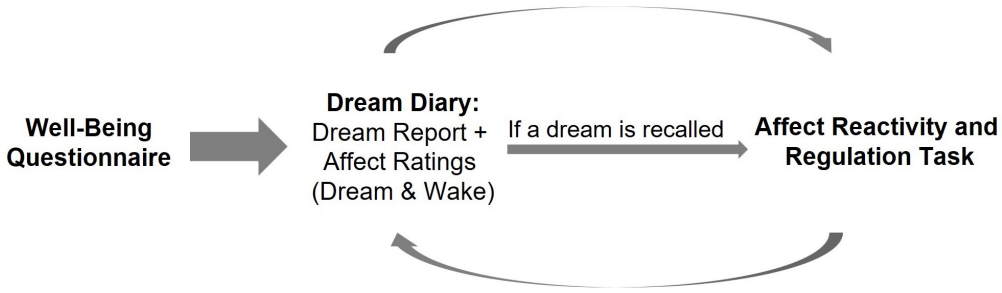

FIGURE 1
Procedure of the study. Participants first completed the well-being questionnaire. Thereafter, every morning upon awakening, they logged on to an online dream diary in which they answered questions about bed-time, waking time, sleep quality, and whether they remembered any dreams that night. If they recalled a dream, participants were asked to provide a narrative dream report and to rate the affect they experienced in the dream using dimensional and discrete affect rating scales. Participants also rated their post-sleep waking affect level. On the mornings when participants recalled a dream and provided dream affect ratings, they were instructed to carry out an affect reactivity and regulation task immediately upon filling in the dream diary. This procedure (i.e., filling in the dream diary and performing the task) was continued each morning until the participants had provided dream affect ratings and carried out the task five times (i.e., on five mornings).

2019). This 20-item scale measures 10 PA categories (e.g., "What is the most amused, fun-loving, or silly you felt?") and 10 NA categories (e.g., "What is the most angry, irritated, or annoyed you felt?") with three items per category. Participants were asked to think back to the dream they had had that night and to rate *the greatest amount* they experienced each of the affect items on a scale from 1 (not at all) to 5 (extremely). The 10 PA and 10 NA items were aggregated to form the PA (Cronbach's $a = 0.88$) and NA (Cronbach's $a = 0.84$) subscales, respectively.

For analyses, the mean scores of dimensional and discrete rating scales (i.e., mean of dimensional NA and discrete NA; mean of dimensional PA and discrete PA) were calculated separately for NA and PA for each dream.

Daily sleep quality

In the diary, participants were asked to rate the quality of their sleep during the preceding night on a scale from 1 (very good) to 4 (very bad). This item derives from the Pittsburgh Sleep Quality Index (Buysse et al., 1989).

Waking affect level

Waking affect level was measured using the same mDES scale as used to measure dream affect. Participants were asked to rate the extent to which they experienced each of the 20 affect items *in the present moment*. The 10 PA and 10 NA items were aggregated to form the PA (Cronbach's $a = 0.91$) and NA (Cronbach's $a = 0.79$) subscales, respectively.

Waking affect reactivity and regulation task

An online affect reactivity and regulation task was carried out *via* the Gorilla Experiment Builder platform[2] (Anwyl-Irvine et al., 2020). The task (see **Figure 2**) was based on previous studies investigating the role of sleep in next-day affect reactivity and regulation (Reddy et al., 2017; Zhang et al., 2019; Shermohammed et al., 2020) and is widely used to manipulate affect reactivity and regulation. Participants were shown a set of affective (negative) and neutral pictures selected from the Nencki Affective Pictures System (NAPS; Marchewka et al., 2014). They were asked either (a) to *view* the picture, try to understand its content, and let themselves freely experience all the feelings it evokes (without trying to change what they were feeling in any way), or (b) to *regulate* (reappraise) the feelings elicited by the picture following previously given instructions. At the beginning of the task, participants were provided information regarding how to regulate their affect using reappraisal. Specifically, they were instructed to look carefully at the picture and try to re-interpret the meaning of the picture so that it would elicit less negative feelings in them. Participants were also provided different examples of how to down-regulate their negative feelings: to imagine that the situation depicted in the picture is not true, but part of a movie ("It's just a movie"); to think that the situation depicted in the picture is getting better ("He will get better soon"); to think of a more positive explanation of the situation depicted in the picture ("Maybe he is tired, rather than lonely"); or to simply view the picture as a detached observer.

Every participant completed five sets of trials, each set performed on a separate day. The order of the sets was counterbalanced across participants. Each set consisted of 60 trials (20 view-neutral, 20 view-negative, and 20 regulate-negative) that were randomized within every set. The instruction ("view" or "regulate") coupled with the negative pictures was randomized across participants so that each negative picture was shown to some participants with the instruction to "view" and to the others with the instruction to "regulate," thus balancing any possible differences between the negative pictures used for each condition. Neutral pictures were always shown with the

2 www.gorilla.sc

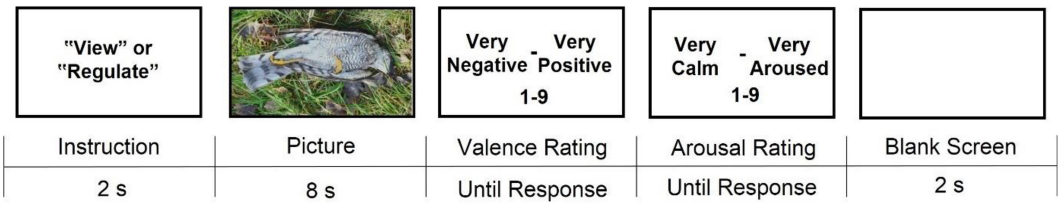

FIGURE 2
Timeline of a trial in the affect reactivity and regulation task. Valence and arousal ratings were accompanied by Self-Assessment Manikins (SAM; Bradley and Lang, 1994). The picture presented in this figure is shown for illustrative purposes only.

instruction to "view." Before completing the first set of trials, participants completed a practice set consisting of one view-neutral, one view-negative, and one regulate-negative trial.

After having seen each picture for 8s, participants were asked to rate the valence and arousal they felt in response to it. These were rated on a 9-point Likert-type scale ranging from 1 (very negative/very calm) to 9 (very positive/very aroused) using the Self-Assessment Manikin (SAM; Bradley and Lang, 1994). A total of 300 NAPS pictures (200 negative, 100 neutral) were selected and divided into the five trial sets based on normative ratings (Marchewka et al., 2014; see **Supplementary material**).

Participants were allowed to carry out the task using either their computer or mobile phone, with the requirement to use the same device on all data collection days.

Affect reactivity was deemed higher when arousal ratings were higher and when valence ratings were lower (i.e., more negative) in response to viewing negative as compared to viewing neutral pictures. Affect regulation was evident when arousal ratings decreased and/or valence ratings increased (i.e., more positive) in response to the instruction to regulate one's feelings when viewing negative pictures compared to when simply viewing negative pictures and freely experiencing the feelings these evoke.

Data reduction

In total, 512 dream diaries were filled in by 51 participants ($M = 10.04$, SD = 5.85, range 2–28).[3] In 69 (13.5%) of the dream diaries, participants reported having no dreams during the night and in 193 (37.7%) of the dream diaries, participants reported thinking they had a dream but not remembering it. A dream was reported and dream affect ratings provided in 250 (48.8%) of the dream diaries ($M = 4.90$, SD = 2.10, range 1–12).

Given that the memory of dream experiences is fleeting and subject to interference, we excluded days on which the dream diary was filled in after more than a 2 h delay between awakening and submitting the dream diary ($n = 13$). To ensure that the affect reactivity and regulation task would be carried out as close as possible to dream experiences, we also excluded days on which the task was performed more than 30 min after submitting the dream diary ($n = 20$). We also excluded days on which (a) there was a delay in submitting both the dream diary and performing the task ($n = 5$), (b) the participant carried out the task before filling in the dream diary ($n = 2$), (c) the participant only submitted the dream diary but failed to perform the task ($n = 8$), (d) there was an incorrect dream diary entry ($n = 4$). After excluding these days, we excluded participants who had dream reports from less than 3 days ($N_{participants} = 11$, $n_{reports} = 18$). Additionally, we excluded a day on which a participant performed the task but did not submit a dream diary ($n = 1$).

As a result of data reduction, 40 participants and 180 dream reports ($M = 4.50$, SD = 1.34, range 3–11 reports) were included in the analyses. Considering that three participants provided more than one report per day, the final data includes, on average, 4.28 (SD = 0.75, range 3–5) dreams and tasks from 171 days (i.e., days with both dream report and task).

Data analyses

All analyses were carried out using IBM SPSS Statistics (v. 20) and R (v. 4.0.2, R Core Team, 2020). We performed linear mixed-effects regression models (also known as multilevel or hierarchical models; Hox, 2010) using the function *lmer* from the packages *lme4* (Bates et al., 2015) and *lmerTest* (Kuznetsova et al., 2017). These models account for the nested nature of the data, i.e., several dream affect ratings and task results per participant. The Bayesian version of the linear mixed-effects model was performed using the *brms* package (Bürkner, 2017), which is based on *Stan* (Carpenter et al., 2017). The Bayes Factors (*BF*) for model comparisons were estimated based on the bridge sampling method (Bürkner, 2017).

To test the relationship between dream affect and post-sleep waking affect level, post-sleep positive and negative affect were specified as outcome variables, whereas dream NA

3 Dream diaries were filled in each morning even when no dreams were recalled. Hence, most participants provided more than five diaries since the requirement was to fill in the diaries until there were dream reports and dream affect ratings from 5 days.

(mean of dimensional and discrete ratings) was included as a predictor. To test task manipulation effectiveness, task valence and arousal ratings were specified as outcome variables, whereas condition (0 = view-neutral; 1 = view-negative; 2 = regulate-negative; contrast-coded) was included as a predictor. To test the relationship between dream NA and task performance, we additionally included dream NA as well as condition *dream NA interaction as predictors. In all models we controlled for age, gender (0 = male, 1 = female, 2 = other), daily sleep quality, and the device (0 = computer; 1 = mobile phone) used to carry out the task. Participant-specific random intercept was also included in all the models (to account for the nested data). All Level-1 predictors (dream NA, daily sleep quality) were group-mean centered because this removes between-participant variation from the predictors and gives a "pure" estimate of the within-participant regression coefficient (Enders and Tofighi, 2007; Nezlek, 2012). Continuous level-2 variables (age) were grand-mean centered.

We used the *anova* function to compare different models. We also calculated marginal and conditional R^2 using the *r.squaredGLMM* function in *MuMIN* package (Barton, 2022). Whereas the marginal R^2 represents the variance explained by the fixed effects, the conditional R^2 represents the variance explained by the whole model, including both fixed and random effects (Nakagawa and Schielzeth, 2013).

We also repeated all the analyses using dream PA (mean of dimensional and discrete ratings) as a predictor. These secondary analyses yielded similar results as with dream NA (see **Supplementary material**).

Results were considered significant if $p < 0.05$. For non-significant results, a follow-up Bayesian analysis was conducted and $BF < 1/3$ indicated substantial evidence in favor of the null hypothesis H_0 (Wetzels and Wagenmakers, 2012).

Results

Dream affect and post-sleep waking affect level

According to emotion regulation theories, dream NA should predict less negative (and more positive) post-sleep affect level, whereas the continuity theories would predict more negative (and less positive) post-sleep affect level. Linear mixed-effects regression models showed that dream NA was positively associated with negative affect in the morning ($B = 0.129$, 95% CI [0.098; 0.160], SE = 0.016, $t = 8.121$, $p < 0.001$, marginal $R^2 = 0.073$, conditional $R^2 = 0.609$) but negatively associated with positive affect in the morning ($B = -0.083$, 95% CI [−0.140; −0.026], SE = 0.029, $t = -2.839$, $p < 0.01$, marginal $R^2 = 0.128$, conditional $R^2 = 0.711$) (see **Figure 3**). Similar results were obtained with dream PA as a predictor (see secondary analyses in **Supplementary material**).

Additionally, sleep quality during the night was a significant predictor of morning affect, with nights rated to have lower sleep quality associated with lower positive affect upon awakening ($B = -0.181$, 95% CI [−0.253; −0.109], SE = 0.037, $t = -4.922$, $p < 0.001$). No significant relationships occurred between sleep quality and negative affect in the morning ($B = 0.034$, 95% CI [−0.005; 0.073], SE = 0.020, $t = 1.688$, $p = 0.092$).

Dream affect and post-sleep waking affect reactivity and regulation

First, we tested the effectiveness of task manipulation. As expected, condition was a significant predictor of task valence. Specifically, viewing negative pictures was associated with lower valence (i.e., more negative) ratings as compared to viewing neutral pictures ($B = -1.731$, 95% CI [−1.846; −1.616], SE = 0.059, $t = -29.572$, $p < 0.001$) (see **Supplementary Figure 1**). Regulating negative pictures was associated with higher valence (i.e., more positive) ratings as compared to viewing negative pictures ($B = 0.739$, 95% CI [0.624; 0.854], SE = 0.059, $t = 12.625$, $p < 0.001$) but with lower valence ratings when compared to viewing neutral pictures ($B = -0.992$, 95% CI [−1.107; −0.877], SE = 0.059, $t = -16.947$, $p < 0.001$). Similar results were obtained for task arousal ratings. Viewing negative pictures was associated with higher arousal ratings as compared to viewing neutral pictures ($B = 1.406$, 95% CI [1.286; 1.527], SE = 0.061, $t = 22.983$, $p < 0.001$). Regulating negative pictures was associated with lower arousal ratings as compared to viewing negative pictures ($B = -0.444$, 95% CI [−0.564; −0.323], SE = 0.061, $t = -7.249$, $p < 0.001$) but with higher arousal ratings when compared to viewing neutral pictures ($B = 0.963$, 95% CI [0.843; 1.083], SE = 0.061, $t = 15.734$, $p < 0.001$). Together, these results indicate that task manipulation was effective: participants' affective reactivity was higher when viewing negative (as compared to viewing neutral) pictures, and they were successful in regulating their affect in response to negative pictures when instructed to do so. However, as indicated by the significant difference between the regulate-negative and view-neutral conditions for both valence and arousal, participants did not manage to fully "neutralize" their affective reactions to negative pictures.

Second, we tested the relationship between dream affect and waking affect reactivity and regulation. According to emotion regulation theories, higher levels of dream NA should predict lower next-day affect reactivity and improved affect regulation ability, whereas the continuity theories would predict higher next-day affect reactivity and lower affect regulation ability. However, results yielded no significant effects of dream NA (valence: $B = -0.100$, 95% CI [−0.236; 0.035], SE = 0.069, $t = -1.454$, $p = 0.147$; arousal: $B = 0.099$, 95% CI [−0.042; 0.241], SE = 0.072, $t = 1.381$, $p = 0.168$) nor condition*dream NA interactions (valence: $F(2, 499) = 0.792$, $p = 0.454$; arousal:

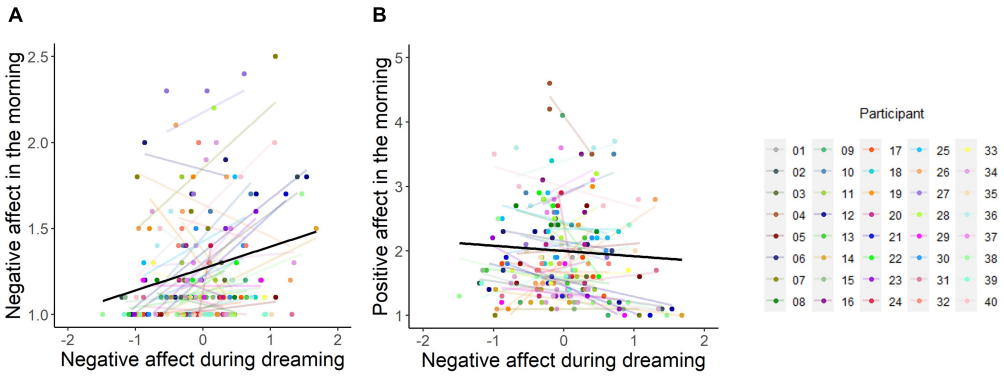

FIGURE 3
Relationship between negative affect experienced in dreams and subjective ratings of post-sleep negative affect **(A)** and positive affect **(B)** the following morning. Figures are displayed for visualization purposes only since analyses were based on linear mixed-effects models with covariates. The black fitted line indicates model prediction, whereas each colored line represents a regression line for each individual participant. Dots of the same color indicate repeated measurements within a participant. Negative affect during dreaming has been group-mean centered, reflecting variation around each participant's own mean values. The y-axis on panel A has been truncated to better visualize individual regression lines.

$F(2, 500) = 0.372$, $p = 0.690$) on either task valence or arousal ratings. Models including condition*dream NA interactions (valence: marginal $R^2 = 0.594$, conditional $R^2 = 0.645$; arousal: marginal $R^2 = 0.268$, conditional $R^2 = 0.819$) were not significantly different from models including condition as the main effect only (valence: marginal $R^2 = 0.592$, conditional $R^2 = 0.643$; arousal: marginal $R^2 = 0.266$, conditional $R^2 = 0.818$), $\chi^2(3) = 2.926$, $p = 0.403$ (valence), $\chi^2(3) = 2.110$, $p = 0.550$ (arousal).

These null effects were confirmed in the Bayesian version of the models (valence: $BF = 0.022$; arousal: $BF = 0.017$).

Discussion

We investigated the within-person relationship between dream affect and next-day affect level, affect reactivity, and affect regulation. Results showed that dream affect was associated with affect level the next morning: participants who experienced higher levels of NA (or lower levels of PA) in their dreams exhibited more negative and less positive post-sleep affect the next morning. These findings corroborate previous studies demonstrating a positive association between dream affect and post-sleep waking affect (Yu, 2007; Schredl and Reinhard, 2009–2010; Mallett et al., 2021). However, hypotheses regarding the relationship between dream NA and next-day affect reactivity and affect regulation were not supported. Although negative pictures induced higher affect reactivity (as reflected in higher arousal and more negative ratings of the pictures) and participants were successful in down-regulating negative affect when instructed to do so, neither affect reactivity nor regulation were associated with dream NA. In fact, Bayesian analyses provided support in favor of the null hypotheses, that is, no relationship between dream NA and waking affect reactivity or regulation.

The findings of the present study fail to provide support for the emotion regulation theories of dreaming, which argue that experiencing NA in dreams contributes to affect regulation in subsequent wakefulness. Instead, results are more in line with the continuity theories of dreaming and suggest affective continuity between dream affect and post-sleep waking affect level. Differences between results regarding self-reported affect level upon awakening versus affect reactivity to stimuli indicates that dream affect is more associated (or continuous) with naturally occurring affect, rather than experimentally manipulated affect. However, it cannot be ruled out that significant correlations between negative dream affect and self-reported post-sleep affect reflect a simple carry-over effect with the physiological arousal evoked by dream affect continuing into wakefulness (Schredl, 2009).

Although the present study did not provide support for the role of dream affect in waking affect reactivity and regulation at the within-person level, it is possible that this relationship exists at the between-individual level. Sterpenich et al. (2019) showed that individuals who tend to experience more NA in dreams display reduced reactivity to affective pictures in wakefulness. Hence, dream affect may be more likely linked to individual differences in habitual affect reactivity and affect regulation (i.e., trait affect reactivity and regulation). This may be especially apparent in those characterized by maladaptive affect regulation (Levin and Nielsen, 2007). Future studies (with appropriate power to evaluate individual differences) investigating the relationship between dream affect and trait affect reactivity and regulation are needed to test this proposition.

Another reason for null findings with regard to affect regulation may be that, in the present study, affect reactivity and

regulation were investigated using subjective ratings of pictures. Previous studies have shown altered brain responses to affective stimuli following sleep loss (Zhang et al., 2019), and in relation to experiencing negative dream affect (Sterpenich et al., 2019), even in the absence of differences in subjective ratings (Zhang et al., 2019). Given the relatively low coherence between the subjective experience and physiological components of affective experiences (Mauss et al., 2005), it is possible that different results would be obtained using physiological measures of affective reactivity and regulation.

It is also possible that waking affect regulation is not associated with dream affect in general but with those affective experiences in dreams that are related to the processing of particularly salient memories of real-life experiences (Malinowski and Horton, 2015). Similarly, it is likely that the affect regulation function is only apparent when individuals experience a certain level of stress during the day that then activates the need for regulation (Levin and Nielsen, 2007; Barbeau et al., 2022b). Although the findings regarding the relationship between pre-sleep affect and dream affect are mixed (e.g., Koulack et al., 1985; Gilchrist et al., 2007; Yu, 2007; cf. Samson-Daoust et al., 2019; Sikka et al., 2019; Conte et al., 2020), accumulated stress over a longer period of time may influence dream affect and, *via* the activation of regulation processes, morning affect. Additionally, affect regulation may not occur within one night, but may be a longer-term process occurring across several nights (akin to the "dream lag" effect; Blagrove et al., 2011), and perhaps even weeks or months (Cartwright, 2010; Goldstein and Walker, 2014). Thus, future studies should strive to manipulate pre-sleep affect, measure both short-term (on the day prior to sleep) and longer-term (days or weeks prior to sleep) stress in the waking life, investigate how dream affect is related to particularly important waking life events that have been incorporated into dreams, and collect data over a longer time period.

The findings of the current study should be considered in light of several limitations. First, since participants rated their waking affect right after rating their dream affect, it is possible that ratings of waking affect were biased by dream affect ratings. While it is not possible to obtain affect ratings while the dream is ongoing, the order of rating dream and waking affect should be counterbalanced in future studies, albeit waking affect ratings may interfere with the dream memory.

Second, we did not measure pre-sleep waking affect. It is likely that affect the next morning would be explained more by pre-sleep waking affect rather than dream affect (Barbeau et al., 2022a), although there is also evidence that the effect of previous-day events on next-day affect occurs *via* dream affect (Schredl and Reinhard, 2009–2010). To better understand the extent to which such cross-state affective continuity depends on the affective nature of dreams, it is important to measure, and control for, pre-sleep affect in future studies.

Third, the fact that this was a home dream study, and data was collected online, made it difficult to control for the exact time when participants filled in the dream diary and carried out the affect reactivity/regulation task. A temporal lag between the actual dream experience and ratings of dream affect may introduce memory biases (e.g., Sikka, 2019). Similarly, a temporal lag between the dream experience and task means that waking events occurring during this lag may have influenced task performance. Although, we tried to control for temporal lags by removing dream diaries filled in too long following awakening and tasks carried out too long after filling in the dream diary, future studies could benefit from tighter experimental control. Relatedly, it was not possible to monitor how well participants followed instructions, especially those pertaining to affect regulation. In future studies, it would be beneficial to obtain participants' evaluations of their regulation success as one indication of task performance.

Fourth, it is also possible that the data collection environment may have influenced the results. Previous studies have demonstrated that differences in the affective content of dreams depend on whether data have been collected in the home or laboratory setting (Sikka et al., 2018). Despite being ecologically more valid, the fact that sleep was not monitored at home means that it was not possible to control for the sleep stage as well as the time of the night from which the dreams (and related affect) derived. The fact that the affect regulation function is specifically postulated to apply to REM sleep, may be one reason for not finding any evidence in support of emotion regulation function of dreaming. Thus, future studies should replicate this study in a laboratory environment as well as in a home environment using sleep monitoring devices.

Finally, our results only pertain to dreams that participants were able to remember and report. This issue is common to almost all dream research since we do not have access to forgotten dreams. If dreams have an affect regulation function, this function should be operative irrespective of whether the dreams are remembered or not. Yet, it may be hypothesized that dream recall is higher when the affect regulation function fails, as in the case of nightmares (Levin and Nielsen, 2007). As a result, we may have access to a biased sample of dreams—those in which the affect regulation function is malfunctioning. However, this argument is not supported in the present study because only 9 of the 180 dreams (i.e., 5%) were rated as nightmares by participants, indicating that the majority of the dreams were so-called normal dreams. Nevertheless, dream recall is influenced by several trait and state variables (e.g., Schredl, 2018), all of which highlights the need to control for these potential factors.

In summary, the findings of the present study fail to provide support for the affect regulation function of dreaming and, instead, speak for affective continuity between dreaming and post-sleep wakefulness.

Data availability statement

The original data set and analysis script can be found in a publicly accessible repository: https://osf.io/hsymd/.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee for Human Sciences at the University of Turku, Finland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PS conceptualized and designed the study and wrote the first manuscript. JG contributed to the study conceptualization. HE contributed to writing the first manuscript. PS and HE collected the data. PS and JZ analyzed the data. All authors reviewed and edited the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Altena, E., Micoulaud-Franchi, J.-A., Geoffroy, P.-A., Sanz-Arigita, E., Bioulac, S., and Philip, P. (2016). The bidirectional relation between emotional reactivity and sleep: From disruption to recovery. *Behav. Neurosci.* 130:336. doi: 10.1037/bne0000128

Alvaro, P. K., Roberts, R. M., and Harris, J. K. (2013). A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* 36, 1059–1068. doi: 10.5665/sleep.2810

Anwyl-Irvine, A. L., Massonnié, J., Flitton, A., Kirkham, N., and Evershed, J. K. (2020). Gorilla in our midst: An online behavioral experiment builder. *Behav. Res. Methods* 52, 388–407. doi: 10.3758/s13428-019-01237-x

Arend, M. G., and Schäfer, T. (2019). Statistical power in two-level models: A tutorial based on Monte Carlo simulation. *Psychol. Methods* 24, 1–19. doi: 10.1037/met0000195

Barbeau, K., Turpin, C., Lafrenière, A., Campbell, E., and De Koninck, J. (2022a). Dreamers' evaluation of the emotional valence of their day-to-day dreams is indicative of some mood regulation function. *Front. Behav. Neurosci.* 16. doi: 10.3389/fnbeh.2022.947396

Barbeau, K., Lafrenière, A., Ben Massaoud, H., Campbell, E., and De Koninck, J. (2022b). Dissociated effects of age and recent troubling experiences on nightmares, threats and negative emotions in dreams. *Front. Psychiatry* 13:770380. doi: 10.3389/fpsyt.2022.770380

Barton, K. (2022). *Mu-MIn: Multi-model inference*. R Package Version 1.46.0. Available online at: https://CRAN.R-project.org/package=MuMIn (accessed September 15, 2022).

Bates, D., Mächler, M., Bolker, B., and Walker, S. (2015). Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* 67, 1–48. doi: 10.18637/jss.v067.i01

Blagrove, M., Fouquet, N. C., Henley-Einion, J. A., Pace-Schott, E. F., Davies, A. C., Neuschaffer, J. L., et al. (2011). Assessing the dream-lag effect for REM and NREM stage 2 dreams. *PLoS One* 6:e26708. doi: 10.1371/journal.pone.0026708

Bradley, M. M., and Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *J. Behav. Ther. Exp. Psychiatry* 25, 49–59. doi: 10.1016/0005-7916(94)90063-9

Bürkner, P. C. (2017). brms: An R package for bayesian multilevel models using Stan. *J. Stat. Softw.* 80, 1–28. doi: 10.18637/jss.v080.i01

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., and Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* 28, 193–213. doi: 10.1016/0165-1781(89)90047-4

Carpenter, B., Gelman, A., Hoffman, M. D., Lee, D., Goodrich, B., Betancourt, M., et al. (2017). Stan: A probabilistic programming language. *J. Stat. Softw.* 76, 1–32. doi: 10.18637/jss.v076.i01

Cartwright, R. (2010). *The twenty-four hour mind: The role of sleep and dreaming in our emotional lives*. Oxford: Oxford University Press.

Cartwright, R. D. (1991). Dreams that work: The relation of dream incorporation to adaptation to stressful events. *Dreaming* 1, 3–9.

Cohen, D. B., and Cox, C. (1975). Neuroticism in the sleep laboratory: Implications for representational and adaptive properties of dreaming. *J. Abnorm. Psychol.* 84, 91–108. doi: 10.1037/h0076938

Conte, F., Cellini, N., De Rosa, O., Caputo, A., Malloggi, S., Coppola, A., et al. (2020). Relationships between dream and previous wake emotions assessed

through the Italian modified differential emotions scale. *Brain Sci.* 10:690. doi: 10.3390/brainsci10100690

De Koninck, J.-M., and Koulack, D. (1975). Dream content and adaptation to a stressful situation. *J. Abnorm. Psychol.* 84, 250–260. doi: 10.1037/h0076648

Domhoff, G. W. (1996). *Finding meaning in dreams: A quantitative approach*. New York, NY: Plenum Press. doi: 10.1007/978-1-4899-0298-6

Domhoff, G. W. (2017). The invasion of the concept snatchers: The origins, distortions, and future of the continuity hypothesis. *Dreaming* 27, 14–39. doi: 10.1037/drm0000047

Domhoff, G. W. (2018). *The emergence of dreaming: Mind-wandering, embodied simulation, and the default network*. Oxford: Oxford University Press.

Enders, C. K., and Tofighi, D. (2007). Centering predictor variables in cross-sectional multilevel models: A new look at an old issue. *Psychol. Methods* 12, 121–138. doi: 10.1037/1082-989X.12.2.121

Fredrickson, B. L. (2013). "Positive emotions broaden and build," in *Advances in experimental social psychology*, Vol. 47, eds G. Devine and E. A. Plant (Cambridge, MA: Academic Press), 1–53.

Gilchrist, S., Davidson, J., and Shakespeare-Finch, J. (2007). Dream emotions, waking emotions, personality characteristics and well-being–a positive psychology approach. *Dreaming* 17, 172–185. doi: 10.1037/1053-0797.17.3.172

Goldstein, A. N., and Walker, M. P. (2014). The role of sleep in emotional brain function. *Ann. Rev. Clin. Psychol.* 10, 679–708. doi: 10.1146/annurev-clinpsy-032813-153716

Hartmann, E. (1996). Outline for a theory on the nature and functions of dreaming. *Dreaming* 6, 147–170. doi: 10.1037/h0094452

Hartmann, E. (2011). *The nature and functions of dreaming*. Oxford: Oxford University Press.

Hox, J. J. (2010). *Multilevel analysis: Techniques and applications*, 2nd Edn. New York, NY: Routledge/Taylor & Francis Group.

Konjarski, M., Murray, G., Lee, V. V., and Jackson, M. L. (2018). Reciprocal relationships between daily sleep and mood: A systematic review of naturalistic prospective studies. *Sleep Med. Rev.* 42, 47–58. doi: 10.1016/j.smrv.2018.05.005

Koulack, D., Prevost, F., and de Koninck, J. (1985). Sleep, dreaming, and adaptation to a stressful intellectual activity. *Sleep* 8, 244–253. doi: 10.1093/sleep/8.3.244

Kramer, M. (1991). The nightmare: A failure in dream function. *Dreaming* 1, 227–285. doi: 10.1037/h0094339

Kramer, M. (1993). "The selective mood regulatory function of dreaming: An update and revision," in *The functions of dreaming*, eds R. Moffitt, A. Kramer, and M. Hoffman (New York, NY: State University of New York Press).

Kuznetsova, A., Brockhoff, P. B., and Christensen, R. H. B. (2017). lmerTest package: Tests in linear mixed effects models. *J. Stat. Softw.* 82, 1–26. doi: 10.18637/jss.v082.i13

Lara-Carrasco, J., Nielsen, T. A., Solomonova, E., Levrier, K., and Popova, A. (2009). Overnight emotional adaptation to negative stimuli is altered by REM sleep deprivation and is correlated with intervening dream emotions. *J. Sleep Res.* 18, 178–187. doi: 10.1111/j.1365-2869.2008.00709.x

Levin, R., and Nielsen, T. A. (2007). Disturbed dreaming, posttraumatic stress disorder, and affect distress: A review and neurocognitive model. *Psychol. Bull.* 133, 482–528. doi: 10.1037/0033-2909.133.3.482

Malinowski, J. E., and Horton, C. L. (2015). Metaphor and hyperassociativity: The imagination mechanisms behind emotion assimilation in sleep and dreaming. *Front. Psychol.* 6:1132. doi: 10.3389/fpsyg.2015.01132

Mallett, R., Picard-Deland, C., Pigeon, W., Wary, M., Grewal, A., Blagrove, M., et al. (2021). The relationship between dreams and subsequent morning mood using self-reports and text analysis. *Affect. Sci.* 3, 400–405. doi: 10.1007/s42761-021-00080-8

Marchewka, A., Żurawski, Ł, Jednoróg, K., and Grabowska, A. (2014). The nencki affective picture system (NAPS): Introduction to a novel, standardized, wide-range, high-quality, realistic picture database. *Behav. Res. Methods* 46, 596–610. doi: 10.3758/s13428-013-0379-1

Mauss, I. B., Levenson, R. W., McCarter, L., Wilhelm, F. H., and Gross, J. J. (2005). The tie that binds? Coherence among emotion experience, behavior, and physiology. *Emotion* 5, 175–190. doi: 10.1037/1528-3542.5.2.175

Nakagawa, S., and Schielzeth, H. (2013). A general and simple method for obtaining R2 from generalized linear mixed-effects models. *Methods Ecol. Evol.* 4, 133–142. doi: 10.1111/j.2041-210x.2012.00261.x

Nezlek, J. B. (2012). "Multilevel modeling analyses of diary-style data," in *Handbook of research methods for studying daily life*, eds M. R. Mehl and T. S. Conner (New York, NY: The Guilford Press), 357–383.

Palmer, C. A., and Alfano, C. A. (2017). Sleep and emotion regulation: An organizing, integrative review. *Sleep Med. Rev.* 31, 6–16. doi: 10.1016/j.smrv.2015.12.006

Perogamvros, L., and Schwartz, S. (2012). The roles of the reward system in sleep and dreaming. *Neurosci. Biobehav. Rev.* 36, 1934–1951. doi: 10.1016/j.neubiorev.2012.05.010

R Core Team (2020). *R: A language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing.

Reddy, R., Palmer, C. A., Jackson, C., Farris, S. G., and Alfano, C. A. (2017). Impact of sleep restriction versus idealized sleep on emotional experience, reactivity and regulation in healthy adolescents. *J. Sleep Res.* 26, 516–525. doi: 10.1111/jsr.12484

Revonsuo, A., Tuominen, J., and Valli, K. (2016). "The simulation theories of dreaming: How to make theoretical progress in dream science: A reply to Martin Dresler," in *Open MIND*, eds T. Metzinger and J. M. Windt (Cambridge, MA: MIT Press), 1341–1348.

Samson-Daoust, E., Julien, S. H., Beaulieu-Prévost, D., and Zadra, A. (2019). Predicting the affective tone of everyday dreams: A prospective study of state and trait variables. *Sci. Rep.* 9:14780. doi: 10.1038/s41598-019-50859-w

Scarpelli, S., Bartolacci, C., D'Atri, A., Gorgoni, M., and De Gennaro, L. (2019). The functional role of dreaming in emotional processes. *Front. Psychol.* 10:459. doi: 10.3389/fpsyg.2019.00459

Schredl, M. (2003). Continuity between waking and dreaming: A proposal for a mathematical model. *Sleep Hypn.* 5, 38–52.

Schredl, M. (2009). Effect of dreams on daytime mood: The effects of gender and personality. *Sleep Hypn.* 11, 51–55. doi: 10.5665/sleep.3646

Schredl, M. (2017). Theorizing about the continuity between waking and dreaming: Comment on Domhoff (2017). *Dreaming* 27, 351–359. doi: 10.1037/drm0000062

Schredl, M. (2018). *Researching dreams: The fundamentals*. London: Palgrave Macmillan.

Schredl, M., and Doll, E. (1998). Emotions in diary dreams. *Conscious. Cogn.* 7, 634–646. doi: 10.1006/ccog.1998.0356

Schredl, M., and Hofmann, F. (2003). Continuity between waking activities and dream activities. *Conscious. Cogn.* 12, 298–308. doi: 10.1016/S1053-8100(02)00072-7

Schredl, M., and Reinhard, I. (2009-2010). The continuity between waking mood and dream emotions: Direct and second-order effects. *Imagin. Cogn. Pers.* 29, 271–282. doi: 10.2190/IC.29.3.f

Shermohammed, M., Kordyban, L. E., and Somerville, L. H. (2020). Examining the causal effects of sleep deprivation on emotion regulation and its neural mechanisms. *J. Cogn. Neurosci.* 32, 1289–1300. doi: 10.1162/jocn_a_01555

Sikka, P. (2019). "How to study dream experiences," in *Dreams: Understanding biology, psychology, and culture*, eds K. Valli and R. J. Hoss (Santa Barbara, CA: ABC-CLIO), 153–166.

Sikka, P., Feilhauer, D., Valli, K., and Revonsuo, A. (2017). How you measure is what you get: Differences in self- and external ratings of emotional experiences in home dreams. *Am. J. Psychol.* 130, 367–384. doi: 10.5406/amerjpsyc.130.3.0367

Sikka, P., Revonsuo, A., Noreika, V., and Valli, K. (2019). EEG frontal alpha asymmetry and dream affect: Alpha oscillations over the right frontal cortex during REM sleep and presleep wakefulness predict anger in REM sleep dreams. *J. Neurosci.* 39, 4775–4784. doi: 10.1523/JNEUROSCI.2884-18.2019

Sikka, P., Revonsuo, A., Sandman, N., Tuominen, J., and Valli, K. (2018). Dream emotions: A comparison of home dream reports with laboratory early and late REM dream reports. *J. Sleep Res.* 27, 206–214. doi: 10.1111/jsr.12555

Sikka, P., Valli, K., Virta, T., and Revonsuo, A. (2014). I know how you felt last night, or do I? Self- and external ratings of emotions in REM sleep dreams. *Conscious. Cogn.* 25, 51–66. doi: 10.1016/j.concog.2014.01.011

Sterpenich, V., Perogamvros, L., Tononi, G., and Schwartz, S. (2019). Fear in dreams and in wakefulness: Evidence for day/night affective homeostasis. *Hum. Brain Mapp.* 41, 840–850. doi: 10.1002/hbm.24843

Tempesta, D., Socci, V., De Gennaro, L., and Ferrara, M. (2018). Sleep and emotional processing. *Sleep Med. Rev.* 40, 183–195. doi: 10.1016/j.smrv.2017.12.005

ten Brink, , M. I., Dietch, J. R., Tutek, J., Gross, J. J., and Manber, R. (2022). Sleep and affect: A conceptual review. *Sleep Med. Rev.* 65:101670. doi: 10.1016/j.smrv.2022.101670

Tousignant, O. H., Glass, D. J., Suvak, M. K., and Fireman, G. D. (2022). Nightmares and nondisturbed dreams impact daily change in negative emotion. *Dreaming* 2, 292–313. doi: 10.1037/drm0000213

Walker, M. P., and van der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135, 731–748. doi: 10.1037/a0016570

Wetzels, R., and Wagenmakers, E. J. (2012). A default bayesian hypothesis test for correlations and partial correlations. *Psychonom. Bull. Rev.* 19, 1057–1064. doi: 10.3758/s13423-012-0295-x

Yu, C. K. C. (2007). Emotions before, during, and after dreaming sleep. *Dreaming* 17, 73–86. doi: 10.1037/1053-0797.17.2.73

Zhang, J., Lau, E. Y. Y., and Hsiao, J. H. W. (2019). Using emotion regulation strategies after sleep deprivation: ERP and behavioral findings. *Cogn. Affect. Behav. Neurosci.* 19, 283–295. doi: 10.3758/s13415-018-00667-y

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Sleep loss suicidal ideation: the role of trait extraversion

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Background: It is known that sleep disturbance is associated with increased suicidal thinking. Moreover, completed suicides, when adjusted for the proportion of the populace that is awake at a given time, are more probable during the late night/early morning hours. Despite these concerns, no studies have examined the role of trait-like individual differences in vulnerability to suicidal ideation during sleep deprivation or insomnia. In two separate studies, we examined whether the trait of extraversion is predictive of changes in suicidal thinking following two nights of sleep deprivation and among individuals meeting the criteria for insomnia.

Methods: Study 1: Twenty-five healthy military personnel (20 males), ages 20–35 completed the NEO-PI-R Extraversion scale and the Suicidal Ideation (SUI) scale of the Personality Assessment Inventory (PAI). Participants completed 77 h of continuous sleep deprivation. After 56 h of sleep deprivation, participants completed the SUI scale a second time. We predicted a change in SUI scores from baseline extraversion. Study 2: 2,061 adults aged 18–79 (900 males) were divided into two groups based on the clinical threshold ($\geq$ 10) on the Insomnia Severity Index (ISI) and completed measures of extraversion and depression, including the suicide item of the Patient Health Questionnaire-9 (PHQ9).

Results: Study 1: After controlling for the caffeine group and changes in PAI Depression, Extraversion scores were used to predict changes in SUI scores using stepwise multiple linear regression. Higher Extraversion was significantly associated with increased non-clinical suicidal ideation following sleep loss, $\beta = 0.463$, partial $r = 0.512$, $p = 0.013$. Study 2: After controlling for depression, the effect of insomnia on suicidal ideation was moderated by trait extraversion ($p < 0.0001$). Overall, the presence or absence of insomnia had little effect on individuals low in trait extraversion (i.e., introverts), but insomnia was associated with significantly higher suicidal ideation among high trait extraverted individuals.

Conclusions: Higher trait extraversion was associated with increased vulnerability to suicidal ideation between rested baseline and total sleep deprivation and was associated with greater suicidal ideation among those meeting criteria for clinically severe insomnia. These findings point to a potential trait-like vulnerability factor that may further our understanding of sleep disruption in the phenomenology of suicide.

KEYWORDS

sleep, suicide ideation, depression, personality, extraversion, individual differences

Introduction

Suicide is currently the 10th leading cause of death in the United States and its incidence steadily increased between 1999 and 2018, with a slight decline in 2019, according to the Centers for Disease Control and Prevention (CDC, 2022). Overall, by 2019, there were 13.9 suicides per 100,000 people, and suicide is now the second leading cause of death among adolescents and younger adults under the age of 35 (CDC, 2022). Suicide has also been a particularly concerning issue for the U.S. military, as the rates have increased from 20.3 suicides per 100,000 active-duty Service members in 2015 to 28.7 per 100,000 as of data available in 2020 (DoD Annual Suicide report). A recent report concluded that since 9/11, military suicides have claimed the lives of more than four times as many U.S. Service members as the number who were killed over the same period as a result of combat operations (Suitt, 2021). While suicide is a major public health issue, the absolute number of individuals who die by completed suicides generally remains around 1.4% around the globe (Bachmann, 2018). Despite the severity of the problem, it has been remarkably difficult to predict completed suicides on an individual level, as the associated factors leading to a decision to commit suicide are complex and multifactorial. Suicidal ideation—thinking about suicide as an option—is relatively common among depressed individuals, but far fewer will actually carry out a suicide attempt. Similarly, suicide attempts are about 30 times more common than completed suicides (Bachmann, 2018). While it is true that most individuals who complete suicide have shown evidence of major depressive disorder or other emotional struggles (Coryell and Young, 2005), most people with depression do not complete or even attempt suicide (Brådvik, 2018). Thus, completed suicide is difficult to predict and is associated with many complex and disparate factors.

It is becoming increasingly apparent that sleep problems and circadian disruption may play a particularly important role in suicidal thinking and behavior. Sleep disorders, including insomnia, parasomnias, and apnea have each been independently associated with increased suicidal tendencies (Pigeon et al., 2012; Bishop et al., 2018, 2020; Britton et al., 2019), and there is growing evidence that being awake at times that are out of sync with one's circadian phase may increase the risk for suicidal ideation and behavior (Perlis et al., 2016a,b; Tubbs et al., 2020). Lack of sleep and being awake at the wrong times both appear to influence neurobehavioral systems that sustain normal emotional homeostasis. Sleep loss has been shown to reduce positive mood state (Grezes et al., 2021; Stenson et al., 2021), degrade emotional intelligence (Killgore et al., 2008, 2021), increase feelings of persecution (Kahn-Greene et al., 2007), and reduce frustration tolerance (Kahn-Greene et al., 2006), all of which can influence an individual's outlook. Without sufficient restorative sleep, people make poorer decisions and take more risks under certain conditions (Killgore et al., 2006; Dickinson et al., 2021), particularly when relying on emotional valuation cues (Whitney et al., 2015). Mechanistically, many of these changes appear to be due to alterations in functional activity and neural communication throughout the brain produced by sleep deprivation (Venkatraman et al., 2007). In particular, neuroimaging findings show that sleep loss weakens the functional connectivity between the regulatory systems of the ventromedial prefrontal cortex and the emotional activating systems of the amygdala, leading to reduced ability to modulate emotional responses to negative stimuli (Yoo et al., 2007). Sleep deprivation also impairs the ability to accurately perceive emotional stimuli such as facial expressions (Van Der Helm et al., 2010; Killgore et al., 2017) and social cues (Dorrian et al., 2019), which can adversely affect the quality of interpersonal relationships and social support. Finally, clinical evidence suggests that sleep disorders contribute indirectly to suicide by virtue of their exacerbating effect on depression, a condition that in-and-of itself increases the likelihood of suicidal behavior (Britton et al., 2019). There is, however, growing evidence that sleep disruption can increase suicide risk exclusive of its effects on depression (Simmons et al., 2020). Overall, when sleep is disturbed or insufficient, positive mood state declines, and critical neurocognitive processes such as emotional awareness, decision-making, and self-regulatory capacities are degraded, which in concert may increase the propensity to contemplate, and perhaps, act on suicidal thoughts.

Despite the clear links between sleep and emotional functioning, the actual associations between sleep disturbance and suicidal thinking and behavior have also remained quite modest. This is not surprising, as considerable evidence suggests that there are stable trait-like interindividual differences in

vulnerability and resilience to sleep loss (Van Dongen et al., 2004; Van Dongen and Belenky, 2009; Dennis et al., 2017; Yamazaki and Goel, 2020). In other words, some people appear to be inherently more susceptible to the adverse effects of insufficient sleep than others. This trait-like vulnerability appears to have some genetic basis (Goel et al., 2011; Casale and Goel, 2021) but has often been difficult to characterize through behavioral metrics. However, an early study by Taylor and colleagues showed that individuals high in the trait of extraversion tended to be more vulnerable to the effects of sleep deprivation on cognitive performance (Taylor and Mcfatter, 2003). Our team subsequently followed up on this work and further established the reliability of these findings, as extraverts were consistently more vulnerable than introverts to psychomotor vigilance decrements during two independent laboratory studies of total sleep deprivation (Killgore et al., 2007; Rupp et al., 2010). Consistent with the idea that extraverts are less resilient to mounting sleep pressure on alertness and vigilance, greater extraversion also appears to be associated with better sleep quality and fewer sleep problems in large population studies (Stephan et al., 2018). These findings are interesting and suggest that there is likely an underlying neurobiological factor associated with the dimension of introversion-extraversion that influences resilience to the effects of sleep loss on alertness and vigilance.

Early theories of personality postulated that extraverts may tend to have lower cortical arousal than introverts (Eysenck, 1967, 1981), a hypothesis that later received some support from neuroimaging studies (Johnson et al., 1999; Kumari et al., 2004). However, extraversion is also associated with higher impulsivity and lack of perseverance (Whiteside and Lynam, 2001), which could conceivably increase vulnerability to distraction and poor performance when sleep is lacking. As sleep deprivation is well known to lead to reductions in prefrontal cortex activity (Thomas et al., 2000, 2003; Wu et al., 2006) and reduced functional regulation of emotional responses (Yoo et al., 2007; Chee and Zhou, 2019), it would be reasonable to expect that individuals higher in extraversion would show more significant declines in cognitive control, attention, and vigilance during periods of sleep deprivation than those with more introverted traits.

Despite growing evidence that extraverts may be more vulnerable to mounting sleep pressure on attention and vigilance, this model has not been extended to potential changes in emotional outlook, such as suicidal ideation. Without sleep, it becomes difficult to regulate emotional responses and negative affect begins to hold greater sway over cognition (Walker and Van Der Helm, 2009). It would, therefore, not be unreasonable to expect that the previously identified vulnerabilities to vigilance decrements among extraverts during sleep deprivation would also extend to the emotional realm, and perhaps even impair the ability to inhibit potentially harmful thoughts/actions (e.g., suicidal ideation or self-harmful behavior) with such emotional dysregulation. Accordingly, we sought to determine the association between the personality trait of extraversion and vulnerability to increases in suicidal thinking during periods of insufficient or disturbed sleep. In a series of two studies, including a laboratory-based study of total sleep deprivation and a nationwide survey study of sleep and personality, we tested the hypothesis that greater trait-extraversion (TE) would be associated with greater suicidal ideation (SI) during total sleep deprivation (TSD) and among those with clinically significant insomnia in the general population.

Study 1: laboratory sleep deprivation

The goal of the first study was to directly examine the association between TE and SI over a controlled period of TSD. As part of a larger investigation on the effects of caffeine and alertness, military participants were recruited to complete an assessment of their personality, followed by three nights of in-laboratory TSD. Assessments of depression and suicidal ideation were collected at rested baseline and again following the second night without sleep. It was hypothesized that higher measured TE would be associated with greater increases in SI over the period of sleep deprivation, regardless of caffeine intake.

Participants

Twenty-five U.S. Army enlisted personnel were recruited to participate in an extensive 5-day in-laboratory study. The sample included 20 males and five females, with a mean age of 25.4 years (SD = 4.1) and an average of 14.1 years (SD = 1.6) of formal education. Separate data from this study have been published previously (Killgore and Kamimori, 2020), but the present findings regarding the association between TE and suicidal ideation are novel and have not been previously reported. All volunteers underwent a physical examination to ensure they were healthy enough to remain awake for three days and potentially consume repeated doses of caffeine. Volunteers were excluded for any past or current physical/mental health/sleep problems, history of drug abuse, or current regular caffeine consumption $\geq$300 mg of caffeine per day, or a self-reported history of caffeine sensitivity, and all were healthy enough for currently active military service. Participants were also required to be on a normal day/night sleep schedule and report sleeping between 7 and 8 h per night, based on self-report. Current nicotine use was exclusionary and was verified by nicotine/cotine testing during the physical examination. Participants were required to abstain from alcohol, stimulants, and other psychoactive drugs for 48 h prior to the study. Written informed consent was obtained from all participants. This study was approved by the Walter Reed Army Institute of Research

Human Use Review Committee and the U. S. Army Human Subjects Research Review Board.

Materials

Participants completed several questionnaires at various points throughout the study. Trait Extraversion-Introversion (TE) was determined by the Extraversion Scale of the Revised NEO Personality Inventory (NEO-PI-R; Costa and Mccrae, 1992). The NEO-PI-R is one of the most widely used instruments for assessing the Big 5 personality traits including introversion-extraversion (De fruyt et al., 2000; Quirk et al., 2003; Sherry et al., 2003; Bagby et al., 2004). The NEO-PI-R includes five primary scales of Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness, which are conceptualized as independent and relatively orthogonal constructs that account for the majority of variance in personality. The scale provides normalized T-scores (i.e., normative Mean = 50, SD = 10) for each facet of personality, including trait Extraversion, or TE, which is the primary focus of the present study. The primary outcome variable, suicidal ideation, was assessed by the Suicidal Ideation (SUI) scale of the Personality Assessment Inventory (PAI; Morey, 2007). The PAI is a multidimensional assessment of various aspects of personality and psychopathological functioning. The inventory comprises 344 statements, each with four response options including: "False, not at all true," "Slightly True," "Mainly True," and "Very True." The SUI items focus on the presence of suicidal thoughts and the imminence of suicidal intentions. The items assess the tendency to think about suicide, the emotional desire to be dead or the belief that one would be better off dead, and the tendency to contemplate ways and means for killing oneself. The SUI scale is reported as a T-score based on comparisons to the normative group reported in the test manual. Higher scores indicate a greater severity and persistence of suicidal thinking. Additionally, because it is well established that depressive mood is associated with sleep problems, we elected to control for depressive mood in the analyses. To provide this control, we extracted the depression (DEP) scores from the PAI to be used as a covariate.

Procedure

Each study session occurred over a 5-day period and participants were run in groups of 3–4 at a time. Participants reported to the lab at 19:00 h on Day 1 and underwent some familiarization and training with various tasks. From 23:00 (Day 1) to 07:00 (Day 2) participants retired to their own private bedrooms to undergo an 8-h baseline sleep opportunity. After awakening at 07:00 h (Day 2) participants remained awake for the next 77 h. At 15:05 on Day 2 (8 h awake), participants began the baseline PAI assessment, which lasted about 30-minutes. Then, at 16:15, they were administered the NEO-PI-R on a desktop computer to provide a baseline assessment of TE. After two days of TSD, at 15:05, participants completed a second administration of the PAI while in the sleep-deprived state (i.e., 56 h of continuous wakefulness).

Additionally, as part of a larger investigation into the effects of caffeine on psychomotor vigilance performance, each participant was randomly assigned to ingest either 200 mg of caffeine or placebo (four times during each overnight session—i.e., at 01:00, 03:00, 05:00, 07:00 h) in a chewing gum formulation (*Military Energy Gum*^{TM}; MarketRight Inc., Plano, IL). While caffeine was expected to have been mostly cleared from the system by the time of the PAI assessment (i.e., the PAI was administered >8 h after the last dose of caffeine) and was not part of the study hypotheses, we nevertheless included caffeine group as a covariate in our analyses to assess and control potential influences of caffeine on outcomes.

Analyses

Change scores from baseline were calculated for the SUI scale. Data were entered in a hierarchical multiple linear regression analysis to predict changes in PAI SUI T-scores using IBM SPSS 28. In the first step, caffeine group and changes in PAI DEP scores were forced into the equation. In the second step, all five primary factors from the NEO-PI-R (i.e., Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness) were entered in a stepwise entry/deletion procedure (probability to enter = 0.05, probability to remove = 0.10). Finally, an interaction term was also entered to examine the interaction between extraversion and caffeine group.

Results and discussion

All SUI scores remained within normal limits (i.e., T score <60) from baseline (min = 43, max = 54) to TSD (min = 43, max = 58), suggesting that any changes were within the sub-clinical range. In the first step, the caffeine group and changes in depression accounted for a non-significant proportion of variance in SUI change scores (R^2 = 0.188, p = 0.102). However, at the second step, stepwise entry and deletion of the Big-5 personality traits resulted in only Extraversion being retained as a significant additional predictor of SUI change (R^2 Change = 0.213, β = 0.463, partial r = 0.512, p = 0.013; see **Figure 1A**). After controlling for covariates, each 10-point T-score increment in TE translates into a 2.32-point T-score increase in SI from the rested to sleep-deprived state. Finally, when the caffeine group was

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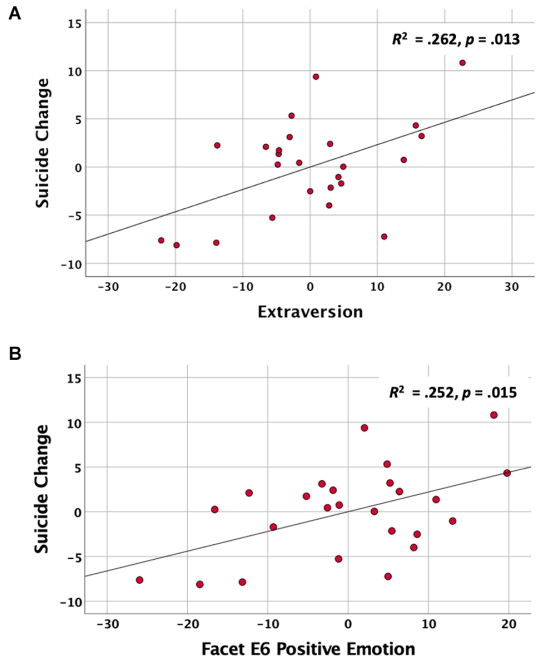

FIGURE 1
The associations between extraversion traits on the NEO-PI-R and change in suicidal ideation (SUI) scores over two nights of total sleep deprivation after controlling for caffeine intake and changes in depression. **(A)** Partial regression plot showing the association between baseline trait extraversion (TE) and change in SUI scores during sleep deprivation. **(B)** Partial regression plot showing the association between the Positive Emotion facet (E6) and changes in SUI scores during sleep deprivation.

included in the model as a categorical moderator, the interaction term was not significant, p = 0.693, and did not add any meaningful improvement in the model (R^2 change = 0.005), suggesting that caffeine did not reliably affect the association between TE and changes in SI over the period of sleep loss. These findings support the primary hypothesis that individuals with higher TE tend to be more vulnerable to increased SI during a period of TSD, regardless of caffeine consumption.

It was also of interest to identify the facets of the extraversion scale that contributed most to the prediction of changes in SUI change. Accordingly, we calculated the partial correlations between SUI change and each of the six Extraversion Facet scores, after controlling for depression change and caffeine group. The Facets of Warmth (E1; partial r = 0.491, p = 0.017), Activity (E4; partial r = 0.436, p = 0.037), and Positive Emotions (E6; partial r = 0.502, p = 0.015) each separately correlated with change in suicide scores, while Gregariousness (E2; partial r = 0.271, p = 0.211), Assertiveness (E3; partial r = 0.233, p = 0.285), and Excitement Seeking (E5; partial r = 0.158, p = 0.472) did not. The heirarchical regression analysis with a stepwise entry of the six Extraversion Facets was used to identify facets that contributed unique variance to the prediction of SUI Change after controlling for changes in depression and caffeine group. This analysis showed that once the facet of Positive Emotions (E6, which measures the tendency to experience happiness, excitement, and joy) was entered into the equation (R^2 change = 0.205, p = 0.015; **Figure 1B**), no other variables added uniquely to the prediction of SUI Change.

Study 2: large scale survey of insomnia

While several nights of TSD within the context of a controlled laboratory setting can allow exceptional control and manipulation of sleep parameters, it is not clear whether similar effects would manifest in a more naturalistic setting, such as when sleep loss is due to chronic insomnia in a non-laboratory environment. Therefore, the goal of the second study was to extend the findings from Study 1, which focused on the association between extraversion and suicidal ideation in the context of TSD, to a more naturalistic setting to examine these associations in the context of self-reported sleep disturbance. Accordingly, in a large nationwide online survey, we collected data regarding insomnia severity, TE, and SI. Moreover, to further broaden the validity and generalizability of these associations, we incorporated alternative assessment metrics of TE and SI. It was hypothesized that higher measured TE would be associated with greater increases in SI among individuals meeting the criteria for clinically significant insomnia relative to those without such complaints.

Participants

A total of 2,061 adults (43.8% male; 56.2% female) aged 18–79 (M = 36.8 years, SD = 12.2) were recruited *via* the Amazon Mechanical Turk (MTurk) online crowdsourcing platform (Litman et al., 2017) and were provided a small financial compensation for their participation. Participants were initially screened to ensure that they were geographically located within the United States (verified by IP address geo-coordinates), were at least 18 years of age, were able to read with at least a 6th grade proficiency and endorsed English as their primary language. No attempt was made to select individuals based on prior mental health, suicidal behavior, or other health-related factor. The racial/ethnic breakdown of the sample included 74.8% describing themselves as white, 10.6% as Black/African-American, 5.9% as Asian, 5.1% as Hispanic/Latino, 1.2% as Native American/American Indian/Native Alaskan, 0.2% as Native Hawaiian/Pacific Islander, and 2.2% responding as Other/Prefer not to answer. All participants provided electronic acknowledgment of informed consent after being provided with a full description of the study. This study was

approved by the Institutional Review Board of the University of Arizona.

Questionnaires and procedures

Participants were asked to complete several online questionnaires *via* the MTurk platform. Items were presented as worded in the original published versions of the questionnaires and responses were collected *via* button clicks in the online portal. There was no time limit imposed for completion, but most participants completed the survey in less than an hour.

Insomnia Severity Index (ISI)

While Study 1 focused on TSD, Study 2 focused on poor sleep due to insomnia. Accordingly, insufficient sleep was assessed with the Insomnia Severity Index (ISI), a well-validated and widely used index of insomnia, including difficulty falling asleep, staying asleep, and early morning awakening (Bastien et al., 2001; Morin et al., 2011). Higher scores on the ISI indicate greater severity of insomnia. For the present analysis, we categorized individuals as having insufficient sleep according to the commonly applied cut-off criterion of $\geq$10 as indicative of clinically significant insomnia (i.e., low or subthreshold sleep problems $<$10; high or clinical sleep problems $\geq$10). This cut-off has been found to have an optimal balance between sensitivity and specificity in population-based samples (Morin et al., 2011).

Eysenck Personality Inventory-Extraversion scale (EPI-E)

In Study 2, we chose to evaluate a different metric of TE than used in Study 1 to further extend the validity of the associations between the core constructs of extraversion, sleep loss, and suicidal ideation. Therefore, TE was assessed with the 24-item Extraversion Scale of the original Eysenck Personality Inventory (EPI; Eysenck and Eysenck, 1964). The Extraversion construct used in Eysenck's scales has been extensively validated (Vingoe, 1968) and has a high correlation with the Extraversion scale of the NEO-PI (Draycott and Kline, 1995). Thus, the EPI provides an alternate but highly related metric of the construct of extraversion. Because of our focused hypothesis on extraversion, we only include the Extraversion Scale and not the other scales of the EPI. For the present analysis, EPI-E scores were calculated by summing the 24 items comprising the scale and were used as a continuous variable.

UCLA Loneliness Scale-3 (LS-3)

The present survey data were collected during the first year of the COVID-19 pandemic during a time when many individuals were required to maintain social distance and self-isolate. Our prior work has shown that many individuals struggled with loneliness during this period and that loneliness was significantly correlated with suicidal ideation during the pandemic (Killgore et al., 2020a,b). Therefore, we elected to also statistically control for the potential contribution of loneliness in the analyses. To provide this control, participants also completed the UCLA Loneliness Scale-3 (Russell, 1996), a well-validated measure of the construct of loneliness. The scale was scored according to standard instructions and was included as a continuous variable covariate in the regression analyses.

Beck Depression Inventory-2 (BDI-II)

Because insomnia is often highly correlated with depression, we wanted to statistically control for depressive mood state using the BDI-II (Beck et al., 1996). The full BDI-II includes 21 items that are each scored from zero to three for severity. The inventory is widely used for assessment of depressive mood and has been shown to have good to excellent psychometric properties (Wang and Gorenstein, 2013). However, since the BDI-II also includes a question about suicidal ideation, it was important to remove any variance associated with this suicide-specific item. Therefore, we calculated the total depression score without Item 9 of the BDI-II. Similarly, we also dropped Item 16 from the BDI-II since this item directly assesses changes in sleep patterns. The total score was the sum of the remaining 19 items, which provided a continuous variable assessing depressive mood, exclusive of suicidal thoughts and sleep problems.

Suicidal Ideation (SI) index

A composite suicidal ideation (SI) index was calculated by summing the total score for the suicidal ideation items from two commonly used screening indices for depression. First, Item 9 from the BDI-II was scored (range 0–3), with higher scores indicating greater severity of suicidal ideation. Second, we also administered the Patient Health Questionnaire (PHQ-9), which is a brief screener for depressive mood and also includes an item (Item 9) assessing the frequency of thoughts of suicide or self-harm. This item asks participants to indicate how often, over the past two weeks, they have been bothered by "thoughts that you would be better off dead or hurting yourself in some way." It is important to note that the item can refer to either suicidal ideation OR other forms of self-harm, so it cannot be interpreted solely as a suicidal thinking item. The individual score for this item ranges from 0 ("not at all") to 3 ("nearly every day"). The SI score was calculated by summing these two items from the two different depression scales, producing an index of suicidal or self-harming ideation that could potentially range from 0 (none) to 6 (high).

Analyses

Data from the survey were analyzed using SPSS version 28. In a hierarchical multiple linear regression for categorical moderators (Aguinis, 2004), with PHQ-9 Suicide scores as the outcome variable, LS-3 and modified BDI-II scores were entered as covariates in the first step, followed by EPI scores and ISI category as the independent variables in the second step, and lastly, an interaction term representing the product of EPI-E score × ISI category was included. To ensure that the outcomes of the categorical analyses were not unduly influenced by the dichotomous nature of the cut-off values, the same analysis was also repeated with continuous values for the ISI. Additionally, to further elucidate the associations at each level of insomnia, a similar regression was calculated for the low and high ISI groups separately.

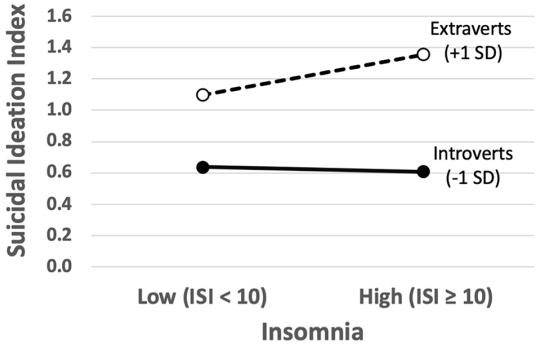

FIGURE 2
The plot of the interaction effect (moderation) between insomnia category (low or high) and trait extraversion from the Eysenck Personality Inventory (EPI) on suicidal ideation scores from the composite Suicide Ideation (SI) index. ISI, Insomnia Severity Index; SD, standard deviation.

Results and discussion

The SI index showed acceptable internal consistency for a simple 2-item scale, with Cronbach's alpha = 0.74. Overall, most participants (64.4%) did not endorse any suicidal ideation on the SI index, while 35.6% indicated some evidence of thoughts about self-harm or suicide. Overall, 13.5% of the sample scored at least a 3 or higher on the 6-point scale.

Not surprisingly, at the first step of the regression analysis, the covariates (i.e., LS-3 loneliness and modified BDI-II depression) accounted for a significant proportion of the variance in SI scores (R^2 = 0.411, $p < 0.00001$). Nonetheless, subsequent simultaneous entry of the primary predictor variables (EPI Extraversion and ISI Insomnia Category) was further associated with a significant improvement in the model (R^2 Change = 0.039, $p < 0.00001$). Finally, the interaction term (i.e., Extraversion × ISI category) was highly significant (R^2 Change = 0.009, $p < 0.0001$), suggesting that the association between extraversion and suicidal ideation differed between those with high and low levels of insomnia, as predicted, even after controlling for depression and loneliness. This interaction was plotted according to standard procedures (Aguinis, 2004) and is represented in **Figure 2**, which shows that for individuals with low extraversion scores (i.e., introverts), suicidal ideation was relatively low and did not differ as a function of insomnia severity, while high levels of extraversion tended to be associated with increased suicidal ideation, particularly for those with clinically elevated levels of insomnia. **Table 1** provides the regression weights for the total model. For completeness in reporting, the model was again reanalyzed using ISI as a continuous variable, with nearly identical results (**Table 2**).

Because the preceding analysis suggested that the associations between extraversion and suicidal ideation differed as a function of insomnia, we calculated the regressions again for the low and high insomnia groups separately. For those without clinically significant insomnia, the initial entry of the covariates (i.e., LS-3 loneliness and modified BDI-II depression) in the first step accounted for a significant proportion of the variance in SI index scores (R^2 = 0.314, $p < 0.00001$). At the second step, EPI Extraversion was further associated with a modest but significant improvement in the model (R^2 Change = 0.008, p = 0.001). As shown in the top panel of **Figure 3**, this analysis yielded a significant partial correlation between extraversion and suicidal ideation (partial r = 0.110, p = 0.001), suggesting that higher extraversion was modestly associated with greater suicidal ideation, even among individuals without sleep issues. Restricting the analysis to only those meeting the cut-off for clinically significant insomnia, we again found that the covariates accounted for significant variance in the SI index (R^2 = 0.362, $p < 0.00001$). Moreover, the inclusion of EPI Extraversion significantly improved the model, accounting for more than twice the variance than the same model in the group without insomnia (R^2 Change = 0.067, $p < 0.00001$). The bottom panel of **Figure 3** shows that this analysis resulted in a significant partial correlation between extraversion and suicidal ideation (partial r = 0.324, $p < 0.00001$). Overall, these findings support the hypothesis that, among individuals with sleep disruption due to insomnia, greater levels of TE were associated with greater SI.

Finally, for completeness in reporting and to allow the full assessment of the robustness of the findings with and without covariates considered, we also ran an exploratory set of analyses that was identical to the preceding analyses, but without the covariates of depression and loneliness included. First, we ran the simpler model (i.e., without covariates) with the ISI as a categorical variable as before. Simultaneous entry of the primary predictor variables (EPI Extraversion and ISI Insomnia Category) was associated with a significant

TABLE 1 Results of hierarchical linear regression predicting the combined suicidal ideation score from trait extraversion and *insomnia category*.

R	R^2	Variable	B	β	Test	Sig.
0.678	0.459	Model			$F_{(5,2051)} = 348.06$	<0.001
		Constant	−1.180		$t_{(2051)} = -9.797$	<0.001
		LS-3	0.011	0.098	$t_{(2051)} = 4.677$	<0.001
		Mod. BDI-II	0.072	0.593	$t_{(2051)} = 26.816$	<0.001
		EPI Extraversion	0.054	0.168	$t_{(2051)} = 9.007$	<0.001
		ISI Category	−0.192	−0.070	$t_{(2051)} = -3.352$	<0.001
		Extraversion x ISI Category	0.034	0.122	$t_{(2051)} = 5.839$	<0.001

LS-3, UCLA Loneliness Scale-3; Mod. BDI-II, Modified BDI-II (i.e., without sleep item and suicide item included); EPI, Eysenck Personality Inventory; ISI, Insomnia Severity Index.

TABLE 2 Results of hierarchical linear regression predicting the combined suicidal ideation score from trait extraversion and *Continuous Insomnia Severity Index (ISI) scores*.

R	R^2	Variable	B	β	Test	Sig.
0.676	0.457	Model			$F_{(5,2051)} = 345.145$	<0.001
		Constant	−0.879		$t_{(2051)} = -5.969$	<0.001
		LS-3	0.010	0.091	$t_{(2051)} = 4.299$	<0.001
		Mod. BDI-II	0.075	0.613	$t_{(2051)} = 26.821$	<0.001
		EPI Extraversion	0.021	0.066	$t_{(2051)} = 2.029$	<0.001
		ISI	−0.037	−0.183	$t_{(2051)} = -4.620$	<0.001
		Extraversion x ISI Score	0.004	0.240	$t_{(2051)} = 5.185$	<0.001

LS-3, UCLA Loneliness Scale-3; Mod. BDI-II, Modified BDI-II (i.e., without sleep item and suicide item included); EPI, Eysenck Personality Inventory; ISI, Insomnia Severity Index.

model (R^2 = 0.118, $p < 0.00001$). Finally, the interaction term (i.e., Extraversion × ISI category) also added significant prediction (R^2 Change = 0.046, $p < 0.0001$), suggesting that the association between extraversion and suicidal ideation differed between those with high and low levels of insomnia, as predicted, even without controlling for depression and loneliness. Similarly, the model was again reanalyzed using ISI as a continuous variable, with nearly identical results. Simultaneous entry of the primary predictor variables (EPI Extraversion and ISI Score) was associated with a significant model (R^2 = 0.164, $p < 0.00001$). Finally, the interaction term (i.e., Extraversion x ISI category) also added significant prediction (R^2 Change = 0.010, $p < 0.0001$). Overall, when the covariates were excluded the results remained similar to the primary analysis that included all covariates. These findings suggest that the results are robust regardless of the inclusion of the covariates of depression or loneliness.

General discussion

Insomnia, short sleep, and other sleep disorders are among several of the leading independent risk factors for suicide (Liu, 2004; Mccall and Black, 2013; Lin et al., 2018; Harris et al., 2020; Simmons et al., 2020). Nevertheless, suicide is a low base rate event relative to the prevalence of clinical sleep disturbance, which means that sleep problems (like most other risk factors) have low specificity and limited practical utility as warning signs for suicide (Harris et al., 2020). Consequently, it is vital to identify additional individual difference factors that may enhance the understanding and prediction of suicide risk in relation to sleep disruption. Here, across two independent studies, each with different data collection methods, assessment tools, and sleep outcome measures, we found converging evidence that the effects of sleep disturbance on suicidal ideation were significantly moderated by the individual's level of introversion-extraversion, with higher levels of TE associated with a greater propensity for suicidal ideation when sleep was disturbed. Study 1 clearly showed that greater TE was associated with correspondingly larger increases in SI following two full nights of laboratory-controlled TSD. Individuals with the highest TE showed the greatest increases in SI from baseline to 56 h of sleep deprivation, whereas those with the lowest TE (i.e., more introverted individuals) tended to show the least increase in SI during sleep deprivation. Moreover, the effect was specific to TE (particularly the tendency to experience positive emotions such as excitement, happiness, and joy), as none of the other personality traits from the Big-5 added any additional predictive power to the model. Then, in Study 2, we extended these findings to a large nationwide sample focused on individuals classified according to self-reported presence or absence of clinically significant insomnia. In that study, we specifically focused on TE and found that the association between insomnia and SI was moderated by TE. Specifically, SI scores did not differ as a function of insomnia for people who were low in TE (i.e., more introverted), but SI differed significantly as a function of insomnia for high TE individuals. Together these findings suggest that there are significant inter-individual differences in how sleep deprivation/disturbance affects SI, which are

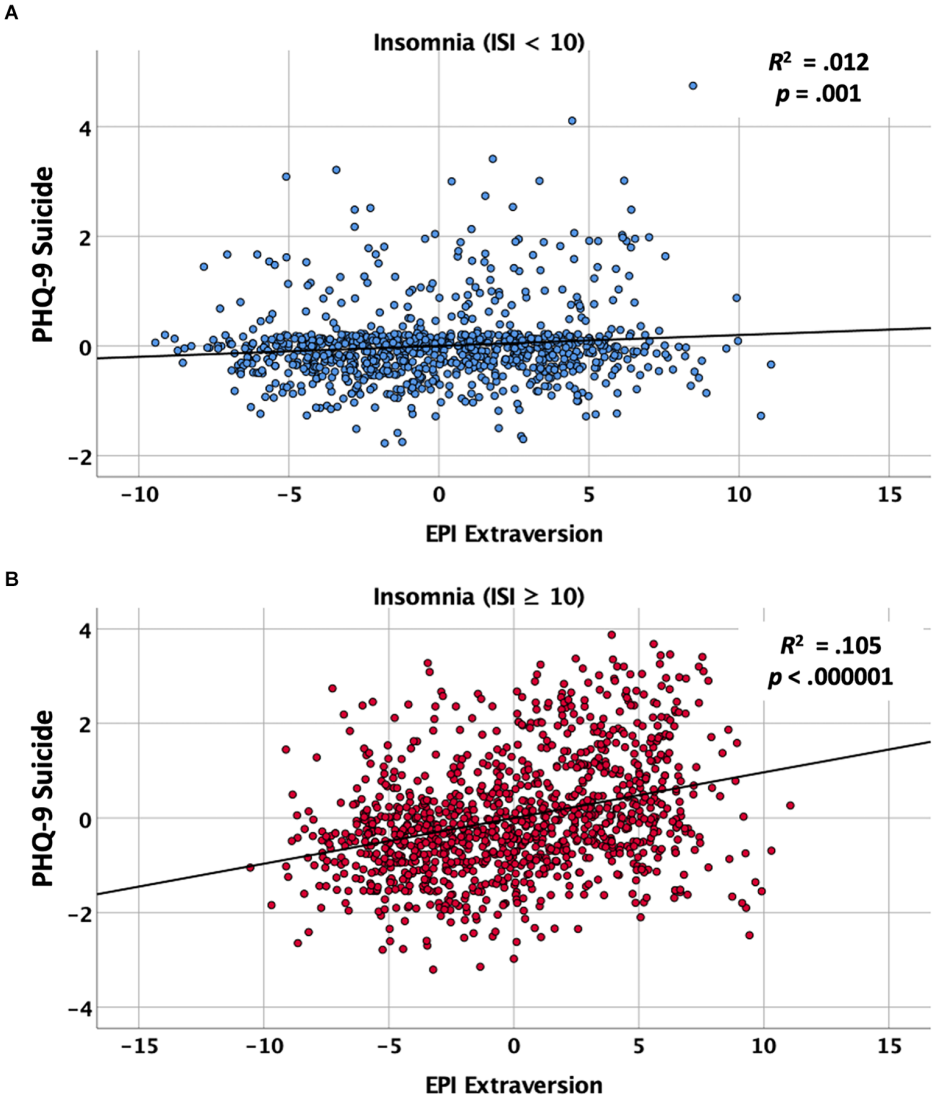

FIGURE 3
Partial regression plots showing the association between baseline trait extraversion as measured by the Eysenck Personality Inventory (EPI) and suicidal ideation on the composite Suicide Ideation (SI) index after controlling for loneliness and depression. **(A)** Partial regression plot for individuals scoring low (< 10) on the Insomnia Severity Index (ISI). **(B)** Partial regression plot for individuals scoring high (≥ 10) on the ISI.

moderated by a person's level of TE. Low TE (i.e., more introverted) individuals appear to be modestly resilient to the effects of sleep disruption on SI, while those high in TE appear to be more vulnerable to increased SI during periods of sleep disruption. These individual difference findings parallel those reported for vigilance decrements during sleep deprivation, which also suggests that extraverted individuals tend to be more vulnerable to the effects of sleep loss on performance compared to more introverted individuals (Taylor and Mcfatter, 2003; Killgore et al., 2007; Rupp et al., 2010).

At present, the underlying mechanisms contributing to the moderating effect of TE on SI during periods of disturbed sleep have yet to be fully elucidated, but we discuss a few potential conceptualizations, none of which are necessarily mutually exclusive. One potential, but antiquated, explanation stems from the early conceptualization of TE, which proposed that the personality dimension of introversion-extraversion is a behavioral manifestation of individual differences in tonic cortical arousal (Eysenck, 1967, 1981). According to this early theory by Eysenck, individuals with greater TE tend to have lower levels of tonic arousal of the reticulo-thalamic-cortical activation system relative to more introverted (i.e., low TE) individuals. According to this early theory, the extraverted person is postulated to seek out social stimulation and excitement to modulate their cortical arousal to sustain an

optimal level, while the introverted individual, whose baseline tonic arousal is inherently higher, avoids such stimulating activities to sustain their arousal within the optimal range. While the neurobiological basis of the theory is a bit obsolete, the general postulates of Eysenck's theory have received support from a handful of neuroimaging studies, which have shown that introverted individuals tend to have greater basal cortical activation within expected brain regions compared to extraverts (Johnson et al., 1999; Kumari et al., 2004). Consistent with this notion, Taylor and McFatter found that individuals higher in extraversion were in fact more vulnerable to vigilance decrements during sleep loss (Taylor and Mcfatter, 2003), a finding that was replicated in two additional studies by our team as well (Killgore et al., 2007; Rupp et al., 2010). As shown in **Figure 4**, this general arousal model could be easily adapted to explain the effects of sleep loss on factors that could relate directly to suicidal ideation or behavior, including executive control, positive affect, or impulsivity. As suggested in the theoretical account outlined in the top panel of **Figure 4**, when normally rested, introverts and extroverts would be expected to function similarly when near their optimal level of arousal and would therefore not differ in terms of performance, positive affect, or impulse control. However, as shown in the bottom panel of **Figure 4**, in accord with the postulated lower level of tonic arousal among extraverts, a decline in arousal due to insufficient sleep might be expected to lead to an earlier and more noticeable decline in performance, positive affect, and/or impulse control than for introverts.

Regardless of the ultimate veracity of the cortical arousal theory of introversion-extraversion put forth by Eysenck, there is considerable evidence suggesting that extroverted individuals tend to be more impulsive than those with more introverted traits (Revelle, 1997). Of note, extraversion appears to correlate with one facet of impulsivity in particular. This facet of the construct is described as "a lack of perseverance," or difficulty ignoring distracting stimuli to remain consistently focused on a specific task (Whiteside and Lynam, 2001). Since a decline in sustained and focused attention is one of the most reliably observed effects of sleep deprivation (Durmer and Dinges, 2005; Lim and Dinges, 2010), it is not surprising that extraverts would show greater vulnerability to this form of impulsivity during sleep loss (Taylor and Mcfatter, 2003; Killgore et al., 2007; Rupp et al., 2010). In a broader sense, impulsivity is a multidimensional construct that has also been used to describe a pattern of behavior characterized by a failure to inhibit inappropriate behavior and respond before considering the consequences of an action (Gvion et al., 2015). While most suicides have usually been contemplated for a while, impulsivity can increase the risk that an individual struggling with mental pain may decide to act on suicidal thoughts (Gvion et al., 2015). Thus, extraversion and associated tendencies toward impulsivity

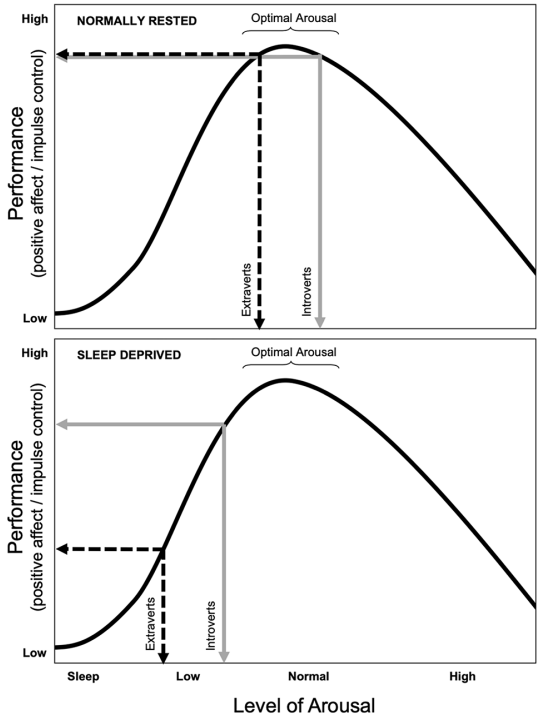

FIGURE 4
Diagram of the hypothesized effects of sleep loss (i.e., decreased arousal) on outcome measures (e.g., performance, positive affect, impulse control) based broadly on Eysenck's theory of cortical arousal (1967, 1981). Top Panel: According to Eysenck's theory, extraverts (dashed black line) function at a lower level of tonic cortical arousal than introverts (solid gray line); when normally rested, this would be expected to lead to similar levels of performance, positive affect, and impulse control. Bottom Panel: During sleep loss, arousal levels would be expected to decline for both groups equally (i.e., shifting both groups to the left), but would be manifested most noticeably among extraverts, as their tonic arousal exists closer to the left side of the curve than for introverts. This is postulated to lead individuals higher in trait extraversion to show greater mood declines and difficulties regulating suicidal impulses when sleep is lacking.

may further increase the vulnerability to suicidal decision processes when a distressed individual perceives no better alternatives.

Our proposition is that sleep disturbance may increase the vulnerability to suicidal decision processes, particularly among those higher in TE. This hypothesis emerges from the well-established evidence that insufficient sleep reduces metabolic activity within the prefrontal cortex (Thomas et al., 2000, 2003; Wu et al., 2006) and weakens functional connectivity among regions that regulate emotional reactivity (Yoo et al., 2007; Chee and Zhou, 2019). These alterations in normal brain functioning can have important consequences for suicidal thinking and behavior. First, the reduced prefrontal regulatory control of the amygdala produced by sleep disruption would be expected to increase the likelihood that life experiences may be viewed as more affectively salient and imbued with negative

emotional tone than when normally rested (Walker and Van Der Helm, 2009). As negative emotions tend to increase during sleep deprivation (Killgore et al., 2008) or following poor quality sleep (Baglioni et al., 2010; Tkachenko et al., 2014), this lack of emotional regulatory capacity could exacerbate existing mental pain and thoughts of suicide for some individuals (Verrocchio et al., 2016). Second, consistent with the well-known role of the prefrontal cortex in higher order executive functioning and cognition, sleep deprivation has been shown to impair critical aspects of cognitive processing, including decision-making and risk propensity (Killgore et al., 2006; Dickinson et al., 2021), cognitive flexibility (Honn et al., 2019), as well as constructive thinking and emotional intelligence (Killgore et al., 2008). Deficits in many of these capacities have also been reported among individuals with chronic sleep disturbances (Cheng et al., 2017; Ballesio et al., 2019; Killgore et al., 2021). It is conceivable that, during a period of sleep disturbance, an individual may evaluate the perceived costs vs. benefits of suicide differently than when well-rested, leading to different decisions and behavioral outcomes. Third, lack of sleep has been shown to decrease metabolic activity in lateral prefrontal cortex regions involved in inhibitory capacity (Thomas et al., 2000; Muzur et al., 2002), which often translates to increased impulsive behavior (Demos et al., 2016; Saksvik-Lehouillier et al., 2020). In one study, sleep-deprived individuals demonstrated enhanced impulsive reactivity to negative stimuli (Anderson and Platten, 2011), which could conceivably amplify the tendency to act on suicidal thoughts, particularly among individuals with higher TE. Together, these findings suggest that insufficient or poor-quality sleep may contribute to functional brain changes that weaken regulatory control over negative emotions, degrade normal decision-making processes, and suppress inhibitory control of behavior—all of which do not portend well for someone in emotional pain and already contemplating suicide, particularly if they are already prone to impulsivity as a facet of high extraversion.

Of course, there are other potential explanations for these findings as well. Notably, we found that in Study 1, the association between TE and changes in suicidal thinking was primarily accounted for by differences in positive emotion (i.e., the tendency to experience high levels of happiness, excitement, and joy), rather than other facets. This raises the possibility that individuals who endorse such extremes in positive emotions may be particularly hard hit by the changes in prefrontal activation and accordant mood shifts produced by sleep loss, leading to greater feelings of hopelessness or despair under such circumstances. This possibility deserves additional investigation. It is also quite possible that individuals who are higher in TE and its accompanying positive emotions are more socially engaged during the day and that increased social interaction produces greater declines in cognitive resources. Social interactions require effort, including sustained self-monitoring and exertion of self-control, which can lead to a state sometimes referred to as "ego depletion," in which the ability to self-regulate behavior becomes diminished (Baumeister, 2014). Ego depletion is known to be moderated by the trait of extraversion (Johnson et al., 2014) and appears to be exacerbated by sleep loss (Pilcher et al., 2015; Guarana et al., 2021). In one study, we demonstrated that social exposure led to greater vigilance decrements during sleep deprivation for extroverts compared to introverts (Rupp et al., 2010). Thus, it is possible that high TE individuals may simply be more vulnerable to a broad range of cognitive and affective declines when sleep deprived due to greater depletion of self-control resources produced by greater social engagement during the day compared to their low TE counterparts. We were not able to assess this possibility here, but the role of social effort and depletion of self-control among those higher in TE should be an area for further research.

While the aforementioned findings do not suggest that a person who is high in TE is destined to engage in suicidal behavior when sleep deprived, these findings do point to a potential contributing factor that may be important to incorporate into a more comprehensive understanding of suicidal phenomena. Consistent with the two-process model (Borbely, 1982), we speculate that during normal daytime hours, the gradual decline in self-control resources is likely offset by the upswing in circadian alertness, but as the period of wakefulness is extended beyond the normal sleep period, it likely becomes progressively more difficult to sustain a positive affective tone and suppress unwanted or unproductive thoughts. For the individual predisposed to a negative outlook, these thoughts may include considerations of self-harm or suicide. With further reductions of prefrontal cortical activation during sleep loss (Thomas et al., 2000) and the incumbent degradation of executive control over affect and behavior that emerges, the individual may find themselves experiencing an excessive negative emotion, self-critical thoughts, and impulsive tendencies. When combined with deficits in decision making, altered moral reasoning, and reduced inhibitory control, the risk for suicide can rise precipitously. Some evidence suggests that, after adjusting for the percent of the populace awake, suicides are most probable in the early morning hours, when sleep is lacking and the individual is functioning outside of their normal circadian phase (Perlis et al., 2016a,b; Tubbs et al., 2020). Moreover, being awake and alone at such times can further increase the risk of suicide as needed social support is absent (Calati et al., 2019), and there are few stimuli available to activate countervailing cognitive resources. Together, these factors can substantially increase the risk of suicide for the vulnerable individual. Our findings suggest that while neither being high in TE nor experiencing sleep disturbance is a sufficient clinical predictor of suicidal risk, when combined these factors do interact such that an individual who is high in TE may show a slightly elevated tendency to engage suicide-related cognitions. Of course, it is important to highlight that despite

the significant interaction between extraversion and insomnia, the main effects of depression tend to explain the largest proportion of the variance, suggesting that careful assessment of depression remains the first line entry point for identifying suicidal thinking.

These findings should be interpreted with appropriate consideration of several limitations. For Study 1, which focused on multiple nights of sleep deprivation, the sample size was quite modest and included only military personnel, the majority of whom were male. Consequently, the generalizability of the findings will require additional replication in larger and more diverse samples. Additionally, the outcome measure was a self-report scale that included items related to suicidal cognition. Endorsing such items does not necessarily translate into suicidal behavior and all scores on the suicide scale were well within normal limits, suggesting that the current findings may not extend to clinically significant suicide. Nonetheless, the fact that significant changes were observed on such a scale in a tightly controlled environment attests to the potential robustness of the effect. Further, the study was extremely well controlled and participants were closely monitored, which allows confident conclusions that the associations were directly relevant to sleep deprivation. For Study 2, the findings are limited by the cross-sectional nature of the data collection, which makes it impossible to determine the directional causality of insomnia and suicidal ideation, although the findings are consistent with the outcomes expected from the experimental manipulation of sleep deprivation conducted in Study 1. Additionally, Study 2 also suffers from a self-report bias, as all metrics were collected online and *via* self-report instruments assessing suicidal ideation and insomnia. It is not possible to determine how these self-reported tendencies may translate into suicidal behavior. A strength of Study 2 is the large sample size, which allows greater confidence in the findings and considerable range in scores, with over 30% indicating that they had recently thought that they "would be better off dead."

With due consideration to the limitations described above, we believe that the present series of studies adds to the understanding of suicide risk. While evidence suggests that suicide risk is greater when an individual is lacking sleep, when they are awake at a time when they should be sleeping, and when they are likely to be alone, our findings further suggest that individuals who are high in TE may be particularly vulnerable to these effects. The extent to which these factors are related to individual differences in brain functioning, arousal, social ego-depletion, or other mechanisms remains to be elucidated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Walter Reed Army Institute of Research Office of Research Management; U.S. Army Human Subjects Research Protection Office; University of Arizona Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WK: primary study design and conceptualization, primary literature search, data analysis, data interpretation, writing of the initial draft, figures, and tables. MG, AT, F-XF, TD, VC, and ND: contributed to study conceptualization, data interpretation, and editing drafts of manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Aguinis, H. (2004). *Regression Analysis for Categorical Moderators*. New York: Guilford.

Anderson, C., and Platten, C. R. (2011). . Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. *Behav. Brain Res.* 217, 463–466. doi: 10.1016/j.bbr.2010.09.020

Bachmann, S. (2018). Epidemiology of suicide and the psychiatric perspective. *Int. J. Environ. Res. Public Health* 15:1425. doi: 10.3390/ijerph15071425

Bagby, R. M., Schuller, D. R., Marshall, M. B., and Ryder, A. G. (2004). Depressive personality disorder: rates of comorbidity with personality disorders and relations to the five-factor model of personality. *J. Pers. Disord.* 18, 542–554. doi: 10.1521/pedi.18.6.542.54796

Baglioni, C., Spiegelhalder, K., Lombardo, C., and Riemann, D. (2010). Sleep and emotions: a focus on insomnia. *Sleep Med. Rev.* 14, 227–238. doi: 10.1016/j.smrv.2009.10.007

Ballesio, A., Aquino, M., Kyle, S. D., Ferlazzo, F., and Lombardo, C. (2019). Executive functions in insomnia disorder: a systematic review and exploratory meta-analysis. *Front. Psychol.* 10:101. doi: 10.3389/fpsyg.2019.00101

Bastien, C. H., Vallieres, A., and Morin, C. M. (2001). Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med.* 2, 297–307. doi: 10.1016/s1389-9457(00)00065-4

Baumeister, R. F. (2014). Self-regulation, ego depletion and inhibition. *Neuropsychologia* 65, 313–319. doi: 10.1016/j.neuropsychologia.2014.08.012

Beck, A. T., Steer, R. A., and Brown, G. K. (1996). *BDI-II: Beck Depression Inventory Manual*. San Antonio, TX: Psychological Corporation

Bishop, T. M., Ashrafioun, L., and Pigeon, W. R. (2018). The association between sleep apnea and suicidal thought and behavior: an analysis of national survey data. *J. Clin. Psychiatry* 79:17m11480. doi: 10.4088/JCP.17m11480

Bishop, T. M., Walsh, P. G., Ashrafioun, L., Lavigne, J. E., and Pigeon, W. R. (2020). Sleep, suicide behaviors and the protective role of sleep medicine. *Sleep Med.* 66, 264–270. doi: 10.1016/j.sleep.2019.07.016

Borbely, A. A. (1982). A two process model of sleep regulation. *Hum Neurobiol* 1, 195–204.

Brådvik, L. (2018). Suicide risk and mental disorders. *Int. J. Environ. Res. Public Health* 15, 1–4. doi: 10.3390/ijerph15092028

Britton, P. C., Mckinney, J. M., Bishop, T. M., Pigeon, W. R., and Hirsch, J. K. (2019). Insomnia and risk for suicidal behavior: a test of a mechanistic transdiagnostic model in veterans. *J. Affect Disord.* 245, 412–418. doi: 10.1016/j.jad.2018.11.044

Calati, R., Ferrari, C., Brittner, M., Oasi, O., Olie, E., Carvalho, A. F., et al. (2019). Suicidal thoughts and behaviors and social isolation: a narrative review of the literature. *J. Affect Disord.* 245, 653–667. doi: 10.1016/j.jad.2018.11.022

Casale, C. E., and Goel, N. (2021). Genetic markers of differential vulnerability to sleep loss in adults. *Genes (Basel)* 12:1317. doi: 10.3390/genes12091317

CDC (2022). *Suicide Prevention: Facts About Suicide* [Online]. Accessed February 27, 2022.

Chee, M. W. L., and Zhou, J. (2019). Functional connectivity and the sleep-deprived brain. *Prog. Brain Res.* 246, 159–176. doi: 10.1016/bs.pbr.2019.02.009

Cheng, P., Tallent, G., Bender, T. J., Tran, K. M., and Drake, C. L. (2017). Shift work and cognitive flexibility: decomposing task performance. *J. Biol. Rhythms* 32, 143–153. doi: 10.1177/0748730417699309

Coryell, W., and Young, E. A. (2005). Clinical predictors of suicide in primary major depressive disorder. *J. Clin. Psychiatry* 66, 412–417. doi: 10.4088/jcp.v66n0401

Costa, P. T., Jr., and Mccrae, R. R. (1992). *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) Professional Manual*. Odessa, FL: Psychological Assessment Resources, Inc.

De fruyt, F., Mervielde, I., Hoekstra, H. A., and Rolland, J. P. (2000). Assessing adolescents' personality with the NEO PI-R. *Assessment* 7, 329–345. doi: 10.1177/107319110000700403

Demos, K. E., Hart, C. N., Sweet, L. H., Mailloux, K. A., Trautvetter, J., Williams, S. E., et al. (2016). Partial sleep deprivation impacts impulsive action but not impulsive decision-making. *Physiol. Behav.* 164, 214–219. doi: 10.1016/j.physbeh.2016.06.003

Dennis, L. E., Wohl, R. J., Selame, L. A., and Goel, N. (2017). Healthy adults display long-term trait-like neurobehavioral resilience and vulnerability to sleep loss. *Sci. Rep.* 7:14889. doi: 10.1038/s41598-017-14006-7

Dickinson, D. L., Brookes, J., Ferguson, C., and Drummond, S. P. A. (2021). The impact of self-selected short sleep on monetary risk taking. *J. Sleep Res.* 31:e13529. doi: 10.1111/jsr.13529

Dorrian, J., Centofanti, S., Smith, A., and Mcdermott, K. D. (2019). Self-regulation and social behavior during sleep deprivation. *Prog. Brain Res.* 246, 73–110. doi: 10.1016/bs.pbr.2019.03.010

Draycott, S. G., and Kline, P. (1995). The big three or the big five-the EPQ-R vs the NEO-PI: a research note, replication and elaboration. *Pers. Individ. Differ.* 18, 801–804. doi: 10.1016/0191-8869(95)00010-4

Durmer, J. S., and Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Semin. Neurol.* 25, 117–129. doi: 10.1055/s-2005-867080

Eysenck, H. J., and Eysenck, S. B. G. (1964). *Manual of the Eysenck Personality Inventory*. London: University of London Press

Eysenck, H. J. (1967). *The Biological Basis of Personality*. Springfield, IL: Charles C. Thomas.

Eysenck, H. J. (1981). "General features of the model," in *A Model for Personality*, (Berlin: Springer).

Goel, N., Banks, S., Lin, L., Mignot, E., and Dinges, D. F. (2011). . Catechol-O-methyltransferase Val158Met polymorphism associates with individual differences in sleep physiologic responses to chronic sleep loss. *PLoS One* 6:e29283. doi: 10.1371/journal.pone.0029283

Grezes, J., Erblang, M., Vilarem, E., Quiquempoix, M., Van Beers, P., Guillard, M., et al. (2021). Impact of total sleep deprivation and related mood changes on approach-avoidance decisions to threat-related facial displays. *Sleep* 44:zsab186. doi: 10.1093/sleep/zsab186

Guarana, C. L., Ryu, J. W., O'Boyle, E. H., Jr., Lee, J., and Barnes, C. M. (2021). Sleep and self-control: a systematic review and meta-analysis. *Sleep Med. Rev.* 59:101514. doi: 10.1016/j.smrv.2021.101514

Gvion, Y., Levi-Belz, Y., Hadlaczky, G., and Apter, A. (2015). On the role of impulsivity and decision-making in suicidal behavior. *World J. Psychiatry* 5, 255–259. doi: 10.5498/wjp.v5.i3.255

Harris, L. M., Huang, X., Linthicum, K. P., Bryen, C. P., and Ribeiro, J. D. (2020). Sleep disturbances as risk factors for suicidal thoughts and behaviours: a meta-analysis of longitudinal studies. *Sci. Rep.* 10:13888. doi: 10.1038/s41598-020-70866-6

Honn, K. A., Hinson, J. M., Whitney, P., and Van Dongen, H. P. A. (2019). Cognitive flexibility: a distinct element of performance impairment due to sleep deprivation. *Accid. Anal. Prev.* 126, 191–197. doi: 10.1016/j.aap.2018.02.013

Johnson, R. E., Lanaj, K., and BarneS, C. M. (2014). The good and bad of being fair: effects of procedural and interpersonal justice behaviors on regulatory resources. *J. Appl. Psychol.* 99, 635–650. doi: 10.1037/a0035647

Johnson, D. L., Wiebe, J. S., Gold, S. M., Andreasen, N. C., Hichwa, R. D., Watkins, G. L., et al. (1999). Cerebral blood flow and personality: a positron emission tomography study. *Am. J. Psychiatry* 156, 252–257. doi: 10.1176/ajp.156.2.252

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., and Killgore, W. D. S. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med.* 8, 215–221. doi: 10.1016/j.sleep.2006.08.007

Kahn-Greene, E. T., Lipizzi, E. L., Conrad, A. K., Kamimori, G. H., and Killgore, W. D. S. (2006). Sleep deprivation adversely affects interpersonal responses to frustration. *Pers. Individual Differences* 41, 1433–1443. doi: 10.1016/j.paid.2006.06.002

Killgore, W. D. S., Balkin, T. J., and Wesensten, N. J. (2006). Impaired decision-making following 49 hours of sleep deprivation. *J. Sleep Res.* 15, 7–13. doi: 10.1111/j.1365-2869.2006.00487.x

Killgore, W. D. S., Balkin, T. J., Yarnell, A. M., Capaldi, V. F., 2nd (2017). Sleep deprivation impairs recognition of specific emotions. *Neurobiol. Sleep Circadian Rhythms* 3, 10–16. doi: 10.1016/j.nbscr.2017.01.001

Killgore, W. D. S., Cloonan, S. A., Taylor, E. C., and Dailey, N. S. (2020a). Loneliness: a signature mental health concern in the era of COVID-19. *Psychiatry Res.* 290:113117. doi: 10.1016/j.psychres.2020.113117

Killgore, W. D. S., Cloonan, S. A., Taylor, E. C., Lucas, D. A., and Dailey, N. S. (2020b). Loneliness during the first half-year of COVID-19 Lockdowns. *Psychiatry Res.* 294:113551. doi: 10.1016/j.psychres.2020.113551

Killgore, W. D. S., Kahn-Greene, E. T., Lipizzi, E. L., Newman, R. A., Kamimori, G. H., and Balkin, T. J. (2008). Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Med.* 9, 517–526. doi: 10.1016/j.sleep.2007.07.003

Killgore, W. D. S., and Kamimori, G. H. (2020). Multiple caffeine doses maintain vigilance, attention, complex motor sequence expression and manual dexterity during 77 hours of total sleep deprivation. *Neurobiol. Sleep Circadian Rhythms* 9:100051. doi: 10.1016/j.nbscr.2020.100051

Killgore, W. D. S., Richards, J. M., Killgore, D. B., Kamimori, G. H., and Balkin, T. J. (2007). The trait of Introversion-Extraversion predicts vulnerability to sleep deprivation. *J. Sleep Res.* 16, 354–363. doi: 10.1111/j.1365-2869.2007.00611.x

Killgore, W. D. S., Vanuk, J. R., Persich, M. R., Cloonan, S. A., Grandner, M. A., and Dailey, N. S. (2021). Sleep quality and duration are associated with greater trait emotional intelligence. *Sleep Health* 8, 230–233. doi: 10.1016/j.sleh.2021.06.003

Kumari, V., Ffytche, D. H., Williams, S. C., and Gray, J. A. (2004). Personality predicts brain responses to cognitive demands. *J. Neurosci.* 24, 10636–10641. doi: 10.1523/JNEUROSCI.3206-04.2004

Lim, J., and Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136, 375–389. doi: 10.1037/a0018883

Lin, H.-T., Lai, C.-H., Perng, H.-J., Chung, C.-H., Wang, C.-C., Chen, W.-L., et al. (2018). Insomnia as an independent predictor of suicide attempts: a nationwide population-based retrospective cohort study. *BMC Psychiatry* 18:117. doi: 10.1186/s12888-018-1702-2

Litman, L., Robinson, J., and Abberbock, T. (2017). TurkPrime.com: a versatile crowdsourcing data acquisition platform for the behavioral sciences. *Behav. Res. Methods* 49, 433–442. doi: 10.3758/s13428-016-0727-z

Liu, X. (2004). Sleep and adolescent suicidal behavior. *Sleep* 27, 1351–1358. doi: 10.1093/sleep/27.7.1351

Mccall, W. V., and Black, C. G. (2013). The link between suicide and insomnia: theoretical mechanisms. *Curr. Psychiatry Rep.* 15:389. doi: 10.1007/s11920-013-0389-9

Morey, L. C. (2007). *Personality Assessment Inventory*. Lutz, FL: Psychological Assessment Resources, Inc.

Morin, C. M., Belleville, G., Belanger, L., and Ivers, H. (2011). . The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 34, 601–608. doi: 10.1093/sleep/34.5.601

Muzur, A., Pace-Schott, E. F., and Hobson, J. A. (2002). The prefrontal cortex in sleep. *Trends Cogn. Sci.* 6, 475–481. doi: 10.1016/s1364-6613(02)01992-7

Perlis, M. L., Grandner, M. A., Brown, G. K., Basner, M., Chakravorty, S., Morales, K. H., et al. (2016a). Nocturnal wakefulness as a previously unrecognized risk factor for suicide. *J. Clin. Psychiatry* 77, e726–e733. doi: 10.4088/JCP.15m10131

Perlis, M. L., Grandner, M. A., Chakravorty, S., Bernert, R. A., Brown, G. K., and Thase, M. E. (2016b). Suicide and sleep: is it a bad thing to be awake when reason sleeps? *Sleep Med. Rev.* 29, 101–107. doi: 10.1016/j.smrv.2015.10.003

Pigeon, W. R., Pinquart, M., and Conner, K. (2012). Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J. Clin. Psychiatry* 73, e1160–e1167. doi: 10.4088/JCP.11r07586

Pilcher, J. J., Morris, D. M., Donnelly, J., and Feigl, H. B. (2015). Interactions between sleep habits and self-control. *Front. Hum. Neurosci.* 9:284. doi: 10.3389/fnhum.2015.00284

Quirk, S. W., Christiansen, N. D., Wagner, S. H., and Mcnulty, J. L. (2003). On the usefulness of measures of normal personality for clinical assessment: evidence of the incremental validity of the revised NEO personality inventory. *Psychol. Assess.* 15, 311–325. doi: 10.1037/1040-3590.15.3.311

Revelle, W. (1997). "Extraversion and impulsivity: the lost dimension," in *The Scientific Study of Human Nature: Tribute to Hans J. Eysenck at Eighty*, ed H. Nyborg (New York, NY: Pergamon/Elsevier Science), 189–212.

Rupp, T. L., Killgore, W. D. S., and Balkin, T. J. (2010). Socializing by day may affect performance by night: vulnerability to sleep deprivation is differentially mediated by social exposure in extraverts vs introverts. *Sleep* 33, 1475–1485. doi: 10.1093/sleep/33.5.1475

Russell, D. W. (1996). UCLA loneliness scale (Version 3): reliability, validity and factor structure. *J. Pers. Assess.* 66, 20–40. doi: 10.1207/s15327752jpa6601_2

Saksvik-Lehouillier, I., Saksvik, S. B., Dahlberg, J., Tanum, T. K., Ringen, H., Karlsen, H. R., et al. (2020). Mild to moderate partial sleep deprivation is associated with increased impulsivity and decreased positive affect in young adults. *Sleep* 43:zsaa078. doi: 10.1093/sleep/zsaa078

Sherry, A., Henson, R. K., and Lewis, J. G. (2003). Evaluating the appropriateness of college-age norms for use with adolescents on the NEO personality inventory-revised. *Assessment* 10, 71–78. doi: 10.1177/1073191102250184

Simmons, Z., Erickson, L. D., Hedges, D., and Kay, D. B. (2020). Insomnia is associated with frequency of suicidal ideation independent of depression: a replication and extension of findings from the national health and nutrition examination survey. *Front. Psychiatry* 11:561564. doi: 10.3389/fpsyt.2020.561564

Stenson, A. R., Kurinec, C. A., Hinson, J. M., Whitney, P., and Van Dongen, H. P. A. (2021). Total sleep deprivation reduces top-down regulation of emotion without altering bottom-up affective processing. *PLoS One* 16:e0256983. doi: 10.1371/journal.pone.0256983

Stephan, Y., Sutin, A. R., Bayard, S., Krizan, Z., and Terracciano, A. (2018). Personality and sleep quality: evidence from four prospective studies. *Health Psychol.* 37, 271–281. doi: 10.1037/hea0000577

Suitt, T. H. (2021). "High suicide rates among United States service members and veterans of teh post-9/11 wars," in *20 Years of War: A Costs of War Research Series*. Providence, RI: Waston Instutute of International and Public Affairs, Brown University

Taylor, D. J., and Mcfatter, R. M. (2003). Cognitive performance after sleep deprivation: does personality make a difference? *Pers. Individual Differences* 34, 1179–1193. doi: 10.1016/s0191-8869(02)00108-3

Thomas, M., Sing, H. S., Belenky, G., Holcomb, H. H., Mayberg, H. S., Dannals, R. F., et al. (2003). Neural basis of alertness and cognitive performance impairments during sleepiness II. effects of 48 and 72 h of sleep deprivation on waking human regional brain activity. *Thalamus Relat. Syst.* 2, 199–229. doi: 10.1016/s1472-9288(03)00020-7

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., et al. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. effects of 24 h of sleep deprivation on waking human regional brain activity. *J. Sleep Res.* 9, 335–352. doi: 10.1046/j.1365-2869.2000.00225.x

Tkachenko, O., Olson, E. A., Weber, M., Preer, L. A., Gogel, H., and Killgore, W. D. S. (2014). Sleep difficulties are associated with increased symptoms of psychopathology. *Exp. Brain Res.* 232, 1567–1574. doi: 10.1007/s00221-014-3827-y

Tubbs, A. S., Harrison-Monroe, P., Fernandez, F.-X., Perlis, M. L., and Grandner, M. A. (2020). When reason sleeps: attempted suicide during the circadian night. *J. Clin. Sleep Med.* 16, 1809–1810. doi: 10.5664/jcsm.8662

Van Der Helm, E., Gujar, N., and Walker, M. P. (2010). Sleep deprivation impairs the accurate recognition of human emotions. *Sleep* 33, 335–342. doi: 10.1093/sleep/33.3.335

Van Dongen, H. P., and Belenky, G. (2009). Individual differences in vulnerability to sleep loss in the work environment. *Ind. Health* 47, 518–526. doi: 10.2486/indhealth.47.518

Van Dongen, H. P., Baynard, M. D., Maislin, G., and Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 27, 423–433. doi: 10.1093/sleep/27.3.423

Venkatraman, V., Chuah, Y. M., Huettel, S. A., and Chee, M. W. (2007). Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. *Sleep* 30, 603–609. doi: 10.1093/sleep/30.5.603

Verrocchio, M. C., Carrozzino, D., Marchetti, D., Andreasson, K., Fulcheri, M., and Bech, P. (2016). Mental pain and suicide: a systematic review of the literature. *Front. Psychiatry* 7:108. doi: 10.3389/fpsyt.2016.00108

Vingoe, F. J. (1968). Validity of the eysenck extraversion scale: replication and extension. *Psychol. Rep.* 22, 706–708. doi: 10.2466/pr0.1968.22.3.706

Walker, M. P., and Van Der Helm, E. (2009). Overnight therapy? the role of sleep in emotional brain processing. *Psychol. Bull.* 135, 731–748. doi: 10.1037/a0016570

Wang, Y. P., and Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Braz. J. Psychiatry* 35, 416–431. doi: 10.1590/1516-4446-2012-1048

Whiteside, S. P., and Lynam, D. R. (2001). The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Pers. Individual Differences* 30, 669–689. doi: 10.1016/s0191-8869(00)00064-7

Whitney, P., Hinson, J. M., Jackson, M. L., and Van Dongen, H. P. (2015). Feedback blunting: total sleep deprivation impairs decision making that requires updating based on feedback. *Sleep* 38, 745–754. doi: 10.5665/sleep.4668

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., Chen, P., Keator, D. B., Khosla Wu, N., et al. (2006). Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. *Neuropsychopharmacology* 31, 2783–2792. doi: 10.1038/sj.npp.1301166

Yamazaki, E. M., and Goel, N. (2020). Robust stability of trait-like vulnerability or resilience to common types of sleep deprivation in a large sample of adults. *Sleep* 43:zsz292. doi: 10.1093/sleep/zsz292

Yoo, S. S., Gujar, N., Hu, P., Jolesz, F. A., and Walker, M. P. (2007). The human emotional brain without sleep–a prefrontal amygdala disconnect. *Curr. Biol.* 17, R877–R878. doi: 10.1016/j.cub.2007.08.007

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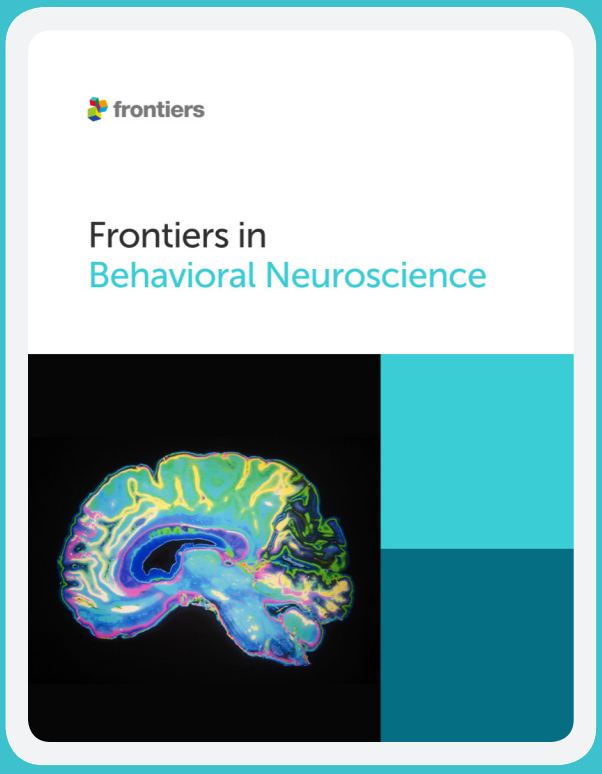

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