# THE INTERPLAY BETWEEN SLEEP AND EMOTION: WHAT ROLE DO COGNITIVE PROCESSES PLAY?

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# THE INTERPLAY BETWEEN SLEEP AND EMOTION: WHAT ROLE DO COGNITIVE PROCESSES PLAY?

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# Editorial: The Interplay Between Sleep and Emotion: What Role Do Cognitive Processes Play?

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## Editorial on the Research Topic

## The Interplay Between Sleep and Emotion: What Role Do Cognitive Processes Play?

Sleep is an intrinsic condition of life. Although "why do we sleep" is still an elusive question, in the last decade several studies have shown that sleep plays a key role in memory and emotional processing. Yet, the specific mechanisms underlying sleep-related memory and emotional processes remain partially unknown, and studies often report contradictory results (Cordi and Rasch, 2020). From a psychopathology point of view, literature is showing how people suffering from sleep problems, such as in insomnia, are often characterized by cognitive dysfunctions and emotion dysregulation (Jansson-Fröjmark et al., 2016; Cellini, 2017; Ballesio et al., 2018). Neuroimaging studies are also supporting this view. As recently summarized by Schiel et al. (2020), insomnia is related to altered amygdala reactivity, morphometry, and adaptation. Moreover, insomnia is associated with aberrant connectivity in the default mode network, alterations in the salience network associated with hyperarousal, maladaptive emotion regulation, and disturbed integration of emotional states. Considering that the ability to adaptively regulate emotions is crucial for healthy functioning, the dysregulation of negative affect circuitry associated or due to insomnia may mediate the impact of insomnia on psychopathology. Indeed, sleep difficulties are often associated with other mental disorders and may be considered a transdiagnostic risk factor (Fairholme et al., 2013), although the role of the mediating factors still needs to be clarified.

The studies collected in the present Research Topic contribute to shed light on the relationship between sleep, cognitive, and emotional processing in healthy and clinical populations, discussing the most advanced development in the field from different perspectives (e.g., neurophysiological, behavioral, clinical). There are nine manuscripts in this special issue, including seven original research studies and two meta-analyses targeting two different aspects of the relationship between sleep and emotions.

Four papers focused their attention on insomnia. Feige et al. addressed the role of physiological arousal showing how evening relaxation positively influences sleep architecture, in particular in patients with insomnia disorders, suggesting how relaxation may be a useful therapeutic target in conjunction with other treatments for insomnia.

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In their opinion paper, Akram et al. focused on the cognitive aspects of insomnia, discussing, in particular, the relationship between attentional bias for sleep-related threat information and insomnia. The authors propose several candidate factors, including mood state and worry, that may influence the sleep-related attentional biases in people suffering from insomnia. The authors also discuss the potential beneficial role of attentional bias modification training for treating insomnia symptomatology. The study of de Almondes et al. investigates the relationship between facial emotion recognition and executive functioning among individuals with insomnia. Results indicate that patients with insomnia disorders show both a lower facial recognition of fear and sadness and impaired executive functions (i.e., inhibitory control, planning capacity, problem-solving, and cognitive flexibility) compared to healthy controls. Impairment in executive functions in individuals with insomnia is also supported by the meta-analysis conducted by Ballesio et al. The authors conducted a systematic review of the literature on three components of executive functions (i.e., inhibitory control, working memory, and cognitive flexibility). Results of the 28 studies included in the meta-analysis indicate small to moderate deficits in executive functions in individuals with insomnia.

Three other papers focused their attention on different aspects of emotional memory in relation to sleep. Jones et al. examined the impact of emotional memory processing during a daytime nap on people's moods. They showed that positive affect decreases after viewing unpleasant pictures, but it recovers after a daytime nap as a function of the sigma activity level. Moreover, the recovery seems to be moderated by the level of emotional memory consolidation, suggesting an interesting relationship between the processing of emotional memories during sleep and post-sleep affect. The study by Cellini et al. investigated the fate of emotional memories over 1 week. Their results indicate that emotional memories are resistant to forgetting, particularly when sleep is disrupted. Moreover, their results indicate that emotional memory consolidation over time seems not to be affected by non-clinical depression symptomatology. The relationship between sleep and emotional memory consolidation is also the focus of the meta-analysis conducted by Lipinska et al.. Analyzing data from 31 articles, the authors showed that sleep preferentially consolidates emotional over neutral memories, but only under specific conditions. For example, studies using free-recall show a more robust effect than studies employing recognition memory tasks.

The remaining two studies targeted different aspects of sleep and emotion/cognition. Ackermann et al. tested the effect of psychosocial stress on subsequent sleep characteristics and cognitive functioning. Using a daytime nap paradigm, they showed that psychosocial stress increases sleep latency and reduce slow-wave activity (i.e., a marker of deep sleep), but the latter effect was short-lasting. Moreover, the stressful situation before a nap did not impair cognitive functioning. Lastly, Simor et al. investigated the time curse of sequence and statistical learning, showing that the knowledge acquired during training is preserved after an off-line period regardless of the presence of sleep, although sleep oscillations seem to modulate memory consolidation at the individual level.

## CONCLUSIONS

The papers included in this Research Topic contributed to shed light on the complex relationship, characterized by reciprocal influences, between sleep and emotional and cognitive processing. They confirm that the alterations of sleep (e.g., due to the chronic effect of insomnia) have a negative impact on cognitive and emotional functioning. However, they also support the negative impact of cognitive and emotional processes on sleep thus suggesting the reciprocal influences of those two domains pertaining to a cycle that only conventionally is divided into wake (cognitive and emotional functioning) and sleep (quality or duration). Nevertheless, more research is needed to further advance our understandings of the relationship between sleep and cognitive and emotional processing, in particular in light of the fundamental role of sleep on physical and mental health. Further studies are also required to better understand the factors that may mediate or moderate the impact of chronic alteration of sleep on psychological functioning and mental health.

## AUTHOR CONTRIBUTIONS

NC and CL have made a substantial, direct and intellectual contribution to the work and approved it for publication.

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OPINION
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# Sleep-Related Attentional Bias in Insomnia: Time to Examine Moderating Factors?

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Prominent cognitive models of insomnia have emphasized the notion that the disorder is in part maintained by an attentional bias for sleep related "threat" cues which may be internal (i.e., bodily sensations) or external (i.e., environmental) in nature (Harvey, 2002; Espie et al., 2006). To support this proposition, a growing number of studies have examined the presence of a sleep-related attentional bias for words and images using experimental tasks including the dot-probe, flicker, Posner, emotional Stroop, and eye-tracking paradigms (see Harris et al., 2015 for a review). Many of these studies have provided encouraging evidence for the presence of such a bias in insomnia. However, the evidence base advocating the presence of such a bias remains mixed with a number of studies yielding no statistically significant effects. While a recent review (Harris et al., 2015) cautiously suggests biased attention for sleep-related threat information to be a likely feature of insomnia, the authors highlight the need to understand the specificity of this bias and its relationship with mechanisms believed to underpin the disorder (e.g., sleep preoccupation). Furthermore, whilst it is possible that the mixed evidence may stem from methodological differences relating to the task or population used, the possible moderating influence of these factors on the relationship between attentional bias for sleep-related threat information and insomnia have only recently been examined (e.g., Zheng et al., 2018). With this in mind, we propose candidate factors that may play a crucial role in addressing moderating questions such as "when," "for whom" and "under which" conditions are sleep-related attentional biases evident in individuals characterized by insomnia.

## 5HTTLPR POLYMORPHISM AND BRAIN REACTIVITY

First, we consider the role of the serotonin transporter polymorphism (5HTTLPR). Some authors have demonstrated the 5HTTLPR short allele to be related to an increased risk for insomnia/poor sleep quality relative to the long allele (Deuschle et al., 2010; Huang et al., 2014), though findings are inconsistent (e.g., Barclay et al., 2011). Others have documented that the association between 5HTTLPR polymorphism and risk for insomnia/poor sleep is moderated by life stress (Brummett et al., 2007; Huang et al., 2014); and recently the short allele has been associated with increased hypothalamic-pituitary-adrenal (HPA) axis reactivity in response to stress (van Dalfsen and Markus, 2015). However, this association is moderated by sleep quality: long-long homozygotes experiencing poor sleep quality exhibit heightened stress reactivity relative to short-short homozygotes (van Dalfsen and Markus, 2015). Regardless of the mechanisms involved, it appears that 5HTTLPR genotype, sleep quality and stress reactivity are intricately linked, and one possibility is that 5HTTLPR genotype may differentially alter an individual's reactivity to stress under different environmental conditions. In the context of attention bias, it is possible that

5HTTLPR genotype differentially affects behavioral outputs, dependent on sleep quality. In other words, it is possible that 5HTTLPR polymorphisms differentially affect biased attention for "threat" relevant stimuli (possibly due to differences in the activity of the HPA axis) in good vs. poor sleepers.

In other psychiatric populations (e.g. anxiety/depression), a relationship between the short allele and an attentional bias for emotionally salient words and images has been evidenced (Beevers et al., 2009; Fox et al., 2009; Perez-Edgar et al., 2010). Specifically, this allelic variation has been linked with difficulty disengaging attention away from response to threat (Beevers et al., 2009), whereas the long allele has been associated with threat avoidance and increased attention for positively valanced stimuli (Hariri et al., 2002; Munafò et al., 2008). It would be worthy to determine whether a similar pattern would occur in insomnia patients, or whether the presence of poor sleep in this population reverses the 5HTTLPR association as would be expected in light of van Dalfsen and Markus's (2015) finding. Either way, we hypothesize that allelic variation in the 5HTTLPR polymorphism to also modulate the relationship between insomnia and attentional bias.

Given that the amygdala is involved in the processing of emotional information, and because one of the roles of serotonin is regulating mood (Ressler and Nemeroff, 2000), researchers have examined whether 5HTTLPR genotype differentially affects neural responses of the amygdala to emotional stimuli. In healthy participants, short allele carriers exhibit greater neural activity in the amygdala, and greater connectivity between the amygdala and ventromedial prefrontal cortex, compared to long-long homozygotes when presented with negatively toned stimuli (Pezawas et al., 2005; Heinz et al., 2007). Given that individuals with insomnia display increased amygdala reactivity in response to sleep-related stimuli (which may be interpreted as negative; Baglioni et al., 2014) it is plausible that 5HTTLPR genotype may underlie this neural response, with genetically vulnerable individuals exhibiting greater sensitivity, and possibly greater attention, to potential threats.

## VALANCE OF MOOD STATE

Second, previous research has statistically controlled for trait-like emotional distress characterized by disposition to experience anxiety or depression (Jansson-Fröjmark et al., 2012; Akram et al., 2018c). However, attentional bias to threat is a transient process (MacLeod et al., 2002) and emotional tone has differential effects. For example, dysphoric mood is often associated with negative cognitive activity (e.g., catastrophising, worry, rumination) whereas this can be attenuated with enhanced mood (Baglioni et al., 2010, 2014). As such, current mood state should be taken into account in future studies rather than just trait-like characteristics. Indeed, inducing a negative mood state in people with insomnia influences the extent to which an attentional bias to threatening information is displayed (Zheng et al., 2018). Specifically, when assigned to a negative mood inducing (i.e., autobiographical recall of poor sleep) or control (i.e., reading recall) condition prior to completing a dot-probe task comprised of images differing in emotional valence and relatedness to sleep (i.e., general threat, sleep positive, sleep negative), an overall attentional bias to all images emerged only amongst individuals with insomnia who were subject to negative mood state induction Despite an absence of evidence for a sleep-related attentional bias in this study, it remains possible that the overall valance of an individual's emotional mood state, as well as its intensity, duration and frequency of occurrence, may act as moderating factors. That said, further research is required to clarify this position, and expand on these novel findings by examining the therapeutic potential of a positive mood state induction.

## SLEEP-RELATED WORRY

Next, we speculate that attentional bias for threatening information might extend particularly to individuals who attribute worry as the main cause of their insomnia. Worry, by definition, is a cognitive process that involves a chain of emotionally negative thoughts about potential future events (Hirsch and Mathews, 2012). Whilst worry may be utilized in a productive manner in terms of solving a specific problem, it appears to be unproductive in the context of sleep, as evidenced by the consistent relationship between worry about sleep and longer sleep onset latency (Harvey, 2002; Harvey and Greenall, 2003; Weise et al., 2013). Indeed, research has consistently evidenced strong relationships between a tendency to worry and high levels of insomnia symptoms (Watts et al., 1994; Jansson and Linton, 2006; Carney et al., 2010; O'Kearney and Pech, 2014). In addition, this population displays a greater propensity to worry during the pre-sleep period, than good sleepers (e.g., Lancee et al., 2017a). Given that by nature, worry is a negative affect-laden process, it is plausible that individuals with insomnia exhibit greater attentional selectivity of emotionally negative information. Therefore, a factor that may moderate this relationship is the degree to which those with insomnia differ in experiencing increased sleep-related worry prior to initiating sleep (e.g., the consequences of not getting enough sleep on functioning; their perceived lack of ability to fix their sleep problem) which is inherently unproductive.

Potentially, a population of those with insomnia who excessively worry about the immediate and longer-term consequences of sleeplessness eventually develop an attentional bias to sleep-related negative information due to an increased personal relevance of this type of information (Espie, 2002). In contrast, those with insomnia who do not worry specifically about sleep are less likely to develop an attention bias to sleep-related negative information. If true, empirical studies would observe a sleep-related attentional bias only in individuals for whom sleep is a major concern on nights where this more profoundly manifested (e.g., attention to signs of wakefulness such as racing heart beat and racing thoughts). While prior research has examined whether cognitive activity in general and worry differentially predict insomnia (Wicklow and Espie, 2000; Harvey and Greenall, 2003), to the best of the author's knowledge no study thus far has examined the specific possibility that differences in the content and intensity of worries (i.e.,

worry about sleep vs. worry about other topics) differentially predict attentional bias in insomnia. However, prior research has obtained suggestive evidence consistent with this latter possibility in the context of catastrophic worry and sleep-related threat (Barclay and Gregory, 2010; Barclay and Ellis, 2013). In particular, Barclay and Gregory (2010) asked poor and good sleepers to: catastrophise (i.e., iterate negative aspects of a problem: Kendall and Ingram, 1987) about their sleep and a personal worry; and to iterate a hypothetical topic in a positive manner. Here, whilst poor sleepers catastrophised more for each topic compared to good sleepers, the frequency of catastrophic worry didn't vary by topic (i.e., sleep-related worry, personal worry, or hypothetical) for poor sleepers. Additionally, these outcomes were mediated by anxiety. The authors suggest that poor sleepers' orientation of catastrophic thoughts may not always be sleep-specific; rather related to a perseverative iterative style, fuelled by anxiety. Next, Barclay and Ellis (2013) observed that poor sleepers were slower to detect sleep-related stimuli compared to non-sleep-related negative stimuli, and this pattern was not observed in good sleepers. The authors speculate that the personal relevance of the "threat" differentially impacts speed of response: sleep-related stimuli hindered performance, whereas conversely non-specific threats facilitated performance. Taken together, these findings suggest that cognitive styles (i.e., worry focused) and personal relevance of the sleep-related stimuli may moderate the attentional bias effect and may account for the inconsistencies in the literature.

Finally, it is relevant to note that worry and rumination come under the broader cognitive process of "repetitive negative thinking" or "recurrent negative thinking" which is now recognized to be a transdiagnostic cognitive process for anxiety and depressive disorders (Gustavson et al., 2018). First, however we propose examining differential aspects of thought and how this is presented in relation to insomnia and then subsequently determining whether these specific insomnia-relevant constructs moderate the relationship between attentional bias and insomnia. In turn, this area could learn whether the "repetitive negative thinking" phenomenon in anxiety and depressive disorders can be extrapolated to insomnia and other sleep disturbances.

## MISPERCEPTION OF SLEEP AND DAYTIME IMPAIRMENT

It is possible that individuals with insomnia exhibiting a sleep-related attentional bias may be experiencing increased misperception pertaining to their nocturnal sleep and the extent of their daytime impairment resulting from poor sleep. Specifically, it is theorized that increased attention toward sleep-related cues during sleep and the pre-sleep period may distort the distinction between sleep and wakefulness resulting in a misperception of sleep (Harvey, 2002). Indeed, it is well-evidenced that some individuals with insomnia often misperceive attributes of sleep: self-reported sleep onset latency is usually overestimated, and total sleep time underestimated, relative to objectively recorded data (e.g., Wicklow and Espie, 2000; Tang and Harvey, 2006; Van Den Berg et al., 2008). This misperception may also extend to daytime impairment and perception of sleep-deficit. Indeed, whilst individuals with insomnia report their perception of daytime cognitive functioning (i.e., attention, working and episodic memory, problem solving) to be in a manner that confirms the presence of a sleep deficit (i.e., an increased daytime impairment: Fortier-Brochu et al., 2012), objective performance on neuropsychological measures of such functioning do not always coincide with their perception (Orff et al., 2007; Goldman-Mellor et al., 2015). In a similar manner, it has also been evidenced that individuals with insomnia consider their facial appearance to appear more physically tired than they actually are (Akram et al., 2016). However, not all those with insomnia misperceive attributes of their sleep and/or the true extent to which daytime functioning is impaired due to poor sleep. This suggests these two forms of sleep misperception (about sleep and daytime consequences) may be functionally underpinned by a third factor. One plausible factor the present commentary has alluded to is worry. It is possible that worry moderates the relationship between sleep misperception and objective measures of sleep, such that increased levels of worry serve to perpetuate misperception of sleep and of the extent to which poor sleep impairs daily functioning. In contrast, a reduced level of worry may result in more accurate perceptions of one's sleep compared with objective measures. Furthermore, worry and misperception of sleep may facilitate attention toward cues pertaining to nocturnal sleep and daytime performance as a counterproductive form of self-assessment. Here, once attention is placed on a particular cue (e.g., heart rate), it may then be interpreted in a way that confirms the sleep disturbance (e.g., "why is my heart *still* racing" during sleep onset) consequently feeding back to accentuate sleep-related worry (e.g., "If it doesn't slow down soon I won't be able to sleep") and misperception of sleep attributes (e.g., "I can't function at work because I slept poorly last night") in a cyclical nature (Harvey, 2002).

## SYMPTOM VARIATION

Several studies investigating the presence of an attention bias in insomnia have found group differences (e.g., insomnia vs. normal-sleepers) in relation to attentional bias outcomes (Spiegelhalder et al., 2008; Jansson-Fröjmark et al., 2012; Barclay and Ellis, 2013; Beattie et al., 2017; Akram et al., 2018a,b,c; Koranyi et al., 2018). However, increased insomnia symptom severity or severity of poor sleep quality do not appear to be related to attentional bias outcomes (Spiegelhalder et al., 2008; Jansson-Fröjmark et al., 2012; Barclay and Ellis, 2013; Beattie et al., 2017; Akram et al., 2018a,b,c; Koranyi et al., 2018). With that in mind, little variation in yielded effect sizes relating to sleep-related attentional bias in insomnia are reported between clinically diagnosed patients, opportunistic samples of individuals meeting diagnostic criteria, and poor sleepers (Harris et al., 2015). That said, Spiegelhalder et al. (2010) demonstrated positive relationships between attentional bias indices and polysomnographically determined total sleep time, sleep efficiency and duration of slow-wave sleep amongst individuals with insomnia when using the dot-probe task. This pattern of findings did not extend to attentional bias when using the Stroop task. Thus, it is possible that objective measures of severity of sleep disturbance may be predictive of attention

bias. Future research should examine the potential role of both subjective and objective variation in sleep continuity as a moderating factor of attention bias.

## TASK AND STIMULI

There is mixed evidence concerning the presence of a sleep-related attentional bias in insomnia and these inconsistencies may stem from variation in the methodological approach used. Indeed, when examining group differences (insomnia/poor-sleeper vs. control) in reaction time tasks, Harris et al. (2015) determined the flicker, dot-probe and Posner tasks to demonstrate moderate to large effects sizes. In contrast, the Stroop task appears less sensitive, with two studies (Spiegelhalder et al., 2008; Barclay and Ellis, 2013) out of five (Lundh et al., 1997; Spiegelhalder et al., 2008, 2010; Zhou et al., 2018) conducted to date demonstrating an attentional bias in insomnia.

Moving forward from reaction time assessments of attentional bias, which can be considered an indirect measure of attention, a number of recent studies have employed eye-tracking paradigms with the aim to examine selective attention in insomnia (Woods et al., 2013; Beattie et al., 2017; Akram et al., 2018c). Here, visual attention can be continuously recorded throughout stimuli presentation, providing a more ecological observation of visual and selective attention relative to reaction time measures (Armstrong and Olatunji, 2012; Marks et al., 2014). Interestingly, using this methodology, only studies using sleep-related and neutral images, rather than words, as part of a free viewing task evidenced increased attention allocated to the spatial location of insomnia salient stimuli (Beattie et al., 2017; Akram et al., 2018c).

A final consideration is whether people with insomnia compared to normal sleepers differ in the extent to which they consider sleep-related stimuli as *threatening*. Moreover, it remains unclear whether this *threat* drives attentional biases in insomnia; or whether perceptions of threat are stimulated by monitoring of the external environment for sleep-related cues. This latter explanation would be consistent with the idea that the attentional bias in insomnia represents a *craving* for sleep rather than interpreting sleep-related stimuli as *threatening*.

## APPLICATION AND SUMMARY

Recent evidence from the anxiety literature shows attentional bias modification (ABM) to be effective in ameliorating disorder consistent symptoms amongst individuals who elicit an attentional bias (MacLeod and Grafton, 2016). In poor sleepers, ABM administered immediately prior to bed improved subjective sleep quality and reduced pre-sleep arousal and sleep onset latency across a single sleep episode, relative to alternative nights where a control task was completed (Milkins et al., 2016). Expanding on this research, Lancee et al. (2017b) evidenced no therapeutic effect of ABM amongst those meeting diagnostic criteria for insomnia. As such, the applicability of ABM to insomnia remains elusive. Therefore, studies assessing the efficacy of ABM for insomnia should incorporate measures to assess factors that potentially moderate not only the relationship between attentional bias and insomnia, but also any therapeutic effect. To that end, an ongoing randomized controlled trial of ABM for insomnia is concurrently examining the role of sleep-related worry and sleep-associated monitoring in the therapeutic potential of ABM (Akram et al., 2018a,b). One can postulate that further steps in this line of enquiry would be to (1) determine the mechanism of action of ABM, if successful even in a subset of patients; and (2) identify moderators of response to ABM. Price et al. (2016) have highlighted the inter-relatedness of moderators and mediators in the therapeutic potential of ABM in relation to anxiety. In other words, is the mechanism of anxiety symptom reduction following ABM due to the successful reduction of attention bias (mediator), and is that successful reduction contingent on particular moderating factors? The same questions can be posed in the insomnia arena. It is possible that potential moderators of response to ABM may overlap with those that predict the presence of attention bias, but it is also possible that there may be distinct moderating factors to consider. For example, as suggested in relation to anxiety (Price et al., 2016), potential moderators of therapeutic response to ABM may be strength of attention bias (i.e., positive responders to ABM may be those exhibiting high attention bias); age; ABM training setting (lab vs. home); and clinician assessed outcomes. These are worthy considerations for future trials examining efficacy of ABM in insomnia.

A recent review tentatively supports the notion of a sleep-related attentional bias in insomnia based on six out of nine studies which confirm group differences in relation to attentional allocation to sleep-related stimuli (Harris et al., 2015). However, the number of studies conducted to date still remains limited. Whilst it is possible that a publication bias exists precluding studies demonstrating null effects, to the best of our knowledge, only a further seven studies have been conducted (Woods et al., 2013; Beattie et al., 2017; Akram et al., 2018a,b,c; Koranyi et al., 2018; Zheng et al., 2018; Zhou et al., 2018), of which four provide additional support (Beattie et al., 2017; Akram et al., 2018a,b,c; Koranyi et al., 2018). Therefore, we suggest that further research is required to clarify the presence of a sleep-related attentional bias in insomnia. Additionally, research should pursue the role of potential factors moderating the sleep-related attentional bias/insomnia relationship. In turn, this may allow a particular sub-set of insomnia patients to benefit therapeutically from ABM through appropriate screening.

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# Deconstructing Procedural Memory: Different Learning Trajectories and Consolidation of Sequence and Statistical Learning

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Procedural learning is a fundamental cognitive function that facilitates efficient processing of and automatic responses to complex environmental stimuli. Here, we examined training-dependent and off-line changes of two sub-processes of procedural learning: namely, sequence learning and statistical learning. Whereas sequence learning requires the acquisition of order-based relationships between the elements of a sequence, statistical learning is based on the acquisition of probabilistic associations between elements. Seventy-eight healthy young adults (58 females and 20 males) completed the modified version of the Alternating Serial Reaction Time task that was designed to measure Sequence and Statistical Learning simultaneously. After training, participants were randomly assigned to one of three conditions: active wakefulness, quiet rest, or daytime sleep. We examined off-line changes in Sequence and Statistical Learning as well as further improvements after extended practice. Performance in Sequence Learning increased during training, while Statistical Learning plateaued relatively rapidly. After the off-line period, both the acquired sequence and statistical knowledge was preserved, irrespective of the vigilance state (awake, quiet rest or sleep). Sequence Learning further improved during extended practice, while Statistical Learning did not. Moreover, within the sleep group, cortical oscillations and sleep spindle parameters showed differential associations with Sequence and Statistical Learning. Our findings can contribute to a deeper understanding of the dynamic changes of multiple parallel learning and consolidation processes that occur during procedural memory formation.

**Keywords: procedural learning, sequence learning, statistical learning, sleep, EEG, consolidation**

## INTRODUCTION

Procedural learning, the development of perceptual and motor skills through extensive practice is a crucial ability that facilitates efficient processing of and automatic responses to complex environmental stimuli. Procedural learning is evidenced by enhanced performance as well as functional changes in the neural network underlying behavior (Howard et al., 2004; Fletcher et al., 2005). Learning performance does not only depend on training during acquisition but also on the post-learning period (Karni et al., 1998; Doyon et al., 2009; Durrant et al., 2011). Nevertheless, there are intensive debates questioning whether the acquired memories are stabilized or enhanced during post-learning, off-line periods (Maquet et al., 2000; Krakauer and Shadmehr, 2006; Peigneux et al., 2006; Rickard et al., 2008; Doyon et al., 2009; Nemeth et al., 2010; Pan and Rickard, 2015; Mantua, 2018). Mixed findings emerging in this field suggest that different processes *within* the procedural learning domain may show different trajectories during learning and off-line periods. At least two processes underlying procedural learning can be distinguished: sequence learning and statistical learning (Nemeth et al., 2013; Kóbor et al., 2018). Sequence learning refers to the acquisition of a series of (usually 5–12) stimuli that repeatedly occur in the same *order* (with no embedded noise in deterministic sequences, or with some embedded noise in probabilistic sequences). In contrast, statistical learning refers to the acquisition of shorter-range relationships among stimuli that is primarily based on *frequency* information (i.e., differentiating between more frequent and less frequent runs (e.g., pairs, triplets, etc.) of stimuli. Previous research has not directly contrasted the consolidation of these two processes. Here, we show - using a visuomotor probabilistic sequence learning task - that performance in sequence learning compared to statistical learning (acquisition of order vs. frequency information) shows marked practice-dependent improvements before and after off line periods.

Studies on sequence learning showed enhanced behavioral performance after an off-line period spent asleep compared to an equivalent period spent awake, especially if individuals acquired an explicit, abstract or complex representation of the sequence (Robertson et al., 2004; Spencer et al., 2006; King et al., 2017). On the other hand, learning probabilistic sequences (Song et al., 2007a; Nemeth et al., 2010), in contrast to deterministic ones, does not seem to benefit from post-learning sleep on the behavioral level, while on a neural level, it has been shown that post-learning sleep is involved in the reprocessing and optimization of the acquired probabilistic sequential information (Peigneux et al., 2003). Importantly, in these probabilistic sequence learning studies the behavioral index of learning encompassed the acquisition of both order- and frequency-based information, thus, the consolidation of sequence learning and statistical learning was not examined separately (Song et al., 2007a,b; Nemeth et al., 2010). There are several studies that investigated the long term retention of statistical learning (Kim et al., 2009; Nemeth et al., 2010; Kóbor et al., 2017), and there is limited evidence that statistical learning in the auditory domain benefits from sleep (Durrant et al., 2011, 2013). Nevertheless, the consolidation, and more specifically, the role of sleep in statistical learning within the visuomotor domain remains largely unexplored.

The Alternating Serial Reaction Time (ASRT) task is a unique tool to investigate statistical and sequence learning within the same experiment (Howard and Howard, 1997; Nemeth et al., 2013). In this perceptual-motor four-choice reaction time (RT) task, participants are required to respond to visual stimuli appearing on the screen. In this task, predetermined sequential (termed as pattern) trials alternate with random ones (e.g., 2R4R3R1R, where numbers correspond to the four locations on the screen presented in the same sequential order during the entire task, and the letter R represents randomly chosen locations) that results in some chunks of stimuli being more frequent than others (see **Figure 1**) and enables us to measure the acquisition of both order and frequency information. Namely, sequence learning is defined as acquiring order information, in that consecutive elements in the sequence (denoted with numbers in the above example) can be predicted with 100% certainty based on the previous sequence element (i.e., the 2nd order transitional probability for the sequence trials is equal to one), while random trials are unpredictable (random stimuli can occur at any of the four possible locations with the same probability). However, as mentioned above, the alternating stimulus structure also results in some chunks of stimuli (three consecutive trials, called *triplets*) occurring more frequently than others (62.5% vs. 12.5%, respectively). For instance, the triplet 2X4 (where X denotes any location out of the four possible ones) would occur more frequently as its first and third item can originate either from sequential/pattern or random stimuli. In contrast, the triplet 2X1 would occur less frequently as this combination can originate only from random stimuli (for more details see **Figure 1** and the section "Materials and Methods"). Statistical learning is defined as acquiring this frequency information [which also represents a 2nd order regularity, where the transitional probability is less than one; for more detailed explanation see (Kóbor et al., 2018)]. To disentangle sequence and statistical learning in the ASRT task, sequence learning is assessed by contrasting sequential/pattern and random stimuli, while controlling for frequency information (i.e., analyzing only high-frequency trials). In contrast, statistical learning is assessed by contrasting high- vs. low-frequency trials while controlling for order information (i.e., analyzing only the random trials) (Nemeth et al., 2013; Kóbor et al., 2018). The learning trajectories for both sequence and statistical learning can be tracked by how different behavioral indices, such as RT and accuracy, change over the course of the task (Howard et al., 2004; Nemeth et al., 2013). To the best of our knowledge, no study has yet tracked the temporal dynamics of learning sequential structures (order information) as well as statistical probabilities (frequency information) within the same experimental design focusing not only on the learning phase but also on consolidation and on further performance changes in a post-consolidation testing phase.

Although sequence learning and statistical learning seem to require different cognitive mechanisms (Nemeth et al., 2013) in everyday learning scenarios, humans might rely simultaneously on both forms of learning. Nevertheless, previous studies

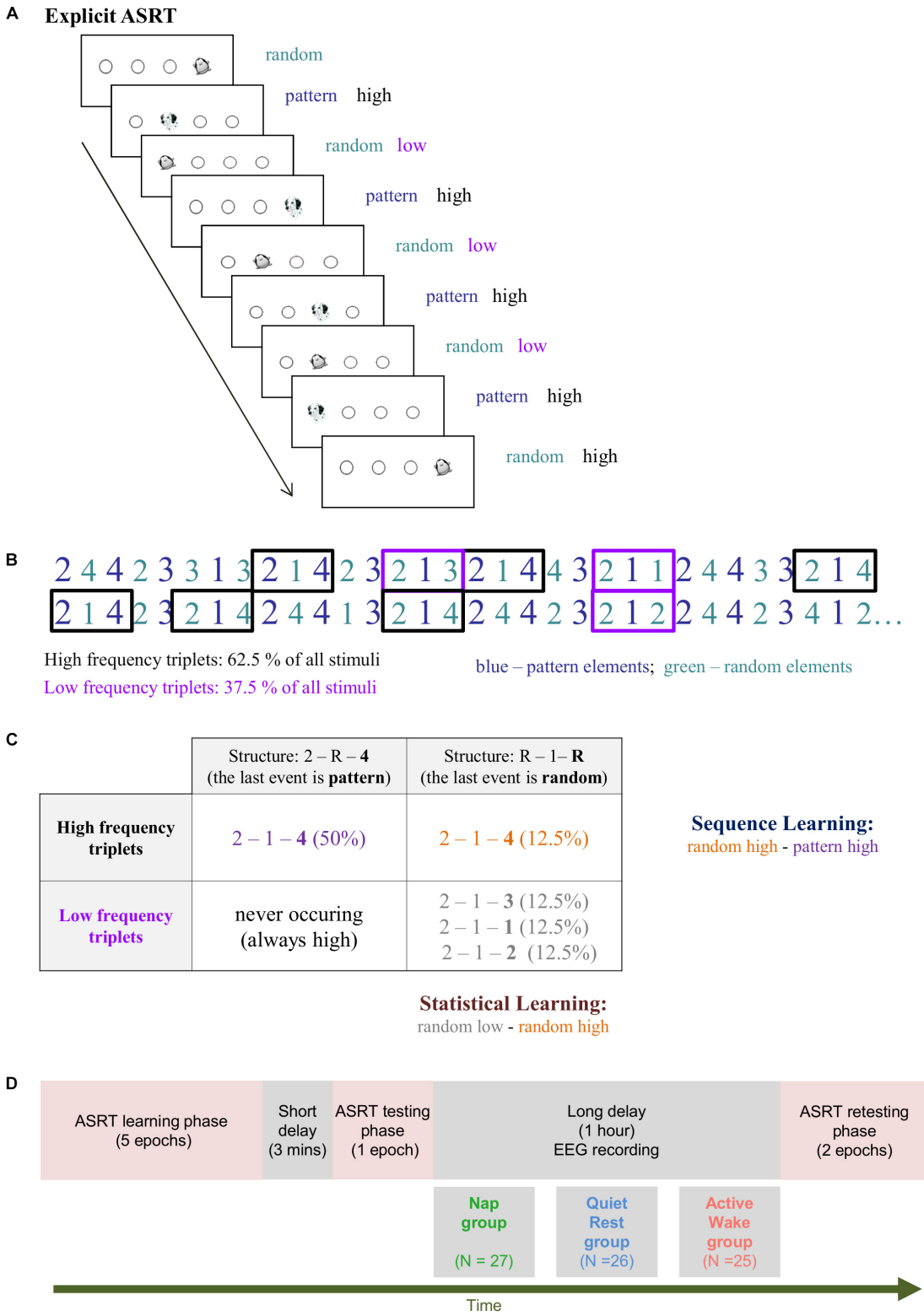


**FIGURE 1 |** The modified Alternating Serial Reaction Time (ASRT) task. **(A)** Pattern and random trials are presented in an alternating fashion. Pattern trials are marked with a picture of a dog, random ones with that of a penguin. Pattern trials always appear in a given location with high probability. Random trials include trials that appear in a given location with high probability and trials that appear in a given location with low probability. **(B)** As the ASRT task contains an alternating

*(Continued)*

**FIGURE 1 |** Continued
sequence structure (e.g., 2R4R3R1R, where numbers correspond to the four locations on the screen and the letter R represents randomly chosen locations), some runs of three consecutive elements (called triplets) occur more frequently than others. For subsequent analyses, we determined for each stimulus whether it was the last element of a high-frequency triplet (black frames) or the last element of a low-frequency triplet (purple frames). **(C)** We assessed *Statistical Learning* by comparing the responses for those random elements that were the last elements of a high frequency triplet, opposite to those that were the last of a low frequency triplet. In contrast, *Sequence Learning* was quantified as the difference between responses for pattern elements (which were always high frequency triplets) vs. random-high frequency triplet elements. **(D)** Study Design. The training phase consisted of five epochs (25 blocks). The testing and retesting phases comprised one and two epochs (that is, 5 and 10 blocks), respectively.

investigated the consolidation of these processes in separate task conditions. Therefore, the first aim of our study was to examine the consolidation of sequence learning and statistical learning simultaneously, in the same experimental context. Previous studies suggest that sequence learning may, whereas statistical learning may not benefit from post-learning sleep or more specific oscillatory activity (slow wave activity and spindles); however, these studies applied awake control groups engaged in daytime activities during the off-line periods (King et al., 2017).

As the amount of interference might influence off-line memory processing (Mednick et al., 2011), our second aim was to examine the off-line change of sequence learning and statistical learning after three different post-learning conditions: active wakefulness, quiet rest, and daytime sleep. We hypothesized that sequence learning would be enhanced after sleep and quiet rest (i.e., due to low interference) compared to active wakefulness, whereas off-line change in statistical learning would be independent from the post-learning condition.

Although post-learning sleep seems to facilitate learning capacity in different cognitive domains (Feld and Diekelmann, 2015), several studies indicate that not sleep *per se*, but specific oscillations during sleep facilitate post-sleep improvements in behavioral performance (Rasch and Born, 2013). Among these oscillations, slow waves and sleep spindles emerge as important candidates that reflect processes of memory consolidation and synaptic plasticity (Diekelmann and Born, 2010; Fogel and Smith, 2011; Ulrich, 2016). Slow waves around 1 Hz and especially fast sleep spindles (13–16 Hz) are considered as hallmarks of the reactivation and neocortical redistribution of hippocampus-dependent memories (Diekelmann and Born, 2010). In addition, slow frequency oscillations ranging between 1 and 8 Hz were linked to the restorative (homeostatic) function of sleep (Achermann et al., 1993; Marzano et al., 2010). In order to examine the associations between cortical oscillations and behavioral performance, we explored the EEG correlates of off-line changes in sequence and statistical learning. We hypothesized that slow frequency oscillations and fast sleep spindles within the sleep group would be positively associated with the post-sleep gains in sequence learning, but not with those of statistical learning.

# MATERIALS AND METHODS

## Participants

Participants (all native Hungarians) were selected from a large pool of undergraduate students from the Eötvös Loránd University in Budapest. The first step of the selection procedure consisted of the completion of an online questionnaire assessing sleep quality and mental health status. Sleep-related questionnaires included the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989; Takács et al., 2016), and Athens Insomnia Scale (AIS, Soldatos et al., 2003; Novák, 2004). Participants that showed poor sleep quality based on previous normative measurements were not included. The Hungarian version of the short (nine item) Beck Depression Inventory (BDI, Rózsa et al., 2001) was used to exclude participants with signs of mild to moderate/severe depression, therefore, participants only with a score less than 10 were included. Respondents reporting current or prior chronic somatic, psychiatric or neurological disorders, or the regular consumption of pills other than contraceptives were also excluded. In addition, individuals reporting the occurrence of any kind of extreme life event (e.g., accident) during the last 3 months that might have had an impact on their mood, affect and daily rhythms were not included in the study. Only right-handed individuals as verified by the Edinburgh handedness inventory (Oldfield, 1971) were invited to the laboratory. At the first encounter with the assistant, participants were instructed to follow their usual sleep-wake schedules during the week prior to the experiment and to refrain from consuming alcohol and all kinds of stimulants 24 h before the day of the experiment. Sleep schedules were monitored by sleep agendas, as well as by the adapted version of the Groningen Sleep Quality Scale (Simor et al., 2009) in order to assess individuals' sleep quality the night before the experiment. The data of participants reporting poor sleep quality the night before the experiment (>7 points) were not considered in the analyses.

After the above selection procedure, 96 right-handed (28 males, $M_{age}$ = 21.66 ± 1.98) participants with normal or corrected-to-normal vision were included in the study. Participants were randomly assigned to one of three groups: an Active Wake, a Quiet Rest, or a Nap group. Individuals unable to fall asleep in the Nap group ($N$ = 10) as well as those falling asleep in the awake groups ($N$ = 5) were excluded from the final analyses. Furthermore, 3 additional participants were excluded due to the absence of learning in the training session. Therefore, the final behavioral analyses were based on the data of 78 participants (20 males, $M_{age}$ = 21.71 ± 1.97), with 25, 26, and 27 participants in the Active Wake, Quiet Rest, and Nap group, respectively (see **Table 1**). In case of the EEG analyses, the data of 12 participants was excluded due to technical artifacts rendering EEG recordings less reliable. Therefore, physiological analyses were restricted to EEG data with sufficient quality (Active Wake, $N$ = 20; Quiet Rest, $N$ = 21, Nap, $N$ = 25). All participants provided written informed consent before enrollment and

**TABLE 1 |** Descriptive characteristics of groups.

| Variable | Active wake group (*N* = 25) Mean (*SD*) | Quiet rest group (*N* = 26) Mean (*SD*) | Nap group (*N* = 27) Mean (*SD*) | *p*-value |
|---|---|---|---|---|
| Age (years) | 22.08 (2.04) | 22.00 (1.94) | 21.15 (1.83) | $p = 0.16$ |
| Gender (male, %) | 28% | 22% | 27% | $p = 0.88$ |
| GSQS | 1.96 (1.72) | 2.31(2.13) | 2.33 (1.96) | $p = 0.75$ |
| Stress scale (before the Learning phase) | 2.65 (2.09) | 2.55 (1.43) | 3.33 (1.98) | $p = 0.35$ |
| Stress scale (before the Retesting phase) | 2.59 (1.28) | 2.00 (1.33) | 1.77 (1.41) | $p = 0.17$ |
| KSS (before the Learning phase) | 6.44 (1.26) | 6.81 (1.13) | 6.19 (1.52) | $p = 0.24$ |
| KSS (before the Retesting phase) | 5.64 (1.19) | 5.96 (1.70) | 6.62 (1.30) | $p = 0.05$ |
| Digit span | 6.32 (1.31) | 5.88 (1.14) | 6.26 (1.06) | $p = 0.36$ |
| Counting span | 3.91 (1.50) | 3.59 (0.72) | 3.48 (0.81) | $p = 0.33$ |
| WCST – number of perseverative errors | 15.67 (9.23) | 14.31 (3.23) | 13.19 (5.86) | $p = 0.40$ |

*GSQS, Groningen Sleep Quality Scale; KSS, Karolinska Sleepiness Scale; WCST, Wisconsin Card Sorting Test. Higher scores in the KSS indicate lower sleepiness.*

received course credits for taking part in the experiment. The study was approved by the research ethics committee of the Eötvös Loránd University, Budapest, Hungary (2015/279). The study was conducted in accordance with the Declaration of Helsinki.

## Task

Behavioral performance was measured by the explicit version of the Alternating Serial Reaction Time (ASRT) task (**Figure 1**, Nemeth et al., 2013). In this task, a stimulus (a dog's head, or a penguin) appeared in one of four horizontally arranged empty circles on the screen, and participants had to press the corresponding button (of a response box) when it occurred. Participants were instructed to respond as fast and accurate as they could. The task was presented in blocks with 85 stimuli. A block started with five random stimuli for practice purposes, followed by an 8-element alternating sequence that was repeated 10 times. The alternating sequence was composed of fixed sequence (pattern) and random elements (e.g., 2-R-4-R-3-R-1-R, where each number represents one of the four circles on the screen and "R" represents a randomly selected circle out of the four possible ones). The response to stimulus interval was set to 120 ms (Song et al., 2007a; Nemeth et al., 2010). In the explicit ASRT task participants are informed about the underlying structure of the sequence, and their attention is drawn to the alternation of sequence and random elements by different visual cues. In our case, a dog always corresponded to sequence elements, and a picture of a penguin indicated random elements (**Figure 1A**). Participants were informed that penguin targets had randomly chosen locations whereas dog targets always followed a predetermined pattern. They were instructed to find the hidden pattern defined by the dog in order to improve their performance. For each participant, one of the six unique permutations of the four possible ASRT sequence stimuli was selected in a pseudo-random manner, so that the six different sequences were used equally often across participants (Howard and Howard, 1997; Nemeth et al., 2010).

The task consisted of a total of 40 blocks. Participants completed 25 blocks during the *training phase*. As the relatively long training phase can introduce fatigue leading to a general decline in performance measures (e.g., slower reaction times at the end of the training phase that do not reflect the acquired knowledge but the effect of fatigue), a retesting session after a long delay (spent asleep or in wakefulness) can result in a spurious increase in performance because of the release from fatigue. This way, the measure of off-line consolidation is confounded by the effect of fatigue (or more specifically, the release from fatigue) (Pan and Rickard, 2015). In order to control for this factor, the training session was followed by a short (3 min long) break in order to minimize the fatigue effect due to massed practice (Rickard et al., 2008; Rieth et al., 2010). After the break, participants were tested on the task for 5 more blocks that constituted the *testing phase*. Subsequently, participants spent an approximately 1-h long off-line period in one of the three conditions (Active Wake, Quiet Rest, and Nap). Finally, they completed a *retesting phase*: 10 more blocks of the same task.

The training phase lasted approximately 30 min, the testing phase 5 min, and the retesting phase 10 min. Awareness of the sequence (pattern elements) was measured after each block. Participants had to type in the regularities they noticed during the task using the same response buttons they used during the ASRT blocks. This method allowed us to determine the duration (in terms of the number of blocks) participants needed to learn the sequence correctly as defined by consistently reporting the same sequence from that point on in the remaining blocks.

## Trial Types and Learning Indices

The alternating sequence of the ASRT task forms a sequence structure in which some of the runs of three successive elements (henceforth referred to as triplets) appear more frequently than others. In the above example, triplets such as 2X4, 4X3, 3X1, and 1X2 (X indicates the middle element of the triplet) occur frequently since the first and the third elements can either be pattern or random stimuli. However, 3X2 and 4X2 occur less frequently since the first and the third elements can only be random stimuli. **Figures 1B,C** illustrate this phenomenon with the triplet 2-1-4 occurring more often than other triplets such as 2–1–3, 2–1–1, and 2–1–2. The former triplet types are labeled as *high-frequency* triplets whereas the latter types are termed as *low-frequency* triplets (see **Figure 1C** and Nemeth et al., 2013).

The third element of a high-frequency triplet is highly predictable (with 62.5% probability) from the first element of the triplet. In contrast, in low-frequency triplets the predictability of the third element is much lower (based on a probability of 12.5%). According to this principle, each stimulus was categorized as either the third element of a high- or a low-frequency triplet. Moreover, trials are differentiated by the cues (dog and penguin) indicating whether the stimulus belongs to the pattern or the random elements. In case of pattern trials, participants can use their explicit knowledge of the sequence to predict the trial, thus we differentiate high-frequency triplets with the last element being a pattern from those triplets in which the last one is a random element. This way, the task consists of three trial types: (1) elements that belong to the explicit sequence and at the same time appear as the last element of a high-frequency triplet are called *pattern* trials; (2) random elements that appear as the last element of a high-frequency triplet are called *random high* trials; and (3) random elements that appear as the last element of a low-frequency triplet are termed *random low* trials (see the example in **Figure 1C**).

To disentangle the two key learning processes underlying performance on the explicit ASRT task, we differentiate *Sequence Learning* and *Statistical Learning* (**Figure 1C**). *Sequence Learning* is measured by the difference in reaction times (RT) between random high and pattern elements (the average RT for random high elements minus the average RT for pattern elements). These elements share the same statistical properties (both correspond to the third element of high-frequency triplets), but have different sequence properties (i.e., pattern vs. random elements). Thus, greater Sequence Learning is determined as faster responses to pattern in contrast to random high trials. *Statistical Learning* is assessed by comparing the responses for those random elements that were the last elements of a high-frequency triplet, opposite to those that were the last of a low-frequency triplet (the average RT for random low elements minus the average RT for random high elements). These elements share the same sequence properties (both are random) but differ in statistical properties (i.e., they correspond to the third element of a high or a low-frequency triplet). Hence, faster responses to random high compared to random low trials yields greater Statistical Learning. In sum, Sequence Learning quantifies the advantage (in terms of RT) due to the awareness of the sequential pattern, whereas Statistical Learning captures purely frequency-based learning (Nemeth et al., 2013).

## Procedure

One to two weeks prior the experiment, participants were invited to the laboratory in order to familiarize them with the environment, and to assess their working memory and executive functions based on the Wisconsin Card Sorting Test (PEBL's Berg Card Sorting Test; Fox et al., 2013) and the Digit Span (Racsmány et al., 2005) and Counting Span (Conway et al., 2005) tasks, respectively. Participants were instructed to complete sleep agendas reporting the schedules, duration and subjective quality of their sleep. On the day of the experiment, participants arrived at the laboratory at 10.00 AM. They completed the GSQS assessing previous nights' sleep quality. Additionally, their subjective stress levels scored on a 10-point Likert scale ("On a scale from 0 to 10 how stressed are you feeling now?"), as well as an item of the Hungarian version of the Karolinska Sleepiness Scale (KSS, Akerstedt and Gillberg, 1990) to measure subjective sleepiness were administered. In the Hungarian version of the scale higher scores indicate a more refreshed state, that is, lower sleepiness. Subsequently, EEG caps with 64 electrodes were fitted by two assistants. Testing started at 11.30 AM and took place in a quiet room equipped with a large computer screen, a response box and EEG recording device. After listening to the instructions, participants had the opportunity to practice the task in order to get familiar with the stimuli and the response box; however, all stimuli appeared in a random fashion during the practice session.

This was followed by the explicit ASRT task composed of the *training phase*, *testing phase*, *off-line period*, and *retesting phase* (**Figure 1D**). In the ASRT task, short breaks were introduced between blocks in the following way: first, at the end of each block, participants were instructed to report the sequence they encountered in that block (which took approximately 6 s on average). Second, they received feedback for their accuracy and RT performance on pattern trials (fixed 3 s). Third, participants were notified (for a fixed 1 s) that the next block can be started by pressing a response button when they are ready; on average, participants continued the next block after approximately 4 s. These breaks were somewhat longer for every fifth blocks (i.e., Block 5, 10, 15, etc.), where participants were instructed to continue the next block after EEG data were saved by the experimenter (which took approximately 20 s on average). Thus, altogether, for the majority of blocks the between-block break was ∼14 s, and for every fifth block it was ∼29 s. Additionally, a 3-min long break was inserted between the learning and the testing phases during which the fitting of the EEG caps were monitored and impedances were reset under 10 kΩ.

The off-line period extended from 12.30 to 13.30. Participants assigned to the Active Wake group were instructed to watch an approximately 1-h long documentary (They were allowed to select from documentaries of different topics such as natural sciences, nature or history). Participants of the Quiet Rest group were asked to sit quietly with eyes closed in a comfortable chair. They were instructed by the assistant to open their eyes for 1 min, every 5 min or in case the EEG recording showed any sign of sleep onset (slow eye movements, attenuation of alpha waves and presence of theta oscillations). Participants in the Nap group had the opportunity to spend a daytime nap in the laboratory. The off-line period took place (in all groups) at the same room in which learning, testing and retesting occurred, and was monitored by EEG. Before the retesting phase, participants were asked to complete again the KSS and the scale assessing the level of stress.

## EEG Recording

The EEG activity was measured by using a 64-channel recording system (BrainAmp amplifier and BrainVision Recorder software, BrainProducts GmbH, Gilching, Germany). The Ag/AgCl sintered ring electrodes were mounted in an electrode cap (EasyCap GmbH, Herrsching, Germany) on the scalp according

to the 10% equidistant system. During acquisition, electrodes were referenced to a scalp electrode placed between Fz and Cz electrodes. Horizontal and vertical eye movements were monitored by EOG channels. Three EMG electrodes to record muscle activity, and one ECG electrode to record cardiac activity were placed on the chin and the chest, respectively. All electrode contact impedances were kept below 10 kΩ. EEG data was recorded with a sampling rate of 500 Hz, band pass filtered between (0.3 and 70 Hz).

In order to remove muscle and eye movement related artifact from the awake EEG data (Active Wake and Quiet Rest groups), EEG preprocessing was performed using the Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) toolbox[1] (Nolan et al., 2010) implemented in EEGLAB (Delorme and Makeig, 2004) under Matlab (The Mathworks). The data was first re-referenced to the Fz electrode, notch filtered at 50 Hz, and band-pass filtered between 0.5 and 45 Hz. Using a predefined *z*-score threshold of ±3 for each parameter, artifacts were detected and corrected regarding single channels, epochs, and independent components (based on the infomax algorithm Bell and Sejnowski, 1995). This way, data was cleared from eye-movement, muscle and heartbeat artifacts. The data was then re-referenced to the average of the mastoid electrodes (M1 and M2). Remaining epochs containing artifacts were removed after visual inspection on a 4-s long basis. In case of the sleep recordings (Nap group), data was re-referenced to the average of the mastoid electrodes, and sleep stages as well as conventional parameters of sleep macrostructure were scored according to standardized criteria (Berry et al., 2012) by two experienced sleep researchers. Periods of NREM sleep (Stage 2 and SWS) were considered for subsequent analyses. Epochs containing artifacts were visually inspected and removed on a 4-s basis. Wrong channels ($N$ = 6 in the dataset of the Nap group) were replaced by the average of the neighboring channels.

Spectral power and sleep spindle analyses of artifact-free segments were performed by a custom made software tool for EEG analysis (FerciosEEGPlus, © Ferenc Gombos 2008–2017). Overlapping (50%), artifact-free, 4-s-epochs of all EEG derivations were Hanning-tapered and Fourier transformed by using the FFT (Fast Fourier Transformation) algorithm in order to calculate the average power spectral densities. The analyzed frequencies spanned between 0.75 and 31 Hz in the Nap group, and between 1.5 and 25 Hz in the awake groups. Low frequencies (0.75–1.5 Hz) were not considered in the awake conditions due to the negligible and unreliable contribution of measurable cortical activity at this frequency range during wakefulness. In addition, frequencies above 25 Hz were unreliable in the awake data due to technical and movement-related artifacts. We summed up frequency bins to generate five frequency bands for the wake groups: delta (1.5–4 Hz), theta (4.25–8), alpha (8.25–13), sigma (13.25–16), and beta (16.25–25 Hz) frequency bands, and five frequency domains for the sleep group: delta (0.75–4 Hz), theta (4.25–8), alpha (8.25–13), sigma (13.25–16), and beta (16.25–31 Hz) frequency ranges. In order to reduce the number of parameters, we averaged bandwise spectral power measures of Frontal (frontal: Fp1, Fpz, Fp2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, frontocentral and frontotemporal: FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8), Central (central, centrotemporal and centroparietal: T7, C5, C3, C1, Cz, C2, C4, C6, T8, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8), and Posterior (parietal, parietotemporal and occipital: P7, P5, P3, Pz, P2, P4, P6, P8, POz, O1, Oz, O2) electrode derivations.

We quantified sleep spindling activity by the Individual Adjustment Method [IAM, (Bódizs et al., 2009; Ujma et al., 2015)] that considers individual spectral peaks to detect spindles in each participant. This method defines frequency boundaries for slow and fast spindles based on the spectral power of NREM sleep. These individualized boundaries are used as frequency limits for slow and fast spindle bandpass filtering (FFT-based, Gaussian filter, 16 s windows) of the EEGs. Thresholding of the envelopes of the band-pass filtered recordings are performed by individual and derivation-specific amplitude criteria (see the description of the method in more detail in Bódizs et al., 2009; Ujma et al., 2015). We used spindle density (spindles/min) and the average amplitude (μV) of slow and fast spindles as different measures of spindling activity. To reduce the number of statistical comparisons, we averaged spindle measures of Frontal, Central, and Posterior electrode derivations similarly to spectral power measures.

## Statistical Analyses

Statistical analyses were carried out with the Statistical Package for the Social Sciences version 22.0 (SPSS, IBM) and R (R Core Team, 2014). The blocks of the explicit ASRT task were collapsed into epochs of five blocks to facilitate data processing and to reduce intra-individual variability. The first epoch contained blocks 1–5, the second epoch contained blocks 6–10, etc. We calculated median reaction times (RTs) for all correct responses, separately for pattern, random high and random low trials for each epoch and each participant. Note that for each response (n), we defined whether it was the last element of a high- or a low-frequency triplet. Two kinds of low-frequency triplets were eliminated: repetitions (e.g., 222, 333) and trills (e.g., 212, 343). Repetitions and trills corresponded to low frequency triplets for all participants and individuals often show pre-existing response tendencies to such triplets (Howard et al., 2004). By eliminating these triplets, we attempted to ensure that differences between high vs. low-frequency triplet elements emerged due to learning and not to pre-existing response tendencies.

To show the performance trajectories of RTs for different trial types, and to explore their differences, we performed a mixed design analyses of variance (ANOVA) with EPOCH (1–8) and TRIAL TYPE (pattern, random high, random low) as within-subject factors, and GROUP (Active Wake, Quiet Rest, Nap) as a between-subject factor. To evaluate the effect of epoch and trial type we performed *post hoc* comparisons (Fisher's LSD).

In order to examine the changes in Statistical and Sequence Learning that occur during the training phase, we applied a mixed-design ANOVA with EPOCH (1–5) and LEARNING

[1] http://sourceforge.net/projects/faster

TYPE (Statistical Learning, Sequence Learning) as within-subject factors, and GROUP (Active Wake, Quiet Rest, and Nap) as a between-subject factor. *Post hoc* comparisons were applied to evaluate changes in performance during the training phase in case of Sequence and Statistical Learning.

To examine off-line changes occurring between testing and retesting sessions we used a similar mixed-design ANOVA with EPOCH (6–8) and LEARNING TYPE (Statistical Learning, Sequence Learning) as within-subject factors, and GROUP (Active Wake, Quiet Rest, and Nap) as a between-subject factor. *Post hoc* comparisons were run to contrast performances of the testing phase (6th epoch) and the retesting phases (7th and 8th epochs).

Greenhouse–Geisser epsilon (ε) correction was used if necessary. Original *df* values and corrected *p*-values (if applicable) are reported together with partial eta-squared ($\eta^2$) as a measure of effect size.

Finally, we aimed to examine the associations between EEG spectral power measured during the off-line period and change in learning performance across the testing and retesting phase, in each group separately. Off-line changes in Sequence and Statistical Learning were defined as the difference between the learning scores of the first retesting (7th epoch) session and the testing session (6th epoch). Thus, a positive value indicated improvement in learning performance after the off-line period. Furthermore, we aimed to examine whether EEG spectral power measured during off-line periods predicted additional performance change after longer re-learning, therefore, we calculated a secondary off-line change score contrasting learning scores of the 8th (2nd half of the retesting session) with those of the 6th epoch (testing session).

The associations between sleep spindles and off-line changes of the above measures were also examined (within the sleep group only). Pearson correlation coefficients or (if normality was violated) Spearman rank correlations were run between spectral power values (of each region and band) and off-line changes in learning scores. The issue of multiple comparisons was addressed by the False Discovery Rate correcting for type 1 error (Benjamini and Hochberg, 1995).

# RESULTS

## Group Characteristics

Groups were matched in age, gender, working memory, executive function, and initial sleepiness and stress level (**Table 1**). However, after the 1 h long off-line period, the groups differed in sleepiness ($F_{2,75}$ = 3.19, $p$ = 0.05). *Post hoc* test showed that the Nap group scored significantly higher on the KSS (indicating lower sleepiness on the Hungarian version of the KSS scale where higher scores indicate a more refreshed state, that is, lower sleepiness) than the Active Wake group ($p$ = 0.02), however, the difference was not significant after FDR correction.

Sleep parameters of the Nap group are listed in **Table 2**. In the Nap group, only one participant reached REM phase during sleep, thus we only report the characteristics of Non-REM sleep.

**TABLE 2 |** Descriptive characteristics of sleep parameters in the Nap group.

| Variable | Mean (*SD*) |
|---|---|
| Sleep duration (min) | 41.16 (12.35) |
| Sleep efficiency (%) | 70.28 (16.27) |
| Wake duration (min) | 16.53 (7.77) |
| S1 duration (min) | 6.02 (3.62) |
| S2 duration (min) | 17.93 (6.59) |
| SWS duration (min) | 16.89 (12.82) |
| Fr. fast spindle density | 6.37 (0.96) |
| Cent. fast spindle density | 7.45 (0.83) |
| Post. fast spindle density | 7.35 (0.93) |
| Fr. fast spindle amp. | 4.56 (1.32) |
| Cent. fast spindle amp. | 6.01 (1.56) |
| Post. fast spindle amp. | 5.38 (1.38) |
| Fr. slow spindle density | 7.31 (1.12) |
| Cent. slow spindle density | 7.33 (1.19) |
| Post. slow spindle density | 7.4 (1.16) |
| Fr. slow spindle amp. | 3.91 (1.85) |
| Cent. slow spindle amp. | 3.28 (1.49) |
| Post. slow spindle amp. | 2.54 (0.96) |

*S1, Stage 1; S2, Stage 2; SWS, Slow Wave Sleep, Fr, Frontal; Cent, Central; Post, Posterior.*

## Are Performance Trajectories of Responses to Different Trial Types Different Between Groups?

Overall, participants in the different groups responded with similar RTs (main effect of GROUP: $F_{2,75}$ = 0.80, $p$ = 0.46, $\eta^2_p$ = 0.02). Irrespectively of trial types, RTs significantly decreased across epochs (main effect of EPOCH: $F_{7,525}$ = 175.26, $p < 0.0001$, $\eta^2_p$ = 0.70), indicating general skill improvements due to practice (**Figure 2**). The GROUP × EPOCH interaction was not significant ($F_{14,525}$ = 1.18 $p$ = 0.32, $\eta^2_p$ = 0.03), suggesting that general skill improvements were similar in the groups. Furthermore, participants showed significant Sequence and Statistical Learning (main effect of TRIAL TYPE: $F_{2,150}$ = 52.04, $p < 0.0001$, $\eta^2_p$ = 0.41): they responded faster to pattern than random high trials ($p < 0.0001$), and faster to random high compared to random low trials ($p < 0.0001$). The GROUP × TRIAL TYPE interaction was not significant ($F_{4,150}$ = 0.80, $p$ = 0.46, $\eta^2_p$ = 0.02) indicating that there was no difference between the groups in performance for different trial types. In addition to that, the EPOCH x TRIAL TYPE interaction was significant ($F_{14,1050}$ = 11.93, $p < 0.0001$, $\eta^2_p$ = 0.14), indicating different learning trajectories in case of the three trial types (see **Figure 2**). Although participants became faster for all trial types during the course of the task, responses to pattern trials showed greater gains in comparison to both random trials: Average reaction times of pattern trials decreased from 357.89 to 257.56 ms ($p < 0.0001$), of random high trials from 370.98 to 326.14 ms ($p < 0.0001$), and of random low trials from 388.26 to 349.65 ms ($p < 0.0001$). Practice-dependent improvement in response to pattern trials was significantly higher than the improvement in case of random high ($t_{77}$ = 4.81, $p < 0.0001$) and random low ($t_{77}$ = 5.45, $p < 0.0001$) trials.

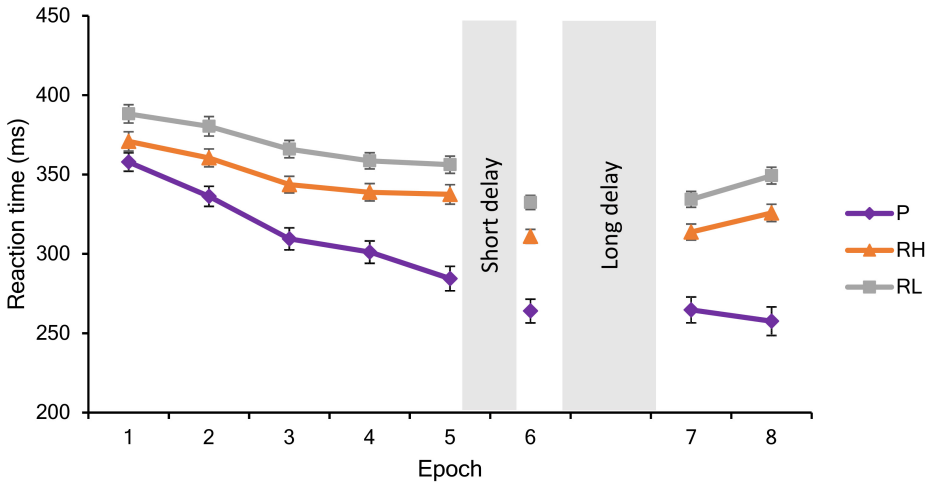


**FIGURE 2 |** Performance during the training (Epochs 1–5), testing (Epoch 6) and retesting (Epochs 7–8) sessions. Mean reaction times and standard errors are visualized in response to pattern (P), random high (RH), and random low (RH) trials during each epoch.

The improvement in responses to random high and random low trials was only marginally different ($t_{77}$ = 1.84, $p$ = 0.07). The GROUP × EPOCH × TRIAL TYPE interaction was not significant ($F_{28,1050}$ = 0.66, $p$ = 0.68, $\eta_p^2$ = 0.02), suggesting that performance trajectories to the different trial types were similar among the groups.

## Do Sequence and Statistical Learning During Training Differ Between Groups?

Sequence and Statistical Learning during the training phase were similar across the groups (main effect of GROUP: $F_{2,75}$ = 1.10, $p$ = 0.34, $\eta_p^2$ = 0.03). Irrespectively of learning type, performance improved across epochs of training (main effect of EPOCH: $F_{4,300}$ = 10.92, $p$ < 0.0001, $\eta_p^2$ = 0.13). The GROUP × EPOCH interaction was not significant ($F_{8,300}$ = 0.59, $p$ = 0.68, $\eta_p^2$ = 0.02), suggesting that improvement during training was similar between the groups. In addition, the main effect of LEARNING TYPE was significant ($F_{1,75}$ = 3.93, $p$ = 0.05, $\eta_p^2$ = 0.05): participants showed greater Sequence Learning compared to Statistical Learning ($M$ = 32.50 vs. $M$ = 19.64, $p$ < 0.0001). The GROUP × LEARNING TYPE interaction was not significant ($F_{2,75}$ = 0.81, $p$ = 0.45, $\eta_p^2$ = 0.02), suggesting that the difference between Sequence and Statistical Learning were similar among the groups. Furthermore, a significant interaction between EPOCH and LEARNING TYPE emerged ($F_{4,300}$ = 5.52, $p$ = 0.002, $\eta_p^2$ = 0.07): as illustrated in **Figure 3**, participants, on average, exhibited a steep increase in Sequence Learning during the training phase [the average learning score increased from 13.09 to 53.31 from the 1st epoch to the 5th ($p$ < 0.001), whereas Statistical learning occurred in the beginning of the task and remained unchanged by the end of the training phase (the average learning score increased from 17.28 to 18.64 from the 1st epoch to the 5th, $p$ = 0.68). The GROUP × EPOCH × LEARNING TYPE interaction was not significant ($F_{8,300}$ = 0.58, $p$ = 0.72, $\eta_p^2$ = 0.02), suggesting that training-dependent patterns of Sequence Learning and Statistical Learning were similar across the groups.

Beyond the group-level results presented in the previous paragraph, we performed an additional analysis to reveal learning trajectories on a subject-by-subject basis. We categorized each subject's learning trajectory during training by a combination of curve fitting and visual inspection. For comparability, we performed the same steps for Sequence and Statistical learning (see **Figures 4A,B**, respectively) and found that ∼33% of participants showed gradually increasing Sequence learning during training, while the trajectory for Statistical learning was gradually increasing only in ∼16% of participants [$\chi^2(1)$ = 3.80, $p$ = 0.05]. Compared to these percentages, a relatively smaller number of participants exhibited a step-like increase in learning performance: ∼10% of participants for Sequence learning and ∼4% of participants of Statistical learning ($p$ = 0.15). Additionally, a small portion of participants exhibited a decreasing pattern, with the best performance at the beginning of the task (∼5% of participants for Sequence learning, and ∼13% of participants for Statistical learning; $p$ = 0.42). The learning trajectory of the majority of participants did not clearly follow any of the patterns described above. These learning trajectories were categorized as 'Other pattern' (∼53% of participants for Sequence learning, and ∼66% of participants for Statistical learning; $p$ = 0.81). These participants exhibited relatively large changes in performance from one epoch to another and then returned to the previous performance level. The timing of these larger changes in performance was evenly distributed across epochs. It is plausible that these participants explored different (explicit or implicit) strategies over the course of learning that may have resulted in large changes in some epochs compared to their overall learning performance. Note, however, that the primary focus of our study was not to test these possible strategies but to compare Sequence and Statistical learning trajectories across the three experimental groups (Quiet Rest, Active Wake, and Nap). Importantly, the distribution of subgroups exhibiting different

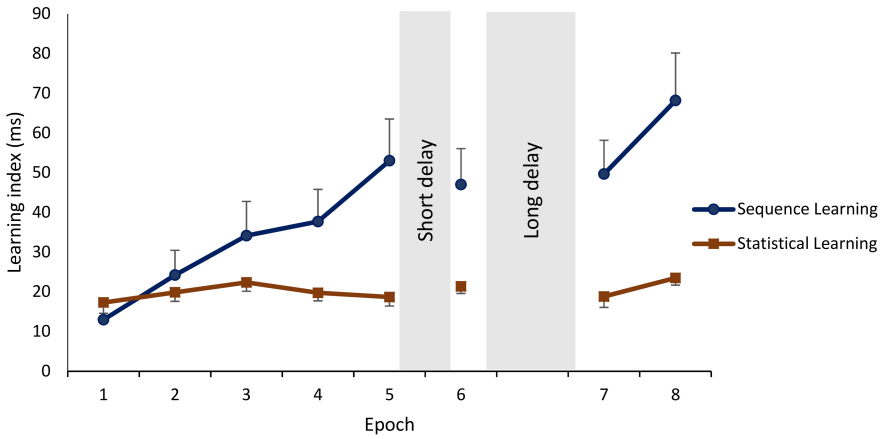


**FIGURE 3 |** Learning and off-line changes in Sequence and Statistical Learning. Sequence Learning is quantified as the difference in reaction times to random high elements vs. pattern elements. Statistical Learning is quantified as the difference in reaction times to random low elements vs. random high elements. Means and standard errors of Sequence Learning and Statistical Learning during each epoch. Sequence Learning exhibited a steep increase during training and additional practice after the off-line periods, whereas Statistical Learning remained unchanged throughout the sessions.

learning trajectories was similar across the three experimental groups both for Sequence learning [$\chi^2(6) = 0.91$, $p = 0.99$] and for Statistical learning [$\chi^2(6) = 1.98$, $p = 0.92$].

## Early Statistical Learning Effects During Training

To provide further insights into the trajectory of Statistical learning, we performed additional analyses by focusing on block-level and below block-level data. The first set of analyses aimed to determine the time point when participants successfully extracted the statistical regularities from the stimulus stream. First, we computed Statistical learning scores for each block of Epoch 1, and tested if these Statistical learning scores were significantly different from zero. We found significant Statistical learning effect already in Block 1 of the ASRT task [$t(73) = 2.12$, $p = 0.04$, Cohen's $d = 0.25$]. Next, we zoomed into Block 1 to further test this learning effect. In this analysis, we split Block 1 into two halves and computed Statistical learning scores for each participant, for each half. This level of granularity seemed the most appropriate so that all participants had at least a few random-high trials (∼4 trials on average, ranging from 2 to 9), enabling us to compute learning scores for all participants. These Statistical learning scores were submitted into one sample *t*-tests, which showed that Statistical learning scores did not reach significance in the first half of Block 1 [$t(73) = 1.11$, $p = 0.269$, Cohen's $d = 0.13$], while they were significant in the second half of Block 1 [$t(73) = 1.99$, $p = 0.05$, Cohen's $d = 0.23$]. This analysis thus demonstrates that statistical regularities are learned (albeit very quickly) and the observed significant Statistical learning scores at the very early phase of the task are not due to other (not learning-related) preexisting tendencies.

This rapid learning effect is in fact not surprising if we consider that 80 trials are presented in the first block, and ∼50 of those trials can be categorized as high frequency triplets (occurring in pattern or random positions). As there are 16 individual triplets that are high frequency, that means that participants encounter each individual triplet approximately four times in the first block already. In contrast, there are 48 individual triplets that are low frequency, and participants encounter these individual triplets approximately (or less than) once in a block. Thus, the observed significant Statistical learning scores (i.e., the difference between the random-high and random-low frequency trials) suggests that participants are so sensitive to the frequency statistics that as little as, on average, four presentations of the same trials are sufficient to show speeded responses to them.

Nevertheless, it is important to highlight that significant learning does not necessarily mean that participants have a stable knowledge about the statistical regularities. Thus, even though the Statistical learning scores are already significant at the early phase of learning and these scores numerically do not change as the task progresses, it is reasonable to assume that more practice can help strengthen the acquired knowledge. We ran an additional analysis to test this assumption. In this analysis, we focused on block-level data and computed Cohen's *d* effect sizes for the block-level Statistical learning scores. These effect sizes were substantially smaller in the first five blocks of the ASRT task (0.27 on average for Blocks 1–5, i.e., Epoch 1) compared to the later blocks (blocks of Epoch 2: 0.45, Epoch 3: 0.51, Epoch 4: 0.53, Epoch 5: 0.50). This difference in the effect sizes suggests that, although participants were able to extract the statistical regularities from the stimulus stream very early in the task, additional training helped them strengthen the acquired statistical knowledge.

## Are Off-Line Changes in Sequence and Statistical Learning Different Across the Groups?

The three groups did not show different patterns of Sequence and Statistical Learning from the testing to the retesting sessions, as neither the main effect of GROUP ($F_{2,75} = 0.65$, $p = 0.53$,

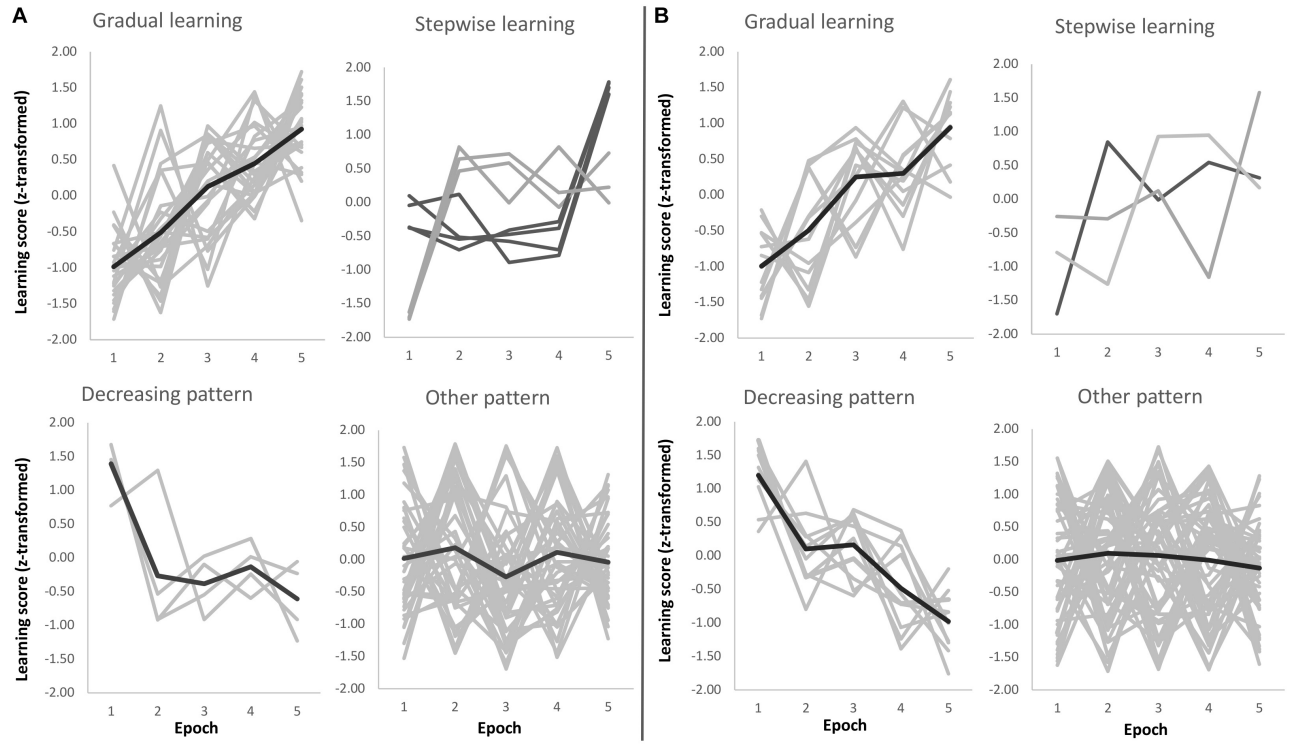


**FIGURE 4 |** Sequence **(A)** and Statistical **(B)** learning trajectories for individual subjects. Each participant's learning trajectory is presented in a light gray color, while the average learning trajectory for that subgroup is presented in a darker gray color for the 'Gradual learning,' 'Decreasing pattern,' and 'Other pattern' panels. For the 'Stepwise learning' panel, the light and dark gray colors represent subgroups of participants depending on the timing of their performance increase (no average learning trajectory is presented).

$\eta_p^2 = 0.02$), nor the interactions GROUP × EPOCH ($F_{4,150} = 0.52$, $p = 0.67$, $\eta_p^2 = 0.01$), GROUP × LEARNING TYPE ($F_{2,75} = 0.65$, $p = 0.53$, $\eta_p^2 = 0.02$), and GROUP × EPOCH × LEARNING TYPE ($F_{4,150} = 0.73$, $p = 0.55$, $\eta_p^2 = 0.02$) emerged as significant predictors. The lack of a group effect is shown in **Figure 5** that illustrates off-line changes (7th minus the 6th epoch) in Sequence and Statistical Learning separately for each group. Similarly to the training phase, participants exhibited higher scores in Sequence Learning than in Statistical Learning (main effect of LEARNING TYPE: $F_{1,75} = 10.72$, $p = 0.002$, $\eta_p^2 = 0.13$). Moreover, learning indices produced robust changes across epochs as indicated by a significant main effect EPOCH ($F_{2,150} = 18.99$, $p < 0.0001$, $\eta_p^2 = 0.20$). More specifically, overall performances (regardless of learning type) were unchanged from the testing phase (6th epoch) to the first retesting epoch (7th) ($p = 0.86$), but improved ($p < 0.0001$) from the testing phase to the end of the retesting session (8th epoch), and from the first retesting epoch to the second (7th epoch vs. 8th epoch) ($p < 0.0001$). Furthermore, Sequence Learning and Statistical Learning scores showed different patterns after the off-line period (see Epoch 7 and 8 in **Figure 3**), as indicated by the significant EPOCH × LEARNING TYPE interaction ($F_{2,150} = 5.31$, $p = 0.009$, $\eta_p^2 = 0.07$). Neither Sequence Learning nor Statistical Learning seemed to show immediate (early) gains after the off-line period. Sequence Learning scores did not significantly change from the testing phase to the first epoch of retesting (6th epoch, $M = 47.02$ vs. 7th epoch, $M = 47.69$, $p = 0.85$). Similarly, Statistical Learning remained unchanged from testing to the first retesting (6th epoch, $M = 21.39$ vs. 7th epoch, $M = 19.96$, $p = 0.56$). Nevertheless, additional practice produced robust changes in Sequence Learning, that increased significantly from the testing phase to the second epoch of the retesting phase (8th epoch, $M = 68.19$, $p = 0.001$), whereas Statistical Learning did not show any significant changes by the end of the retesting phase (8th epoch: $M = 23.51$, $p = 0.41$).

To further explore potential group differences during the off-line period we ran additional ANOVAs separately for Sequence and Statistical learning scores considering their different learning curves. Based on these ANOVAs, we found no group differences in the consolidation (6th epoch vs. 7th epoch) of the acquired knowledge (Sequence learning: $p = 0.35$, Statistical learning: $p = 0.78$). Similarly, no group differences emerged in the additional increase between 7th epoch and 8th epoch (Sequence learning: $p = 0.65$, Statistical learning: $p = 0.36$).

## Awareness of the Sequence in the Groups

For the analysis of sequence awareness, two participants' data had to be excluded due the technical issues during collection of sequence reports (one data from the active wake and one data

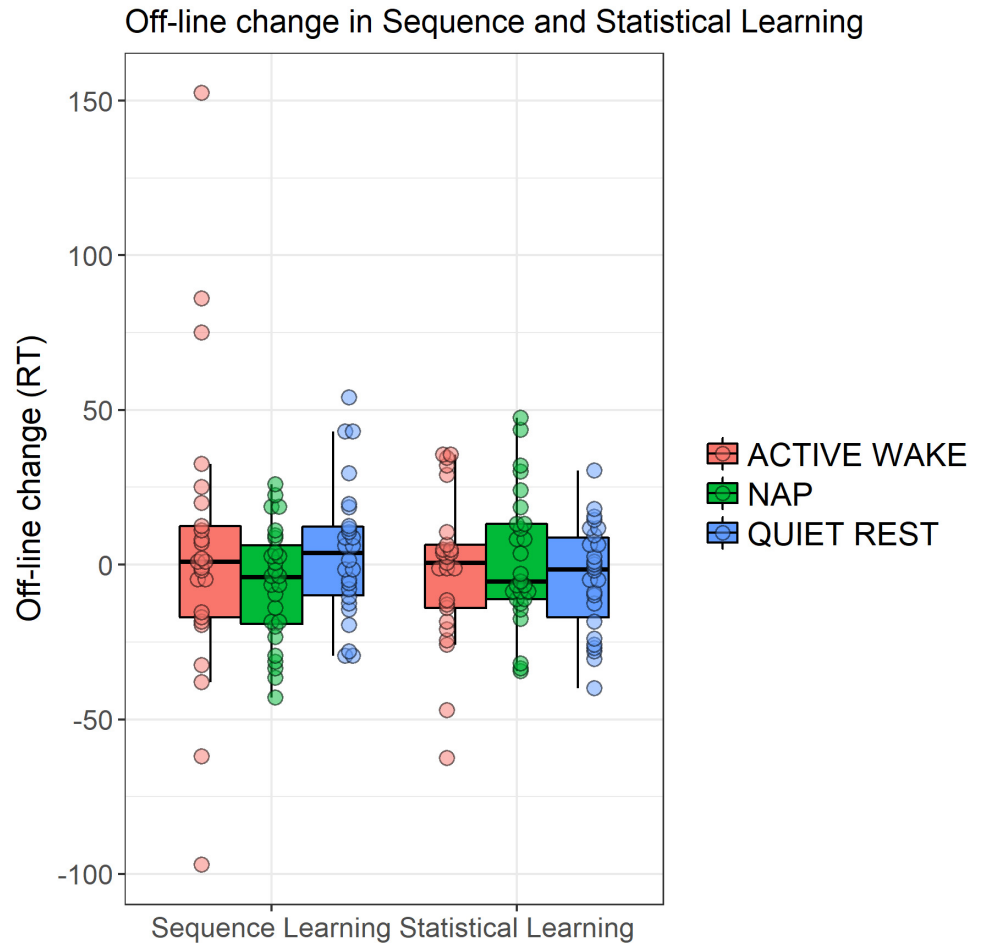


**FIGURE 5 |** Off-line changes in learning indices within the three groups. Off-line changes were calculated by the learning scores of the 7th epoch minus the respective learning scores of the 6th epoch. Dots show individual data points, the vertical line within the boxes show the medians, boxes represent the first and third quartiles, whiskers indicate the interquartile range of 1.5.

from the nap group). Additionally, eleven participants could not report the correct sequence consistently during training ($N$ = 3 in the active wake, $N$ = 3 in the nap, and $N$ = 5 in the quiet rest group), and therefore they were also excluded from the following analyses. Importantly, there were no group differences in the number of participants who could or could not report the correct sequence consistently and were excluded (chi-square = 1.77, $p = 0.78$).

On average, participants could report the correct sequence consistently from the 6th block ($M$ = 6.58, $SD$ = 7.04), with no differences across the groups ($F_{2,64} = 1.53$, $p = 0.23$). Overall, the block number from which participants could consistently report the correct sequence showed a significant negative correlation with the Sequence learning scores ($r = -0.28$, $p = 0.02$). Thus, the earlier participants could find the correct sequence and report consistently thereafter, the better their overall Sequence learning was. No association was observed between the block number and the Statistical learning scores ($r = -0.06$, $p = 0.63$), suggesting that sequence awareness primarily affected Sequence learning but not Statistical learning.

Finally, we conducted an ANOVA for the Sequence learning scores of the training phase (Epoch 1–5), including the block number from which participants could consistently report the correct sequence as a covariate to check how sequence awareness affected the time course of learning across groups. The ANOVA revealed a significant main effect of EPOCH ($F_{4,244} = 10.53$, $p < 0.001$, $\eta_p^2 = 0.147$), indicating better Sequence learning scores as learning progressed. This effect was modulated by the block number on a trend level ($F_{4,244} = 2.58$, $p = 0.08$, $\eta_p^2 = 0.041$), suggesting that the earlier participants could report the correct sequence, the better their Sequence learning became across training. Importantly, no significant group differences emerged either in overall learning or in the trajectory of learning even after taking into account the block number as a covariate ($ps > 0.21$).

A similar ANOVA was conducted for the consolidation analysis (Epoch 6–8). This ANOVA also revealed a significant main effect of EPOCH ($F_{2,122} = 8.34$, $p < 0.001$, $\eta_p^2 = 0.120$), which is consistent with the previous ANOVA conducted for these epochs, showing increase in Sequence learning scores due to additional training (Epoch 7 vs. Epoch 8, see **Figure 3**).

This effect was not modulated by the block number ($p = 0.49$). Furthermore, no significant group differences emerged either in overall learning scores or in the trajectory of learning scores across these epochs, even after taking into account the block number as a covariate ($ps > 0.32$). These results altogether suggest that, although the timing when participants gained explicit knowledge about sequence affects their Sequence learning scores, this effect is similar across the groups both during training and consolidation.

## Associations Between EEG Spectra and Off-Line Changes

Off-line changes in Sequence Learning as indexed by the difference scores between the 7th (first half of retesting phase) and the 6th epochs' (testing phase) scores were positively associated with frontal theta power ($r = 0.44$ $p = 0.028$) within the nap group. Off-line changes in Sequence Learning were not associated with spectral EEG power measures in the either of the awake (AW, QR) groups. Additional off-line-changes in Sequence Learning as indexed by the difference scores between the 8th (second half of retesting phase) and the 6th epochs' (testing phase), showed a positive association with frontal theta power ($r = 0.52$, $p = 0.008$) within the nap group only. Nevertheless, these correlations did not reach statistical significance after FDR correction of multiple comparisons (all $ps > 0.05$). Since region-wise averaging of electrodes might not capture associations between behavioral measures and spectral power of a more local nature, we examined (on an exploratory level) the associations between theta activity and off-line changes (7th vs. 6th epoch and 8th vs. 6th epoch) in Sequence Learning within the nap group. As shown in **Figure 6**, associations with theta band power were prominent at frontal electrode sites, peaking at left frontopolar locations in case of immediate off-line changes (**Figure 6A**), as well as in case of additional off-line changes in performance (**Figure 6B**). Finally, we examined the associations between off-line (7th vs. 6th epoch and 8th vs. 6th epoch) changes in Sequence Learning and bin-wise EEG spectral power averaged across all electrodes (within the Nap group). Immediate (7th vs. 6th epoch) and delayed (8th vs. 6th epoch) post-sleep improvement in Sequence Learning correlated only with slow frequency activity between 2 and 7.75 Hz (all bins $p < 0.01$).

Immediate and additional off-line changes (7th vs. 6th epoch and 8th vs. 6th epoch) in Statistical Learning were not associated with spectral power measures within the nap group, and no other associations emerged within the Quiet Rest and Active Wake groups.

In sum, individual differences in off-line changes in Statistical Learning assessed immediately after the long delay (6th vs. 7th epoch) and after extended practice, (6th vs. 8th epoch) were not associated with spectral EEG power measures in any of the three groups. On the other hand, immediate and delayed post-sleep improvements in Sequence Learning were predicted by high delta and theta activity during sleep within the Nap group. Nevertheless, these correlations did not remain significant after correction for multiple comparisons.

## Associations Between Sleep Spindles and Off-Line Changes

Off-line change (7th vs. 6th epoch) in Sequence Learning showed a negative correlation with slow spindle density at Frontal ($r = -0.52$, $p = 0.008$), Central ($r = -0.54$, $p = 0.006$), and Posterior ($r = -0.53$, $p = 0.006$) derivations. Slow spindle amplitude, fast spindle density and amplitude were not associated with the off-line change in Sequence Learning. Negative correlations between slow spindle density and off-line change in Sequence Learning remained significant after FDR correction ($p = 0.036$).

Off-line change in Statistical Learning was negatively correlated with fast spindle amplitude (Frontal: $r = -0.43$, $p = 0.03$; Central: $r = -0.47$, $p = 0.02$; Posterior: $r = -0.44$, $p = 0.03$), but was not related either to fast spindle density or slow spindle density/amplitude. Correlations between fast spindle amplitude and off-line change in Statistical Learning were not significant after FDR correction (all $ps > 0.05$).

To examine whether the negative correlation between off-line changes in performance and spindle parameters were linked to overall Sequence/Statistical Learning ability, we applied partial correlations with learning performance of the training phase as a covariate. Learning performance here was computed as the differences in Sequence and Statistical learning between the 5th and the 1th epochs of the training phase. Slow spindle density remained a negative correlate of off-line change in Sequence Learning even after controlling for this initial Sequence Learning performance (Frontal: $r = -0.5$, $p = 0.006$; Central: $r = -0.52$, $p = 0.009$; Posterior: $r = -0.51$, $p = 0.005$).

Similarly, partial correlations were computed between fast spindle amplitude and off-line change in Statistical Learning with Statistical Learning performance as a covariate. The correlations showed trends after partialling out this initial Statistical Learning performance (Frontal: $r = -0.37$, $p = 0.07$; Central: $r = -0.43$, $p = 0.03$; Posterior: $r = -0.36$, $p = 0.08$).

Additional (delayed) off-line-changes in Sequence and Statistical Learning as indexed by the difference scores between the 8th (second half of retesting phase) and the 6th epochs' (testing phase) were not associated to any of the extracted spindle parameters.

# DISCUSSION

Our aim was to investigate performance trajectories in Sequence and Statistical Learning during extensive practice and after off-line periods spent in different vigilance states. In order to examine these processes in the same experimental context, we applied a paradigm that simultaneously measured sequence and statistical learning by delineating order and frequency-based information. Our findings indicate that Sequence and Statistical Learning follow different learning curves. Whereas performance in Sequence Learning exhibited an increase during training, Statistical Learning was rapidly acquired and remained unchanged throughout training. During the off-line period, both forms of learning were preserved as no significant off-line changes emerged in either Sequence or Statistical Learning.

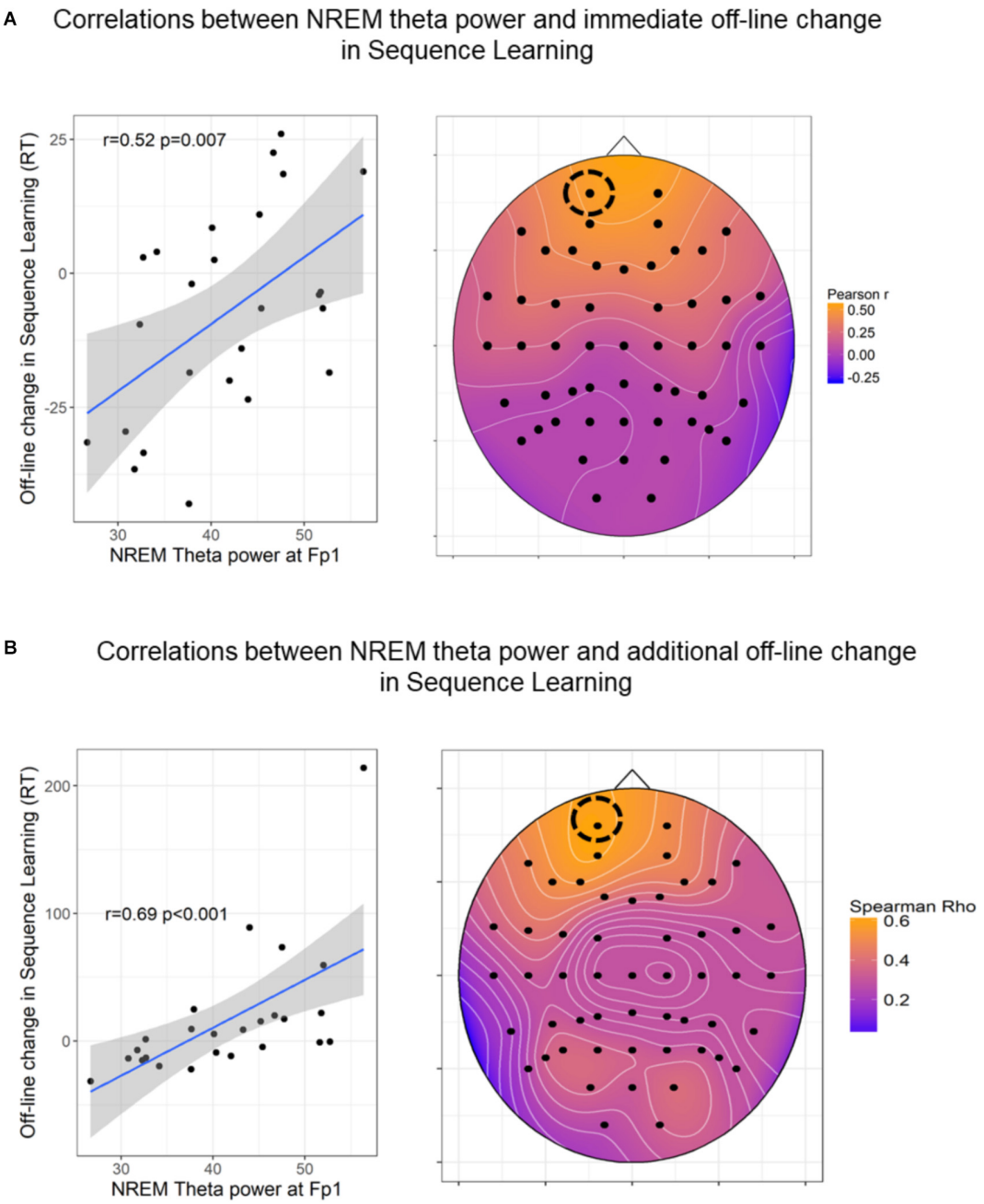


**FIGURE 6 |** Associations between NREM theta power and off-line changes in Sequence Learning. **(A)** Pearson correlations between NREM theta band power and immediate (7th vs. 6th epoch) post-sleep changes in Sequence Learning. **(B)** Spearman Rho correlations coefficients between NREM theta band power and delayed (8th vs. 6th epoch) post-sleep changes in Sequence Learning. The heat plots on the right indicate the magnitude of correlation coefficients, the scatterplots on the left show the association in a prominent (left frontal) electrode site. In case of 6B the correlation coefficient remained unchanged ($r = 0.64$, $p < 0.001$) after the exclusion of the outlier. The figures show uncorrected $p$-values (before FDR correction). For the immediate off-line changes, only Fp1, Fp2, AF3, AF4 locations remained significant after FDR correction. For the additional off-line changes, frontal channels Fp1, Fpz, Fp2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8 as well as FC4, FC5, CP5, and P5 locations remained significant after FDR correction.

Nevertheless, Sequence Learning improved after additional practice (i.e., in the retesting phase), whereas Statistical Learning remained stable regardless of further training compared to the testing phase. Performance trajectories were similar across the groups: Performance during training and consolidation did not differ between the Active Wake, Quiet Rest, and Nap groups. EEG spectral power assessed during the off-line periods was not associated with off-line changes in Sequence and Statistical Learning in the awake groups. Within the Nap group we found a trend indicating a positive association between frontal

theta band power and off-line change in Sequence Learning. In addition, frontal theta power predicted further improvements in Sequence Learning after additional practice. Within the Nap group, slow spindle density was negatively associated with post-sleep improvement in Sequence Learning, and fast spindle amplitude was negatively associated with post-sleep improvement in Statistical Learning.

Our data suggests that sequence and statistical learning are markedly different sub-processes of procedural learning. Frequency-based information is acquired rapidly and appears to undergo less prominent changes during further training compared to the acquisition of order-based information that may exhibit further performance improvements. Our fine-grained analyses revealed that statistical learning occurs already in the first block of the task. This finding suggests that participants are so sensitive to the frequency statistics that as little as, on average, four presentations of the same trials are sufficient to show speeded responses to them. Nevertheless, the further analysis of effect sizes showed that, although participants were able to extract the statistical regularities from the stimulus stream very early in the task, additional training helped them strengthen the acquired statistical knowledge.

Rapid statistical learning has also been reported before: for instance, in the ASRT study of Szegedi-Hallgató et al. (2017), statistical learning was apparent already in the first epoch in the Explicit group but seemed to have larger individual differences in the Implicit groups as only one of the two Implicit groups exhibited significant statistical learning in the first epoch (see Supplementary results and figures in Szegedi-Hallgató et al., 2017). Similarly, in Kóbor et al. (2018) study, statistical learning was observed in the first epoch of the explicit version of the ASRT task, along with a significant sequence learning as well. Consequently, a possible explanation for the very rapid statistical learning is that, in an explicit condition, the instructions and motivation to learn can have an overarching effect, providing a cognitive state, in which not only the instructed sequential but also the uninstructed statistical regularities can be learned quickly. Although this was not in the primary focus of these previous studies, if we take a closer look at the learning trajectories, it appears that statistical regularities are extracted very early and no (or very little) further gains may be observed during training if explicit instructions are given for the *sequential* information (Szegedi-Hallgató et al., 2017; Kóbor et al., 2018). In contrast, in the implicit conditions, statistical learning may undergo further improvements during training (Szegedi-Hallgató et al., 2017), above and beyond the strengthening of the acquired knowledge as suggested in the previous paragraph. These observations support the interpretation that explicit instructions and the motivation to learn can have an overarching effect in that not only the instructed sequential but also the uninstructed statistical regularities can be learned more quickly. Interestingly, a recent study showed that, if the task is fix-paced instead of self-paced, no such overarching effect can be observed, suggesting a complex interplay of multiple factors that may influence the effect of explicit instructions on learning (Horváth et al., 2018). Further studies should directly test these factors.

Nevertheless, it is important to note that statistical learning typically occurs implicitly (i.e., without conscious intent to learn and without awareness about the learning situation itself or about the actual regularities) and relatively quickly, already in one learning session (e.g., Song et al., 2007a; Nemeth et al., 2013; Kóbor et al., 2017). In contrast, it has been previously shown that acquiring the alternating sequence structure (frequently referred to as higher-order sequence learning) in the ASRT task typically occurs after 4 days of practice if learning is implicit (Howard and Howard, 1997; Howard et al., 2004), while this can be substantially faster if explicit instruction is provided to the participants (Nemeth et al., 2013). Accordingly, participants quickly formed explicit knowledge about the sequence. Therefore, we think that the current study design was suitable to measure both sequence and statistical learning, bringing them in the same time frame of acquisition (i.e., showing significant learning in one learning session for both measures).

The present study narrows down the concept of statistical learning by regarding it as only one of the processes that is the sensitivity to frequency information. From a theoretical perspective, however, it is important to note that at the level of transitional probabilities, statistical learning (in this narrow sense) and sequence learning could be considered as similar. Namely, both are statistical learning in a broader sense. When acquiring frequency information (statistical learning in the narrow sense), a 2nd order probabilistic sequence should be learned, in which there are always one probable continuation and some less probable continuations for the first two elements of a given three-element stimulus chunk (Szegedi-Hallgató et al., 2017; Kóbor et al., 2018). When acquiring order information (sequence learning), the 2nd order transitional probability is equal to one; namely, consecutive elements in the sequence could be predicted with 100% certainty from the previous sequence element (Kóbor et al., 2018).

Our finding of different learning trajectories within one learning session is in line with the results of Kóbor et al. (2018) well as corroborates earlier data (Nemeth et al., 2013) that showed different developmental trajectories of sequence and statistical learning between 11 and 40 years of age but did not analyze the time course of these learning types. Beyond the group-level results, we performed an additional analysis to characterize learning trajectories on a subject-by-subject basis. This analysis revealed that one-third of participants showed gradually increasing Sequence learning during training, and this proportion was significantly higher than the number of participants who exhibited gradually increasing Statistical learning, confirming differences in learning trajectories for Sequence vs. Statistical learning beyond the group-level findings. Nevertheless, the majority of participants exhibited a learning trajectory other than gradual. It is plausible that these participants explored different strategies over the course of learning that may have resulted in large changes in some epochs compared to their overall learning performance. Further investigations should directly focus on individual level heterogeneity and test which factors/characteristics predict learning trajectories on the individual level.

We had a special focus on the off-line change and the effect of sleep on Sequence Learning and Statistical Learning. In order to differentiate between the specific effects of sleep and from the indirect effect of reduced interference during off-line periods, we included a quiet rest control group into the design. On the behavioral level, we found no sleep-dependent consolidation neither in Sequence Learning nor in Statistical Learning. The lack of evidence for the beneficial influence of sleep on statistical learning is in line with previous studies that used probabilistic sequence learning tasks (Peigneux et al., 2003, 2006; Song et al., 2007a; Nemeth et al., 2010; Hallgató et al., 2013), however, we should note that these studies did not differentiate between order-based and frequency-based learning mechanisms. Here, we aimed to investigate the influence of sleep on pure (frequency-based) statistical learning in the perceptual-motor domain. Other studies examined sleep-dependent consolidation on statistical learning in the auditory domain (Durrant et al., 2011, 2013) and contrary to our results, found improved performance after sleep compared to wakefulness. Discrepancies between these studies and our findings might stem from methodological differences (overnight sleep and longer daytime naps in Durrant and colleagues' study) as well as the examined modality (auditory system vs. perceptual-motor system). Nevertheless, it is important to highlight that Durrant et al. (2011) did not include a quiet rest condition that might be favorable in napping studies.

Interestingly, and contrary to our expectations sleep did not facilitate off-line improvement in Sequence Learning either. In case of perceptual-motor sequence learning, Robertson and colleagues (Robertson et al., 2004) reported sleep-dependent consolidation in the explicit version of the Serial Reaction Time task using deterministic sequences. Discrepant findings between the present and Robertson and colleagues' study can be the result of different sequence structures applied in the SRT and ASRT task. In addition, other confounding factors, such as the effects of fatigue or reactive inhibition (Török et al., 2017) might have a different impact on these tasks. For instance, effects of fatigue are typical to occur in learning tasks (Rickard et al., 2008; Brawn et al., 2010; Pan and Rickard, 2015), however, ASRT learning scores seem to be relatively immune against the influence of fatigue (Török et al., 2017). Furthermore, recent studies raised concerns about the reliability of the deterministic SRT task (Stark-Inbar et al., 2017; West et al., 2017) while the ASRT proved to be a more reliable measure of sequence learning (Stark-Inbar et al., 2017).

Performance in Sequence and Statistical Learning did not show off-line improvements immediately after the long delay period; however, performance in Sequence Learning exhibited further gains after additional practice, suggesting that post-sleep increases in our case were also largely dependent on further practice. Interestingly, delayed (training-dependent) off-line improvements were associated with slow oscillatory activity within the Nap group. This finding suggests that not sleep *per se*, but low-frequency oscillations are associated with delayed performance gains after sleep and additional practice. Our findings indicate that slower oscillatory activity including the (high) delta and the theta frequency ranges (from 2 to 7.75 Hz) during daytime sleep might be predictive of post-sleep improvements in Sequence Learning. Slow frequency oscillations peaking at anterior locations and spanning between 1 and 8 Hz reflect the homeostatic and restorative capacity of sleep as power in these frequencies is increased after prolonged wakefulness (Borbély et al., 1981; Marzano et al., 2010) in fronto-central derivations. Furthermore, the homeostatic increase in spectral power between 2 and 7 Hz is state-independent (Marzano et al., 2010) making these oscillations likely candidates to reflect restorative processes during a daytime nap, with lower homeostatic pressure. Whether the association between slow frequency activity and further improvement in Sequence Learning reflects processes of sleep-related memory consolidation or a non-specific effect of restorative sleep facilitating performance remains a question of further research.

Sleep spindle parameters within the Nap group were negatively associated with off-line changes in performance: slow spindle density and fast spindle amplitude showed negative associations with early off-line changes in Sequence Learning and Statistical Learning, respectively. These findings are hard to interpret as they are at odds with the majority of previous findings that reported a positive association between spindle parameters, general cognitive abilities, and off-line gains in performance in a variety of declarative and procedural learning tasks (see Rasch and Born, 2013 for a comprehensive review). Still, negative correlations were also reported to some extent although in samples including children (Chatburn et al., 2013), and psychiatric patients (Nishida et al., 2016). In our study, associations between spindle parameters and off-line changes in performance might not simply stem from trait-like effects, as associations were unchanged if we controlled for the confounding effects of training-dependent learning performance. Nevertheless, given the lack of baseline EEG measurements, we cannot fully discern trait- and state-like effects in the present study. Moreover, only the association between slow spindle density and the off-line change in Sequence Learning remained significant after the correction for multiple comparisons, whereas previous studies mainly linked sleep-dependent cognitive benefits to fast spindle activity. In sum, off-line changes in Sequence Learning and Statistical Learning were associated with different spindle parameters, nevertheless, the relevance of these associations should be examined in further studies, including baseline sleep measurements without pre-sleep learning experience.

To conclude, here we were able to assess the time-course of two fundamental learning processes, namely Sequence Learning and Statistical Learning separately and showed that Statistical Learning is acquired rapidly and remains unchanged even after extended practice, whereas Sequence Learning may develop more gradually. On the behavioral level, both sequence and statistical knowledge were retained and were independent of whether the off-line period included sleep or not. Although our measures of cortical oscillations assessed during the off-line period showed associations with behavioral performance within the sleep group to some extent, the influence of sleep-specific oscillations on Sequence and Statistical learning should

be examined in future studies. Nevertheless, our findings suggest that sleep does not have an all-in-one-effect on memory consolidation, and future studies should focus on mapping systematically which learning and memory mechanisms might and might not benefit from sleep and related oscillatory activity. Learning and memory should be assessed on a process level (such as Sequence Learning and Statistical Learning in the current study) in order to characterize the time-course of these processes on the behavioral level as well as their neural correlates more precisely.

## AUTHOR CONTRIBUTIONS

DN, KJ, and PS conceived the original idea and designed the study. KJ programmed the experimental tasks. ZZ, NÉ, KH, OP, and CT performed the experiments, collected and preprocessed the data. PS, ZZ, KJ, FG, and NÉ analyzed the data. PS, ZZ, KJ, FG and DN wrote the manuscript. All authors discussed the results and commented on the manuscript.

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# The Relationship Between PSG and Morning/Evening Emotional Parameters in Patients With Insomnia Disorder and Good Sleepers

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**Objectives and Introduction:** It is as yet unclear how polysomnographically determined sleep parameters determine emotional well-being both generally and particularly in patients with Insomnia Disorder (ID). ID is a frequent and disabling health condition associated with both day- and nighttime hyperarousal, linked to negative sleep-related ruminations as a cognitive component. Information on the immediate influence of objective sleep quality on emotional parameters is important for therapeutic approaches.

**Methods:** The relationship between objective sleep parameters and two emotional questionnaire items obtained both for evening and morning, relaxation and emotional balance, was determined for both sleep lab nights in 161 ID patients and 161 age and gender matched good sleepers (retrospective sample from the Freiburg data base, 98 female, 63 male in each group, age ID: 42.16 ± 11.55, GSC: 41.91 ± 11.30 years). Multivariate mixed effects analysis, corrected for global influences of group, age and first/second night, was employed to determine between- and within-subject influences of sleep and emotional parameters.

**Results:** Main effects: Within-subject, relaxation in the evening was strongly associated with sleep efficiency, REM latency and low arousal index in NREM sleep. No such influence was significant for emotional balance. Also between subjects, evening relaxation was related to increased sleep efficiency. Group interactions: Patients with larger relaxation values in the evening showed a larger reduction of the number of wake periods and the awakening index in NREM sleep than GSC subjects.

**Discussion:** Unexpectedly, no general influence of emotional balance on sleep was found. The subjective feeling of relaxation, however, was associated with sleep efficiency, REM latency and low NREM sleep arousal index. While the first association may be obvious, a direct link to REM latency and NREM arousal index has not previously been shown. We could also directly observe that the number of wake periods in the PSG is more strongly influenced by evening relaxation in ID patients than in good sleepers, asserting the importance of sleep perception and attitude toward sleep in the therapeutic process.

**Keywords: PSG (Polysomnography), insomnia, emotion, questionnaire, good sleepers**

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## INTRODUCTION

Theories of chronic insomnia emphasize the role of cognitive, emotional, and physiological hyperarousal for its development and maintenance (Harvey, 2002; Espie et al., 2006). Own work (Riemann et al., 2010, 2011, 2012, 2015) summarized that hyperarousal processes seem to play a key role in its pathophysiology. Autonomous, neuroendocrine, neuroimmunological, electrophysiological, neuroimaging, and psychological studies deliver converging evidence for increased levels of arousal in ID without comorbidity compared to good sleepers. Corresponding to the subjective experience of patients with insomnia having difficulties to "shut down" or to disengage from wakefulness (especially when trying to sleep), physiological data reflect increased levels of arousal both during day- and nighttime compared to good sleepers. It is assumed that the permanent hyperarousal in chronic insomnia—linked to habit formation or alternatively to an (epi-) genetic lack in the ability to down-regulate arousal (e.g., Palagini et al., 2014)—is triggered by stressful life events and maintained by sleep-preventing learned associations and maladaptive coping strategies (neurocognitive model of insomnia as formulated by Perlis et al., 1997).

Little is known on the concrete relationship between cognitive and emotional state in the evening and in the morning and objective measures of sleep. It is well-known that in Insomnia Disorder (ID) subjective sleep perception is often worse than objective sleep measures suggest, while healthy subjects tend to overestimate their sleep time (Carskadon et al., 1976; Frankel et al., 1976; Edinger and Fins, 1995; Means et al., 2003). This bad perception of sleep has been linked to qualitatively different REM sleep (Feige et al., 2008, 2018; Riemann et al., 2012). The studies on sleep perception are based upon subjective assessments in the morning after a sleep night. When assessing state variables such as cognitive and emotional state, however, two different aspects are equally important: The state at bedtime (evening) and the state change from evening to morning. The state at bedtime may influence sleep in the successive night, while the state change across the night may be influenced by the objective characteristics of sleep.

Sleep and affective phenomena have been linked before. People suffering from ID often do not feel refreshed and feel impaired in relevant areas of life as stated in DSM-IV (American Psychiatric Association, 2000) and DSM-5 (American Psychiatric Association, 2013). They also report worse mood than healthy controls and negative mood in ID correlates positively with subjective sleep latency (Buysse et al., 2007). Additionally, epidemiological studies show that insomnia increases the risk of developing depression (Baglioni et al., 2011) and anxiety disorders (Morphy et al., 2007; Neckelmann et al., 2007). A model by Walker (2009) allows to explain this relationship between sleep and affective disorders. He suggests that sleep plays a crucial role in emotion regulation and that memories and emotion are disentangled during sleep. If this disentanglement does not work properly, the risk of developing chronic anxiety and depression increases. Wassing et al. (2016) examined correlations between REM sleep disruption, hyperarousal, insomnia, and the resolution of emotional distress. They found a positive correlation between insomnia severity, restless REM sleep and duration of emotional distress (specifically shame) overnight. In the current study we aimed at the relationship between objective sleep parameters and more general emotional states as rated using the SF-A sleep questionnaire (Schlaffragebogen-A, Görtelmeyer, 1981).

This questionnaire is similar to a sleep diary in that it contains evening and morning items filled for each night. It measures subjective quality of sleep, feeling recuperated after sleep, psychological balance before going to sleep and psychosomatic symptoms during sleep. In addition, identical evening and morning items are available for relaxation and emotional balance. Combined with sleep laboratory examinations, it therefore allows to directly assess the relationship between the latter items—both state in the evening and change across the night with PSG (polysomnographic) parameters. Relaxation can be viewed as inverse arousal, thereby providing a link to the hyperarousal theories of insomnia. Emotional balance may provide an assessment of the importance of emotional processes.

Assessing two nights of every subject in addition allows us to discriminate between- and within-subject, i.e., trait- and state- like influences: Subjects generally reporting low emotional balance may, for example, show certain sleep characteristics by trait; this does not necessarily mean that targeting emotional balance therapeutically will change sleep as well. A within-subject relationship (between the nights) however, provides a better hint at a possible therapeutic pathway. At the same time we can control for a first night effect, which itself is thought to result from elevated arousal during the first night in a sleep laboratory (Agnew et al., 1966; Wauquier et al., 1991).

As most studies on sleep and emotion refer to subjective sleep data, the aim of this study was to explore potential relationships between subjective emotional states (relaxation and emotional balance) and objective sleep patterns in ID ad GSC using data from first and second night's sleep assessed at the sleep laboratory.

## MATERIALS AND METHODS

### Participants and Procedure

#### Patients With Insomnia Disorder (ID)

This comparative observational study was based on a chart and data review of clinical patients with insomnia complaints evaluated between 1995 and 2012 at the sleep center of the Department of Psychiatry and Psychotherapy, Freiburg University Medical Center. During this period, 304 patients had been examined for two nights and diagnosed with Insomnia Disorder (ID; to ensure continuity, the diagnosis was primary insomnia after DSM-IV before DSM-5 and ID after DSM-5 thereafter, with exclusion criteria ensuring that this corresponded to primary insomnia after DSM-IV).

All patients had been referred from their primary care physician or medical specialist for evaluation of their sleep complaint. Two weeks before consultation in our outpatient sleep disorders clinic, patients received a questionnaire screening package by mail which included, among others, the Beck Depression Inventory (BDI, Beck and Steer, 1987; German version by Hautzinger et al., 1994) and the Pittsburgh Sleep

Quality Index (PSQI, Buysse et al., 1989; German version by Riemann and Backhaus, 1996, see below). During the 1-h intake interview in the outpatient facility, patients were interviewed about: onset and duration of insomnia, sleep habits as well as history of medical illnesses, psychiatric disorders, use of medication, drugs, tobacco and alcohol, sleep disorders in first degree relatives (parents, siblings, and children) as well as education and social background.

A preliminary diagnosis was given on the basis of this interview and a decision was made about the necessity of a sleep laboratory examination (e.g., in case of: chronicity, persistence of insomnia despite adequate therapy, suspicion of possible underlying organic causes). Patients were then scheduled for a PSG evaluation approximately 4 to 8 weeks after the first outpatient contact.

During their 2-day stay in the sleep center, all patients underwent a thorough physical, psychiatric (repeating the interview taken 4–8 weeks earlier) and neurological examination, routine blood tests (blood cell count, liver, renal, and thyroid function), ECG, EEG, and urine drug screen (opiates, barbiturates, benzodiazepines, amphetamines and cannabis, and viral/bacterial infection).

Exclusion criteria for the present data analysis were: Presence of any other sleep disorder (e.g., sleep apnea syndrome, restless-legs syndrome, narcolepsy, circadian rhythm disorders, organic or psychiatric insomnia as defined by DSM-IV); A sleep apnea-/PLMS (period leg movements in sleep)-index with arousal $\geq$ 5.0/TST (total sleep time); Clinically relevant medical or neurological disorders or a positive urine drug screen; Consumption of hypnotic medication or medication known to affect sleep in the 2 weeks before or during sleep laboratory examination; Pregnancy; Any history of psychiatric disorder, of serious medical illness (e.g., hepatitis), substance abuse or shift work in the past.

During the two nights of sleep laboratory examinations patients had to refrain from alcohol. Decaffeinated coffee was only allowed in the morning for breakfast (maximum: two cups).

179 patients with confirmed insomnia disorder (ID) fulfilling the in- and exclusion criteria were finally eligible for statistical analysis.

### Good Sleeper Controls (GSC)

One hundred and ninety-eight good sleeper controls (GSC) were available for the current study. They were selected retrospectively from our database of healthy subjects who participated in healthy volunteer studies of our sleep center. Control subjects underwent the same routine procedure of examinations as ID patients to ensure physical and psychiatric health. In addition to the exclusion criteria applying to the patients, good subjective sleep quality was required to be reflected in a PSQI sum score below 6. Medical problems including sleep apnea or restless legs syndrome were excluded. Written informed consent was obtained from all healthy subjects prior to the investigation in the sleep center.

### Matched Groups for Final Analysis

From the ID and GSC groups described above, 161 ID patients and 161 GSC subjects could be matched using automated pair matching for gender and mean age within each gender group.

The final matched sample consisted of 63 men and 98 women of each group aged 42.16 $\pm$ 11.55 years (ID, 19–67 years) and 41.91 $\pm$ 11.30 years (GSC, 20–69 years). The age distribution did not differ (Wilcoxon W = 13122, $p = 0.847$).

## Polysomnography

All polysomnographic investigations were carried out using a standardized procedure. All subjects underwent two consecutive nights of PSG sleep monitoring. Sleep was recorded on 14-channel Nihon-Kohden EEG-polysomnographs for 8 h from "lights out" (23:00 h) until "lights on" (7:00 h) and digitized at a rate of 200 Hz. All recordings included EEG (C3A2; C4A1), EOG (horizontal and vertical) and EMG (submental) and were scored visually by experienced raters according to Rechtschaffen and Kales (1968) criteria. Inter-rater reliability is regularly evaluated and ensured to be above 0.9 as part of laboratory routine. During the first night, all subjects were screened for apneas and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oxymetry, and bilateral tibialis anterior EMG.

Sleep recordings were evaluated for the following parameters of sleep continuity and architecture: total sleep time (TST), sleep efficiency (SEI): ratio of TST to time in bed (TIB) x 100%; sleep onset latency (SOL): time from lights out until sleep onset (defined as first epoch of stage N2). Arousals were analyzed according to the criteria of the American Sleep Disorders Association (Sleep Disorders Atlas Task Force of the American Sleep Disorders Association, 1992). The arousal index is the number of arousals per hour. We evaluated both the arousal index within TST and sleep stage specific indices (stage N2, REM). In addition, short awakenings within N2 and REM sleep were captured accordingly as awakening index. Sleep architecture variables included: amounts of stages wake (W), N1, N2, slow wave sleep (SWS), and REM expressed as percentage of sleep period time (SPT: time from sleep onset until final awakening). REM sleep variables were REM latency (time from sleep onset until the first epoch of REM sleep, possible wake time not counted) and REM density, calculated as the ratio of 3 s REM mini-epochs including rapid eye movements (REMs) to the total amount of REM mini-epochs x 100%. REMs were defined using separate vertical and horizontal EOG traces, requiring a steepness of excursions of at least 70 $\mu$V/s.

## Subjective Sleep Scales

The PSQI (Buysse et al., 1989; Riemann et al., 1996) assesses sleep habits and quality in the preceding 2 weeks. Variables reported for group descriptives are the subjectively reported sleep onset latency, total sleep time, and (derived) sleep efficiency as well as the PSQI sum score (ranging from 0 to 21, highest values denoting severely impaired sleep).

The SF-A (Schlaffragebogen-A, Görtelmeyer, 1981, in its revised form Görtelmeyer, 2011) captures subjective aspects of sleep in the preceding night. It was administered in the morning after each sleep recording, after subjects were awake for some minutes. The questionnaire contains subjective estimates of wake times (SOL and wake after sleep onset, WASO) as well as the frequency of awakenings. Of the additional 5-level items (values 1-5) asked regarding to experiences in the evening prior to sleep and in the morning after sleep, "relaxation" and "emotional

balance" are formulated identically for evening and morning and therefore can be directly compared. Both items are part of the SF-A factor scales "psychological balancedness in the evening" and "feeling of recuperation in the morning. "The German term "Ausgeglichenheit" translated here as "balance" or "balancedness" means absence of disturbing thoughts or emotions and could also be translated as "calmness of the mind. "The questions are "how relaxed/how emotionally balanced did you/do you feel". The relationship of these two variables with PSG sleep is the major topic of this study. Descriptive subjective sleep quality data for both groups is given in **Table 1**.

## Statistical Analysis

Two-tailed non-parametric Wilcoxon tests were employed to ensure that the groups did not systematically differ in age. $\chi^2$ tests were used to compare dichotomous variables between groups. For descriptive purposes, means and standard deviations were calculated for PSG and subjective sleep parameters. Group differences (ID vs. GSC), night (first, second) and age effects were assessed using mixed-effects MANOVAs with between-subject factor GROUP and covariate AGE as well as within-subject factor NIGHT. Multivariate statistics were based on Wilk's Lambda. $P < 0.05$ was considered to be significant, proceeding from significant multivariate effects to univariate effects of the same independent variable. For univariate effects, we report $F$ and $p$ values as well as $B$ values (betas) of the linear model, i.e., coefficients or differences between factor levels. For the NIGHT effect this is Night2-Night1 and for the GROUP effect ID-GSC.

For the main analysis of the influence of relaxation and emotional balance which were assessed before and after each night, mixed-effects MANOVAS were used with between-subject factor GROUP and covariate AGE as well as within-subject factor NIGHT and covariates morning values as well as changes across the night (morning-evening) of relaxation and emotional balance. Only the terms involving the target variables alone and their GROUP interactions are reported. The remaining terms are regarded as nuisance effects in this analysis. This pertains to the terms identical to the previous, more descriptive model (**Table 2**) and the NIGHT interactions.

The rationale for using evening scores and differences across the night instead of evening and morning scores was that evening and morning scores can be expected to be related to some degree; also, the difference across the night can be hypothesized to be determined by some property of the intervening sleep. If evening and morning scores were entered independently into an analysis, this important change aspect would be reflected only in an interaction term of these covariates, rendering analysis and conclusions more complex.

All statistical analyses were performed using the statistical software suite "R" version 3.5.1 (R Core Team, 2018).

# RESULTS

## Main Effects for Group, Night, and Age

**Table 2** shows the more descriptive MANOVAs separately for the PSG variables and the target variables relaxation and emotional balance. For PSG, multivariate effects are seen for GROUP, NIGHT, and AGE but not NIGHT x GROUP. The GROUP effect shows the typical reductions in total sleep time (TST) and sleep efficiency index (SEI) in the ID group as well as an increased awakening index in NREM sleep. The NIGHT effect shows reduced sleep onset latency (SOL), increased TST and SEI, reduced number of wake periods (NWP) as well as arousal and awakening indices in NREM sleep (AI/N and AWI/N) in the second relative to the first night. Increased AGE is associated with reduced TST and SEI, increased NWP as well as increases in arousal and awakening indices in both NREM and REM sleep.

**TABLE 1 |** Descriptives of subjective sleep quality for both groups.

| | | GSC | ID | Group | | | Age | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SD | Mean ± SD | *B* | *F* | *p* | *B* | *F* | *p* |
| | Multivariate statistics (Wilk's Lambda) | | | | 0.36 | **0.000** | | 0.85 | **0.000** |
| PSQI | SOL | 14.25 ± 10.93 | 41.89 ± 47.50 | 27.39 | 42.11 | **0.000** | 0.16 | 0.71 | 0.401 |
| | TST | 431.69 ± 56.28 | 302.17 ± 88.38 | −126.30 | 216.97 | **0.000** | −1.45 | 13.99 | **0.000** |
| | SEI | 87.79 ± 25.03 | 60.31 ± 26.19 | −27.86 | 242.58 | **0.000** | −0.16 | 4.20 | **0.041** |
| | PSQI sum score | 3.68 ± 2.12 | 10.96 ± 3.37 | 7.23 | 461.27 | **0.000** | 0.02 | 2.70 | 0.101 |
| SF-A | SOL | 11.35 ± 11.32 | 22.20 ± 17.90 | 10.86 | 36.50 | **0.000** | 0.08 | 1.00 | 0.317 |
| | TST | 452.92 ± 29.85 | 408.01 ± 61.61 | −44.95 | 58.30 | **0.000** | −0.29 | 1.20 | 0.274 |
| | SEI | 94.25 ± 6.13 | 84.90 ± 12.80 | −9.35 | 58.43 | **0.000** | −0.05 | 1.01 | 0.315 |
| | SQ | 3.58 ± 0.67 | 2.90 ± 0.74 | −0.69 | 67.28 | **0.000** | −0.01 | 3.03 | 0.083 |
| | R_MOR | 3.60 ± 0.72 | 2.80 ± 0.82 | −0.84 | 82.36 | **0.000** | 0.01 | 5.35 | **0.021** |
| | WB_EVE | 3.92 ± 0.64 | 3.53 ± 0.66 | −0.41 | 27.67 | **0.000** | 0.00 | 0.00 | 0.964 |
| | EX_EVE | 2.60 ± 0.67 | 2.92 ± 0.70 | 0.29 | 11.88 | **0.001** | −0.01 | 2.99 | 0.085 |
| | PS | 1.49 ± 0.48 | 1.87 ± 0.47 | 0.38 | 52.92 | **0.000** | 0.01 | 13.50 | **0.000** |

*The SF-A of the second night is used. For the Group effect, B=ID-GSC. GSC, Good Sleeper Controls; ID Patients with Insomnia Disorder; PSQI, Pittsburgh Sleep Quality Index; min, Minutes; SOL, Sleep Onset Latency; TST, Total Sleep Time; SEI, Sleep Efficiency Index %; SF-A, Schlaffragebogen-A; SQ, Sleep Quality; R_MOR, Recovery in the morning; WB_EVE, Wellbeing in the evening; EX_EVE, Exhaustion in the evening; PS, Psychosomatic Symptoms. p values below p = 0.05 are set in bold font.*

**TABLE 2 |** Characteristics of PSG data and the variables on relaxation and emotional balance.

| | Adaptation night | | Baseline night | | Effects | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GSC | ID | GSC | ID | Group | | | Night | | | Night x Group | | | Age | | |
| | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* |
| Multivariate statistics (Wilk's Lambda) | | | | | | 0.84 | **0.000** | | 0.55 | **0.000** | | 0.96 | 0.714 | | 0.66 | **0.000** |
| SOL (min) | 22.87 ± 19.86 | 25.39 ± 22.10 | 17.44 ± 15.38 | 15.85 ± 11.97 | 0.45 | 0.08 | 0.778 | −5.43 | 45.49 | **0.000** | −4.11 | 3.42 | 0.065 | 0.05 | 0.55 | 0.461 |
| TST (min) | 391.71 ± 51.29 | 361.24 ± 64.06 | 419.22 ± 33.04 | 396.90 ± 47.24 | −26.08 | 33.75 | **0.000** | 27.51 | 125.10 | **0.000** | 8.15 | 2.08 | 0.150 | −1.29 | 41.57 | **0.000** |
| SEI (%) | 81.61 ± 10.58 | 75.35 ± 13.27 | 87.33 ± 6.85 | 82.67 ± 9.81 | −5.40 | 33.71 | **0.000** | 5.72 | 125.86 | **0.000** | 1.61 | 1.92 | 0.167 | −0.27 | 42.61 | **0.000** |
| NWP | 29.27 ± 13.80 | 31.68 ± 14.95 | 27.50 ± 14.34 | 29.56 ± 14.57 | 2.14 | 2.65 | 0.105 | −1.77 | 8.41 | **0.004** | −0.35 | 0.07 | 0.795 | 0.39 | 42.72 | **0.000** |
| W (%SPT) | 12.95 ± 9.08 | 17.92 ± 11.92 | 8.49 ± 5.61 | 12.68 ± 9.39 | 4.52 | 30.85 | **0.000** | −4.46 | 83.18 | **0.000** | −0.78 | 0.54 | 0.461 | 0.26 | 50.73 | **0.000** |
| N1 (%SPT) | 9.30 ± 4.92 | 9.98 ± 4.92 | 8.02 ± 4.65 | 8.64 ± 4.22 | 0.62 | 2.05 | 0.153 | −1.28 | 44.32 | **0.000** | −0.06 | 0.02 | 0.877 | 0.14 | 47.00 | **0.000** |
| N2 (%SPT) | 51.96 ± 8.43 | 50.39 ± 9.51 | 54.93 ± 7.24 | 53.04 ± 9.12 | −1.71 | 4.04 | **0.045** | 2.98 | 44.52 | **0.000** | −0.32 | 0.14 | 0.706 | −0.07 | 3.38 | 0.067 |
| N3 (%SPT) | 7.02 ± 6.55 | 5.05 ± 5.81 | 7.97 ± 6.78 | 6.24 ± 7.06 | −1.80 | 8.01 | **0.005** | 0.94 | 26.04 | **0.000** | 0.24 | 0.33 | 0.566 | −0.20 | 50.39 | **0.000** |
| REM (%SPT) | 18.44 ± 5.44 | 16.55 ± 5.44 | 20.39 ± 4.91 | 19.25 ± 4.57 | −1.49 | 10.10 | **0.002** | 1.94 | 71.57 | **0.000** | 0.76 | 1.90 | 0.169 | −0.12 | 31.20 | **0.000** |
| REML (min) | 101.51 ± 48.39 | 107.84 ± 60.51 | 76.50 ± 33.55 | 72.94 ± 30.44 | 1.34 | 0.13 | 0.719 | −25.01 | 86.81 | **0.000** | −9.89 | 2.37 | 0.125 | 0.16 | 0.88 | 0.348 |
| REMD (%) | 24.96 ± 7.51 | 25.97 ± 8.77 | 25.36 ± 7.83 | 26.94 ± 7.41 | 1.30 | 2.61 | 0.107 | 0.40 | 3.54 | 0.061 | 0.58 | 0.63 | 0.429 | −0.04 | 1.32 | 0.252 |
| AI/REM | 18.19 ± 9.32 | 18.50 ± 9.38 | 17.59 ± 9.10 | 17.76 ± 9.03 | 0.22 | 0.07 | 0.795 | −0.60 | 2.41 | 0.121 | −0.14 | 0.03 | 0.872 | 0.09 | 4.47 | **0.035** |
| AI/N | 12.30 ± 6.23 | 13.72 ± 7.95 | 10.33 ± 5.52 | 10.91 ± 6.07 | 0.98 | 2.28 | 0.132 | −1.97 | 74.12 | **0.000** | −0.85 | 2.34 | 0.127 | 0.09 | 9.83 | **0.002** |
| AWI/REM | 3.49 ± 3.78 | 3.66 ± 3.33 | 3.58 ± 3.69 | 3.75 ± 3.46 | 0.16 | 0.25 | 0.620 | 0.09 | 0.24 | 0.624 | −0.01 | 0.00 | 0.985 | 0.06 | 13.94 | **0.000** |
| AWI/N | 3.90 ± 1.78 | 4.37 ± 2.20 | 3.38 ± 1.76 | 3.68 ± 1.89 | 0.38 | 4.67 | **0.031** | −0.52 | 39.24 | **0.000** | −0.16 | 0.73 | 0.393 | 0.05 | 39.06 | **0.000** |
| Multivariate statistics (Wilk's Lambda) | | | | | | 0.76 | **0.000** | | 0.91 | **0.000** | | 0.96 | **0.019** | | 0.96 | **0.006** |
| Relaxation Evening | 3.80 ± 0.77 | 3.22 ± 0.90 | 3.84 ± 0.81 | 3.48 ± 0.80 | −0.47 | 36.28 | **0.000** | 0.04 | 9.19 | **0.003** | 0.21 | 4.61 | **0.033** | 0.00 | 0.34 | 0.560 |
| Em.Balance Evening | 3.87 ± 0.78 | 3.47 ± 0.87 | 3.93 ± 0.83 | 3.45 ± 0.91 | −0.44 | 29.63 | **0.000** | 0.06 | 0.19 | 0.662 | −0.07 | 0.47 | 0.492 | 0.01 | 3.54 | 0.061 |
| Relaxation M-E | −0.09 ± 0.91 | −0.49 ± 1.12 | −0.01 ± 0.90 | −0.39 ± 0.90 | −0.39 | 22.23 | **0.000** | 0.08 | 1.71 | 0.192 | 0.02 | 0.02 | 0.892 | 0.00 | 1.65 | 0.200 |
| Em.Balance M-E | −0.10 ± 0.85 | −0.47 ± 1.04 | 0.01 ± 0.81 | −0.16 ± 0.95 | −0.27 | 11.06 | **0.001** | 0.11 | 10.53 | **0.001** | 0.20 | 2.55 | 0.111 | 0.01 | 3.16 | 0.077 |

*For the Group effect, B=ID-GSC. For the Night effect, B=Night 2 - Night 1. p values below p = 0.05 are set in bold font.*

## Target Variables (Relaxation and Emotional Balance)

For the target variables (lower part of **Table 2**), all multivariate effects are significant. Patients with ID show reductions in all four variables (relaxation and emotional balance, both evening values and differences morning-evening). In the second night, relaxation in the evening and the emotional balance difference morning-evening are increased. As evidenced by the NIGHT x GROUP effect, the increase in evening relaxation across nights was significantly higher in ID patients. Finally, age tended to increase both emotional balance in the evening and its morning-evening difference, not reaching significance.

### Between-Subject Effects

**Table 3** shows the between-subject relationships between the target variables and PSG, i.e., whether subjects with different sleep characteristics tend to also show different values on relaxation and emotional balance. Multivariate significance is seen for evening relaxation and the evening relaxation x GROUP interaction. Subjects with larger evening relaxation show reduced SOL and increased TST, SEI, and stage N3 % SPT. Patients with larger evening relaxation show reduced NWP and awakening index in NREM sleep (AW/N) relative to the control group. **Figures 1**, **2** show the relationship between evening relaxation and SEI as well as NWP, respectively.

### Within-Subject Effects

**Table 4** shows the within-subject relationships between the target variables and PSG, i.e., whether nights with different sleep characteristics within the same subject tend to show different values on relaxation and emotional balance. This is generally more valuable than between-subject effects, since possible different response tendencies across subjects are factored out and within-subject effects are more suitable to predict treatment effects.

Across groups, relaxation in the evening was strongly related to within-subject PSG sleep quality: Reduced SOL, increased TST and SEI as well as REM % SPT and REM latency (REML) and a reduced arousal index in NREM sleep were related to increased evening relaxation. The awakening index in REM sleep was, surprisingly, slightly positively related to evening relaxation.

Unexpectedly, the influence of the Morning-Evening relaxation difference is for the most part of opposite direction to the evening value, albeit with lower amplitude. This indicates that evening relaxation is more important than morning relaxation; with the scores limited between 1 and 5, a positive Morning-Evening difference can only be attained if the evening relaxation value is less than 5, associated with a negative impact on sleep quality. **Figure 3** shows these relationships graphically for the example of SEI.

No other main effects or interactions reached significance, particularly no relationship could be found between the scales of emotional balance and any PSG sleep parameter.

# DISCUSSION

In the current study, we reported an extensive multivariate analysis of the relationship between relaxation and emotional balance in a large population of patients with insomnia and matched healthy controls.

The level of relaxation, particularly in the evening, was found to enhance sleep both between subjects and within subjects. This suggests that relaxation can be an important therapeutic target for treating sleep problems.

A single significant group interaction was identified: Evening relaxation reduced the number of wake periods and, specifically, the awakening index in NREM sleep more strongly in patients with insomnia disorder. In fact, relaxation techniques are important components in current cognitive-behavioral treatments for insomnia (CBT-I, Trauer et al., 2015; Riemann et al., 2017a,b; Friedrich and Schlarb, 2018), although clearly only responsible for part of its therapeutic efficacy (Norell-Clarke et al., 2015). Bertisch et al. (2012) have found that relaxation techniques are generally under-used for sleep problems in the general population. However, the therapeutic effect of relaxation alone may not be sustainable, requiring other components of CBT-I for a lasting effect.

The level of emotional balance as assessed by the SF-A could not be linked to objective sleep parameters in this multivariate analysis. This is interesting by and of itself, as ID patients showed clearly reduced levels of emotional balance as a group, an effect which has been partialled out of the emotional balance—PSG relationships in our analysis. Therefore, the finding means that, within each group, differences in emotional balance were related to PSG parameters neither between- nor within subjects. It is well-known that emotional reactivity is impaired in insomnia, as well as some aspects of emotional valence (sleep in good sleepers being distinguished by increased positive but not necessarily reduced negative emotions; Baglioni et al., 2010). Since these were group studies comparing insomnia patients to good sleepers and the current study found clear group differences in SF-A emotional balance as well, it may still be that the latter construct captures the deficiencies in emotional processing characteristic to insomnia to some degree. In this case the current finding could be extended to emotional reactivity and valence as well. This in turn would indicate that targeting emotional reactivity, valence or balance itself would rather not present a viable therapeutic approach. Further studies making this link explicit are, however, needed to support this conclusion.

Generally, mutual relationships between sleep and emotions have to be considered (Kahn et al., 2013). Complicating the matter further, reappraisal processes may be involved (cf. Palmer and Alfano, 2017), for example general dissatisfaction with sleep leading to more negative responses to any sleep-related question. This could be a potential mechanism for the more negative judgments on both the relaxation and emotional balance scale in ID patients (**Table 3**).

Wassing et al. (2016) reported that the overnight resolution of emotional distress contributes to hyperarousal. They specifically targeted shame. Overnight resolution of emotional distress

**TABLE 3 |** Between-subject effects of relaxation and emotional balance variables.

| | Between | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Evening | | | | | | Morning–Evening | | | | | | Evening x Group | | | | | | Morning–Evening x Group | | | | | |
| | Relaxation | | | Emotional balance | | | Relaxation | | | Emotional balance | | | Relaxation | | | Emotional balance | | | Relaxation | | | Emotional balance | | |
| | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* |
| Multivariate statistics (Wilk's Lambda) | | 0.92 | **0.049** | | 0.92 | 0.064 | | 0.98 | 0.963 | | 0.95 | 0.405 | | 0.90 | **0.014** | | 0.95 | 0.407 | | 0.95 | 0.389 | | 0.94 | 0.211 |
| SOL (min) | −20.44 | 10.66 | **0.001** | 13.99 | 0.05 | 0.829 | −11.51 | 0.14 | 0.708 | −2.10 | 1.46 | 0.227 | −13.53 | 1.72 | 0.191 | 12.73 | 0.19 | 0.665 | −4.89 | 1.44 | 0.231 | 22.86 | 0.30 | 0.584 |
| TST (min) | 32.15 | 8.28 | **0.004** | −20.01 | 1.68 | 0.195 | −4.63 | 1.14 | 0.287 | 34.51 | 0.59 | 0.443 | 62.94 | 0.97 | 0.325 | −57.56 | 3.63 | 0.058 | 67.81 | 0.28 | 0.597 | −58.81 | 0.22 | 0.639 |
| SEI (%) | 6.13 | 7.87 | **0.005** | −4.58 | 1.53 | 0.218 | −1.05 | 1.17 | 0.281 | 6.91 | 0.48 | 0.490 | 13.94 | 0.76 | 0.383 | −11.13 | 3.82 | 0.052 | 13.96 | 0.33 | 0.568 | −11.54 | 0.28 | 0.597 |
| NWP | −0.82 | 0.08 | 0.779 | 13.46 | 0.00 | 0.945 | 3.04 | 0.10 | 0.747 | 3.35 | 0.03 | 0.854 | −11.95 | 5.59 | **0.019** | −12.59 | 5.17 | **0.024** | −12.42 | 1.93 | 0.165 | −2.95 | 0.02 | 0.896 |
| W (%SPT) | −0.64 | 2.90 | 0.089 | −0.08 | 1.47 | 0.226 | 3.61 | 1.50 | 0.222 | −8.71 | 0.20 | 0.653 | −11.74 | 0.16 | 0.691 | 9.21 | 4.45 | **0.036** | −12.63 | 0.07 | 0.793 | 9.63 | 1.95 | 0.164 |
| N1 (%SPT) | −2.07 | 2.52 | 0.113 | 0.66 | 0.34 | 0.558 | 2.08 | 0.01 | 0.926 | −2.05 | 0.02 | 0.879 | 1.17 | 1.96 | 0.162 | −1.38 | 0.86 | 0.356 | −2.99 | 1.57 | 0.212 | 0.55 | 1.84 | 0.176 |
| N2 (%SPT) | −3.82 | 0.01 | 0.909 | −2.56 | 0.26 | 0.613 | −5.35 | 0.65 | 0.422 | 0.11 | 6.14 | **0.014** | 11.26 | 0.03 | 0.860 | −5.49 | 6.95 | **0.009** | 14.06 | 0.03 | 0.868 | −4.23 | 0.12 | 0.728 |
| N3 (%SPT) | 3.47 | 5.85 | **0.016** | 1.01 | 0.91 | 0.340 | 1.02 | 0.10 | 0.747 | 5.53 | 6.70 | **0.010** | −2.04 | 1.58 | 0.210 | 3.15 | 0.23 | 0.633 | −2.11 | 1.45 | 0.230 | −2.98 | 0.01 | 0.921 |
| REM (%SPT) | 2.66 | 1.61 | 0.205 | 0.81 | 0.04 | 0.843 | −1.30 | 0.84 | 0.360 | 4.26 | 0.02 | 0.892 | 1.42 | 0.61 | 0.434 | −4.96 | 0.37 | 0.545 | 3.43 | 0.06 | 0.806 | −1.94 | 0.28 | 0.597 |
| REML (min) | 8.77 | 0.71 | 0.401 | −29.24 | 1.88 | 0.171 | −9.95 | 0.53 | 0.468 | −15.46 | 0.09 | 0.763 | −40.13 | 2.23 | 0.137 | 39.68 | 0.16 | 0.687 | −23.79 | 0.98 | 0.324 | −6.26 | 1.23 | 0.268 |
| REMD (%) | −10.69 | 0.51 | 0.475 | 3.31 | 2.89 | 0.090 | −9.03 | 0.75 | 0.386 | 3.30 | 0.14 | 0.712 | 4.59 | 2.76 | 0.098 | −9.80 | 0.40 | 0.530 | 2.11 | 1.31 | 0.252 | −2.11 | 0.16 | 0.691 |
| AI/REM | −3.80 | 1.19 | 0.276 | 5.89 | 0.33 | 0.566 | −5.26 | 0.00 | 0.954 | 8.23 | 0.23 | 0.630 | 11.28 | 0.83 | 0.364 | −3.03 | 0.49 | 0.483 | 8.18 | 1.58 | 0.210 | −10.00 | 0.03 | 0.873 |
| AI/N | −2.90 | 0.18 | 0.673 | 5.04 | 9.32 | **0.002** | 0.22 | 0.57 | 0.452 | −0.39 | 0.07 | 0.797 | −7.50 | 1.35 | 0.246 | 3.15 | 3.09 | 0.080 | −4.57 | 2.53 | 0.113 | −3.14 | 0.02 | 0.888 |
| AWI/REM | 0.83 | 0.45 | 0.504 | 2.87 | 2.40 | 0.122 | 0.40 | 0.04 | 0.845 | 0.97 | 0.02 | 0.887 | −1.70 | 0.64 | 0.423 | −2.86 | 2.35 | 0.126 | −0.66 | 0.16 | 0.689 | 0.34 | 0.01 | 0.908 |
| AWI/N | −0.86 | 0.12 | 0.730 | 1.87 | 0.87 | 0.353 | 0.25 | 0.50 | 0.481 | −0.02 | 0.45 | 0.502 | −1.72 | 4.31 | 0.039 | −1.07 | 4.03 | 0.046 | −2.11 | 1.26 | 0.262 | 0.26 | 0.00 | 0.988 |

*p values below p = 0.05 are set in bold font.*

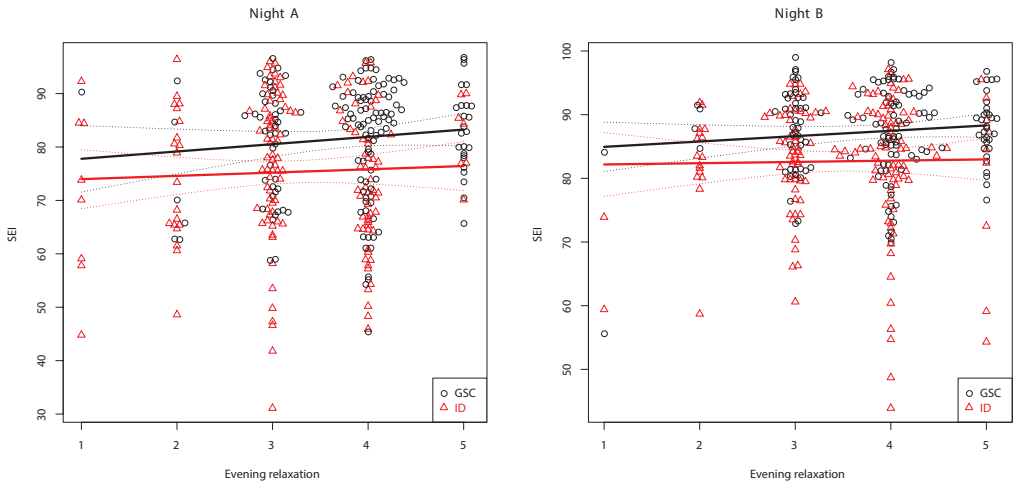


**FIGURE 1 |** Relationship between evening relaxation and SEI (%) for the two groups in first **(Left)** and second **(Right)** nights.

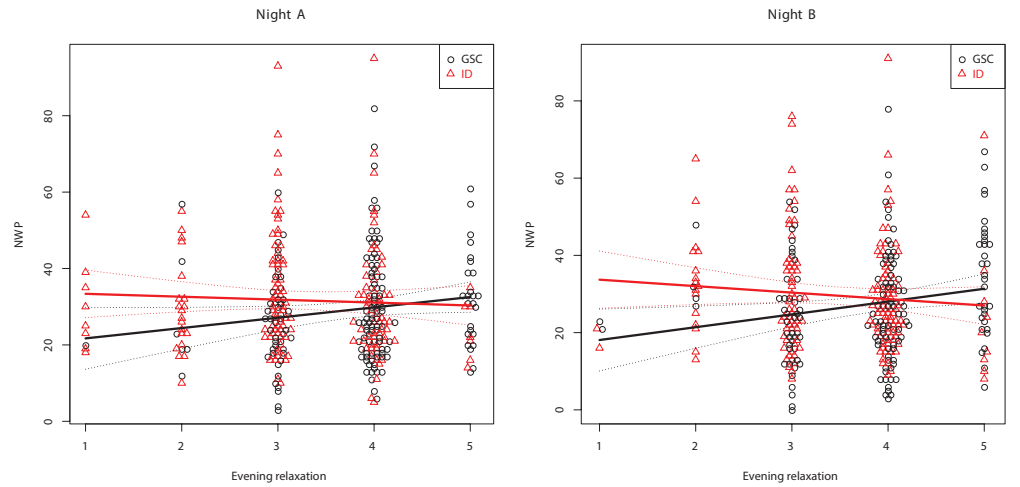


**FIGURE 2 |** Relationship between evening relaxation and NWP for the two groups in first **(Left)** and second **(Right)** nights.

means an amelioration of values during sleep (positive Morning-Evening difference in our study). We did not see an influence of emotional balance (or its difference across the night) on sleep parameters, but a measure of (inverse) hyperarousal (i.e., relaxation) was included in the same model and apparently correlated better with objective sleep parameters than emotional balance itself. Thus, for the SF-A emotional balance construct it appears that its change across the night is rather not related to hyperarousal or objective sleep parameters. Since there is a clear group difference in emotional balance, it is possible that impaired emotional balance over longer periods of time (e.g., weeks) leads to increased hyperarousal. This notion cannot be tested using the data of the current study but should be addressed by future studies.

In summary, in the current study we could separately assess state- and trait- like influences of two emotional parameters, relaxation and emotional balance, on PSG in large matched samples of patients with ID and good sleeper controls. While both parameters were lower in ID patients ("trait"), particularly increased evening relaxation had a strong within-subject influence on PSG sleep quality as a main effect across both groups and was additionally linked to a reduced number of wake periods in the ID patients, suggesting relaxation as a useful therapeutic target in conjunction with other CBT-I elements.

## LIMITATIONS

While interpreting the results of this study some limitations should be taken into account. First of all we used pre-existing data which on the one hand lead to a large sample size but on the other hand restricted the measurement of the emotional state to two subjective items without defined valence. To assess

**TABLE 4 |** Within-subject effects of relaxation and emotional balance variables.

| | Within | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Evening | | | | | | Morning–Evening | | | | | | Evening x Group | | | | | | Morning–Evening x Group | | | | | |
| | Relaxation | | | Emotional balance | | | Relaxation | | | Emotional balance | | | Relaxation | | | Emotional balance | | | Relaxation | | | Emotional balance | | |
| | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* | *B* | *F* | *p* |
| Multivariate statistics (Wilk's Lambda) | | 0.84 | **0.000** | | 0.96 | 0.608 | | 0.78 | **0.000** | | 0.94 | 0.216 | | 0.94 | 0.209 | | 0.95 | 0.476 | | 0.95 | 0.369 | | 0.95 | 0.541 |
| SOL (min) | −7.48 | 15.25 | **0.000** | 1.69 | 2.38 | 0.124 | 1.53 | 6.91 | **0.009** | −2.92 | 0.58 | 0.445 | 2.78 | 1.39 | 0.240 | 0.93 | 1.42 | 0.234 | 1.60 | 0.70 | 0.404 | 7.48 | 0.89 | 0.345 |
| TST (min) | 17.49 | 12.08 | **0.001** | −1.14 | 2.56 | 0.111 | −2.66 | 29.05 | **0.000** | 8.90 | 4.55 | **0.034** | 6.47 | 3.90 | **0.049** | −28.64 | 1.21 | 0.272 | 7.87 | 2.90 | 0.090 | −12.99 | 0.15 | 0.699 |
| SEI (%) | 3.24 | 12.06 | **0.001** | 0.05 | 2.50 | 0.115 | −0.93 | 31.70 | **0.000** | 2.11 | 4.47 | **0.035** | 2.22 | 3.51 | 0.062 | −6.45 | 1.76 | 0.186 | 2.00 | 3.35 | 0.068 | −3.02 | 0.13 | 0.718 |
| NWP | 0.08 | 0.09 | 0.771 | −0.86 | 0.02 | 0.895 | 3.96 | 8.72 | **0.003** | −5.38 | 1.70 | 0.194 | −4.80 | 0.76 | 0.384 | 5.77 | 0.44 | 0.509 | −9.67 | 1.50 | 0.222 | 6.99 | 1.89 | 0.170 |
| W (%SPT) | −0.68 | 3.04 | 0.082 | −1.12 | 0.79 | 0.375 | 1.24 | 33.53 | **0.000** | −2.48 | 0.96 | 0.329 | −5.90 | 3.35 | 0.068 | 9.40 | 0.07 | 0.785 | −4.16 | 4.42 | **0.036** | 3.78 | 0.85 | 0.358 |
| N1 (%SPT) | −1.00 | 10.62 | **0.001** | 2.03 | 0.15 | 0.699 | 0.05 | 4.30 | **0.039** | 0.46 | 2.74 | 0.099 | −0.29 | 1.39 | 0.240 | −1.21 | 0.73 | 0.392 | −1.03 | 1.72 | 0.190 | 0.62 | 3.31 | 0.070 |
| N2 (%SPT) | 2.56 | 3.07 | 0.081 | −0.78 | 1.57 | 0.212 | −0.32 | 26.12 | **0.000** | 0.28 | 0.04 | 0.844 | 2.89 | 2.75 | 0.098 | −4.40 | 0.38 | 0.541 | 4.11 | 1.07 | 0.302 | −2.25 | 0.10 | 0.751 |
| N3 (%SPT) | −1.70 | 0.00 | 0.999 | 0.46 | 0.60 | 0.438 | −0.37 | 5.72 | **0.017** | 1.84 | 0.94 | 0.334 | 2.64 | 1.07 | 0.302 | −1.64 | 0.01 | 0.910 | 0.35 | 0.32 | 0.573 | −1.58 | 0.07 | 0.798 |
| REM (%SPT) | 0.37 | 8.54 | **0.004** | −0.15 | 0.60 | 0.439 | −0.82 | 7.85 | **0.005** | 0.07 | 2.50 | 0.115 | 1.00 | 6.35 | **0.012** | −2.58 | 1.37 | 0.244 | 0.90 | 8.55 | **0.004** | −0.73 | 0.46 | 0.499 |
| REML (min) | 7.36 | 10.28 | **0.001** | −5.38 | 0.03 | 0.869 | 18.87 | 16.62 | **0.000** | −16.70 | 2.11 | 0.147 | −49.62 | 2.69 | 0.102 | 30.47 | 0.82 | 0.365 | −12.41 | 4.59 | **0.033** | 8.09 | 0.02 | 0.885 |
| REMD (%) | −2.33 | 3.86 | 0.050 | −0.19 | 1.34 | 0.248 | −0.55 | 0.15 | 0.696 | 2.65 | 0.43 | 0.510 | 2.43 | 0.71 | 0.400 | 2.74 | 1.04 | 0.309 | 1.39 | 4.16 | **0.042** | −3.00 | 0.73 | 0.394 |
| AI/REM | 4.25 | 1.23 | 0.268 | −1.85 | 0.00 | 0.975 | −0.06 | 0.03 | 0.858 | −0.30 | 0.36 | 0.551 | −7.13 | 0.11 | 0.738 | 4.27 | 0.00 | 0.979 | −2.65 | 0.37 | 0.541 | 3.48 | 0.54 | 0.465 |
| AI/N | −1.10 | 20.80 | **0.000** | 0.46 | 2.37 | 0.125 | 0.19 | 14.21 | **0.000** | −1.41 | 1.46 | 0.228 | −3.28 | 1.21 | 0.272 | 3.04 | 0.11 | 0.737 | −0.74 | 5.22 | **0.023** | 0.84 | 0.00 | 0.997 |
| AWI/REM | 2.20 | 3.94 | **0.048** | −1.65 | 0.71 | 0.400 | 1.53 | 2.82 | 0.094 | −0.80 | 0.21 | 0.648 | −1.89 | 0.20 | 0.657 | 2.05 | 0.00 | 0.994 | −1.55 | 1.34 | 0.248 | 1.15 | 0.17 | 0.682 |
| AWI/N | −0.36 | 3.69 | 0.056 | 0.07 | 0.21 | 0.651 | 0.43 | 17.06 | **0.000** | −0.58 | 1.50 | 0.221 | −0.53 | 4.06 | **0.045** | 0.86 | 0.07 | 0.790 | −1.30 | 0.76 | 0.385 | 1.01 | 3.03 | 0.083 |

*p values below p = 0.05 are set in bold font.*

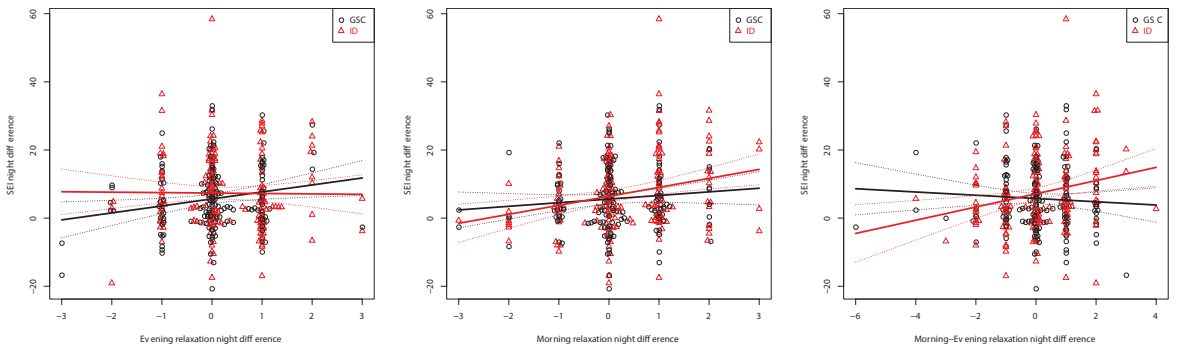


**FIGURE 3 |** Within-subject relationships to the SEI captured as differences between nights: Evening **(Left)**, Morning **(Middle)**, and Morning-Evening **(Right)** relaxation.

the emotional state more broadly, another procedure should be chosen in future studies. Buysse et al. (2007) presented a possible procedure that additionally avoids ground effects. Furthermore the evening data as used here was assessed in the following morning and could therefore be influenced by the morning emotional state. To avoid such bias future studies should assess the emotional state in the actual evening. Possibly, more questionnaires for sample description would have been useful.

Just like in every other sleep laboratory study the ecological validity of the results can be questioned. The time needed for adjustment to the changed sleep environment is not known exactly, although an adaption phase of one night is usually assumed (Le Bon et al., 2001). Since good signal quality and monitoring options are still lacking for the home environment, sleep laboratory data in general may lack ecological validity. This is, however, partially true also for sleep studies conducted at home, because the presence of the recording equipment is a factor in the "First Night Effect" as well (Blackwell et al., 2017). In the current study we analyzed both between- and within-subject influences between PSG and emotional parameters. The "First Night Effect" generates welcome within-subject variability in this respect (it can be interpreted as a "stress probe" for sleep). Part of our within-subject results could be due to this special situation with an unusually disturbed first night.

Finally, most of our data has been collected during clinical routine. Therefore characteristics like personality traits or chronotype have not been assessed systematically for all subjects although these characteristics could be related to potential subgroup-differences and should therefore be assessed in future studies.

## ETHICS STATEMENT

The current study is a retrospective analysis of studies carried out in accordance with the recommendations of the ethics committee of the University of Freiburg Medical Center with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of the University of Freiburg Medical Center.

## AUTHOR CONTRIBUTIONS

BF and DR devised the study. BF devised the data analysis, interpreted the data and wrote the manuscript. BB and DM analyzed and interpreted the data. All authors contributed to the manuscript.

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# Psychosocial Stress Before a Nap Increases Sleep Latency and Decreases Early Slow-Wave Activity

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Sleep disturbances are an important risk factor for stress-related diseases such as burnout or depression. In particular, slow-wave activity (SWA) during sleep might be eminently relevant for optimal maintenance of mental health and cognitive functioning. In spite of the clinical importance and the pertinence of stress-related processes in everyday life, the physiological mechanisms of the association between stress, sleep, and cognition are not well-understood. In the present study, we carefully mapped the time course of the influence of a psychosocial stressor on sleep architecture and sleep-related oscillations during a midday nap. We induced stress using a psychosocial laboratory stressor, the Montreal Imaging Stress Task, vs. a neutral control task. Afterward, participants were allowed to take a 90-min nap ($n$ = 20) or stayed awake ($n$ = 19) and cortisol was measured via saliva samples. We hypothesized that stress would decrease sleep efficiency and SWA in a time-dependent manner, with impairing effects on cognitive functioning. Psychosocial stress resulted in increased cortisol levels, which were elevated throughout the study interval. In the nap group, psychosocial stress increased sleep latency, but had only minor effects on sleep architecture. Still, SWA in the first 30 min of sleep was significantly reduced, whereas alpha activity was enhanced. These effects vanished after approximately 30 min. No impairing effect on cognitive functioning occurred. Our results show that psychosocial stress before sleep has an impact on sleep latency and early SWA during sleep. In contrast to our hypothesis, the effects were rather small and short-lasting. Importantly, cognitive functioning was maintained. We conclude that the effects of psychosocial stress before a nap are possibly better compensated than previously believed.

**Keywords: sleep, stress, cortisol, cognition, emotion**

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## INTRODUCTION

Sleep is critical for our mental health and well-being, and sleep disturbances are an important risk factor for stress-related syndromes such as burnout or depression (Hall et al., 2000; Söderström et al., 2004, 2012; Ekstedt et al., 2006, 2009; Sonnenschein et al., 2007; Armon et al., 2008; Willert et al., 2010).

In particular, slow-wave sleep (SWS) is important to maintain physical and mental health, and its characteristic slow-wave activity (SWA) has been shown to be functionally related to optimal recovery and brain plasticity (Finelli et al., 2001; Anderson and Horne, 2003; Tononi and Cirelli, 2006). In addition, SWS and SWA are critical for processes of sleep-associated memory consolidation and vigilance (Van Der Werf et al., 2009, 2011; Diekelmann and Born, 2010; Ackermann and Rasch, 2014).

Psychosocial stress has been reported to play a major role for the development and maintenance of sleep disturbances (Åkerstedt, 2006; Kim and Dimsdale, 2007). In previous studies, psychosocial stress and perseverative cognition [e.g., rumination (thoughts of past stressful events) and/or worry (feared events in the future)], that go along with psychosocial stress (Brosschot, 2010), have been associated with prolonged sleep onset latency, worse sleep efficiency, shorter as well as more fragmented sleep, more stage 1 sleep, less REM sleep, less SWS and prolonged SWS latency (Kecklund and Åkerstedt, 2004; Åkerstedt et al., 2007, 2014; Vandekerckhove et al., 2011; Wuyts et al., 2012). Moreover, in a sample of subjects with primary insomnia, higher stress levels were associated with decreased SWA during non-REM sleep (Hall et al., 2000).

As a physiological consequence stress alters hypothalamic–pituitary–adrenal (HPA) axis activity, and acute stress and stress induction lead to increased activation of the HPA axis, resulting in an increase in cortisol levels (Dickerson and Kemeny, 2004). Thus, effects of stress on sleep might be largely due to prolonged increases in cortisol due to the stressful experience. Interestingly, the reported effects of cortisol on sleep architecture are not completely consistent. On the one hand, four studies in humans focusing on acute stress and the association of HPA axis reactivity and sleep reported associations between subjective sleep measures and the cortisol response to a physiological (Goodin et al., 2012) or a psychosocial stressor (Räikkönen et al., 2010; Pesonen et al., 2012; Bassett et al., 2015). On the other hand, effects of cortisol administration on sleep show inconsistent results (Friess et al., 1995). In a study focusing on the effects of glucocorticoids on memory consolidation across sleep, mere direct infusion of a low dose of cortisol during early SWS-rich sleep did not change sleep architecture (Plihal and Born, 1999). Also administration of fludrocortisone before sleep or infusion of hydrocortisone during night sleep did not alter sleep architecture, except for a reduction of REM sleep after the infusion of hydrocortisone (Groch et al., 2013). It is thus questionable if cortisol release after stress induction can explain the effects of stress on sleep. Interestingly, sleep-associated memory consolidation was impaired in both above-mentioned studies, possibly due to a more fine-grained cortisol-related alteration on brain oscillations during sleep.

In the present study we focus on the effects of a psychosocial laboratory stressor on cortisol response and sleep measured with polysomnography. We were interested on the exact time course of the effect of acute stress on sleep architecture and sleep-related brain oscillations, in particular SWA. In addition, cortisol responses and cognitive functioning were measured. We hypothesize that a higher stress-level, going along with an increase in cortisol levels, is associated with worse sleep efficiency and lower SWA, leading to an impaired performance in cognitive tests.

# MATERIALS AND METHODS

## Participants

Forty subjects took part in all sessions of the experiments. One subject in the wake group was excluded due to missing saliva samples. The remaining 39 participants were aged between 18 and 33 years (mean age 23.69 $\pm$ 3.76 years [standard deviation]). 20 subjects were in the nap group (10 women, 10 men) and 19 subjects were in the wake group (13 women, 6 men).

Participants were students or employees from the Zurich area and received 200 CHF for their participation. They did not take any medication (except hormonal contraceptives) and reported no neurological or mental illness. None of the participants had shift work or intercontinental flights within 6 weeks prior to participation in the study, had irregular night-day rhythms nor was habitually taking naps. Participants were asked to refrain from caffeine and alcohol on the days the experimental session took place. This study was carried out in accordance with the recommendations of the guidelines of the ethics committee of the University of Zurich with written informed consent from all subjects prior to participation. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of the University of Zurich.

## Procedure

All subjects spent an adaption nap in the sleep laboratory 1 week before the first experimental session (sleep data see **Table 1**) and kept sleep diaries between each experimental session. Each subject took part in two experimental sessions (stress vs. control session) separated by 1 week, according to a balanced cross-over design (**Figure 1**). Each session started with application of electrodes, during which participants filled in questionnaires (see Materials and Methods). Afterward, participants performed one of two versions of the picture memory task, and short-delay free recall of the picture memory task was tested after 10 min (see Materials and Methods for an explanation of the tasks). During these 10 min, participants performed a working memory task (n-Back). Then either the laboratory stressor or the control condition was applied. 18 subjects started with the stress condition, 21 subjects started with the control condition. This task was followed by either a 90 min nap period (nap group) or a period of wakefulness (wake group). The wake group watched a documentary during the 90 min interval. Afterward, participants freely recalled the pictures again. Psychomotor vigilance was tested, and the session ended with filling in further questionnaires. Testing started always between 11:30 and 13:00 and ended between 17:00 and 19:00. Naps started between 14:10 and 16:05 and ended between 15:40 and 17:35.

## Psychosocial Stress Test

For stress induction we used the Montreal Imaging Stress Task (MIST) (Dedovic et al., 2005; Marca et al., 2011) as this task could be applied in the sleep laboratory while participants sat in front of a computer monitor. The MIST is a standardized computerized stress task combining challenging arithmetic problems and social-evaluative threat in the stress condition (MIST-S). The control condition (MIST-C) contains neither time pressure nor social evaluation.

Before the MIST-S started, the experimenter introduced an investigator impersonating a fictitious study leader who came by to check if everything was going well with the study. Then the experimenter explained the task to the subject and told her/him that data could only be used if she/he was performing well and fast. The difficulty of the task adapted to the performance of the subjects, in order to create a 45 to 50% performance range. A mock performance indicator showed the subjects that their task performance was poor compared to a control sample. One round had a duration of 4 min.

After the first round the experimenter entered the room and told the subject, that her/his performance was bad and asked the subject what the reason for the bad performance was (e.g., was there a problem?). The experimenter also told the study leader that it was an exception that the task did not go well and put pressure on the subject by telling her/him that it is very important that is concentrating on the task. After the second round, the experimenter called the study leader, who entered the room and put additional pressure on the participants (e.g., What is the problem?/Your performance was quite bad/Did you have math problems in the past?/It is important that you are doing well, the study costs a lot of energy and money for us). During the third round the study leader stayed in the room and repeatedly asked the subjects if she/he was stressed, looked for reasons why the subject was performing so bad and commented on what would have been the correct solution of the math problem. After the third round the study leader commented that the subjects performed bad again and left the room and told the experimenter to go on with the experiment.

In the control condition (MIST-C) the participants also had to solve math problems but they received neutral feedback after each round and were told, that their performance will not be analyzed. They were neither under time pressure nor did they receive any social evaluation nor was the study leader present.

Participants took part in the stress and the control condition in random order. If the participants performed on the stress condition in the first experimental session, they got following debriefing after the experimental session: "the next experimental session will be similar but with one big difference: there will be no more stress tasks and you will take part in the control condition. Thus, we are able to compare effects of stress vs. no stress on sleep. Do you have any questions?" After the second experimental session all subjects received a detailed debriefing about the MIST.

## Cortisol and Salivary Alpha-Amylase

Cortisol was measured via saliva samples using Salivette collection tubes (Sarstedt, Sevelen, Switzerland). In the nap group as well as in the wake group saliva samples (**Figure 1A**) were taken before the start of the MIST (sample 1, used as baseline sample), directly after the MIST (sample 2), 10 min after the MIST (sample 3), 100 min after the MIST (directly after 90 min of nap/wake; sample 8) and 140 min after the MIST (sample 9). In the wake group, we took four additional samples during the time the nap group took the nap: 15 min (sample 4), 30 min (sample 5), 45 min (sample 6), and 60 min (sample 7) after the third saliva sample. Cortisol and salivary alpha-amylase (sAA) values were baseline corrected with respect to sample 1 before the analysis (also see paragraph Stress Induction and Cortisol results section). After saliva collection salivettes were stored in the fridge and then frozen at −20°C. Cortisol and sAA levels were analyzed by the laboratory of the division of clinical psychology and psychotherapy of the University of Zurich. For cortisol and sAA analysis, saliva samples were centrifuged at 3000 rpm for 10 min after thawing. Concentrations of salivary free cortisol were measured using a commercially available enzyme immunoassay (IBL, Hamburg, Germany) with intra- and inter-assay precision of 3.2 and 4.2%, respectively.

Concentrations of sAA were measured using a commercially available assay (Alpha-Amylase EPS Sys. Roche Diagnostics).

## Sleep Data

### Polysomnographic Recordings

The electroencephalogram (EEG), the electromyogram (EMG), and the electrocardiogram (ECG) were recorded in the wake as well as the nap group throughout the whole experimental session. We only analyzed data of the nap group during the nap. EEG was recorded using a high-density 128-channel Geodesic Sensor Net (Electrical Geodesics, Eugene, OR, United States) with a sampling rate of 500 Hz. The maximum for the electrical impedance was set at 50 kOhm. Electrodes were physically referenced to Cz and re-referenced to both mastoids during preprocessing. Data was preprocessed with Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany).

### Sleep Scoring

In the nap group EEG data was visually scored between the markers lights-off and lights-on by two independent raters using standardized criteria following the manual published by the American Academy of Sleep Medicine (AASM) (Iber et al., 2007). Accordance rate between the raters was 92.69 ± 4.96% (mean ± SD) for the whole nap and 94.78 ± 3.05% for N2 epochs. Both did not differ between stress vs. control condition (both $p > 0.20$). For sleep stage analysis, data was referenced to the mastoids and filtered according to the recommendations in the AASM manual. For the total time in bed, every 30-s epoch was scored as NREM sleep stages 1, 2, 3, or REM sleep. Sleep onset was defined by the first period in stage 1 sleep which was followed by stage 2 sleep. SWS latency and REM sleep latency were determined with reference to sleep onset.

For a more fine-grained analysis we additionally segmented the nap into 15 min episodes starting from lights-off. This allowed investigating the time course of possible stress effects on sleep simultaneously to cortisol probes in the wake group.

### Fast Fourier Transformation

To investigate power differences across the whole nap period as well as within NREM sleep and the single 15-min segments, we subjected the data to spectral analysis using a fast Fourier transformation (FFT). Data was preprocessed by filtering between 0.1 and 35 Hz. The EEG signal was then segmented into equal sized episodes with 4096 data points (ca. 8 s) with 409 points overlap to compensate for later window-related data reductions. Artifact afflicted segments were deleted manually. The FFT was run with a 10% Hanning window and a resolution of 0.2 Hz. Power values for total power (0.5–50 Hz), SWA (0.5–4.5 Hz), theta (4.5–8 Hz), alpha (8–11 Hz), slow spindle (11–13 Hz), and fast spindle (13–15 Hz) were exported. This was done for the whole sleep episode, for only NREM sleep and for 15 min segments of the nap. Data was imported to SPSS. Based on topography (frontal, central, parietal), we created three regions by averaging electrode assemblies (see **Figure 2** for more details). Topography "FCP" (frontal, central, parietal) was taken as within-subjects factor into the ANOVA.

## Heart Rate

Electrocardiogram was analyzed using Kubios HRV Version 3.1 (Tarvainen et al., 2014). Here, we used the automatic artifact correction on unfiltered data, eliminating ectopic beats and artifacts based on dRR series. We then segmented the data into 15 min episodes starting from lights off and corresponding to the sleep sections (see next paragraph). Within these segments, movement-related artifacts were eliminated in 5 min segments. Heart rate (HR) was then analyzed for each segment.

## Cognitive Tasks

### Picture Memory Task

The picture memory task consisted of 90 pictures taken from the International Affective Picture System (IAPS) (Lang et al., 2008) as well as from the emo-pics set (Wessa et al., 2010) as well as from in-house standardized picture sets (some of the neutral pictures). Stimuli consisted of two sets (picture set 1 and picture set 2) of 30 positive, 30 negative, and 30 neutral pictures. In addition, four pictures showing neutral objects were presented to control for primacy and recency effects (two pictures were shown in the beginning of the presentation, the other two at the end). These pictures were not included in the analysis. Picture set 1 was presented in experimental session 1, picture set 2 was presented in experimental session 2. The two sets were counterbalanced for ratings of arousal [mean set 1: 4.66 $\pm$ 1.34 (SD), mean set 2 4.73 $\pm$ 1.31 (SD)] and valence [mean set 1: 4.87 $\pm$ 3.00 (SD), mean set 2 4.95 $\pm$ 2.15 (SD)] as well as for visual complexity and presence of humans.

The pictures were presented in a quasirandomized order so that a maximum of four pictures of the same category followed consecutively. A fixation-cross appeared for 500 ms before each picture. Then the picture was presented for 2.5 s. After presentation of each picture, subjects rated the presented picture according to its emotional valence [from 1 (very negative) to 5 (very positive)] and arousal [from 1 (low) to 5 (high)] to ensure deeper encoding of the pictures. Trials were separated by variable intertrial periods (9–12 s). Participants were told to memorize the pictures (intentional encoding).

For the free recall task, participants had to write down a short description of each picture. The participants were instructed to recall as many pictures as possible. The participants were given 20 to 25 min for this task. Participants were not told how many pictures they saw during picture presentation; therefore, no expectation of the number of pictures to be recalled was mentioned. Two independent and blind raters analyzed the recalled pictures and decided for each picture whether it could be recognized as one of the presented pictures. Afterward, a third independent and blind rater decided on pictures with diverging ratings.

Participants recalled the pictures 10 min after encoding (short-delay free recall) as well as approximately 120 min after encoding (long-delay free recall; after the nap or wake period). Memory retention over the nap or wake period was calculated as relative retrieval performance of picture set 1 with learning performance before the retention interval (short delay recall picture) set to 100% (long delay free recall/short delay free recall * 100%).

### Working Memory Task

Between picture presentation and recall, participants performed the 0- and 2-back versions of the n-Back working memory task (Gevins and Cutillo, 1993). Results of this task are not reported.

### Psychomotor Vigilance Task

To assess vigilance, participants performed a psychomotor vigilance task (Dinges and Powell, 1985). One subject of the nap group had a missing value in this task due to technical problems.

## Questionnaires

For subjective sleep measures we used a subjective sleep quality questionnaire, the Schlaffragebogen A, revised version (SF-A/R) (Görtelmeyer, 2011) referring to the nap instead of the night. To measure circadian rhythm we used the German version of the Morningness-Eveningness Questionnaire (Horne et al., 1976). To check for depressive symptoms we used the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974). To assess anxiety, we used the German Version of the State and Trait Anxiety Inventory (STAI) (Laux et al., 1981).

To assess the chronic daily stress levels we used the Trier Inventory for the Assessment of Chronic Stress (TICS) (Schulz and Schlotz, 1999).

To assess the influence of the stress or control task on positive and negative affect, subject filled in the German version of the Positive and Negative Affect Schedule (PANAS) (Breyer and Bluemke, 2016) in the beginning of the experimental session as well as before (missing in one subject of the wake group and in one subject of the nap group) and after the MIST (missing in one subject of the wake group). In addition, after the MIST, subjects rated (on a visual analog scale) how uncomfortable it felt to solve the math problems. This information is missing in three subjects of the wake group.

## Statistical Analysis and Data Reduction

We used SPSS (IBM SPSS Statistics Version 25) for data analysis. Unless indicated differently, values are presented as mean ± standard error of the mean (SEM).

Data was analyzed with mixed model repeated measures analysis of variance (ANOVA) and repeated measures ANOVAs. Significant main effects and interactions were further explored using uncorrected paired sample *t*-tests. To correct for multiple comparisons, we used the Fisher–Hayter procedure. Associations were explored with Pearson correlations and corrected for multiple testing according to the Bonferroni method. Chi-square tests were used to compare frequencies of traits between groups. $p < 0.05$ was considered significant.

# RESULTS

## Questionnaires

### Sleep Diaries Before Experimental Sessions and Circadian Rhythm

Subjective total sleep time did not differ between conditions, neither on the night before the experiment (7:28 vs. 7:10 h, for stress vs. control) nor during the entire week before the experiment (7:33 vs. 7:39 h, for stress vs. control, both $p > 0.40$). Similarly, subjective sleep quality did not differ between stress and control conditions, neither the night before the experiment (2.22 ± 1.20 vs. 2.44 ± 1.33) nor across the week before the experiment (2.50 ± 0.78 vs. 2.45 ± 1.01, both $p > 0.60$).

Morning and evening types, as measured with the D-MEQ, were equally distributed between the nap and the wake group ($p = 0.996$).

### Mood and Anxiety

The wake and the nap group did neither differ in respect to the BDI ($p = 0.862$) nor the STAI state (measured before the adaption and the two experimental sessions, all $p \geq 0.30$) nor the STAI trait ($p = 0.522$).

**TABLE 1 |** Sleep parameters in the adaptation nap.

| Sleep parameters | Baseline |
|---|---|
| Sleep length (min) | 77.98 ± 2.18 |
| Sleep efficiency | 76.88 ± 3.82 |
| %Wake | 12.34 ± 3.06 |
| %S1 | 11.20 ± 1.91 |
| %S2 | 41.10 ± 2.88 |
| %SWS | 29.58 ± 4.94 |
| %REM | 5.77 ± 1.78 |
| Sleep latency (min) | 11.55 ± 1.98 |
| Wake (min) | 9.00 ± 2.18 |
| S1 (min) | 8.63 ± 1.54 |
| S2 (min) | 32.05 ± 2.33 |
| SWS (min) | 23.53 ± 4.06 |
| REM (min) | 4.78 ± 1.49 |

### Subjective Stress Perception and Affect

Subjective stress levels increased after stress induction (question about MIST: "How uncomfortable did it feel to solve the math problems?"). Subjects in the nap as well as the wake group rated the stress condition as significantly more uncomfortable than the control condition [$F(1,34) = 98.09$, $p < 0.001$]. The interaction group * condition as well as the main effect group did not reach significance (both $p > 0.30$).

In respect to positive and negative affect, as measured with the PANAS, subjects in the nap group as well as in the wake group did not differ in their scores before stress induction or the control condition (all $p \geq 0.217$). After stress induction subjects scored higher on the negative affect scale in the stress condition than the control condition in the nap as well as the wake group (both $p \leq 0.003$). In the wake group, in addition subjects scored lower on the positive affect scale after stress induction than after the control condition [$t(17) = 2.40$, $p = 0.028$]. The nap and the wake group did not differ in any of the measures (all $p \geq 0.10$).

We also checked for differences in the chronic stress levels using the TICS. The subjects in the wake and the nap group didn't differ in any of the subscales (all $p \geq 0.09$).

### Stress Induction and Cortisol

Because in the control condition, the nap and the wake group differed in cortisol levels before stress induction [sample 1; control condition: $F(1,38) = 5.15$, $p = 0.029$, stress condition: $F(1,38) = 2.96$, $p = 0.093$], we used sample 1 as baseline and used baseline-corrected cortisol values for all subsequent analyses. We show the time course of cortisol (baseline corrected samples 2 to 9) in **Figure 1B**.

We first conducted an analysis for the wake group including all eight time points of cortisol measurements (first measurement was used for baseline-correction, see **Figure 1A** for time points of cortisol measurements) including the factors condition and time. The interaction between stress and time reached significance [$F(7,126) = 2.13$, $p = 0.045$, $\eta_p^2 = 0.106$]. In addition, we found significant main effects of stress [$F(1,18) = 8.76$, $p = 0.008$, $\eta_p^2 = 0.327$] and time [$F(1,126) = 9.15$, $p < 0.001$, $\eta_p^2 = 0.337$]. Following up on the significant interaction, exploratory uncorrected *t*-tests showed a significant increase in baseline-corrected cortisol levels 10 min after the stress test as compared to the control condition [baseline-corrected sample 3, $t(18) = 2.38$, $p = 0.028$, see **Figure 1B**]. Cortisol responses remained elevated almost throughout the entire experimental period [baseline-corrected sample 4: $t(18) = 2.74$, $p = 0.013$, sample 5: $t(18) = 3.13$, $p = 0.006$, sample 6: $t(18) = 3.14$, $p = 0.006$, sample 7: $t(18) = 2.80$, $p = 0.012$], and were still marginally elevated in baseline-corrected sample 8 [$t(18) = 1.97$, $p = 0.064$] and became non-significant only 140 min after stress induction [baseline-corrected sample 9: $t(18) = 0.699$, $p = 0.493$], indicating a relatively long-lasting effect of stress induction on cortisol levels. Findings for baseline-corrected samples 4 to 7 also survived the control for multiple comparisons using the Fisher–Hayter Procedure ($q_{(0.05,15,120)} = 4.898$, $Diff_{crit.} = 2.72$).

We then conducted the same analysis for the nap group. As no cortisol was collected during sleep, four time points

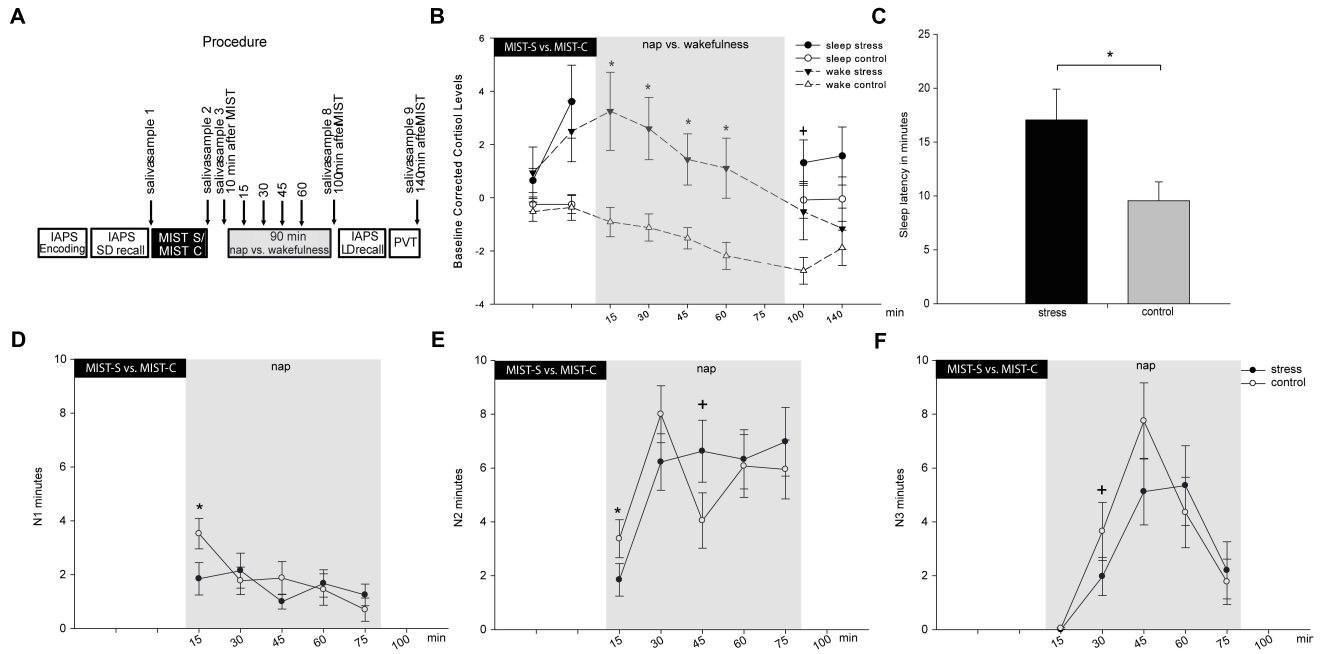


**FIGURE 1 |** Displays the procedure of the experimental sessions and the main results on cortisol and sleep. **(A)** Procedure of the experiment. IAPS, picture memory task; SD, short delay; LD, long delay; PVT, psychomotor vigilance task. In **(B)** Baseline (sample 1) corrected cortisol values for wake and nap groups are reported for both conditions (stress in black versus control in white) separately. **(C)** Shows the overall effect of stress condition on sleep latency. **(D)** Shows effects in N1, **(E)** shows effects in N2 and **(F)** shows effects in N3 across the nap in 15 min segments. Asterisks indicate significant differences with $p \leq 0.05$, trends are marked with +. The error bars represent standard errors of the marginal estimated means.

were analyzed (samples 2 and 3 before the nap, samples 8 and 9 after the nap, see **Figure 1A**). We found a trend for an interaction between condition and time [$F(3,57) = 2.33$, $p = 0.084$, $\eta_p^2 = 0.109$]. In addition, the main effect condition reached significance [$F(1,18 = 5.06$, $p = 0.037$, $\eta_p^2 = 0.210$]. Following up on the interaction showed a significant difference between the stress and control condition for the increase in cortisol levels 10 min after stress induction [baseline-corrected sample 3, $t(19) = 3.01$, $p = 0.007$ exploratory uncorrected $t$-tests]. This finding also survived the control for multiple comparisons using the Fisher–Hayter Procedure ($q_{(0.05,7,48)} = 4.351$, Diff $_{crit.} = 2.65$).

Descriptively, cortisol levels were still higher after the nap in the stress as compared to the control condition, although no significant differences occurred [baseline-corrected sample 8: $t(19) = 1.36$, $p = 0.189$; baseline-corrected sample 9: $t(19) = 1.08$, $p = 0.293$, exploratory uncorrected $t$-tests].

In a third step, we conducted an overall analysis across both groups (nap and sleep) and the within factors "condition" (stress vs. control) and "time" (baseline-corrected samples 2, 3, 8, and 9). Neither the three way interaction between condition, time and group nor the two way interaction condition and time reached significance [$F(3,111) = 0.69$, $p = 0.559$ and $F(1,37) = 0.01$, $p = 0.932$, respectively].

However, the interaction between time and group was significant [$F(3,111) = 3.06$, $p = 0.031$, $\eta_p^2 = 0.076$]. Following up on this interaction, cortisol levels were higher in sleep group as compared to the wake group after the 90 min period [baseline-corrected sample 8: $t(38) = 2.21$, $p = 0.034$, sample 9: $t(38) = 2.45$ $p = 0.019$, exploratory uncorrected $t$-tests]. These findings also survived the control for multiple comparisons using the Fisher–Hayter Procedure ($q_{(0.05,7,80)} = 4.277$, Diff $_{crit.} = 1.986$). The nap and the wake group did not differ in respect to cortisol before the nap or wake period respectively (both $p \geq 0.708$).

Also, the interaction between condition and time [$F(3,111) = 3.06$, $p = 0.031$, $\eta_p^2 = 0.076$] reached significance. Following up on this interaction, cortisol levels in the stress condition were higher than in the control condition after the MIST [baseline-corrected sample 2: $t(38) = 2.10$ $p = 0.042$, sample 3: $t(38) = 3.867$, $p = 0.000$] as well as directly after the 90-min period [baseline-corrected sample 8: $t(38) = 2.395$, $p = 0.022$, sample 9: $t(38) = 1.301$, $p = 0.201$, exploratory uncorrected $t$-tests]. These findings also survived the control for multiple comparisons using the Fisher–Hayter Procedure ($q_{(0.05,7,80)} = 4.277$, Diff $_{crit.} = 1.786$). Cortisol in the stress and control condition did not differ 140 min after stress induction ($p = 0.201$).

In addition, the main effect condition [stress vs. control; $F(1,37) = 9.56$, $p = 0.004$, $\eta_p^2 = 0.205$], the main effect time [$F(3,111) = 6.76$, $p < 0.001$, $\eta_p^2 = 0.155$] and the main effect group [nap vs. wake; $F(1,37) = 4.81$, $p = 0.035$, $\eta_p^2 = 0.115$] reached significance.

To get one measure for the course of the cortisol levels over time (i.e., samples 1, 2, 3, 8, and 9) we additionally

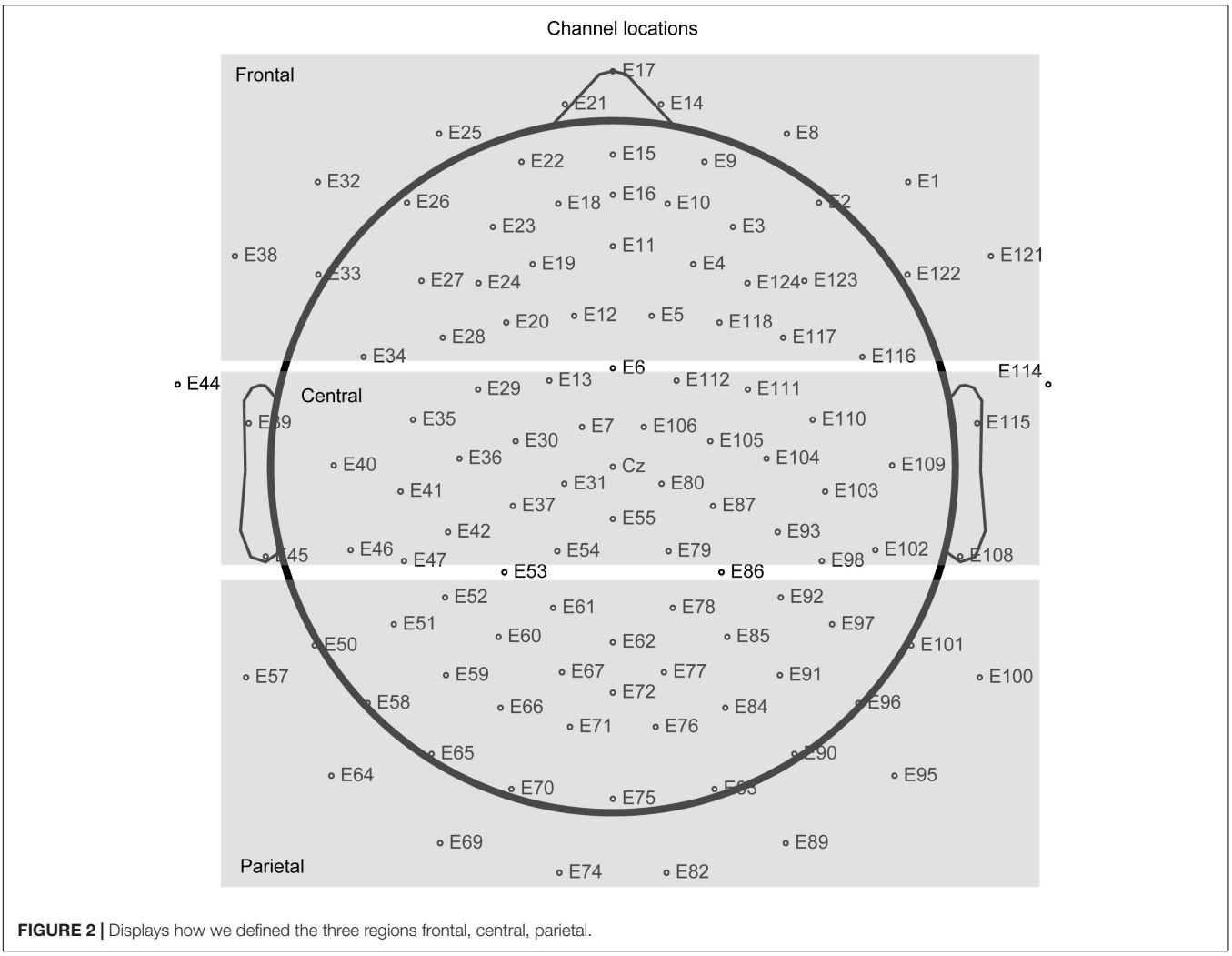


**FIGURE 2 |** Displays how we defined the three regions frontal, central, parietal.

computed the area under the curve with respect to increase (AUCi) using the formula suggested by Pruessner et al. (2003). The interaction between the nap vs. wake group and stress vs. control did not reach significance ($p > 0.90$). As expected, in both groups the AUCi was larger in the stress condition as compared to the control condition [$F(1,37) = 11.00$, $p = 0.002$, $\eta_p^2 = 0.229$]. The main effect group (nap vs. wake) reached a trend level [$F(1,37) = 3.79$, $p = 0.059$, $\eta_p^2 = 0.093$], with a generally larger AUCi in the nap group than the wake group.

**TABLE 2 |** Stress effects on sleep in total nap time.

| Sleep parameters | Stress | Control | *p* |
|---|---|---|---|
| Sleep length (min) | 66.35 ± 4.16 | 72.50 ± 4.45 | 0.320 |
| Sleep efficiency | 71.41 ± 4.44 | 75.48 ± 5.06 | 0.508 |
| Sleep latency (min) | 17.05 ± 2.87 | 9.03 ± 1.50 | 0.005* |
| Wake (min) | 2.63 ± 0.67 | 3.90 ± 1.45 | 0.427 |
| S1 (min) | 10.83 ± 1.87 | 10.48 ± 1.43 | 0.822 |
| S2 (min) | 32.13 ± 3.07 | 35.10 ± 2.80 | 0.531 |
| SWS (min) | 16.28 ± 3.13 | 17.98 ± 3.51 | 0.591 |
| REM (min) | 4.33 ± 1.45 | 4.88 ± 1.37 | 0.772 |

*Displays sleep parameters for the whole duration of the nap for the stress versus the control condition. p-Values indicate the within group-comparison between those two conditions.*

## Stress Induction and Cortisol, Including Sex as Factor

We conducted an additional analysis adding sex as a between-factor to the model, as this factor may influence cortisol levels. The results are comparable to the ANOVA not including sex (see previous paragraph).

The three way interaction between the factors "condition," "time," and "group" did not reach significance [$F(3,105) = 1.08$, $p = 0.361$], neither did the two way interaction between condition and group [$F(1,35) = 0.012$; $p = 0.913$].

In contrast to the analyses not controlling for influences of sex, the two way interaction between condition and time only reached a trend [$F(3,105) = 2.36$, $p = 0.075$, $\eta_p^2 = 0.063$].

As in the previous analysis, the two way interaction between time and group [$F(3,105) = 3.74$, $p = 0.026$, $\eta_p^2 = 0.097$] as

**TABLE 3 |** Sleep stage differences in 15 min segments.

| | Stress | Control | *p* |
|---|---|---|---|
| 0–15 min | Mean ± SEM | Mean ± SEM | |
| Wake minutes | 0.15 ± 0.13 | 0.30 ± 0.22 | 0.57 |
| N1 minutes | 1.85 ± 0.60 | 3.53 ± 0.57 | 0.026* |
| N2 minutes | 1.85 ± 0.60 | 3.38 ± 0.71 | 0.053* |
| N3 minutes | 0.00 ± 0.00 | 0.05 ± 0.03 | 0.163 |
| REM minutes | 0.00 ± 0.00 | 0.00 ± 0.00 | N/A |
| 15–30 min | | | |
| Wake minutes | 0.35 ± 0.33 | 0.73 ± 0.39 | 0.49 |
| N1 minutes | 2.15 ± 0.65 | 1.78 ± 0.51 | 0.61 |
| N2 minutes | 6.23 ± 1.05 | 8.00 ± 1.06 | 0.26 |
| N3 minutes | 1.98 ± 0.71 | 3.65 ± 1.08 | 0.07$^{+}$ |
| REM minutes | 0.00 ± 0.00 | 0.00 ± 0.00 | N/A |
| 30–45 min | | | |
| Wake minutes | 0.63 ± 0.37 | 1.28 ± 0.49 | 0.25 |
| N1 minutes | 1.00 ± 0.27 | 1.88 ± 0.62 | 0.188 |
| N2 minutes | 6.63 ± 1.15 | 4.05 ± 1.03 | 0.074$^{+}$ |
| N3 minutes | 5.13 ± 1.24 | 7.75 ± 1.41 | 0.092 |
| REM minutes | 0.00 ± 0.00 | 0.00 ± 0.00 | N/A |
| 45–60 min | | | |
| Wake minutes | 1.10 ± 0.36 | 2.98 ± 1.09 | 0.101 |
| N1 minutes | 1.68 ± 0.51 | 1.45 ± 0.58 | 0.724 |
| N2 minutes | 6.33 ± 1.10 | 6.08 ± 1.16 | 0.887 |
| N3 minutes | 5.35 ± 1.48 | 4.35 ± 1.31 | 0.512 |
| REM minutes | 0.50 ± 0.35 | 0.35 ± 0.35 | 0.343 |
| 60–75 min | | | |
| Wake minutes | 2.65 ± 1.07 | 3.58 ± 1.35 | 0.559 |
| N1 minutes | 1.25 ± 0.40 | 0.70 ± 0.43 | 0.374 |
| N2 minutes | 6.98 ± 1.28 | 5.95 ± 1.10 | 0.577 |
| N3 minutes | 2.20 ± 1.06 | 1.78 ± 0.84 | 0.696 |
| REM minutes | 1.88 ± 0.83 | 2.95 ± 1.05 | 0.441 |
| 75–90 min | | | |
| Wake minutes | 4.10 ± 1.37 | 3.35 ± 1.30 | 0.70 |
| N1 minutes | 2.95 ± 0.75 | 2.10 ± 0.82 | 0.211 |
| N2 minutes | 3.73 ± 0.77 | 7.25 ± 1.07 | 0.017* |
| N3 minutes | 1.53 ± 0.73 | 0.40 ± 0.23 | 0.160 |
| REM minutes | 2.30 ± 0.93 | 1.50 ± 0.54 | 0.417 |

*Displays sleep parameters in the six 15 min segments (15 min after lights-off, minutes 15–30, 30–45, 45–60, 60–75, and 75–90) for the stress versus the control condition. p-Values indicate the withingroup-comparison between those two conditions. Reported results are explorative uncorrected t-tests. Asterisks indicate significant differences with $p \leq 0.05$, trends are marked with +. $^{+}$Indicates a trend of $p > 0.05 < 0.08$. No comparison remained significant when correcting for multiple comparisons using the Fisher–Hayter correction ($q_{(0.05,11,80)} = 4.686$, $Diff_{crit} = 4.537$).*

well as the main effect condition [$F(1,35) = 8.22$, $p = 0.007$, $\eta_p^2 = 0.190$], the main effect time [$F(3,105) = 6.71$, $p > 0.005$, $\eta_p^2 = 0.161$], and the main effect group [nap vs. wake; $F(1,35) = 6.19$, $p = 0.018$, $\eta_p^2 = 0.150$] reached significance.

In respect to sex, none of the interactions reached significance (trend for an interaction between group and sex: $F(1,35) = 2.97$, $p = 0.094$; all other $p \geq 0.203$). Neither did the main effect of sex reach significance [$F(1,35) = 0.03$, $p = 0.858$].

### Stress Induction and Salivary Alpha-Amylase

As an overall analysis we conducted a mixed model repeated measures ANOVA with the within factors "condition" (stress vs. control) and "time" (baseline-corrected samples 2, 3, 8, and 9) and the between subjects factor "group" (nap vs. wake). The three way interaction between condition, time and group did not reach significance [$F(3,111) = 1.55$, $p = 0.215$].

Neither did any of the two way interactions (all $F \leq 1.50$, all $p \geq 0.22$) nor any of the main effects reach significance (all $F \leq 1.38$, all $p \geq 0.25$).

## Sleep Parameters

When focusing on the total nap time, we found condition-related differences in sleep latency (see **Table 2**). After stress induction, subjects had a significantly longer sleep latency (17.05 ± 2.87 min) as compared to sleep latency after the control condition (9.03 ± 1.50 min), $t(19) = 3.20$, $p = 0.005$, see **Figure 1C**. This result also survived Bonferroni-correction for multiple comparisons (corrected significance threshold $p = 0.006$). However, we did not find any differences in any other sleep parameter (all $p > 0.30$). We also did not find differences in subjective sleep latency between the stress condition and the control condition [$t(18) = 1.18$, $p = 0.255$].

Because we were interested in the time course of the influence of stress induction on sleep parameters, we conducted a more detailed analysis of sleep progression. Therefore, we segmented sleep into 15-min epochs starting after lights-off. We found a trend for an interaction between condition and time in N1 [$F(5,95) = 2.07$, $p = 0.076$], a significant interaction of condition and time in N2 [$F(5,95) = 2.58$, $p = 0.031$, $\eta_p^2 = 0.119$] and a trend for an interaction of condition and time in N3 [$F(5,95) = 2.19$, $p = 0.062$].

The most pronounced stress-related differences in sleep parameters appeared in the first 15 min after lights-off, with lower amounts of N1 and N2 sleep in the stress condition as compared to the control condition (see **Figures 1D,E** and **Table 3**). Those marked differences diminished in minute 15–30 and completely abolished across the following 15-min episodes. In addition, a trend for reduced SWS after stress occurred after 15–30 min and after 30–45 min (see **Figure 1F**). No other effects were significant, except an increase in N2 sleep in the control group in the last 15-min segment of the nap (not displayed in the Figure, but see **Table 3**). However, none of the *post hoc* comparisons remained significant when correcting for multiple comparisons using the Fisher–Hayter correction.

## Frequency Analysis

We calculated repeated measure ANOVAs with the within-subject factors "condition" (stress vs. control) and "FCP" (frontal vs. central vs. parietal topography). Neither for the entire nap period ($p = 0.45$) nor the analyses based on NREM sleep episodes ($p > 0.90$), did total power differ depending on stress condition or control condition. We still corrected for possible general and unspecific power differences between the sessions by reporting

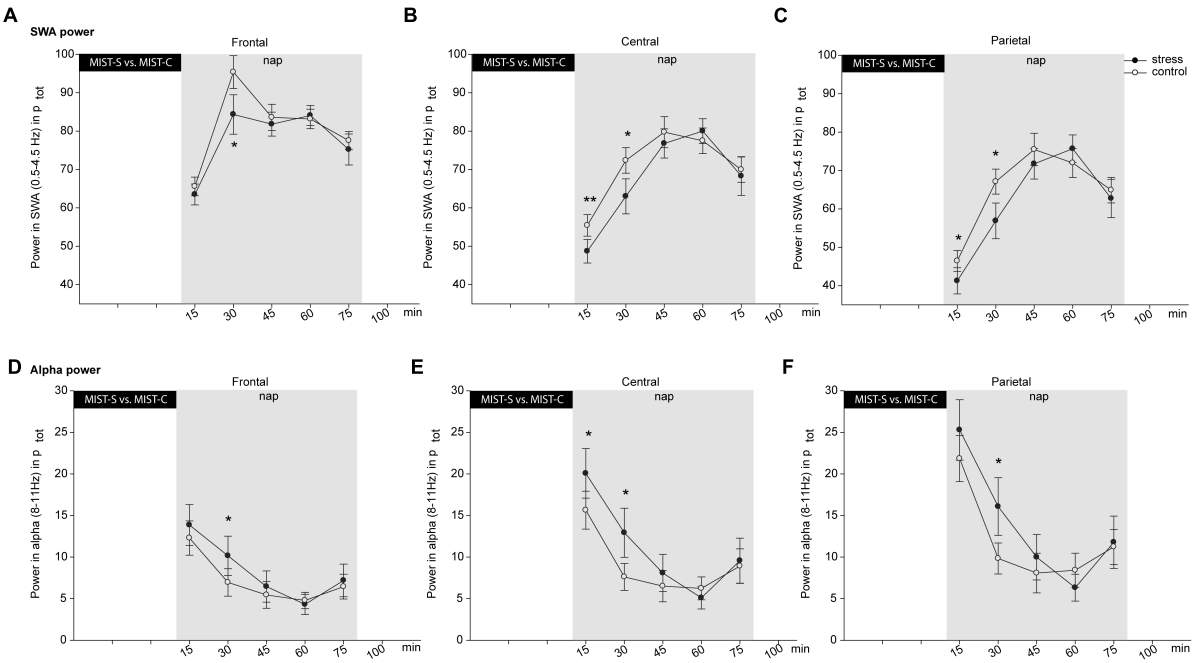


**FIGURE 3 |** Effects of stress (black dots) versus control (white dots) on relative SWA **(A–C)** and alpha power **(D–F)** separately for frontal **(A,D)**, central **(B,E)** and parietal **(C,F)** regions. Asterisks indicate significant stress effects in a within-subjects ANOVA with $p \leq 0.05$. All indicated significant *post hoc* comparisons survived the correction for multiple comparisons using the Fisher–Hayter Procedure. The error bars represent standard errors of the marginal estimated means.

relative values for which we set the amount of total power (0.5–50 Hz) to 100%. The reported values are thus percentage of power in the respective bands relative to total power during the session.

## Frequency Analysis for the Whole Nap Period and NREM Sleep

We analyzed and compared differences in power in frequency bands of SWA (0.5–4.5 Hz), theta (4.5–8 Hz), alpha (8–11 Hz), slow (11–13 Hz), and fast spindles (13–15 Hz). No significant main effects or interactions with stress appeared in any of the frequency bands, neither in the entire nap period (all $p > 0.07$) nor NREM sleep episodes (all $p > 0.15$).

## Frequency Analysis for the Course of Sleep, Measured by 15 min Segments

We analyzed the power differences between conditions in the 15 min nap segments in repeated measure ANOVAs with the within-subject factors "time" (five segments, excluding the last 90 min in which data of one subject was missing), "condition" (stress vs. control) and "FCP" (frontal vs. central vs. parietal topography). We analyzed the relative power in the frequency bands by setting total power (0.5–50 Hz) of each segment to 100%. This took account for potential overall power differences between the two sessions. Thus, reported values are percentage of power relative to total power in that segment.

For power in the SWA frequency band, a significant three-way interaction between all three factors appeared [$F(8,152) = 2.39$, $p = 0.019$, $\eta_p^2 = 0.11$]. Also, the time * condition interaction was significant [$F(4,76) = 2.73$, $p = 0.035$, $\eta_p^2 = 0.13$]. Following up on this interaction showed that SWA power after stress is lower (51.16 ± 2.93%) than after control (55.82 ± 2.57%) in the first 15 min [$t(19) = -2.67$, $p = 0.015$] and the second segment [$t(19) = -2.39$, $p = 0.027$, 68.08 ± 4.66 vs. 78.28 ± 3.48%], but not in later segments (all $p > 0.35$, exploratory uncorrected $t$-tests). Only the difference in the second segment survived the control for multiple comparisons using the Fisher–Hayter Procedure ($q_{(0.05,9,60)} = 4.55$, $\text{Diff}_{\text{crit.}} = 8.89$). For the three-way interaction, differences in the first and second time segment were observed in central and parietal recording sites, in frontal electrodes at the first time point, corrected for multiple comparisons using the Fisher–Hayter Procedure (see **Figures 3A–C**).

For the theta band, the three-way interaction between the three factors was only a statistical trend [$F(8,152) = 1.77$, $p = 0.088$, $\eta_p^2 = 0.09$]. The other effects with condition were $p > 0.20$.

Also, for alpha power we found a significant three-way interaction [$F(8,152) = 3.25$, $p = 0.002$, $\eta_p^2 = 0.15$, $q = 5.5$, $\text{Diff}_{\text{crit.}} = 2.18$] and a significant time by condition interaction [$F(4,76) = 2.51$, $p = 0.049$, $\eta_p^2 = 0.12$]. Follow-up analyses showed that alpha power was higher after stress (19.74 ± 2.91 and 13.05 ± 2.83%) than control (16.59 ± 2.31 and 8.13 ± 1.68%) in the first [$t(19) = 2.23$, $p = 0.038$] and second segment [$t(19) = 2.33$, $p = 0.031$], but not later (all $p > 0.30$, exploratory uncorrected $t$-tests). No difference survived the control for multiple comparisons using the Fisher–Hayter

Procedure ($q_{(0.05,9,60)}$ = 4.55, Diff $_{crit.}$ = 6.67). For the three-way interaction, corrected significant *post hoc* differences were observed in central and parietal sites at the first and second time point, and in frontal sites at the second time point (see **Figures 3D–F**).

For slow spindle power, only the three-way interaction was significant [$F(8,152) = 3.63$, $p = 0.001$, $\eta_p^2 = 0.16$], while all others were $p > 0.10$. Follow-up analyses however revealed no condition-related differences in frontal, central, nor parietal electrodes (all $p > 0.10$).

No effects appeared in fast spindle power (all $p > 0.20$).

## Cortisol and Sleep

We correlated differences of cortisol increases after the stress vs. control condition of the MIST (i.e., baseline-corrected sample 3, stress minus control condition) with differences in sleep measures over the whole duration of the nap in the stress versus the control condition. Cortisol levels were not associated with any sleep measures (all $p_{uncorrected} \geq 0.27$).

As we found time dependent effects in sleep parameters when comparing the stress condition and the control condition, we also conducted the same cortisol and sleep parameter correlations per 15 min of sleep (Bonferroni-corrected for multiple comparisons, corrected significance threshold $p = 0.0016$). We observed one negative correlation that survived correction for multiple testing: higher cortisol increase after stress induction vs. control significantly predicted a stronger reduction in N1 sleep in the stress vs. the control condition between 45 and 60 min ($r = -0.70$, $p_{uncorrected} = 0.001$). No further correlations did survive Bonferroni correction for multiple comparisons. Following correlations were significant on a nominal level: a negative correlation between cortisol increase after stress induction vs. control and N1 sleep in the stress vs. the control condition between 30 and 45 min ($r = -0.486$, $p_{uncorrected} = 0.030$) and a positive correlation cortisol between increase after stress induction vs. control and N1 sleep in the stress vs. the control condition between 60 and 75 min ($r = 0.526$, $p_{uncorrected} = 0.017$).

In addition, we correlated sleep parameters over the whole duration of the nap (stress – control condition) with cortisol levels after the nap (i.e., baseline-corrected samples 8 and 9, stress minus control condition), as sleep may influence cortisol as well. Sleep measures were not associated with the cortisol levels after the nap (all $p_{uncorrected} \geq 0.079$).

Also, here we conducted cortisol and sleep parameter correlations per 15 min of sleep (Bonferroni-corrected for multiple comparisons, corrected significance threshold $p = 0.00083$).

Following correlations were significant on a nominal level: a positive correlation between N1 sleep in the first 15 min and cortisol after the nap (baseline-corrected sample 8) in the stress vs. control condition ($r = 0.479$, $p_{uncorrected} = 0.033$), negative correlations between N1 sleep between 15 and 30 min and cortisol levels after the nap (with baseline-corrected sample 8: $r = -0.465$, $p_{uncorrected} = 0.039$, with baseline-corrected sample 9: $r = -0.528$, $p_{uncorrected} = 0.017$).

## Heart Rate and Sleep

We analyzed heart rate during the nap and also segmented it into the same 15 min segments. Artifacts were rejected in 5-min epochs. In the ANOVA with stress condition by time, the main effect of time [$F(4,72) = 4.23$, $p = 0.004$, $\eta_p^2 = 0.19$], of stress condition [$F(1,18) = 6.94$, $p = 0.017$, $\eta_p^2 = 0.28$] and their interaction were significant [$F(4,72) = 2.99$, $p = 0.024$, $\eta_p^2 = 0.14$]. Follow-up exploratory uncorrected *t*-tests showed that for 15, 30, and 45 min, heart rate was faster in the stress than control condition [59.50 ± 1.90 vs. 55.55 ± 1.66, $t(18) = 3.81$, $p = 0.001$; 57.23 ± 1.72 vs. 54.08 ± 1.52, $t(18) = 3.38$, $p = 0.003$ and 57.15 ± 1.52 vs. 53.88 ± 1.54, $t(18) = 3.43$, $p = 0.003$]. All time points remained significant when correcting for multiple comparisons using the Fisher–Hayter Procedure ($q_{(0.05,9.60)}$ = 4.55, Diff $_{crit.}$ = 2.55). Later time windows did not differ depending on stress condition (all $p \geq 0.25$).

The difference in heart rate between stress vs. control did not correlate with difference in alpha power between stress vs. control (all $p_{uncorrected} > 0.15$). With SWA power difference, only in the episode of 45 min sleep the correlation was significant, indicating that a higher difference in heart rate between the conditions is associated with a lower SWA power difference. Correcting these analyses for multiple comparisons would however nullify it. All other correlations were $p_{uncorrected} > 0.20$.

## Subjective Stress Levels and Sleep

We analyzed whether acute (question about the MIST) and chronic [screening subscale of chronic stress (SSCS) of the TICS] subjective stress levels are associated with the sleep parameters as well as the memory parameters (per valence) in the stress versus the control condition. None of the correlations between the subjective stress parameters and the sleep parameters reached significance (all $p_{uncorrected} \geq 0.154$). In respect to the memory parameters, we found a significant negative correlation between the acute stress level (stress minus control) and recall of negative pictures (stress minus control; $r = -0.523$, $p_{uncorrected} = 0.018$) in the nap group and a significant positive correlation between the acute stress level (stress minus control) and recall of positive pictures (stress minus control; $r = 0.646$, $p_{uncorrected} = 0.007$). However, these associations did not survive correction for multiple testing (Bonferroni corrected significance threshold $p = 0.002$).

## Cognitive Measures

### Picture Memory Performance

We did not find a significant three-way interaction of condition (stress/control), group (nap/wakefulness), and valence (positive, negative, neutral) on memory consolidation ($p = 0.718$). Neither did any of the two-way interactions or main effects reach significance (all $p \geq 0.12$).

In addition, we correlated recall of pictures (stress condition minus control condition) per valence (positive, negative, neutral) with sleep parameters (stress condition minus control condition). We found a nominally significant positive correlation between minutes non-REM sleep and recall of neutral pictures ($r = 0.483$,

$p_{uncorrected} \geq 0.031$). However, this correlation did not survive correction for multiple testing (Bonferroni corrected significance threshold $p = 0.0006$).

### Psychomotor Vigilance Task

There was neither an effect of condition nor group nor the interaction of both factors on average reaction time measured in the PVT (all $p > 0.20$) or on error rate (all $p > 0.20$).

## DISCUSSION

In the present study, we investigated, whether stress induction using a psychosocial stressor is associated with worse sleep quality during a nap and higher cortisol levels and whether these effects are time-dependent. Stress induction lead to a significant increase in cortisol levels which was present almost throughout the entire experiment. In the wake group, we detected stress-induced cortisol elevations throughout the wakefulness period until 100 min after stress-induction. However, in the nap group, changes in sleep-related EEG activity were only detectable until 45 min after stress-induction. These results may indicate that stress effects on sleep oscillations are not as long lasting as stress-induced cortisol elevations as measured in the wake group. One possibility is that the stress-induced differences in SWA and alpha activity vanish in spite of increased cortisol levels during sleep, suggesting that similar sleep depth can be achieved after stress while cortisol levels are still increased. An alternative explanation is that the increases in cortisol after stress induction vanish quicker as compared to wakefulness, so that cortisol and EEG changes during sleep occur in parallel. Future studies measuring cortisol also during the sleep period are needed to answer these questions.

In the present study we observed higher cortisol levels after the nap as compared to a period of wakefulness. This difference was statistically significant in the control group, whereas in the stress condition we saw this effect only on a descriptive level. Increase in cortisol values after a period filled with sleep might be possibly due to a cortisol awakening response (CAR) (Fries et al., 2009; Clow et al., 2010). Previous studies have shown that the CAR is larger after night time sleep as compared to 90 min naps (Devine and Wolf, 2016). These authors also showed associations between sleep stages and CAR after night time sleep (stage 2) as well as after a morning nap (stage 1), while there were no associations with CAR after afternoon naps. Interestingly, no CAR was observed after a nap duration of 60 or 50 min (Federenko et al., 2004; Devine and Wolf, 2016). According to these results, our nap duration might have been rather short to elicit a strong CAR (mean TST of $66.35 \pm 4.16$ min in the stress condition and $72.50 \pm 4.45$ min in the control condition). Furthermore, in the present study we report a negative association between cortisol after stress induction and N1 sleep toward the end of the nap.

Results indicate influences of psychosocial stress on sleep quality in a nap, in particular on sleep onset latency and sleep shortly after sleep onset. We found several time-dependent effects of stress induction on sleep. After the control condition, subjects show more N1 sleep and N2 sleep in the first 15 min of the nap than after the stress condition. In the last 15 min of the nap, subjects again have more N2 sleep after the control condition than after the stress condition. In addition, a trend for reduced SWS after stress occurred after 15–30 and 30–45 min. Sleep frequency analyses show that power in the SWA frequency band is lower and the alpha frequency band is higher after the stress condition than after the control condition in the first and second 15 min of nap. These results show a time-dependency of the effects of an acute psychosocial stressor on subsequent nap. To our knowledge, this is the first study showing time-dependent effects of psychosocial stress-induced cortisol changes on sleep. However, the effects are rather small and short-lasting.

Our results show parallels to previous studies on stress effects on sleep. Several studies focusing on psychosocial stress or pre-sleep arousal and its impact on sleep showed increased sleep onset latency and more stage 1 sleep (Wuyts et al., 2012; Åkerstedt et al., 2014).

Moreover, we found effects on SWA, which has also been associated with stress in a sample of patients with primary insomnia (Hall et al., 2000). SWA is crucial for optimal recovery, brain plasticity (Finelli et al., 2001; Anderson and Horne, 2003; Tononi and Cirelli, 2006) and sleep-associated memory consolidation and vigilance (Van Der Werf et al., 2009, 2011).

In the present study we were also interested, whether stress induction affects cognition in the nap and the wake group differently. However, in contrast to our hypothesis, we did not find any interactions of stress and sleep on a declarative memory task or on vigilance. In our study, effects of a psychosocial stressor on memory recall are not modulated by sleep nor does it impact on memory performance or vigilance. Even though in the present study sleep parameters change to some extend with elevated cortisol levels, this does not affect memory consolidation.

These findings stand in contrast to a previous study, showing that basal pre-learning cortisol levels influence memory consolidation across night sleep but not across the same period of wakefulness (Bennion et al., 2015). However, this study uses a different memory paradigm (scenes including a neutral or negative object) and recognition memory while in the present study we focus on free recall. Moreover, the effects of stress induction, as was done in the present study, may differ from effects of basal cortisol on memory. In an evening nap study, post-learning infusion of cortisol during sleep or wakefulness neither affected memory retention, which was tested after cortisol levels had returned to normal values. Cortisol had effects on the recall of temporal order; it was positively influenced in the wake group and negatively in the nap group (Wilhelm et al., 2011). However, the design as well as the memory task in our study differed from above mentioned studies. In addition, in the present study, cortisol was still elevated at time of recall which may also have influenced memory recall (also see de Quervain et al., 2009; Wolf, 2009 for reviews of cortisol effects on memory). Our results may also point to a different process when focusing on a psychosocial stressor as compared to basal cortisol or pharmacologically elevated cortisol during sleep. To answer these questions, studies using the same design and memory tasks for investigating effects of basal cortisol or cortisol elevation (through stress induction or

pharmacologically induced) on memory consolidation and sleep are needed.

Moreover, the effect of stress on memory consolidation may be driven by cortisol and may be more pronounced in cortisol responders than non-responders (Stock and Merz, 2018), therefore this possibility should be analyzed in a larger sample.

In spite of the clinical importance and the pertinence of stress-related learning processes in everyday life, the behavioral, physiological as well as molecular mechanisms of the association between stress, sleep and memory are not well-known and merit more research.

As both the nap and the wake period took place at the same circadian time (midday – afternoon), we did not expect circadian differences in cortisol levels between the two groups. However, sleep architecture, time of day as well as nap duration may have a specific effect on cortisol levels, in particular on cortisol after waking up (Devine and Wolf, 2016). Future studies need to measure cortisol also during sleep to get more information on the course of cortisol during sleep.

In addition, it is not clear whether we can generalize the effects reported here to nighttime sleep. The effects of a stressor on a nap may differ from effects on night sleep due to circadian rhythmicity of cortisol. During the day, cortisol levels are higher, gradually decreasing throughout the day with lowest levels during the first half of the night (Fries et al., 2009; Clow et al., 2010). Moreover, although sleep architecture in naps generally follows the same pattern as sleep during the night (Maron et al., 1964), time of day may also influence sleep architecture (Karacan et al., 1970).

A further limitation of the study are confounding factors that may determine cortisol changes. All of our female participants used hormonal contraceptives due to practical reasons. In a large study investigating effects of basal cortisol on memory, results did not differ between naturally cycling women and women taking oral contraceptives (Ackermann et al., 2013). However, as compared to naturally cycling women, hormonal contraceptives have been shown to attenuate cortisol effects on memory (Kuhlmann and Wolf, 2005) and blunt the cortisol response to stress induction (Kirschbaum et al., 1999; Nielsen et al., 2013). Therefore, the effects of stress induction and sleep on memory might have been larger in naturally cycling women.

We did not include any women not taking hormonal contraceptives due to the larger variability it would have added to the sample and due to the fact, that the different menstrual phases may influence cortisol levels and response to the stressor (Kirschbaum et al., 1999; Maki et al., 2015).

A laboratory stressor probably has different effects on sleep than an everyday stressor, due to various differences such as duration. However, using a laboratory stressor allows for standardization of stress induction. Looking at everyday stressors, it cannot be concluded whether effects of stress lead to sleep impairments or whether effects of sleep impairments are a cause for increased stress perception. It is most likely a bidirectional relationship (Van Laethem et al., 2015).

In sum, stress induction using a psychosocial stressor only affects sleep stages and power spectra in the first 15 to 30 min of the nap. Cortisol levels normalize later across sleep to the level of the control condition. Therefore, we conclude that effects of a psychosocial stressor on sleep are time-dependent. Moreover, changes in sleep stages and power spectra are paralleled by changes in cortisol levels induced by stress. We conclude that the effects of psychosocial stress before a nap are possibly better compensated than previously believed.

## AUTHOR CONTRIBUTIONS

SA and BR developed the study design. SA and RLM prepared the study and collected the data. SA and MC analyzed the data. All authors wrote the manuscript.

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SYSTEMATIC REVIEW
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# Executive Functions in Insomnia Disorder: A Systematic Review and Exploratory Meta-Analysis

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**Background:** Executive functions (EFs) are involved in the control of basic psychological processes such as attention and memory and also contribute to emotion regulation. Research on the presence of EFs impairments in insomnia yielded inconsistent results. Therefore, we performed a systematic review of the literature on three EFs: inhibitory control, working memory, and cognitive flexibility in adults with insomnia in order to investigate the presence and magnitude of insomnia-related EFs impairments.

**Methods:** PubMed, Scopus, Medline, and PsycINFO were searched. Risk of bias assessment of included studies was performed by two independent researchers. Findings were summarised using both a narrative approach and meta-analysis. Cohen's *d* was calculated at 95% confidence interval (CI) as effect size of between groups differences.

**Results:** Twenty-eight studies comparing adult individuals with a diagnosis of insomnia and healthy controls on neuropsychological measures of EFs were included. Narrative synthesis revealed substantial variability across study findings. Factors that were primarily hypothesised to account for this variability are: objective sleep impairments and test sensitivity. Exploratory meta-analysis showed impaired performance of small to moderate magnitude in individuals with insomnia as compared to controls in reaction times, but not accuracy rates, of inhibitory control ($d = -0.32$, 95% CI: −0.52 to −0.13) and cognitive flexibility tasks ($d = -0.30$, 95% CI: −0.59 to −0.01). Performance in working memory tasks was also significantly impacted ($d = -0.19$, 95% CI: −0.38 to −0.00). Effects sizes were larger when insomnia was associated with objective sleep impairments, rather than normal sleep.

**Conclusions:** We gathered evidence supporting small to moderate deficits in EFs in individuals with insomnia. Due to the small sample size results should be considered preliminary and interpreted carefully.

**Keywords: insomnia, executive functions, inhibition, working memory, flexibility, prefrontal cortex, cognition**

# INTRODUCTION

## Rationale

Insomnia disorder is defined by difficulty falling asleep, maintaining sleep or early morning awakenings (American Psychiatric Association, 2013). Concomitant daytime consequences such as fatigue, reduction in motivation and energy, mood instability, and cognitive impairments are crucial components of insomnia (Shekleton et al., 2010). Symptoms should present at least three times a week over a period of 3 months to meet the diagnostic criteria for insomnia (American Psychiatric Association, 2013). Epidemiological data estimate the prevalence of insomnia disorder from 6 to 20% in industrialised societies, with rates varying depending on country under study and methodological quality (Calem et al., 2012; Chaput et al., 2018).

Deficits in the control of cognitive and emotional processes are key characteristics of insomnia, as highlighted by influential models on the disorder (Perlis et al., 1997; Harvey, 2002; Espie et al., 2006). For instance, according to Harvey (2002), patients with insomnia are unable to exert control over night-time intrusive cognitions and engage in diurnal repetitive and unwanted thoughts, such as ruminations, i.e., passively and repetitively focusing on the consequences of insomnia. Impairments in the domain of concentration, memory, attention, and emotion regulation are also generally reported in this population (Kyle et al., 2013; Harris et al., 2015; Cellini, 2016). Taken together, these findings raise the question of whether executive functions (EFs), the higher order cognitive processes which exert top-down control over basic psychological functions like attention, memory, and contribute to emotion regulation (Diamond, 2013; Yang et al., 2016), are also impacted in insomnia. To answer this question, we aimed to conduct a systematic review and exploratory meta-analysis of the literature examining EFs in insomnia disorder in an adult population. Before introducing our study, we discuss conceptual models of EFs, their clinical correlates and the role of EFs in insomnia.

EFs are considered top-down, higher-order cognitive processes needed to control and coordinate lower-level mental processes such as memory encoding and retrieval, orienting attention, and emotion regulation, which together enable self-regulation and contribute to goal-directed behaviour (Diamond, 2013; Snyder et al., 2015). Neuropsychological and neuroimaging studies in clinical and healthy populations suggest that the prefrontal cortex (PFC) as well as parietal and cerebellar networks subserve EFs (Nowrangi et al., 2014; Yuan and Raz, 2014). However, the definition and conceptualisation of EFs remains inconsistent in the literature. Indeed, there is a lack of agreement regarding whether EFs should be considered unitarily (e.g., Duncan, 2010) or as a number of different and independent cognitive processes (e.g., Miyake et al., 2000). Moreover, conceptualisation and definition of EFs varies substantially depending on the field of study and the population of interest. This is reflected by the prevalent use of the term EFs in neuropsychology (aimed at the assessment of patients) and the term control processes in the cognitive sciences (typically aimed at investigating in healthy populations the cognitive mechanisms underlying the EFs). Given the clinical nature of this review, we use the terms EFs throughout the text.

Different conceptualisations and classifications of EFs have been developed over several decades (see Gratton et al., 2017 for a review). Recently, an influential model hypothesised that the performance on complex EF tasks is underpinned by three core EFs: inhibitory control, working memory, and cognitive flexibility (Miyake et al., 2000; Diamond, 2013). Inhibitory control refers to the ability to reduce the effect of strong internal predispositions, automatic schemata or responses when they are not useful for accomplishing the task goal. Inhibitory control is therefore needed to suppress thoughts, emotions, motor responses and irrelevant stimuli (Aron et al., 2004). Working memory involves the ability to hold and manipulate goal-related information in mind (Repovs and Baddeley, 2006). Finally, cognitive flexibility refers to the ability to readily change perspective, demands or priorities, and to quickly adjust from set-shifting (Miyake et al., 2000). Given its wide use in cognitive and clinical literature, we decided to focus the present systematic review on the tripartite model of EFs, based on inhibitory control, working memory, and cognitive flexibility. This tripartite model of EFs also overlaps with the model of "executive control" adopted in insomnia research by Vgontzas et al. (2013) in their attempt to identify different phenotypes of insomnia from symptom severity and biological correlates, as further described below.

Although individuals with insomnia commonly report subjective difficulties in different cognitive functions involving executive control like attention, memory, and concentration (Kyle et al., 2013; Harris et al., 2015; Cellini, 2016), objective EFs deficits have been difficult to capture through standardised measures in laboratory settings. Additionally, few reviews on EFs in insomnia have been published to date. A review on daytime impairments in insomnia concluded that on tests of attentional shifting and working memory, individuals with insomnia generally perform worse than good sleepers (Shekleton et al., 2010). However, the authors did not include these tests within the EFs domain and instead included planning, reasoning, flexibility, and multitasking in this category. Performance on these EFs were mostly preserved in individuals with insomnia.

Recent evidence suggests relevant clinical correlates of EFs impairments that may be of particular interest for insomnia research. For instance, EFs have been associated with poor cognitive self-regulatory strategies, including rumination. A recent meta-analysis of correlational studies showed that poorer inhibitory control and cognitive flexibility were significantly associated with higher rumination in the general population (Yang et al., 2016). This finding may be particularly relevant for insomnia, as most theoretical models suggest a role of repetitive negative thinking such as rumination and the implementation of thought control strategies in the maintenance of the disorder (e.g., Harvey, 2002). In line with this, we recently found that rumination about symptoms of insomnia was associated with poor EFs in a clinical sample (Ballesio et al., 2018). Additionally, poor EFs have been associated with significant impairment in instrumental activities of daily living (Vaughan and Giovanello,

2010), which may contribute to lower quality of life in insomnia patients (Kyle et al., 2013) and increase indirect costs associated with insomnia (e.g., due to errors in workplace; Gustavsson et al., 2011). These potential clinical correlates of EFs in insomnia are therefore further grounds to systematically review the literature on EFs in this population.

To date, only one meta-analysis has investigated executive performance in insomnia (Fortier-Brochu et al., 2012). This included cross-sectional studies investigating daytime cognitive performance in adults with insomnia and good sleepers and published up to 2009. Findings showed that individuals with insomnia perform significantly worse than controls on tasks measuring manipulation and retention of information in working memory, with effect sizes of medium magnitude ($d = 0.42$). Small and non-significant effects were found with respect to tasks assessing inhibitory control ($d = 0.19$) and cognitive flexibility ($d = 0.16$). However, 6 years have passed since Fortier-Brochu et al.'s (2012) systematic review and meta-analysis on cognitive functions in insomnia, raising the need to appraise and summarise the state of the evidence again.

Among the factors that were previously hypothesised to account for variability between studies' findings, objective sleep received particular attention. In a large population-based study, Fernandez-Mendoza et al. (2010) concluded that only individuals with insomnia with objective short sleep duration, measured through polysomnographic records, showed impairments in executive control tasks. A subsequent theoretical review suggested that impairments in higher order cognitive processes in insomnia may be present only when the disorder is associated with shortened sleep duration (Vgontzas et al., 2013). This hypothesis may partly explain the inconsistency found in previous research on EFs. Nevertheless, it has never been tested in a systematic search of the literature. Other factors have been hypothesised to account for variability in previous results. For instance, it has been suggested that individuals with insomnia may engage increased cognitive effort in high cognitive load tasks to compensate for their deficits (Schmidt et al., 2014). Moreover, "time of the day" has been considered a confounding factor, since it is possible that individuals with insomnia and good sleeper controls have different underlying circadian rhythms, and by extension differentially affecting patterns of cognitive performance (see Shekleton et al., 2010 for a review).

## Objective

To conduct a systematic review of the literature on inhibitory control, working memory, and cognitive flexibility in individuals with insomnia.

## Research Questions

1) Are inhibitory controls, working memory, and cognitive flexibility impacted in individuals with a diagnosis of insomnia disorder?
2) Is there a relationship between objective sleep and EFs deficits in insomnia disorder?

# METHODS

## Study Design

This study was conducted according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (Moher et al., 2009) (see the PRISMA Checklist reported in **Document S1**).

## Participants, Interventions, Comparators

The following inclusion criteria were applied to identified records: (1) presence of a group of adult individuals with clinical insomnia, (2) presence of a control group, (3) presence of at least one neuropsychological test assessing inhibitory control and/or working memory and/or cognitive flexibility. Given that EFs may be affected by psychoactive substances (Killgore et al., 2009, 2014), studies which allowed participants to take psychoactive medication, as well as caffeine and/or alcohol were excluded. Moreover, given that comorbid disorders may similarly affect EFs (Snyder et al., 2015), studies conducted on insomnia-comorbid samples were excluded. Studies dealing with sleep-related attentional bias were not included, as they have been recently systematically reviewed elsewhere (Harris et al., 2015). Additionally, only studies providing data to compute effect sizes were included in the meta-analytic calculations.

## Search Strategy

The literature search was performed by the first author using two strategies. First, PubMed, Scopus, Medline, and PsycINFO were searched from inception to 10th August 2018 using the following keywords: "insomnia" or "sleep disturbance" and "executive function*" or "inhibition" or "inhibitory control" or "working memory" or "flexibility." Second, the reference lists of relevant review articles were searched. When titles of studies appeared relevant to the present review, abstracts and full-texts were screened against the eligibility criteria by the first author.

## Data Sources, Studies Sections, and Data Extraction

For the qualitative synthesis, data on a number of procedural variables were extracted by the first author from included studies including demographic and clinical characteristics of the sample, as well as methodological variables. Given the importance of objective sleep duration which is hypothesised to contribute to executive dysfunction (Fernandez-Mendoza et al., 2010; Vgontzas et al., 2013), information about group differences between individuals with insomnia and controls on total sleep time (TST) based on polysomnographic or actigraphic recordings were extracted, together with information about objective sleep efficiency (SE). TST is generally calculated as time spent in bed during the night (total bed time, TBT) minus the time needed to fall asleep, the wake after sleep onset and early morning awakenings. SE is then calculated as TST/TBT*100 (Carney et al., 2012). For the meta-analysis, means and standard deviations of the indices of performance reported in the included studies were extracted by the first author to compute effect sizes. When means and standard deviations were not reported in the studies, effect sizes were computed from means and standard errors.

Effect sizes were not estimated from graphs. To identify and categorise the neuropsychological tests, we referred to recent systematic reviews on the topic (Diamond, 2013; Snyder et al., 2015) and consulted systematic reviews and meta-analyses on cognitive impairment in insomnia (Shekleton et al., 2010; Fortier-Brochu et al., 2012). Due to variations in test categorisation in the domain of EFs, we decided to follow the categorisation used in the meta-analysis of Fortier-Brochu et al. (2012), drawn by two independent neuropsychologists.

## Data Analysis

Two independent investigators (AB, RA) assessed risk of bias using the checklist for assessing the quality of quantitative studies (Kmet et al., 2004). This tool appraises studies on different potential areas of bias, including appropriateness of the design, method of subject selection, blinding procedure, sample size, and data analysis. Disagreements between the investigators was resolved by consensus discussion.

Given the high variability of EFs measures, findings were first summarised and discussed using narrative synthesis (Popay et al., 2006). This allowed for the discussion of the differences in study findings and how clinical and methodological variables might have influenced study results, including between group differences on objective sleep.

When variability in EFs measures was limited, and there was a relevant number of studies to analyse (at least 3), meta-analysis was used in addition to the narrative synthesis to statistically estimate the presence and magnitude of EFs impairments. This was possible for the EFs assessed through reasonably comparable tasks (i.e., similar paradigms and outcomes) and for studies providing data to calculate effect sizes. To limit the impact of outcome measures' variability, analyses were run separately according to outcome type, i.e., reaction times and accuracy. When there was a relevant number of studies to analyse (at least 3), we ran sensitivity analysis to investigate the impact of objective sleep impairments on EFs.

For the meta-analytic calculations, standardised mean differences (Cohen's $d$) were estimated at 95% confidence intervals for group differences on cognitive tasks performance. Cohen's $d$ was derived by subtracting the mean for control groups from the mean for insomnia groups and dividing the result by the pooled standard deviation. The direction of effect size values was adjusted so that negative effects always indicate poorer performance in individuals with insomnia compared to controls. Meta-analytic calculations were computed using the statistical software "Comprehensive Meta-Analysis" version 2. A fixed effects model was used following the procedure of other authors (Fortier-Brochu et al., 2012). To test heterogeneity of effects distribution (i.e., variability in the distribution of effect sizes across studies included in a meta-analysis), Cochran's $Q$ and Higgins's $I^2$ were calculated. Cochran's $Q$ is computed as a weighted sum of squared differences between single study effects and the pooled effect across studies. Significant values indicate high level of heterogeneity between effects that need to be further investigated. Higgins's $I^2$ assesses the variability in effect estimates that is due to between-study heterogeneity rather than to chance. Low percentages of $I^2$ are indicative of low heterogeneity while percentages over 75% represent considerable levels of heterogeneity.

Additionally, we performed a series of subgroup analyses including either studies that reported significant sleep differences (objective TST or SE) between those with insomnia and good sleepers or studies reporting comparable sleep values between groups in order to investigate the differences in effect sizes between these sets of studies. This allowed us to investigate the effects of insomnia with objective sleep impairment vs. insomnia with normal sleep on EFs.

# RESULTS

## Study Selection and Characteristics

The study selection flowchart is reported in **Figure 1**. A detailed description of study characteristics is provided in **Table 1**. Database search yielded 2012 studies (PubMed = 493, PsycINFO = 405, Medline = 467, Scopus $n$ = 647). After removing duplicates, 1,625 records were identified. Reference screening yielded 16 additional records. In sum, 429 abstracts and 65 full-texts were screened against the eligibility criteria. Thirty-six studies were excluded because of the absence of: measures of inhibitory control, working memory or cognitive flexibility ($n$ = 7), a group of individuals with standardized diagnosis of insomnia disorder ($n$ = 15), and a control group ($n$ = 5). A further eight studies were excluded as these allowed participants to take drugs or psychoactive substances (e.g., caffeine or alcohol) prior to assessment. Furthermore, one study was excluded due to it being a secondary analysis of a study already included for review (see **Document S1** for excluded studies). Finally, 28 studies met the inclusion criteria and were included in the systematic review.

Data from 901 participants with insomnia and 859 controls were qualitatively evaluated. Mean percentage of females was 58.9 in the insomnia group and 58.5 in the controls. Mean age was 45.6 years in the insomnia group and 44.4 years in the controls.

## Synthesized Findings

### Narrative Synthesis

#### *Inhibitory control*

Thirteen studies reported a neuropsychological measure of inhibitory control as an outcome (Crenshaw and Edinger, 1999; Edinger et al., 2000, 2008; Szelenberger and Niemcewicz, 2001; Backhaus et al., 2006; Sagaspe et al., 2007; Haimov et al., 2008; Covassin et al., 2011; Joo et al., 2013; Siversten et al., 2013; Fortier-Brochu and Morin, 2014; Liu et al., 2014; Perrier et al., 2015). Three of these measured inhibitory control through the continuous performance test (Crenshaw and Edinger, 1999; Edinger et al., 2000, 2008) and one through the continuous performance test II (Fortier-Brochu and Morin, 2014). Two studies used the Stroop test (Haimov et al., 2008; Joo et al., 2013), one a similar colour-word interference test (Siversten et al., 2013) and two the stop-signal task (Sagaspe et al., 2007; Covassin et al., 2011). The attention network test, which evaluates three attention networks (alerting, orienting, executive control) was used by two studies (Liu et al., 2014; Perrier et al., 2015). Finally, one study used the go/no-go paradigm (Backhaus et al., 2006).

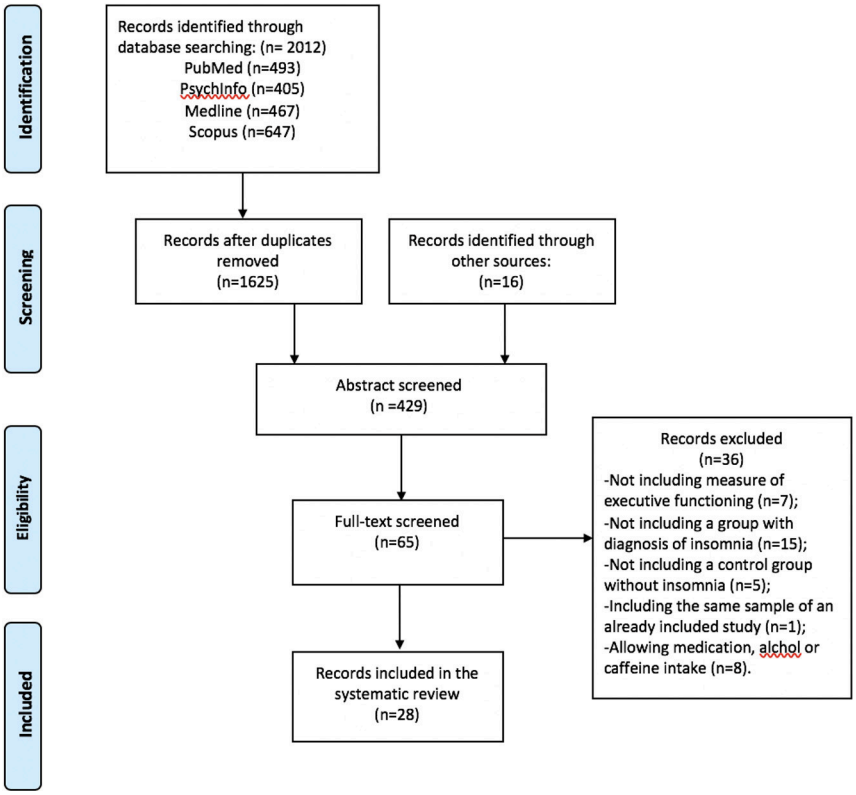


**FIGURE 1 |** Flow chart for study selection.

Six of thirteen studies reported significant differences between individuals with insomnia and controls on inhibitory performance and objective sleep (see below, Haimov et al., 2008; Covassin et al., 2011; Joo et al., 2013; Fortier-Brochu and Morin, 2014; Liu et al., 2014; Perrier et al., 2015).

Covassin et al. (2011) found that young adults with insomnia showed longer reaction times at the stop trials of the stop-signal task indicating poorer inhibitory control. However, in terms of accuracy, no differences were found. In contrast, Fortier-Brochu and Morin (2014) found that participants with insomnia differed from good sleepers in the number of perseverative errors of the continuous performance task II, but not on mean reaction times. Haimov et al. (2008) reported that individuals with insomnia showed longer reaction times in the Stroop test, consistent with Joo et al. (2013). Liu et al. (2014) found that adults with insomnia showed impaired functioning in the executive control performance of the attentional network test. In contrast, Perrier et al. (2015) found intact performance on the same task, but increased reaction times (RTs) in the incongruent Flankers compared to congruent and neutral Flankers, that they interpreted as a conflict resolution deficit. With respect to objective sleep, four of these studies reported significant shorter TST (Covassin et al., 2011; Joo et al., 2013; Fortier-Brochu and Morin, 2014; Liu et al., 2014) and two lower SE in insomnia as compared to controls (Haimov et al., 2008; Perrier et al., 2015).

Three of the eight studies that found no significant differences between individuals with insomnia and controls on inhibitory control tasks found no differences between groups on TST (Crenshaw and Edinger, 1999; Edinger et al., 2000, 2008), one in both TST and SE (Crenshaw and Edinger, 1999); three did not report information on objective sleep data (Szelenberger and Niemcewicz, 2001; Sagaspe et al., 2007; Siversten et al., 2013). Only in the study of Backhaus et al. (2006), participants with insomnia objectively slept less and worse than controls, although no effects on inhibitory control were found. Findings on inhibitory control are summarised in **Table 2**.

## Working Memory

Seventeen studies assessed working memory (Bonnet and Arand, 1995; Randazzo et al., 2000; Rosa and Bonnet, 2000; Vignola et al., 2000; Varkevisser et al., 2007; Haimov et al., 2008; Noh et al., 2012; Joo et al., 2013; Lovato et al., 2013; Siversten et al., 2013; Cellini et al., 2014; Fortier-Brochu and Morin, 2014; Shekleton et al., 2014; Chen et al., 2016; Guo et al., 2017; Khassawneh et al., 2018; Son et al., 2018). Eight of these measured working memory through digit or spatial span backward tests (Randazzo et al., 2000; Vignola et al., 2000; Haimov et al., 2008; Noh et al., 2012; Joo et al., 2013; Lovato et al., 2013; Fortier-Brochu and Morin, 2014; Khassawneh et al., 2018). Four studies used the n-back memory task (Varkevisser et al., 2007; Cellini et al., 2014; Shekleton et al., 2014; Son et al., 2018); two used the memory

**TABLE 1** | Study characteristics.

| Author (year) | Diagnostic criteria | Insomnia duration | Assessment | Comorbidity | *N* insomnia | *N* controls | %Female insomnia | % Female controls | Age insomnia (M) | Age controls (M) | Pharmaco intake | Caffeine intake | Alcol intake | Time of testing |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Altena et al., 2008 | RDC, Lichstein criteria | >2.5 years | Questionnaire | Subclinical psychiatric symptoms | 21 | 12 | 80.9 | 75 | 61 | 60 | Excluded | n/a | n/a | PM |
| Backhaus et al., 2006 | DMS-IV | 9.2 years | Clinical interview | Excluded | 15 | 13 | 50 | 61.3 | 41.6 | 40.1 | Excluded | n/a | n/a | AM |
| Bonnet and Arand, 1995 | SOL>45 or WASO>60 min, 4 nights per week for 1 year | 8 years | Questionnaire | Excluded | 10 | 10 | n/a | n/a | 38.3 | 38.6 | Excluded | Excluded | n/a | Repeated testing |
| Cellini et al., 2014 | RDC | n/a | Clinical interview, questionnaire | Excluded | 13 | 13 | 61.5 | 46.1 | 23.3 | 24.3 | Excluded | Excluded | Excluded | PM |
| Chen et al., 2016 | ICSD-3 | >6 months | Questionnaire | Excluded | 21 | 20 | 71.4 | 65 | 41.8 | 38.1 | n/a | n/a | n/a | AM |
| Covassin et al., 2011 | DSM-IV | n/a | Clinical interview, questionnaire | Excluded | 8 | 8 | 50 | 50 | 22.9 | 24.8 | Excluded | Excluded | Excluded | Repeated testing |
| Crenshaw and Edinger, 1999 | DMS-III-R | n/a | Clinical interview | Excluded | 32 | 32 | 50 | 50 | 67.7 | 67.5 | Excluded | n/a | n/a | Repeated testing |
| Edinger et al., 2000 | DMS-III-R | >6 months | Clinical interview | Excluded | 27 | 31 | 44.4 | 51.6 | 49.7 | 46.4 | Excluded | n/a | n/a | Repeated testing |
| Edinger et al., 2008 | DSM-IV | n/a | Clinical interview | Excluded | 79 | 84 | 54.4 | 48.8 | 50 | 48.6 | Excluded | n/a | n/a | Repeated testing |
| Fang et al., 2008 | DSM-IV | n/a | Questionnaire, actigraphy | Excluded | 18 | 21 | 66.7 | 66.7 | 34.1 | 27.8 | n/a | Excluded | Excluded | PM |
| Fortier-Brochu and Morin, 2014 | DSM-IV, ICD-10 | 17.3 years | Clinical interview, diary | Excluded | 25 | 16 | 56 | 50 | 44.4 | 42.8 | Excluded | Excluded | Excluded | AM |
| Guo et al., 2017 | DSM-IV | n/a | Questionnaire | Excluded | 40 | 48 | 77.5 | 72.9 | 37.3 | 39.8 | Excluded** | n/a | n/a | n/a |
| Haimov et al., 2008 | Lichstein criteria | n/a | Questionnaire, actigraphy | Excluded | 35 | 64 | 57.1 | 67.2 | 73.6 | 71.6 | Excluded | n/a | n/a | PM |
| Joo et al., 2013 | ICSD-2 | >1 year | Clinical interview, diary, questionnaire | Excluded | 27 | 27 | 92.5 | 85 | 52.3 | 51.7 | Excluded | Excluded | Excluded | n/a |
| Khassawneh et al., 2018 | DSM-5, ICSD-3 | n/a | Clinical interview, questionnaire, psg | Excluded | 35 | 54 | 71.4 | 70.4 | 40.6 | 31.5 | Excluded | n/a | n/a | Repeated testing |

*(Continued)*

**TABLE 1** | Continued

| Author (year) | Diagnostic criteria | Insomnia duration | Assessment | Comorbidity | *N* insomnia | *N* controls | %Female insomnia | % Female controls | Age insomnia (M) | Age controls (M) | Pharmaco intake | Caffeine intake | Alcol intake | Time of testing |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liu et al., 2014 | DSM-IV | 6.4 years | Clinical interview, questionnaire | Excluded | 36 | 26 | 58.3 | 61.5 | 42.9 | 40.5 | Excluded | Excluded | Excluded | n/a |
| Lovato et al., 2013 | DSM-IV | n/a | Clinical interview, questionnaire | Excluded | 49 | 49 | 55.2 | 55.2 | 69.4 | 70 | Excluded | n/a | n/a | n/a |
| Noh et al., 2012 | ICSD-2 | 7.6 years | Clinical interview | Excluded | 20 | 20 | 90 | 90 | 50.8 | 50.4 | Excluded | Excluded | Excluded | n/a |
| Perrier et al., 2015 | DSM-IV | n/a | Clinical interview, questionnaire | Excluded | 21 | 16 | 57.1 | 62.5 | 48.7 | 48.3 | Excluded | n/a | n/a | PM |
| Randazzo et al., 2000 | DSM-IV | n/a | n/a | Excluded | 35 | 35 | 71.4 | 77.1 | 43.6 | 43.5 | n/a | n/a | n/a | n/a |
| Rosa and Bonnet, 2000 | SOL>45 or WASO>60 min, 4 nights per week for 1 year | 7.9 years | Questionnaire, psg | Excluded | 121 | 56 | 38 | 32 | 35 | 36 | Excluded | Excluded | n/a | Repeated testing |
| Sagaspe et al., 2007 | ICSD-2 | >6 months | Clinical interview, psg | n/a | 13 | 13 | 38.4 | 38.4 | 47.4 | 47.4 | Excluded | n/a | n/a | PM |
| Son et al., 2018 | DSM-5 | 4.9 years | Clinical interview, questionnaire | Excluded | 21 | 26 | 57.1 | 57.7 | 36.6 | 33.2 | Excluded | n/a | n/a | AM |
| Shekleton et al., 2014 | RDC | n/a | Clinical interview, questionnaire | Excluded | 76 | 20 | 57.8 | 70 | 35.7 | 34.7 | Excluded | Excluded | n/a | Repeated testing |
| Siversten et al., 2013 | DSM-IV | n/a | Questionnaire | Excluded | 30 | 91 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Szelenberger and Niemcewicz, 2001 | DSM-IV | 8.2 years | Questionnaire, actigraphy, psg | Excluded | 14 | 14 | 57.1 | 57.1 | 41.2 | 36.2 | Excluded | n/a | n/a | AM |
| Varkevisser et al., 2007 | ICSD-2 | n/a | Clinical interview, diary | n/a | 39 | 20 | 58.9 | 50 | 40.9 | 42.6 | n/a | n/a | n/a | Repeated testing |
| Vignola et al., 2000 | ICSD, DSM-IV | n/a | Clinical Interview, questionnaire, diary | Excluded | 20 | 20 | 10 | 10 | 61.7 | 63.3 | Excluded benzodiazepine | n/a | n/a | AM |

*AM, morning; DSM, diagnostic and statistical manual of mental disorders; ICD, international classification of diseases; ICSD, international classification of sleep disorders; n/a, not available; PM, afternoon/evening; PSG, polysomnography; RDC, research diagnostic criteria; SEI, sleep efficiency index; SOL, sleep onset latency; TST, total sleep time, WASO, wake after sleep onset. X= no group differences, **excluded if could impact cognitive function or reaction times.*

**TABLE 2 |** Comparison of individuals with insomnia and controls on tasks of inhibitory control.

| Author (year) | *n* Insomnia; controls | Task | Outcome | Group difference | Group differences TST | Group difference SEI |
|---|---|---|---|---|---|---|
| Backhaus et al., 2006 | 15; 13 | Go/no-go | Response times | X | $p < 0.05$ | $p < 0.05$ |
| | | | Number of correct responses | X | | |
| Covassin et al., 2011 | 8; 8 | Stop-Signal task | Go reaction times | X | $p < 0.05$ | $p < 0.05$ |
| | | | Stop reaction times | $p < 0.05$ | | |
| | | | Accuracy | X | | |
| | | | Errors | X | | |
| Crenshaw and Edinger, 1999 | 32; 32 | Continuous performance task | Response latency | X | X | X |
| Edinger et al., 2000 | 27; 31 | Continuous performance task | Response latency | X | X | $p < 0.05$ |
| Edinger et al., 2008 | 79; 84 | Continuous performance task | Response latency | X | X | $p < 0.05$ |
| Fortier-Brochu and Morin, 2014 | 25; 16 | Continuous performance task II | Perseverative errors | $p < 0.05$ | $p < 0.05$ | $p < 0.05$ |
| Haimov et al., 2008 | 35; 64 | Stroop | Response times | $p < 0.05$ | n/a | $p < 0.05$ |
| Joo et al., 2013 | 27; 27 | Stroop | Response times | $p < 0.05$ | $p < 0.05$ | $p < 0.05$ |
| Liu et al., 2014 | 36; 26 | Attention network test | Response times (executive control) | $p < 0.05$ | $p < 0.05$ | $p < 0.05$ |
| Perrier et al., 2015 | 21; 16 | Attention network test | Response times (executive control) | X | X | $p < 0.05$ |
| | | | Response times* | $p < 0.05$ | | |
| Sagaspe et al., 2007 | 13; 13 | Stop-signal task | Go reaction times | X | n/a | n/a |
| | | | Stop reaction times | X | | |
| | | | Accuracy | X | | |
| | | | Errors | X | | |
| Siversten et al., 2013 | 30; 91 | Color-word interference task | Response times | X | n/a | n/a |
| Szelenberger and Niemcewicz, 2001 | 14; 14 | Continuous attention task | Response times | X | n/a | n/a |
| | | | Omission errors | X | | |
| | | | Commission errors | X | | |

*Significant differences between groups are shown as $p < 0.05$. No group differences are shown as X. *Response times in incongruent compared to congruent and neutral Flankers.*

and search task (Bonnet and Arand, 1995; Rosa and Bonnet, 2000) two used the letter-number sequencing test (Randazzo et al., 2000; Siversten et al., 2013), one used the Corsi block test backward (Noh et al., 2012), one used the nine box maze test to measure spatial and object working memory (Chen et al., 2016) and one the Montreal cognitive assessment battery (Guo et al., 2017).

Nine out of seventeen studies showed significant differences between individuals with insomnia and good sleeper controls on performance (Bonnet and Arand, 1995; Randazzo et al., 2000; Vignola et al., 2000; Haimov et al., 2008; Noh et al., 2012; Joo et al., 2013; Lovato et al., 2013; Cellini et al., 2014; Chen et al., 2016). Of these nine, sleep was objectively impaired in four (Bonnet and Arand, 1995; Haimov et al., 2008; Joo et al., 2013; Cellini et al., 2014). Seven out of seventeen studies did not report information on objective sleep (Randazzo et al., 2000; Varkevisser et al., 2007; Lovato et al., 2013; Siversten et al., 2013; Shekleton et al., 2014; Chen et al., 2016; Guo et al., 2017). With respect to the tasks, performance was consistently impaired in digit and spatial span backward tests, with the exception of two studies (Randazzo et al., 2000; Fortier-Brochu and Morin, 2014). However, Randazzo et al. (2000) found significant impairments in insomnia vs. controls on spatial, but not digit span tasks. The two studies using the two-back memory task failed to find significant differences between individuals with insomnia and controls (Varkevisser et al., 2007; Son et al., 2018). The majority of the studies (five out of eight) which did not report significant differences between subjects with insomnia and controls did not report data on objective sleep (Randazzo et al., 2000; Varkevisser et al., 2007; Siversten et al., 2013; Shekleton et al., 2014; Guo et al., 2017). Findings on working memory are summarised in **Table 3**.

## Cognitive Flexibility

Twelve studies reported a measure of cognitive flexibility (Edinger et al., 2000, 2008; Vignola et al., 2000; Altena et al., 2008; Fang et al., 2008; Noh et al., 2012; Joo et al., 2013; Siversten et al.,

**TABLE 3 |** Comparison of individuals with insomnia and controls on tasks of working memory.

| Author (year) | *n* Insomnia; controls | Task | Outcome | Group difference | Group differences TST | Group difference SEI |
|---|---|---|---|---|---|---|
| Bonnet and Arand, 1995 | 10; 10 | Memory and search task | Correct responses | $p < 0.05$ | $p < 0.05$ | $p < 0.05$ |
| Cellini et al., 2014 | 13; 13 | N-back memory task | Accuracy | $p < 0.05$ | $p < 0.05$ | $p < 0.05$ |
| | | | Number of errors | $p < 0.05$ | | |
| | | | Reaction times | X | | |
| Chen et al., 2016 | 21;20 | Nine box maze test-spatial working memory | Number of errors | $p < 0.05$ | n/a | n/a |
| | | Nine box maze test-object working memory | Number of errors | X | | |
| Fortier-Brochu and Morin, 2014 | 25; 16 | Digit span backward | Number of recalled | X | $p < 0.05$ | $p < 0.05$ |
| Haimov et al., 2008 | 35; 64 | Digit span backward | Number of recalled | $p < 0.05$ | n/a | $p < 0.05$ |
| | | Spatial span backward | Number of recalled | $p < 0.05$ | | |
| Guo et al., 2017 | 40;48 | Montreal cognitive assessment battery-attention, concentration, and working memory* | Accuracy | X | n/a | n/a |
| Joo et al., 2013 | 27; 27 | Digit span backward | Number of recalled | $p < 0.05$ | $p < 0.05$ | $p < 0.05$ |
| Khassawneh et al., 2018 | 35;54 | Spatial working memory test | Number of errors | X | $p < 0.05$ | X |
| | | | Reaction times | X | | |
| | | | Strategy | X | | |
| Lovato et al., 2013 | 49; 49 | Double span backward | Number of recalled | $p < 0.05$ | n/a | n/a |
| Noh et al., 2012 | 20; 20 | Digit span backward | Number of recalled | $p < 0.05$ | X | X |
| | | Corsi block test backward | Number of recalled | $p < 0.05$ | | |
| Randazzo et al., 2000 | 35; 35 | Digit span backward | Number of recalled | X | n/a | n/a |
| | | Spatial span backward | Number of recalled | $p < 0.05$ | | |
| | | Letter number sequencing test | Correct units in a string | $p < 0.05$ | | |
| Rosa and Bonnet, 2000 | 121; 56 | Memory and search task | Correct responses | X | X | X |
| Shekleton et al., 2014 | 76; 20 | N-back memory task | Reaction times | X | n/a | n/a |
| Siversten et al., 2013 | 30; 91 | Letter number sequencing test | Correct units in a string | X | n/a | n/a |
| Son et al., 2018 | 21;26 | Two-back memory task | Reaction times | X | $p < 0.05$ | $p < 0.05$ |
| | | | Accuracy | X | | |
| Varkevisser et al., 2007 | 39; 20 | Two-back memory task | Reaction times | X | n/a | n/a |
| | | | Accuracy | X | | |
| Vignola et al., 2000 | 20; 20 | Digit span backward | Number of recalled | $p < 0.05$ | X | X |

*Significant differences between groups are shown as $p < 0.05$. No group differences are shown as X.*

2013; Fortier-Brochu and Morin, 2014; Shekleton et al., 2014; Guo et al., 2017; Khassawneh et al., 2018). Four studies measured flexibility through switching attention tasks (Edinger et al., 2000, 2008; Shekleton et al., 2014; Khassawneh et al., 2018) and using verbal fluency tasks (Vignola et al., 2000; Siversten et al., 2013; Fortier-Brochu and Morin, 2014). The Wisconsin card sorting test was used in two studies (Vignola et al., 2000; Fang et al., 2008), as well as the controlled oral word association test (Noh et al., 2012; Joo et al., 2013). The trail making test B was used in two studies (Joo et al., 2013; Siversten et al., 2013). Finally, one study used the "visuospatial and executive function" subtest of the Montreal cognitive assessment battery, based on the trail making test B, verbal fluency task and verbal abstraction task (Guo et al., 2017).

Four of twelve studies reported significant differences between individuals with insomnia and good sleepers in some aspects of performance (Edinger et al., 2000, 2008; Noh et al., 2012; Khassawneh et al., 2018). Of these, three also reported between group differences on objective sleep. Specifically, Edinger et al. (2000, 2008) found significant shorter TST and Khassawneh et al. (2018) lower SE in insomnia as compared to controls. Sleep was comparable between the groups in the study of Noh et al. (2012).

Edinger et al. (2000) found that individuals with insomnia showed longer response latency in the switching attention test

**TABLE 4 |** Comparison of individuals with insomnia and controls on tasks of cognitive flexibility.

| Author (year) | *n* Insomnia; controls | Task | Outcome | Group difference | Group differences TST | Group difference SEI |
|---|---|---|---|---|---|---|
| Altena et al., 2008 | 21; 12 | Verbal fluency | | | n/a | n/a |
| | | Letter | Number of words produced | X | | |
| | | Category | Number of words produced | X | | |
| Edinger et al., 2000 | 27; 31 | Switching attention task | | | X | $p < 0.05$ |
| | | Part IIIA | Response latency | X | | |
| | | Part IIIB | Response latency | $p < 0.05$ | | |
| Edinger et al., 2008 | 79; 84 | Switching attention task | | | X | $p < 0.05$ |
| | | Part IIIA | Response latency | $p < 0.05$ | | |
| | | Part IIIB | Response latency | $p < 0.05$ | | |
| Fang et al., 2008 | 18; 21 | Wisconsin card sorting test | Perseverations | X | $p < 0.05$ | $p < 0.05$ |
| | | | Errors | X | | |
| | | | Conceptual level responses | X | | |
| | | | Number of categories competed | X | | |
| | | | Failure to maintaining set | X | | |
| | | | Learning to learn | X | | |
| Fortier-Brochu and Morin, 2014 | 25; 16 | Verbal fluency | Number of words produced | X | $p < 0.05$ | $p < 0.05$ |
| | | | Set lost errors | X | | |
| | | | Repetition errors | X | | |
| Guo et al., 2017 | 40;48 | Montreal cognitive assessment- visuospatial and executive function* | Number of correct responses | X | n/a | n/a |
| Joo et al., 2013 | 27; 27 | Controlled oral word association test | Number of words produced | X | $p < 0.05$ | $p < 0.05$ |
| | | Trail making test B | Complation time | X | | |
| Khassawneh et al., 2018 | 35;54 | Attention switching task | Response latency | $p < 0.05$ | $p < 0.05$ | X |
| | | | Number of incorrect trials | $p < 0.05$ | | |
| | | | Number of commission errors | X | | |
| Noh et al., 2012 | 20; 20 | Trail making test B | Complation time | X | X | X |
| | | Controlled oral word association test | Number of words produced | $p < 0.05$ | | |
| Shekleton et al., 2014 | 76; 20 | Switching attention task | | | n/a | n/a |
| | | Part IIIA | Response latency | X | | |
| | | Part IIIB | Response latency | X | | |
| Siversten et al., 2013 | 30; 91 | Verbal fluency | Number of words produced | X | n/a | n/a |
| | | Trail making test B | Completion time | X | | |
| Vignola et al., 2000 | 20; 20 | Trail making test B | Completion time | X | X | X |
| | | Wisconsin card sorting test | Number of categories competed | X | | |
| | | | Number of perseverative errors | X | | |

*Significant differences between groups are shown as $p < 0.05$. No group differences are shown as X. *Based on Trail making test B, verbal fluency task, and verbal abstraction task.*

part III, and the result was replicated by a later study by the same group (Edinger et al., 2008). Similarly, Khassawneh et al. (2018) found slower response latency and higher number of incorrect trials in a similar task. However, Shekleton et al. (2014) replicated the result only in individuals with insomnia and short sleep duration, and no changes to performance was found in subjects with insomnia and normal sleep duration. Fortier-Brochu and Morin (2014) failed to find between group differences in a verbal fluency test. Instead, Noh et al. (2012) found that individuals with insomnia produced less words than controls in the controlled oral association test, reflecting poorer flexibility. However, other researchers failed to replicate these results using similar tests (Altena et al., 2008; Siversten et al., 2013). Performance on the trail making test B (Noh et al., 2012; Joo et al., 2013) and the

Wisconsin card sorting test (Vignola et al., 2000; Fang et al., 2008) of individuals with insomnia remained comparable to the controls.

Only three of the eight studies which failed to find significant differences between individuals with insomnia and controls on EFs reported significant differences in TST and SE (Fang et al., 2008; Joo et al., 2013; Fortier-Brochu and Morin, 2014). Vignola et al. (2000) reported no differences on objective TST and SE between those with insomnia and controls, while Altena et al. (2008), Siversten et al. (2013) and Guo et al. (2017) did not provide data on objective sleep measurement. Findings on cognitive flexibility are summarised in **Table 4**.

## Exploratory Meta-Analysis

### Inhibitory Control

Nine of thirteen studies measuring inhibitory control provided data to compute effect sizes (Crenshaw and Edinger, 1999; Edinger et al., 2000; Szelenberger and Niemcewicz, 2001; Backhaus et al., 2006; Sagaspe et al., 2007; Covassin et al., 2011; Siversten et al., 2013; Liu et al., 2014; Perrier et al., 2015). These reported reaction times as an outcome. Additionally, four of nine studies included a measure of accuracy of the performance (Szelenberger and Niemcewicz, 2001; Backhaus et al., 2006; Sagaspe et al., 2007; Covassin et al., 2011). Thus, we conducted separate analyses for reaction times and accuracy. Reaction times were significantly slower for individuals with insomnia ($n = 303$) than controls ($n = 355$) ($d = -0.32$, 95% CI: $-0.52$ to $-0.13$). Heterogeneity statistics were non-significant, showing that the distribution of effects across studies was homogeneous ($Q = 3.328$, df $= 8$, $p = 0.912$; $I^2 = 0.000\%$). Forest plot of analysis is reported in **Figure 2**.

We investigated whether the effect size was larger for studies including participants with insomnia and objective sleep impairment (shorter TST or lower SE compared to the controls) by including only these studies in the analysis (Edinger et al., 2000; Backhaus et al., 2006; Covassin et al., 2011; Liu et al., 2014; Perrier et al., 2015). Results showed a significant and larger effect ($d = -0.41$, 95% CI: $-0.69$ to $-0.13$). Heterogeneity statistics were non-significant ($Q = 1.436$, df $= 4$, $p = 0.838$; $I^2 = 0.000\%$). In contrast, including only studies which failed to find significant differences between insomnia and control groups or missed to report information on objective sleep (Crenshaw and Edinger, 1999; Szelenberger and Niemcewicz, 2001; Sagaspe et al., 2007; Siversten et al., 2013), results showed a smaller effect ($d = -0.24$, 95% CI: $-0.51$ to $-0.03$), with low and non-significant heterogeneity ($Q = 1.144$, df $= 3$, $p = 0.766$; $I^2 = 0.000\%$).

Results on accuracy showed that the performance of individuals with insomnia was significantly more accurate than that of controls ($d = 0.504$, 95% CI: 0.082 to 0.925). Nevertheless, effects distribution was significantly heterogenous between studies ($Q = 19.162$, df $= 3$, $p < 0.001$; $I^2 = 84.344\%$). We repeated the analysis removing one potential outlier (Covassin et al., 2011, $d = 0.4.21$, 95% CI: 2.38–5.85). Results showed smaller and no longer significant effect ($d = 0.27$, 95% CI: $-0.15$ to 0.71). Heterogeneity tests were low and no longer significant, reflecting a homogeneous distribution of the effects across studies ($Q = 1.345$, df $= 2$, $p = 0.510$; $I^2 = 0.000\%$). Forest plot of the analysis is reported in **Figure 3**. Given the small number of studies, we were limited in performing further sensitivity analyses.

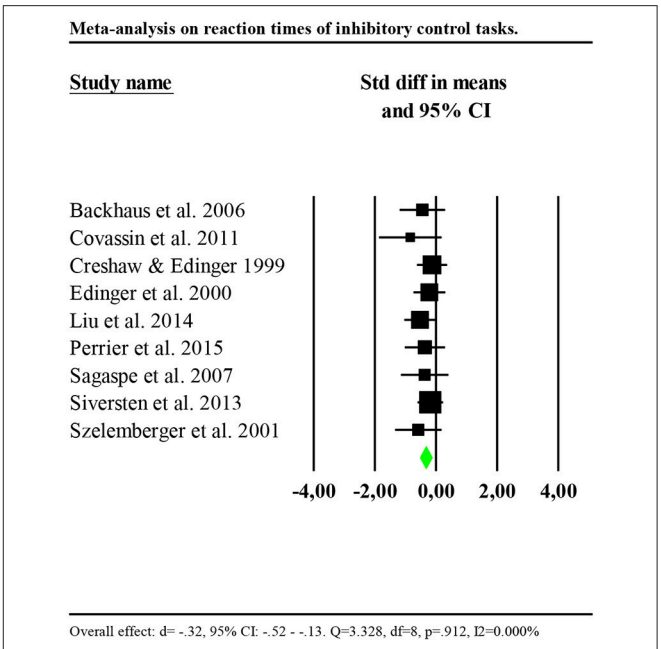


**FIGURE 2 |** Forest plot of the meta-analysis on reaction times of inhibitory control. Results are presented as standardised mean differences (Std diff) and 95% confidence intervals (CI).

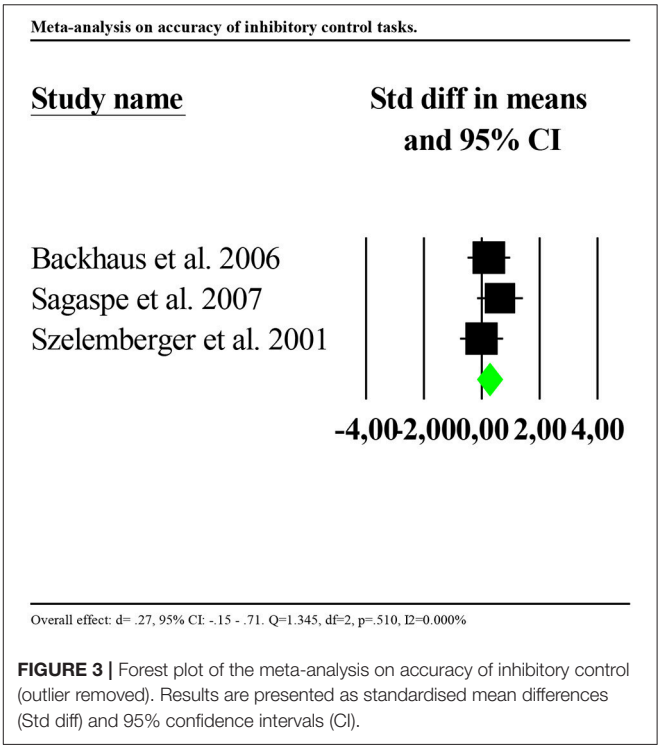


**FIGURE 3 |** Forest plot of the meta-analysis on accuracy of inhibitory control (outlier removed). Results are presented as standardised mean differences (Std diff) and 95% confidence intervals (CI).

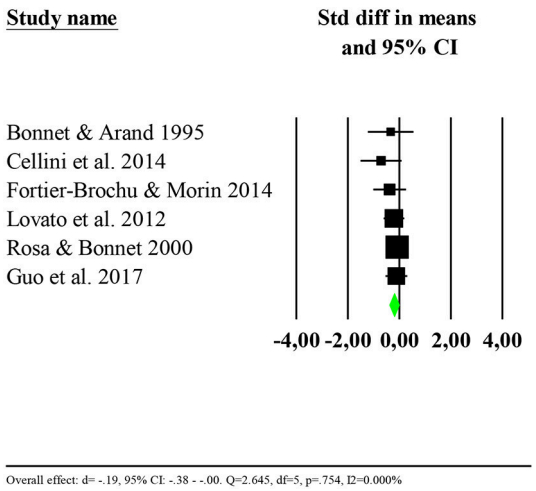


**FIGURE 4 |** Forest plot of the meta-analysis on accuracy of working memory (outlier removed). Results are presented as standardised mean differences (Std diff) and 95% confidence intervals (CI).

## Working Memory

Eight studies reported data of accuracy of the performance (Bonnet and Arand, 1995; Rosa and Bonnet, 2000; Lovato et al., 2013; Cellini et al., 2014; Fortier-Brochu and Morin, 2014; Guo et al., 2017; Khassawneh et al., 2018; Son et al., 2018). Only one study reported data for reaction times (Cellini et al., 2014). Consequently, we performed the analysis for accuracy only. Analysis showed no significant results ($d = -0.034$, 95% CI: −0.211 to 0.144) and high heterogeneity ($Q = 42.678$, df = 6, $p < 0.001$; $I^2 = 85.941\%$). We repeated the analysis removing one potential outlier (Khassawneh et al., 2018, $d = -1.161$, 95% CI: −1.93 to −0.98). Results showed a small significant effect ($d = -0.19$, 95% CI: −0.38 to −0.00). Heterogeneity statistics were not significant ($Q = 2.645$, df = 5, $p = 0.754$; $I^2 = 0.000\%$). Forest plot of this analysis is reported in **Figure 4**.

We investigated whether the effect was larger for studies including participants with insomnia and objective sleep impairment (shorter TST or lower SE compared to the controls) by including only these in the analysis (Bonnet and Arand, 1995; Cellini et al., 2014; Fortier-Brochu and Morin, 2014). Results showed a significant and larger effect ($d = -0.46$, 95% CI: −0.03 to −0.89). Heterogeneity statistics were non-significant ($Q = 0.525$, df = 2, $p = 0.769$; $I^2 = 0.000\%$). In contrast, including only studies which failed to find significant differences between insomnia and control groups, or missed to report information on objective sleep, showed a smaller and non-significant effect ($d = -0.13$, 95% CI: −0.08 to 0.34), with low and non-significant heterogeneity ($Q = 0.240$, df = 2, $p = 0.887$; $I^2 = 0.000\%$).

## Cognitive Flexibility

Four studies reported reaction times (Edinger et al., 2000; Vignola et al., 2000; Siversten et al., 2013; Khassawneh et al., 2018) and four accuracy (Fang et al., 2008; Fortier-Brochu and Morin, 2014; Guo et al., 2017; Khassawneh et al., 2018) as outcomes. Consequently, we ran separate analyses for reaction times and accuracy. Reaction times were significantly slower for individuals with insomnia as compared to controls ($d = -0.77$, 95% CI: −1.03 to −0.51). Nevertheless, the distribution of effects was highly and significantly heterogenous between studies ($Q = 54.954$, df = 3, $p < 0.001$; $I^2 = 94.541$). We repeated the analysis removing one potential outlier (Khassawneh et al., 2018, $d = -2.689$, 95% CI: −3.26 to −2.10). Results showed a significant effect ($d = -0.30$, 95% CI: −0.59 to −0.01). Heterogeneity tests were low and no longer significant ($Q = 2.920$, df = 2, $p = 0.232$; $I^2 = 31.496$). Forest plot of this analysis is reported in **Figure 5**.

Accuracy was significantly poorer for individuals with insomnia than controls ($d = -0.602$, 95% CI: −0.873 to −0.330). Again, the distribution of effects was highly and significantly heterogenous between studies ($Q = 67.580$, df = 3, $p < 0.001$; $I^2 = 95.561$). We repeated the analysis removing one potential outlier (Khassawneh et al., 2018, $d = -2.733$, 95% CI: −3.31 to −2.14). Results showed no significant effects ($d = -0.017$, 95% CI: −0.32 to 0.28). Heterogeneity tests were low and no longer significant ($Q = 2.576$, df = 2, $p = 0.276$; $I^2 = 22.375$). Forest plot of this analysis is reported in **Figure 6**.

In addition, since three studies reported the same outcome using the same task (the number of words produced in the verbal fluency task) (Altena et al., 2008; Siversten et al., 2013; Fortier-Brochu and Morin, 2014), we ran a separate analysis on verbal fluency tasks. Results showed a slight and marginally significant tendency toward a better performance for individuals with insomnia as compared to controls ($d = 0.313$, 95% CI: −0.000 to 0.617). Heterogeneity tests were low and non-significant ($Q = 3.371$, df = 2, $p = 0.176$; $I^2 = 42.380$).

## Risk of Bias

Risk of bias assessment ratings are reported in **Figures 7**, **8**. In general, studies were judged as having low risk of bias. Small sample size of individual studies emerged as a potential source of bias. Blinding of outcome assessors and participants were judged as two areas of partially biased.

# DISCUSSION

The present systematic review aimed to examine the presence and magnitude of inhibitory control, working memory and cognitive flexibility impairments in individuals with insomnia vs. controls. Using combined narrative synthesis and meta-analysis, we gathered evidence supporting impaired functioning in several aspects of EFs in insomnia. Due to few studies reporting data to compute effect sizes, small sample sizes and high heterogeneity of effects distribution, results from the present review should be interpreted carefully.

Meta-analytic findings support the presence of impaired performance of individuals with insomnia as compared to controls in reaction time-based tasks assessing inhibitory control and cognitive flexibility, with effects sizes ranging from small to moderate in magnitude. In contrast, accuracy rates (i.e., correct responses), were found intact in insomnia with respect to

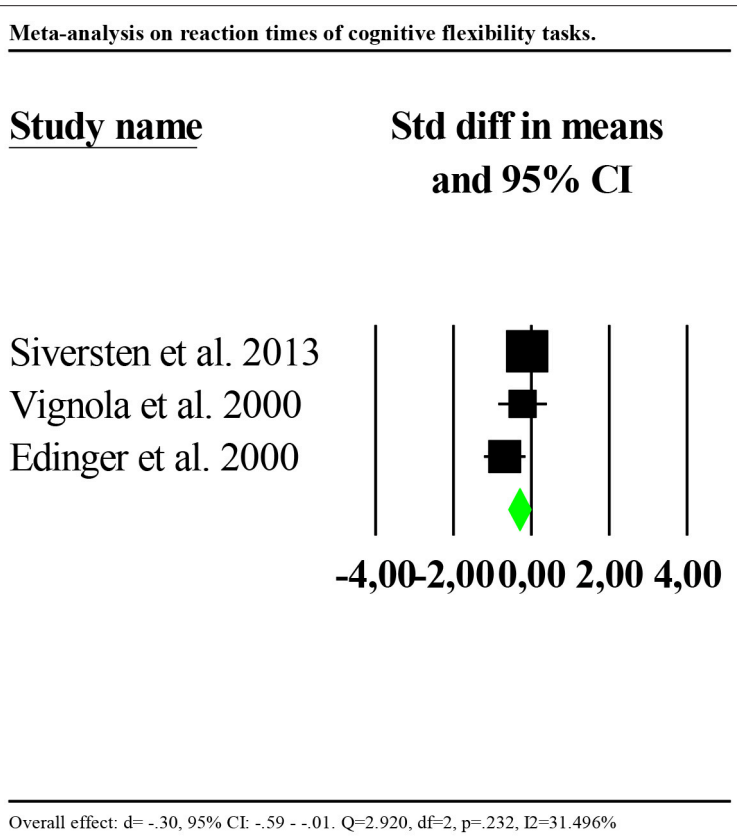


**FIGURE 5 |** Forest plot of the meta-analysis on reaction times of cognitive flexibility (outlier removed). Results are presented as standardised mean differences (Std diff) and 95% confidence intervals (CI).

inhibitory control and cognitive flexibility tasks but impaired in working memory tasks. The present work advances knowledge on cognitive functioning in insomnia, updating previous meta-analytic work (Fortier-Brochu et al., 2012) and providing a more detailed assessment of executive processes. In particular, our findings corroborate the results of Fortier-Brochu's review with respect to insomnia-related working memory deficits and provide further evidence for inhibitory control and cognitive flexibility impairments. This advancement is due to the great number of studies ($n = 14$) published on this topic after Fortier-Brochu's meta-analysis.

## Objective Sleep Impairments

To examine the hypothesis that EFs are impaired only in insomnia with objective sleep impairments (i.e., shortened TST and/or reduced SE; Fernandez-Mendoza et al., 2010; Vgontzas et al., 2013), which may explain conflicting study findings (Shekleton et al., 2010), we extracted data on the difference between individuals with insomnia and good sleepers on TST and SE. Consequently, we investigated the relationship between presence of EFs impairments and objective sleep impairments. Both narrative synthesis and meta-analysis highlighted that the magnitude of EFs impairments was larger in studies including participants with insomnia and objective shorter TST and/or lower SE as compared to the controls rather than in studies which failed to report significant between group differences in objective sleep or did not report this information. More specifically, this hypothesis was statistically verified for reaction times in inhibitory control tasks and accuracy rates in working memory tasks. Due to the small number of studies, it was not possible to statistically test the objective sleep hypothesis for cognitive flexibility tasks. Nevertheless, these findings could have important implications for treatment development; in particular, tailoring treatment for varying needs, and differential effects of treatment on populations of diverse clinical characteristics.

These results, therefore, are apparently consistent the hypothesis that higher order neuropsychological functions may be quite preserved in individuals with insomnia with normal sleep and provide partial evidence for the theory that only the phenotype of insomnia with objective sleep impairment is associated with worst objective neuropsychological deficits (Fernandez-Mendoza et al., 2010; Vgontzas et al., 2013). This is also in line with sleep deprivation literature demonstrating an impairment of EFs after sleep loss (Nilsson et al., 2005; Couyoumdjian et al., 2010; Martella et al., 2011).

Nevertheless, due to the small number of studies included in the meta-analytic calculations, these results should be interpreted carefully. Larger trials conducted in both insomnia with normal sleep and objective sleep impairments and including both

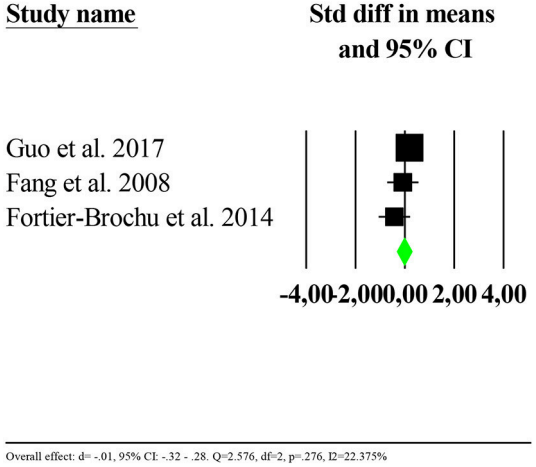


**FIGURE 6 |** Forest plot of the meta-analysis on accuracy of cognitive flexibility (outlier removed). Results are presented as standardised mean differences (Std diff) and 95% confidence intervals (CI).

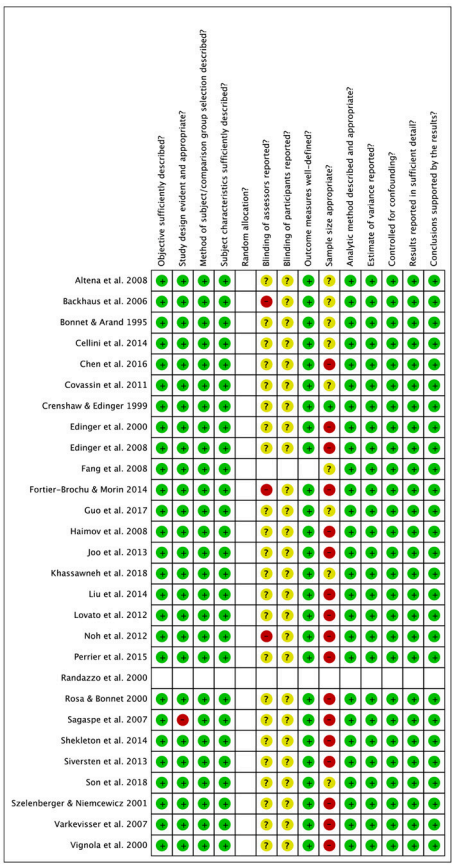


**FIGURE 7 |** Risk of bias summary.

reaction times and accuracy indices are needed to confirm our findings. Moreover, as discussed in detail below, it is desirable for future studies to elucidate the potentially differential effects of sleep quality and sleep quantity on EFs, that we were unable to investigate due to the small number of studies available.

## Cognitive Tests

Many neuropsychological tests used to assess EF, such as the trail making test and the Wisconsin card sorting test, have been validated to assess deficits of large magnitude in patients with brain injuries or neurological disorders and are therefore unlikely to detect minor impairment experienced by those without brain injury, such as those with insomnia. Although deficits in the trail making test are reported in samples with severe psychiatric disorder like major depression or bipolar disorder (Pattanayak et al., 2012; Cotrena et al., 2016), other neuropsychological tests such as the colour-word interference tests, backward memory span tasks, and switching attention tasks may be more sensitive to detecting less severe deficits such as those affecting subjects with insomnia. In fact, individuals with insomnia consistently showed impaired performance in these tasks. Thus, future studies of EFs in insomnia samples would benefit from considering for test sensitivity. Importantly, future research on EFs in insomnia would benefit from including tasks with reasonably similar paradigms (i.e., similar instructions and procedure of assessment, similar outcomes). The presence of varied tasks used to assess the same cognitive functions (e.g., 5 different tasks on 13 studies to assess inhibitory control), is a potential source of bias. It would be therefore important for insomnia research to standardise cognitive assessment procedures in order to reduce variability in studies' methodology.

## Age

A variable that may have potentially influenced the results is age. It has been suggested that different executive processes decline with increasing age, and this decline has been associated with changes in brain areas including frontal lobes and their connections with other brain areas (e.g., Jurado and Rosselli, 2007 for a review). In our sample, about the 60% of the studies reported significant differences between insomnia those with insomnia and controls on EFs, without remarkable differences between studies conducted in adult and elderly populations. Only two studies were conducted on young adults (Covassin et al., 2011; Cellini et al., 2014), and both reported significantly impaired performance in those with insomnia compared to controls respectively on tasks of inhibitory control and working memory. However, the studies were conducted by the same research group and this may potentially limit the generalization of the results. Moreover, differences in age between those with insomnia and controls were limited, with the exception of one study including participants with insomnia 10 years older than controls (Khassawneh et al., 2018). In summary, age is a variable that should be further investigated in cognitive studies conducted in insomnia. Also, there is a dearth of literature on EFs in elderly and young adults with insomnia.

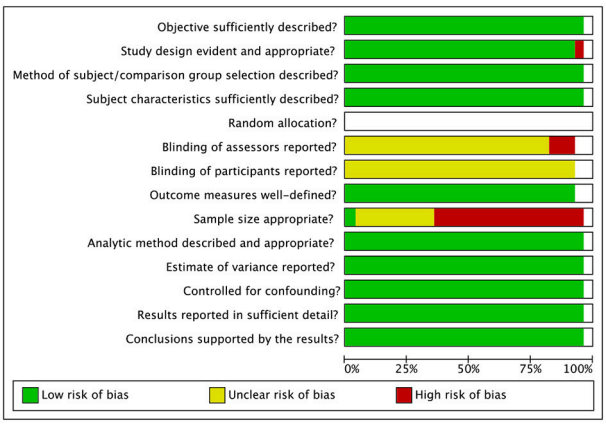


**FIGURE 8 |** Risk of bias graph.

## Limitations

Although the current review provides a comprehensive synthesis of the literature concerning EFs and insomnia, there are several limitations which should be acknowledged. Consistent with Cochrane guidelines for systematic reviews (Higgins and Green, 2011), we searched three databases. It is possible that searching additional databases (e.g., EMBASE) may have produced additional studies, although our other approaches (e.g., searching reference lists of included papers) make this less likely. Also, in this review, we adopted the definition of EFs based on inhibitory control, working memory, and cognitive flexibility (Miyake et al., 2000; Diamond, 2013), a very influential classification recently used in the context of insomnia research (Fernandez-Mendoza et al., 2010; Vgontzas et al., 2013). However, as aforementioned, controversies and divergences on the definition and conceptualisation of EFs, with many other models of EFs previously proposed (see Gratton et al., 2017 for a review); thus, future systematic reviews integrating those models may highlight further important findings and achieve different conclusions. Additionally, the identification and categorisation of executive tasks used in this review may also present some limitations. We decided to base the identification and categorisation of the tests on recent literature (Fortier-Brochu et al., 2012; Diamond, 2013; Snyder et al., 2015) whilst other researchers in the field have used different classifications (Shekleton et al., 2010). Thus, it is possible that slightly different results may emerge due to the use of different classifications of the tasks. Also, we decided to extract data on objective sleep derived from both actigraphy and polysomnography and to consider these measures in the same analysis. Although both measures allow to objectively assess TST and SE, the two measures are based on different psychophysiological processes. Actigraphy is based on body movements while polysomnography is based on a combination of electroencephalogram, electrooculogram and electromyogram, which also permits derivation of sleep architecture information. It has been observed in validation studies, that TST and SE derived from the two methods of assessment correlate ($r = 0.87$ for TST and $r = 0.56$ for SE; e.g., Lichstein et al., 2006; Williams et al., 2018). However, contrasting evidence also suggested limited validity of actigraphy when compared to polysomnography (e.g., Sànchez-Ortun o et al., 2010; Natale et al., 2014). We decided to pool them in the same analysis to reach a sufficient number of effect sizes to analyse. However, given contrasting literature, the two measures may be ideally considered in different analyses in future studies with larger samples. Relatedly, we focussed on TST and SE as two measures reflecting night-time symptoms of insomnia (i.e., longer time needed to fall asleep, frequent and long nocturnal awakenings). While TST is a measure of sleep duration, SE is generally considered a measure of general sleep quality. Thus, the two measures may potentially have differential effects on EFs. Given the limited number of studies included in this review, we were limited in investigating the differential effect of SE and TST on EFs in meta-analysis. Again, it is important for future studies to include objective measures of SE and TST to better elucidate their effects on EFs performance in insomnia.

## Conclusions

The study of EFs has dramatically increased in recent years in the context of mental health. However, EFs are still under-investigated in insomnia. To make a comparison, a recent and already cited review of meta-analytic literature (Snyder et al., 2015) found that ten meta-analyses were conducted studying EFs in bipolar, eight in schizophrenia, seven in substance use, four in anxiety and two in depressive disorders, while only one meta-analysis was conducted in samples with insomnia (Fortier-Brochu et al., 2012). This discrepancy is particularly surprising given the well documented detrimental effects of insomnia on daytime variables in which EFs may play an important role, such as memory, attention and concentration and emotion regulation (Kyle et al., 2013; Harris et al., 2015; Cellini, 2016) and the consideration of insomnia as a transdiagnostic process across mental disorders (Harvey, 2009; Dolsen et al., 2014). Future studies with comparable procedures of neuropsychological assessment are needed to clarify the nature and strength of the association between insomnia and EFs deficits. Such standardisation of assessments could lead to important clinical and research applications. Interventional studies, aiming at investigating whether EFs impairments in insomnia are reversible are needed. Randomised controlled trials of cognitive behavioural therapy for insomnia showed promising results on core EFs (Herbert et al., 2018). Nevertheless, replication studies are needed to consolidate these results and evaluate the cost-effectiveness of such treatment approaches on factors including healthcare utilisation and burden of illness (e.g., absenteeism, workplace errors, quality of life). Additionally, it is yet to be explored whether improvement in EFs after insomnia treatment is associated with ameliorate subjective functioning (Kyle et al., 2013; Ballesio et al., 2018). Future research is particularly needed on elderly and young adults which are under-investigated populations. Moreover, researchers should consider variables that are largely neglected in this field, including, besides objective sleep, the time of testing, that may influence study results due the

fluctuations of circadian rhythm (e.g., Varkevisser and Kerkhof, 2005).

## AUTHOR CONTRIBUTIONS

AB run the literature searches, extracted qualitative and quantitative data, assessed the risk of bias, run the analyses, and wrote the draft of the manuscript. MRJVA screened the abstracts and full-texts, assessed the risk of bias, and revised the draft. SK, FF, and CL provided intellectual and analytical advices, supervised the work, and revised the manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.00101/full#supplementary-material

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# The Fate of Emotional Memories Over a Week: Does Sleep Play Any Role?

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Although there is a wide consensus on how sleep processes declarative memories, how sleep affects emotional memories remains elusive. Moreover, studies assessing the long-term effect of sleep on emotional memory consolidation are scarce. Studies testing subclinical populations characterized by REM abnormalities are also lacking. Here we aimed to (i) investigate the fate of emotional memories and the potential unbinding (or preservation) between content and affective tone over time (i.e., 1 week), (ii) explore the role of seven nights of sleep (recorded via actigraphy) in emotional memory consolidation, and (iii) assess whether participants with self-reported mild-moderate depressive symptoms forget less emotional information compared to participants with low depression symptoms. We found that, although at the immediate recognition session emotional information was forgotten more than neutral information, a week later it was forgotten less than neutral information. This effect was observed both in participants with low and mild-moderate depressive symptoms. We also observed an increase in valence rating over time for negative pictures, whereas perceived arousal diminished a week later for both types of stimuli (unpleasant and neutral); an initial decrease was already observable at the immediate recognition session. Interestingly, we observed a negative association between sleep efficiency across the week and change in memory discrimination for unpleasant pictures over time, i.e., participants who slept worse were the ones who forgot less emotional information. Our results suggest that emotional memories are resistant to forgetting, particularly when sleep is disrupted, and they are not affected by non-clinical depression symptomatology.

**Keywords: actigraphy, arousal, emotional memory, sleep, valence, time**

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## INTRODUCTION

In the last two decades, several studies have shown that sleep plays an important role in memory processing (Rasch and Born, 2013), including emotional memory, which can be defined as the memory of an event or experience that evokes an emotional response (Kensinger, 2009). According to the active system consolidation model (Diekelmann and Born, 2010), information initially encoded during wakefulness is repeatedly reactivated and reorganized during the subsequent sleep period in order to transform the labile memory trace into long-lasting memories. A key role in this

process seems to be played by non-rapid eye movement (NREM, composed by N1, N2, and N3 stages) sleep, whose physiology seems to promote the reactivation of specific information at the hippocampal level and its reorganization and consolidation at cortical level (Staresina et al., 2015; Klinzing et al., 2016). However, while there is a wide consensus on how sleep, especially NREM sleep, processes declarative memory and, to a certain degree, procedural memories, how sleep affects emotional memories remains elusive (Ackermann and Rasch, 2014; Cellini and Capuozzo, 2018).

Although some recent studies have suggested a key role of NREM sleep in emotional memory processing (Hauner et al., 2013; Cellini and Parma, 2015; Diekelmann and Born, 2015; Cellini et al., 2016), most of the studies have focused on the role of REM sleep (Tempesta et al., 2017) due its unique state characterized by the suppression of adrenergic activity coupled with a large activation in the amygdala-hippocampal networks (Genzel et al., 2015; Pace-Schott et al., 2015). However, as recently highlighted by Bolinger et al. (2018), two contrasting hypotheses have been put forward about the role of REM sleep in emotional processing.

The first hypothesis, which is based on the "Sleep to Forget and Sleep to Remember" model (SFSR; Walker and van Der Helm, 2009), proposes that sleep depotentiates the emotional tone of experience while preserving the content of that event. Therefore, this model suggests that over several REM cycles the emotional tone (e.g., indexed by neural, peripheral, and subjective arousal) should decrease. The second hypothesis ("emotional salience view") stems from studies showing a conservation of the emotional content after a sleeping period (Pace-Schott et al., 2011; Baran et al., 2012; Werner et al., 2015; Cellini et al., 2017) suggesting that REM sleep may instead preserve the emotional component of an experience during the consolidation of its content. In a recent review of the literature, Genzel et al. (2015) tried to merge these two hypotheses suggesting that REM sleep may promote the optimal process (preservation or reduction) depending on the nature of the information to be processed, in order to promote the most adaptive behavioral response during the next wakefulness.

The main issue about these models is that the majority of studies trying to test them have used a single-night (or nap) designs that could be insufficient to entirely capture the critical modulating role of sleep in emotional processing over time. Indeed, it seems plausible that several sleeping periods are needed to unbind the content and the emotional experience of an event. Moreover, given the focus of these models on the REM sleep, it is surprising that studies with clinical and subclinical populations characterized by abnormal REM sleep, such as narcolepsy (Cellini, 2017) or depression (Pillai et al., 2011; Palagini et al., 2013) are lacking. To our knowledge, there are only two studies, from the same group, investigating the relationship between sleep and emotional memory in a subclinical population with depressive symptoms (Harrington et al., 2018a,b). In one study, the authors tested two groups of participants with either minimal or mild-to-moderate depressive symptoms [based on the Beck Depression Inventory (BDI-II; Beck et al., 1996) scores] on a memory recognition task with emotional pictures and a within-subjects split-night design (Harrington et al., 2018a). In this paradigm, memory testing occurred after an N3-rich sleep in the first half of the night or a REM-rich sleep in the second half of the night, allowing them to differentiate (although with some limitations due to circadian and fatigue confounds) the role of N3 and REM sleep in emotional memory processing. They found a benefit for N3 sleep on neutral stimuli, and a marginal benefit for REM sleep on unpleasant pictures in the participants with mild-to-moderate depressive symptoms compared to the minimal depressive symptoms group. Also, they showed that participants with mild-to-moderate depressive symptoms had a greater REM density (number of rapid-eye movements/REM sleep duration), and a marginally greater number of rapid-eye movements in the second half of the night compared to the minimal depression group. In addition, the number of rapid-eye movements and REM density were positively associated with the discrimination of unpleasant pictures at the delayed recognition session. In the other study (Harrington et al., 2018b), the authors used the same groups and the same task but with a different protocol: participants underwent either a 12-h sleep or 12-h sleep deprivation between the encoding and the delayed recognition sessions. This time they found no differences in emotional memory consolidation between the two groups and no association between REM sleep and the consolidation of memories of unpleasant pictures. However, participants with mild-to-moderate depressive symptoms showed a lower memory retention in the sleep deprivation condition compared to the normal sleep condition for negative and neutral images (but not positive), whereas the minimal depressive symptom group showed no differences in the consolidation of negative and neutral images across conditions (although sleep deprivation impaired their ability to consolidate positive images). Whilst these findings suggest that emotional memory processing during sleep is affected by depressive symptomatology, further research is needed on this topic.

Based on this literature, here we aimed to (i) investigate the fate of emotional memories and the potential unbinding (or preservation) between emotional content and affective tone over time (i.e., 1 week); (ii) explore the impact of seven nights of sleep (recorded via actigraphy) on emotional memory consolidation; and (iii) assess whether participants with self-reported mild-moderate depressive symptoms forget less emotional memory information compared to participants with low depressive symptoms.

# MATERIALS AND METHODS

## Participants

Forty-eight university students (27 F, Mean age ± Standard Deviation = 23.10 ± 2.53 years) participated in the study. All participants were enrolled through advertisements posted at the University of Padua and they underwent an online screening to ensure they met the eligibility criteria for the study. Exclusion

criteria for all participants were the presence of psychiatric (e.g., clinical depression, anxiety disorders) or somatic diseases as evaluated by the screening questionnaires.

Based on their BDI-II scores, they were divided into lower depressive symptoms (LDS; $N$ = 30) and higher depressive symptoms (HDS; $N$ = 18) groups. The LDS group had BDI-II scores lower than 13 (i.e., the Italian BDI-II cut-off for minimal depression; Ghisi et al., 2006), whereas the HDS group had BDI-II scores between 13 and 28 (i.e., mild-moderate depression).

The study protocol was approved by the Ethics Committee of the Department of Psychology, University of Padua, and all the participants signed a written informed consent before participating in the study.

## Self-Reported Questionnaires

### Pittsburg Sleep Quality Index (PSQI)

The level of self-reported sleep disturbances was assessed using the Pittsburg Sleep Quality Index (PSQI), a widely used questionnaire composed of 19 items (Buysse et al., 1989; Mollayeva et al., 2016). The scores range from 0 to 21, with 0 indicating no difficulties and 21 severe sleep difficulties. The commonly used cut-off to differentiate good from bad sleepers is >5 (Buysse et al., 1989; Curcio et al., 2013; Mollayeva et al., 2016).

### Beck Depression Inventory-II (BDI-II)

The Beck Depression Inventory-II (BDI-II) is a 21-item questionnaire to assess the severity of depressive symptomatology (Beck et al., 1996). The total score ranges from 0 to 63, with the higher scores indicating more severe depressive symptoms. For the Italian version of the BDI-II, a score of 13 is considered as the optimal cut-off to discriminate individuals with and without depressive symptoms (Ghisi et al., 2006).

### State-Trait Anxiety Inventory Y2 (STAI-Y2)

The trait anxiety level was assessed using the State-Trait Anxiety Inventory version Y2 (STAI-Y2) (Spielberger, 2010). This self-report questionnaire is composed of 20 items, with a total score ranging from 20 to 100. Higher scores indicate greater anxiety levels.

### Circadian Preferences

Circadian preferences were assessed using the reduced version of morningness–eveningness questionnaire (MEQr, Adan and Almirall, 1991), translated into Italian (Natale, 1999; Natale et al., 2006a,b). This questionnaire assesses self-reported chronotype using 5 items, with a total score ranging from 4 to 35, which categorize participants into evening (scores <11), intermediate (scores between 11 and 18), and morning types (scores >18).

## Emotional Memory Task

All the participants performed an emotional memory task divided into encoding and two recognition sessions (immediate and delayed recognition sessions). One-hundred and sixty digitized pictures were selected from the International Affective Picture System (IAPS) (Lang et al., 2008) based on their normative arousal and valence ratings and were organized in four sets of 40 pictures, each composed of 20 unpleasant stimuli (attacking humans and animals, injuries, and mutilations; mean normative ratings: arousal 5.75, valence 2.71) and 20 neutral stimuli (household objects, neutral faces and urban landscapes; mean normative ratings: arousal 3.11, valence 4.96). The sets were balanced in terms of normative valence and arousal ratings (see **Supplementary Material**). The presentation of the sets and the sequence of the blocks within each set were counterbalanced across participants using a Latin square design.

During the encoding task (**Figure 1**), participants were exposed to a set of 40 neutrals and 40 unpleasant pictures. At the beginning of each trial, a gray cross (+) appeared at the center of a black screen (duration: 1 s) followed by the presentation of one of the pictures for 2 s. After that, participants were asked to decide (no time limit) whether in the pictures there were one or more persons or not, by pressing the "A" or the "L" button, respectively, on a QWERTY keyboard. This request was aimed to force participants to attend to the features of the images, and

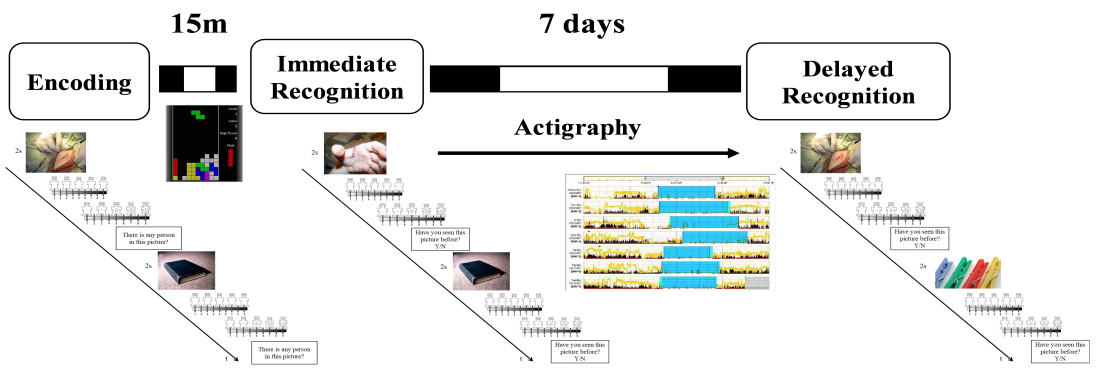


**FIGURE 1 |** Schematic representation of the experimental procedure. During the encoding session, participants were exposed to 40 neutral (objects, neutral faces) and 40 negative (injuries, attacking humans, and animals) pictures. They were asked whether a person was present in the picture or not. After each picture they rated how they felt in term of valence and arousal. After the task they played Tetris for 15 min before performing an immediate recognition session. During the immediate (15 min later) and the delayed (7 days later) recognition task, half of the pictures previously presented were randomly rearranged and intermixed with 40 new pictures similar in term of content, and normative valence and arousal ratings. Participants had to decide whether they had seen or not the picture in the previous session. Between the immediate and the delayed recognition sessions participants wore an actigraph and complete a daily sleep log.

also as a check to ensure that the participants remained focused during the task. Afterward, participants rated their subjective valence (i.e., state of pleasantness) and arousal (i.e., state of activation) evoked by picture viewing using two 9-point graphic scales (from 1 to 9) of the computerized version of the Self-Assessment Manikin (Lang et al., 2008). The 80 pictures were presented in a random order for all the participants.

In both the immediate and the delayed recognition tasks, participants were exposed again to 80 pictures, 40 already presented in the encoding task (20 neutral and 20 unpleasant) intermixed with 40 new pictures (20 neutral and 20 unpleasant). In this case, after picture presentation, participants had to decide whether they had already seen the pictures before or not, by pressing the "A" or the "K" button, respectively. The task was implemented and run with E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, United States).

Performance in this task was computed using signal detection theory (Macmillan and Creelman, 2004). For each participant and for each recognition session, we computed the following variables separately for neutral and unpleasant stimuli: Hits (i.e., the number of old pictures correctly defined as seen), Correct Rejections (i.e., the number of novel pictures correctly defined as never seen), Misses (i.e., the number of old pictures mistakenly defined as never seen), and False Alarms (i.e., the number of novel pictures mistakenly defined as seen). From these variables we calculated the Hit Rate (HR), the False Alarm Rate (FAR), and the memory discrimination index (*d*') as the difference between the z-transformed (normalized) probabilities of Hit Rate and False Alarm Rate [*d*' = z(HR) – z(FAR)]. Since *d*' cannot be calculated when HR = 1 or FAR = 0, we replaced HR values of 1 and FAR values of 0 with 1 – 1/(2N) and 1/2N, respectively, where N equals the number of targets (Macmillan and Creelman, 2004).

## Actigraphic Recording

Participants' sleep patterns were assessed using the Actiwatch-64 (AW-64; Philips Respironics, Portland, OR, United States), a reliable actigraph to objectively measure sleep parameters based on the level of physical activity (Cellini et al., 2013). Actigraphic data were collected for 7-days in 1-min epochs. Participants were instructed to continuously wear the actigraph on the non-dominant wrist and to press the AW-64 marker button every time they switched off/on the light to sleep and to get up from the bed, or when they had to remove the AW-64 for any reason (e.g., coming in contact with water). Actigraphic data were analyzed using the Actiware 6.2 software (Phillips Respironics, Portland, OR, United States), using the Medium threshold setting (40 activity counts/epoch to define a wake state). All analyses were confined to the period between lights off and lights on, which was defined based on both the presence of marker placement and bedtimes and waketimes reported by the participants in their sleep diary. For each participant and for every night we calculated the total sleep time (TST, min), defined as the number of minutes scored as sleep between lights off and lights on; sleep onset latency (SOL, min), the number of minutes between lights out and the first epoch scored as sleep; wake after sleep onset (WASO, min), the number of minutes scored as WASO; and sleep efficiency (SE, %), the ratio between TST and total time spent in bed.

## Procedure

Participants completed online a battery of questionnaires including the BDI-II, the PSQI, the STAI-Y2, and the rMEQ. Then, participants were scheduled for the experimental session in the lab where they first performed the encoding session and, 15 min after the end of the encoding, they had the immediate recognition session (**Figure 1**). Between the encoding and the immediate recognition sessions, participants played with a freely available version of Tetris in order to avoid active rehearsal of the pictures. Before leaving the lab, participants received a sleep diary, a wrist actigraph, and the instruction to use these instruments during the following 7 days. A week later, they returned to the laboratory at the same time as the week before to give back the sleep diary and the actigraph, and to perform the delayed recognition session.

## Statistical Analysis

Demographics and sleep variables were compared between the two groups using independent *t*-tests and $\chi^2$ for continuous and categorical data, respectively.

Separate 2 × 2 × 2 ANOVAs with *Group* (LDS, HDS) as a between-subject factor, and *Category* (Unpleasant, Neutral) and *Session* (Immediate, Delayed) as within-subject factors were run to assess group differences in the memory parameters (i.e., Schematic representation, HR, FAR).

For the analysis of the self-rated arousal and valence, we calculated separately the mean valence and arousal ratings from the encoding session for images that subsequently appeared in the immediate and delayed recognition test ("old" images). Then we analyzed these data with separate 2 × 2 × 2 ANOVAs with *Group* (LDS, HDS) as a between-subjects factor and *Category* (Unpleasant, Neutral) and *Session* (Encoding, Immediate, or Delayed Recognition Test) as within-subject factors for the self-rated arousal and valence. This approach, focusing only on target images, allowed us to assess the presence of any habituation effect due to the mere re-exposure to similar images (immediate recognition test) or to slower emotional processing that may occur across the 7-day interval.

Fisher's Least Significant Difference test was used for *post hoc* comparisons and partial eta squared ($\eta_p^2$) was reported as estimate of effect size.

Pearson's correlations were run to explore potential associations between sleep parameters averaged across the week (see **Table 1**) and the change (computed as delayed minus immediate test score) in behavioral variables (d', HR, FAR, arousal, and valence).

# RESULTS

Descriptive statistics of the sample are presented in **Table 1**.

The HDS group showed a higher BDI-II score, reflecting the selection criteria, as well as higher STAI-Y2 and PSQI scores, which are usually positively associated with BDI-II scores (e.g., Demirci et al., 2015; Mollayeva et al., 2016; Çelik et al., 2018). At the objective sleep level, the only differences were observed for the sleep onset latency: on average, HDS

**TABLE 1 |** Demographics, psychological measures, and sleep parameters of the sample.

| | LDS | | HDS | | | | |
|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | $t_{(45)}$ | *p* | **Cohen's *d*** |
| **Demographics and baseline measures** | | | | | | | |
| Age | 23.32 | 3.01 | 22.74 | 1.46 | 0.77 | 0.443 | 0.23 |
| Gender (F/M) | 19/11 | | 8/10 | | 1.63* | 0.20* | |
| BDI-II | 5.93 | 3.72 | 18.72 | 4.74 | −10.39 | <0.001 | −3.10 |
| STAI-Y2 | 38.47 | 8.38 | 56.56 | 10.65 | −6.54 | <0.001 | −1.95 |
| PSQI | 5.67 | 2.06 | 7.82 | 2.63 | −3.12 | 0.003 | −0.95 |
| MEQr | 14.00 | 2.65 | 13.29 | 4.25 | 0.70 | 0.490 | 0.21 |
| **Sleep parameters** | | | | | | | |
| Bed time (hh:mm) | 1:02 | 00:59 | 1:16 | 1:15 | −0.65 | 0.517 | −0.20 |
| Wake time (hh:mm) | 8:43 | 00:59 | 8:41 | 00:44 | 0.12 | 0.906 | 0.04 |
| Time in bed (min) | 454.81 | 36.99 | 445.16 | 48.75 | 0.71 | 0.483 | 0.21 |
| Sleep latency (min) | 6.62 | 7.96 | 11.24 | 5.64 | −2.32 | 0.025 | −0.70 |
| WASO (min) | 49.82 | 23.53 | 43.20 | 26.02 | 0.87 | 0.391 | 0.26 |
| Total sleep time (min) | 398.37 | 48.22 | 390.72 | 47.34 | 0.53 | 0.600 | 0.16 |
| Sleep efficiency (%) | 87.55 | 6.10 | 87.69 | 5.71 | −0.08 | 0.938 | −0.02 |

*BDI-II, Beck Depression Inventory-II; STAY-Y2, State-Trait Anxiety Inventory Y2; PSQI, Pittsburg Sleep Quality Index; MEQr, reduced version of morningness–eveningness questionnaire; WASO, wake after sleep onset.* $^*\chi^2$ *value.*

took longer to fall asleep than LDS. No other significant difference was observed. Comparing objective (actigraphy) and subjective (sleep diary) sleep parameters, we observed longer reported time spent in bed, asleep, trying to fall asleep and higher sleep efficiency for the subjective measures (see **Supplementary Material** for the full statistics). This is likely due to the tendency of the participants to "round up" the reported time (e.g., instead of 7 h and 20 min spent in bed they tend to report 7 h and 30 min). Nevertheless, no differences between the two depressive symptom groups were observed for sleep diary parameters (all *p*'s > 0.29, **Supplementary Table S2**).

## Valence and Arousal Ratings

### Immediate Recognition Test

The analysis on valence ratings (**Figure 2A**) showed a significant Session main effect ($F_{1,46}$ = 19.23, $p$ < 0.001, $\eta_p^2$ = 0.20), with a general increase in the valence of the images in the immediate test compared to the encoding session. A significant Session × Category interaction was found ($F_{1,46}$ = 10.01, $p$ = 0.003, $\eta_p^2$ = 0.18, **Figure 2B**), with a significant increase in valence for the unpleasant stimuli (i.e., they became less unpleasant) in the immediate test compared to the encoding session ($p$ < 0.001). We also observed a significant Category main effect ($F_{1,46}$ = 338.569, $p$ < 0.001, $\eta_p^2$ = 0.88), with higher valence ratings for neutral than unpleasant pictures, and a Group main effect ($F_{1,46}$ = 4.26, $p$ = 0.045, $\eta_p^2$ = 0.08, **Figure 2C**), with a generally higher self-reported valence for the HDS group than the LDS group. This latter result seems to be driven specifically by the higher valence for unpleasant stimuli (i.e., less unpleasant) in the HDS compared to the LDS group ($p$ = 0.005), even if the Group × Category interaction did not reach statistical significance ($F_{1,46}$ = 3.41, $p$ = 0.071, $\eta_p^2$ = 0.07).

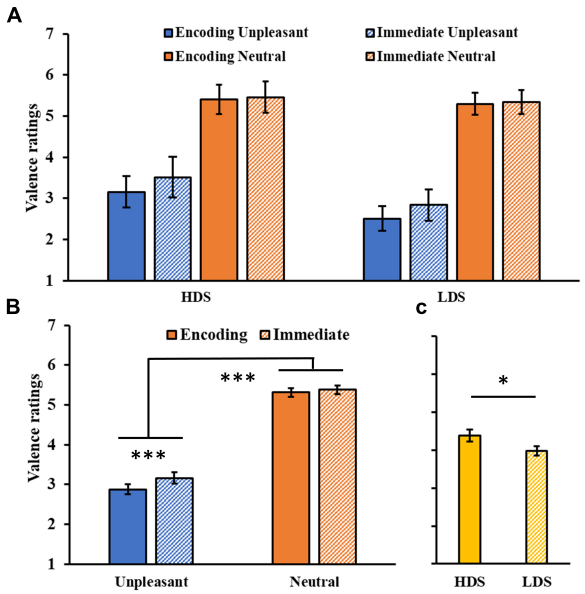


**FIGURE 2 | (A)** Valence ratings as a function of the group and of the category of stimuli (unpleasant and neutral pictures) at the encoding and at the immediate recognition sessions. **(B)** Session (encoding and immediate recognition sessions) × Category (unpleasant and neutral pictures) interaction for the valence ratings. **(C)** Group (HDS and LDS) main effect for valence ratings. LDS: participants with lower depression symptoms; HDS: participants with higher depression symptoms. Error bars represent standard error of the mean. *$p$ < 0.05; ***$p$ < 0.001.

The analysis of the arousal ratings (**Figure 3A**) showed a significant Category main effect ($F_{1,46}$ = 142.43, $p$ < 0.001, $\eta_p^2$ = 0.76), with higher arousal ratings for unpleasant than neutral pictures, and a significant Group × Category interaction

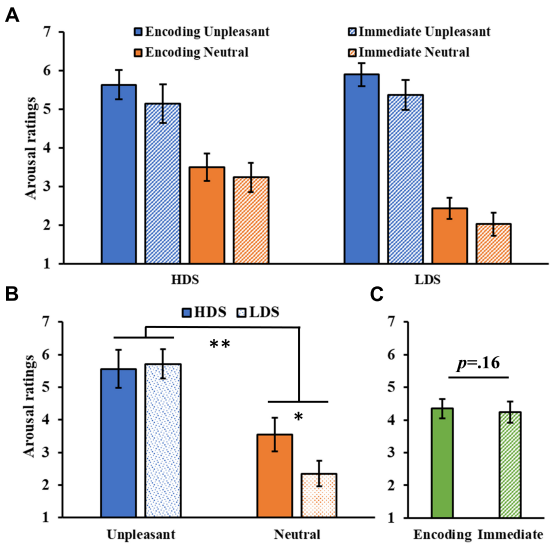


**FIGURE 3 | (A)** Arousal ratings as a function of the group and of the category of stimuli (unpleasant and neutral pictures) at the encoding and at the immediate recognition sessions. **(B)** Group (HDS and LDS) × Category (unpleasant and neutral pictures) interaction for the arousal ratings. **(C)** Session (encoding and immediate recognition sessions) main effect for arousal ratings. LDS: participants with lower depression symptoms; HDS: participants with higher depression symptoms. Error bars represent standard error of the mean. *$p < 0.05$; **$p < 0.01$.

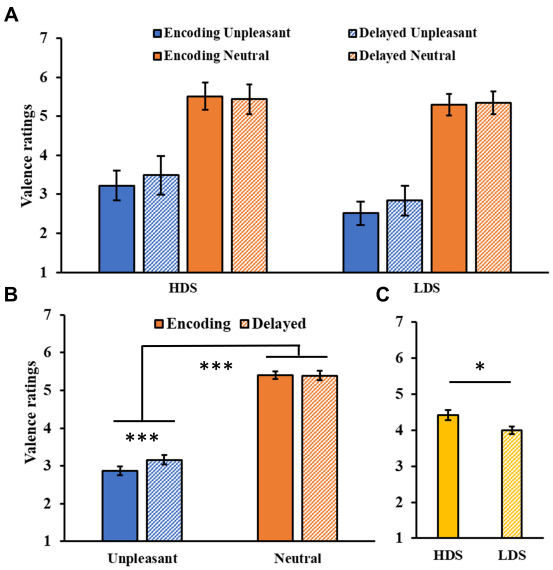


**FIGURE 4 | (A)** Valence ratings as a function of the group and of the category of stimuli (unpleasant and neutral pictures) at the encoding and at the delayed recognition sessions. **(B)** Session (encoding and delayed recognition sessions) × Category (unpleasant and neutral pictures) interaction for the valence ratings. **(C)** Group (HDS and LDS) main effect for valence ratings. LDS: participants with lower depression symptoms; HDS: participants with higher depression symptoms. Error bars represent standard error of the mean. *$p < 0.05$; ***$p < 0.001$.

($F_{1,46}$ = 9.02, $p$ = 0.004, $\eta_p^2$ = 0.16, **Figure 3B**), with the HDS group showing higher arousal scores for neutral pictures compared to the LDS group ($p$ = 0.017). No main effect of Session was observed ($F_{1,46}$ = 2.06, $p$ = 0.16, $\eta_p^2$ = 0.04, **Figure 3C**).

### Delayed Recognition Test

The analysis of valence ratings (**Figure 4A**) showed a significant Session main effect ($F_{1,46}$ = 6.21, $p$ = 0.016, $\eta_p^2$ = 0.12), and a significant Session × Category interaction ($F_{1,46}$ = 15.00, $p < 0.001$, $\eta_p^2$ = 0.25, **Figure 4B**), with a significant increase in valence for the unpleasant stimuli (i.e., they became less unpleasant) in the delayed recognition test compared to the encoding session ($p < 0.001$). The analysis also showed a significant Category main effect ($F_{1,46}$ = 285.31, $p < 0.001$, $\eta_p^2$ = 0.86), with higher valence ratings for neutral than unpleasant pictures, and a Group main effect ($F_{1,46}$ = 5.46, $p$ = 0.024, $\eta_p^2$ = 0.11, **Figure 4C**), with a generally higher self-reported valence for the HDS group. Again, this latter result seems to be driven specifically by the higher valence for unpleasant stimuli (i.e., less unpleasant) in the HDS compared to the LDS group ($p$ = 0.004), even if the Group × Category interaction did not reach statistical significance ($F_{1,46}$ = 3.48, $p$ = 0.068, $\eta_p^2$ = 0.07). No other significant differences were observed.

The analysis of the arousal ratings (**Figure 5A**) showed a significant Category main effect ($F_{1,46}$ = 155.09, $p < 0.001$, $\eta_p^2$ = 0.77), with higher arousal ratings for unpleasant than neutral pictures. A significant Group × Category interaction ($F_{1,46}$ = 10.01, $p$ = 0.003, $\eta_p^2$ = 0.18, **Figure 5B**), revealed that the HDS group showed higher arousal scores for neutral pictures compared to the LDS group ($p$ = 0.023). Unlike the immediate test results, this time we observed a main effect of Session ($F_{1,46}$ = 9.67, $p$ = 0.003, $\eta_p^2$ = 0.17, **Figure 5C**), with a general decrease in arousal for both category of stimuli in the delayed recognition test compared to the encoding session. No other significant differences were observed.

## Memory Performance

### Encoding

During the encoding phase, participants detected the presence of one/more person with an accuracy of (Mean ± SD) 94.25 ± 4.96%, indicating a high level of attentional focus on the pictures presented on the screen.

### Memory Discrimination (*d'*)

The analysis of the consolidation of the stimuli over time (i.e., the discriminability of the encoding pictures in the immediate and delayed recognition sessions) showed a significant Session main effect ($F_{1,46}$ = 246.85, $p < 0.001$, $\eta_p^2$ = 0.84), with *post hoc* tests indicating a lower memory discrimination index (*d'*) for the stimuli at the delayed compared to the immediate recognition session ($p < 0.001$). We also observed a significant Session × Category interaction ($F_{1,46}$ = 4.08, $p$ = 0.049, $\eta_p^2$ = 0.08, **Figure 6A**), with a higher memory discrimination index for neutral stimuli relative to unpleasant pictures at the immediate ($p$ = 0.019), but not the delayed recognition session ($p$ = 0.450), indicating less forgetting of the unpleasant stimuli. To confirm this result, we compared the memory consolidation score (i.e.,

delayed minus immediate *d*' score) of the two stimuli category, showing the same result ($t_{96} = 2.13$, $p = 0.036$, **Figure 6B**).

### Hit Rate and False Alarm Rate

The analysis of the hit rate showed only a significant main Session effect ($F_{1,46} = 115.97$, $p < 0.001$, $\eta_p^2 = 0.71$), with a decrease in hit rate in the delayed session compared to the immediate one (**Figure 7A**).

The analysis of the false alarm rate showed a significant main Category effect ($F_{1,46} = 8.08$, $p = 0.007$, $\eta_p^2 = 0.15$, **Figure 7B**), with a higher false alarm rate for the unpleasant stimuli. A significant main Session effect ($F_{1,46} = 12.60$, $p < 0.001$, $\eta_p^2 = 0.22$) revealed an increased false alarm rate in the delayed session compared to the immediate one (**Figure 7C**).

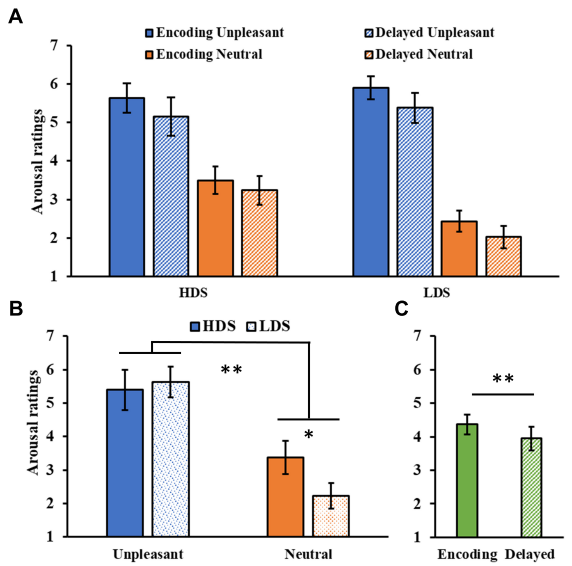


**FIGURE 5 | (A)** Arousal ratings as a function of the group and of the category of stimuli (unpleasant and neutral pictures) at the encoding and at the delayed recognition sessions. **(B)** Group (HDS and LDS) × Category (unpleasant and neutral pictures) interaction for the arousal ratings. **(C)** Session (encoding and delayed recognition sessions) main effect for arousal ratings. LDS: participants with lower depression symptoms; HDS: participants with higher depression symptoms. Error bars represent standard error of the mean. *$p < 0.05$; **$p < 0.01$.

## Correlational Analyses on Performance and Sleep Parameters

We observed a negative association between sleep efficiency (SE, %) and memory consolidation score of unpleasant stimuli over time in the HDS group ($r = -0.57$, $p = 0.018$), but not in the LDS group, which showed a similar pattern without reaching a statistical significance ($r = -0.21$, $p = 0.274$, **Figure 8**). This association was also present when the two groups were merged ($r = -0.32$, $p = 0.026$, **Supplementary Figure S1**), and by correcting the correlation of the whole sample for the BDI-II scores (partial correlation with BDI-II as covariate, $r = -0.33$, $p = 0.026$). These results indicate that in the participants with higher symptoms of depression, lower sleep quality was associated with less forgetting of emotional stimuli. Comparing the two correlation slopes with the Fisher's r-to-z transformation (Cohen et al., 2003), we did not observe a significant difference between the groups ($Z = -1.35$; $p = 0.18$, two tails).

## DISCUSSION

In the current study, we aimed to investigate the potential role of sleep in the consolidation of emotional memories over 7 days. Moreover, we wanted to assess emotional memory processing over time in a population at risk of REM abnormality, i.e., individuals with self-reported mild-moderate depressive symptoms.

We found that, although at the immediate recognition session emotional information was forgotten more than neutral information, a week later emotional information was forgotten less than neutral information. This effect was observed both in participants with low and mild-moderate depressive symptoms. We also observed an increase in valence ratings both at the immediate and at the delayed recognition session, suggesting a

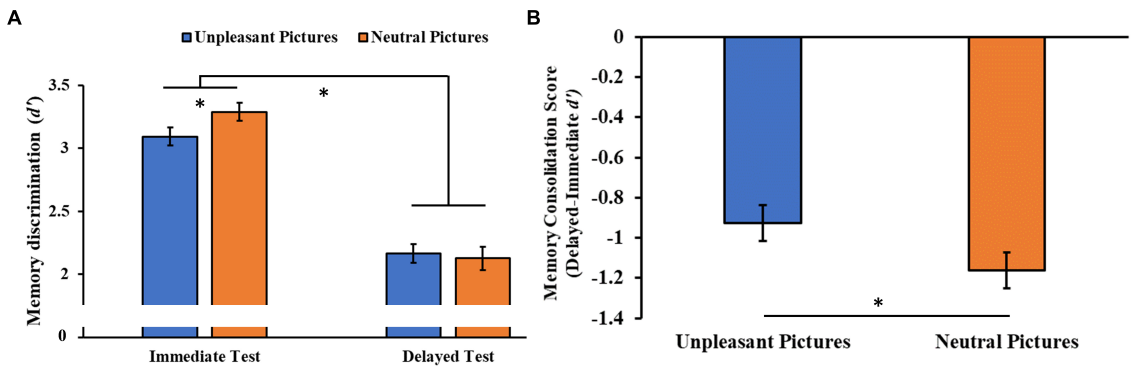


**FIGURE 6 | (A)** Memory discrimination (*d*') as a function of the testing session (immediate and delayed recognition sessions) and of the type of stimuli (unpleasant and neutral pictures). **(B)** Memory consolidation score (delayed minus immediate test *d*' score) as a function of the type of stimuli. Error bars represent standard error of the mean. *$p < 0.05$.

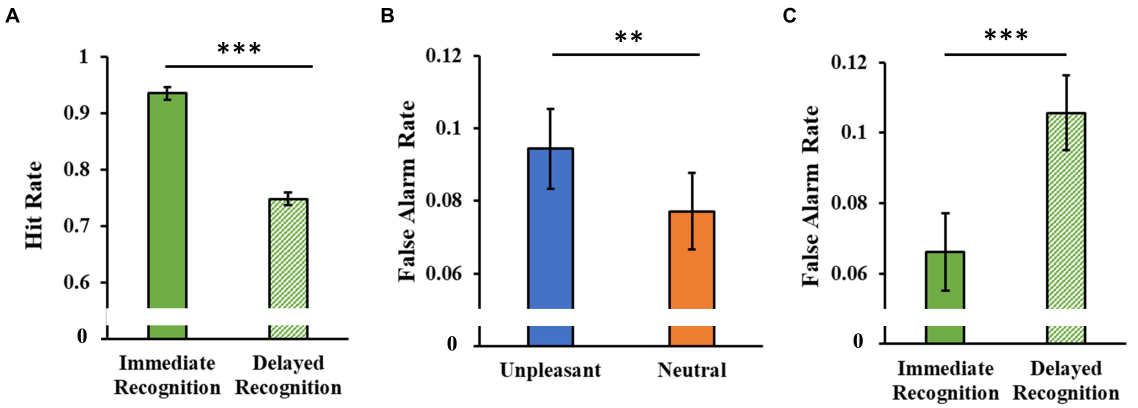


**FIGURE 7 | (A)** Hit rate as a function of the experimental session (immediate and delayed recognition sessions). **(B)** False alarm rate as a function of the type of stimuli (unpleasant and neutral pictures). **(C)** False alarm rate as a function of the experimental session (immediate and delayed recognition sessions). Error bars represent standard error of the mean. $^{**}p < 0.01$; $^{***}p < 0.001$.

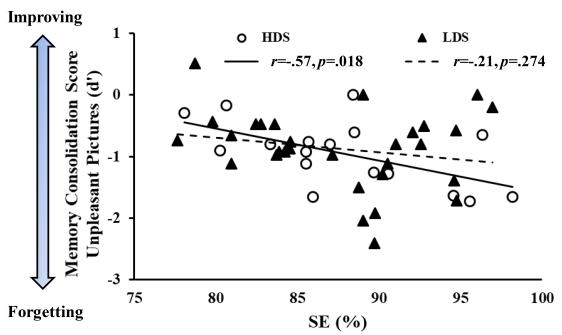


**FIGURE 8 |** Memory consolidation score (*d'* of the delayed minus *d'* of the immediate recognition session) of the unpleasant pictures as a function of sleep efficiency (SE) in the two groups.

habituation effect to these stimuli. Perceived arousal decreased a week later (but not during the first re-exposure to the images, i.e., immediate session) for both types of stimuli (unpleasant and neutral), suggesting a potential role of sleep in the processing of all the stimuli. Interestingly, we observed a negative association between sleep efficiency across the week and change in memory discrimination for unpleasant pictures over time, i.e., participants who slept worse were the ones who forgot less (remembered more) emotional (unpleasant) information. This latter effect was significant for the participants with self-reported mild-moderate depressive symptoms, but the participants with low depressive symptoms showed the same trend.

Regarding memory performance, we observed, consistent with previous studies from our groups (Cellini et al., 2016; Mercurio et al., 2018) and others (Wagner et al., 2007; McKeon et al., 2012), that neutral stimuli are encoded better than the unpleasant ones. This result may seem unexpected given the wide literature about the memory advantage for emotional events (Kaplan et al., 2016). However, an explanation of this finding may be linked to the nature of the task and of the stimuli and the level of their arousal. We used a recognition task, which required encoding the details of the pictures presented (the IAPS pictures); these stimuli are known to reliably evoke an emotional response both at the subjective and physiological levels (Lang et al., 2008). Neutral pictures, due to their low arousal level, may be scanned profoundly, resulting in a better encoding of the picture details. Instead, highly arousing unpleasant pictures can only capture the attention of the participants on the general perspective of the picture (e.g., this is a black spider), leaving limited attentional resources to explore the details of the pictures (e.g., this spider has eight legs). When the participants are exposed to similar pictures (a black spider in a different position with four legs), the limited encoding of the details may increase the number of errors, i.e., the false alarm rate, as observed in the current and in previous studies (see Groch et al., 2014; Cellini et al., 2016). This effect may be similar, to some extent, to the emotional memory narrowing (Kensinger, 2009) and the weapon focus effect (Loftus et al., 1987), characterized by an attentional trade-off for central versus peripheral details of the emotional events (Kaplan et al., 2016).

Interestingly, over the week, the memory of the unpleasant stimuli decayed to a lesser degree, i.e., they were forgotten less. This result is intriguing since it suggests that details of emotional events may be harder than neutral to be encoded, but then they become resistant to forgetting. This result fits well with a study by Dolcos et al. (2005), which showed that memory for unpleasant pictures was greater than for neutral ones 1 year after encoding, and the memory benefit was driven by enhanced recollection (i.e., the process of retrieving contextual information about an event) rather than familiarity (i.e., the feeling of having experienced an event). Another study (Wagner et al., 2006) showed that the content of emotional memory (i.e., emotional texts) can be recognized up to 4 years after the encoding if the participants slept after the encoding. These results suggest that once the details of emotional events are correctly encoded, then this memory become more resistant to forgetting compared to neutral information.

One of the aims of the current study was to test the relationship between sleep and emotional memory in individuals with mild-moderate depressive symptoms. This idea stems from

recent work by Harrington et al. (2018a,b), which was grounded in the observation that individuals with depression show marked changes in sleep pattern, for example, modification in the REM characteristics such as its latency, proportion, and density (Pillai et al., 2011; Palagini et al., 2013). Considering the theories postulating a key role of REM sleep in emotional memory processing (Walker and van Der Helm, 2009; Genzel et al., 2015; Tempesta et al., 2017), alterations in REM sleep should change the emotional processing, for example, by strengthening the salience of emotional information. However, similarly to the sleep condition in the second Harrington et al. (2018b), study here we did not observe any difference in emotional memory consolidation between the groups with different level of depressive symptomatology. Taken together, these results suggest that, at least in a non-clinical population, the level of depressive symptomatology may not affect emotional memory consolidation over time.

Nevertheless, we observed that participants with higher level of depressive symptomatology rated the unpleasant pictures as less unpleasant than the participants with lower BDI-II score, both at the immediate and at the delayed recognition session. Although this may seem the opposite of what one might expect to observe, it is in line with the *emotion context-insensitivity hypothesis* proposed by Rottenberg and Gotlib (2004) which suggests that individuals with depression tend to show less affective modulation (see Rottenberg et al., 2005). This seems to be related to dysfunctional emotional regulation, which makes the emotional response to stimuli more insensitive and less adequate to the context. Although Rottenberg et al. (2005) based their hypothesis on major depressive disorder, it is possible that participants with higher BDI-II scores may have experienced a similar insensitivity (at least to some extent) to the emotional pictures presented in the current study.

From a theoretical perspective, the current data can partially fit the different hypotheses concerning the role of sleep in emotional memory processing (Walker and van Der Helm, 2009; Pace-Schott et al., 2011; Baran et al., 2012; Werner et al., 2015). Emotional pictures were more likely to be retained than neutral pictures across the 7-day interval, which is in line with all the models suggesting a stronger long-term consolidation of emotional over neutral memories. Moreover, the valence ratings of the unpleasant pictures increased over time (i.e., they were perceived as less unpleasant). However, this effect was already present at the immediate recognition session, therefore questioning the role of sleep in reducing the unpleasantness of these memories. Also, while the SFSR hypothesis would predict an arousal decrement only for unpleasant pictures over a week (Walker and van Der Helm, 2009), and the emotional salience view would expect a preservation of the arousal ratings (Pace-Schott et al., 2011; Baran et al., 2012; Werner et al., 2015), here we observed a reduction of perceived arousal over a week for both types of stimuli. Moreover, whilst sleep was associated with memory forgetting, it did not play a critical role in modulating perceived arousal and valence ratings (as indicated by the lack of any correlation between sleep parameters and change in affective ratings). Overall, based on the results of the current study, whether sleep induced a modification in the emotional tone over a week (including several REM cycles, as proposed by the SFSR and the other theoretical models) remains unclear; the current results cannot clearly be interpreted within one of the current models regarding sleep and memory processing.

Nevertheless, our results demonstrate that sleep efficiency was linearly associated with memory forgetting. Although this result may seem counterintuitive, it should be interpreted in the context of a laboratory study. It is plausible that, over time, the brain would get rid of non-useful information (Davis and Zhong, 2017), such as the stimuli used in the current study, to make room for more salient information, in line with the synaptic homeostasis hypothesis (Tononi and Cirelli, 2014). However, as recently proposed by Feld and Born (2017), the sleeping brain sculpts memories by, on the one hand, actively deleting non-useful memory traces (such as neutral non-arousing stimuli) and, on the other hand, by protecting salient arousing information. However, it is plausible that the salience of a memory (useful or non-useful) may change across time, depending on how much individuals use that memory. Indeed, it has been shown that the protective effect of sleep seems to be a function of the time from the encoding to the retrieval, for example, it seems that there is a "protecting" effect of memories in the 24-h after the encoding, but then the sleep benefit begins to disappear (Schönauer et al., 2015; Abel et al., 2018), with forgetting following a log-linear curve over the next days (Murre and Dros, 2015). In the case of emotionally arousing stimuli, such as in the unpleasant pictures of the current study, we can speculate that sleep (at least nocturnal sleep, see Cunningham and Payne, 2017) may promote a stronger initial consolidation of these stimuli to the detriment of neutral ones. This will result in the normal decay for neutral information, which can reach a "plateau" level about 7 days after the encoding (Murre and Dros, 2015). Afterward, it seems that there is a second forgetting phase (Fisher and Radvansky, 2018). Instead, the forgetting curve of unpleasant stimuli may be delayed and it is plausible that a sleep-related forgetting mechanism may still be active about 7 days after the encoding. This delay may explain the positive relationship between sleep efficiency and forgetting observed only for unpleasant stimuli. Moreover, this delay may also be worsened in the HDS group due to potential impairment of neural plasticity, which has been reported in patients with major depressive disorder, and has been associated with maladaptive synaptic downregulation (Wolf et al., 2016). Nevertheless, it should be stressed that since we did not collect memory performance across the week (e.g., after 1–3–5 days after the encoding), this explanation should be considered as mere speculation.

The current results should be interpreted in the context of the study's limitations. For example, we used actigraphy instead of polysomnography (PSG) to assess sleep pattern over a week. Although standard actigraphy is considered a reliable tool to objectively assess sleep, it also has some limits, such as low specificity (i.e., the ability to correctly detect wakefulness) and cannot differentiate across sleep stages, not allowing assessment of the potential role of REM sleep in emotional memory processing over a week. Therefore, the association between sleep efficiency over a week and memory retention should be considered with some caution. Further studies employing

standard PSG, which allow not only the differentiation of sleep stages but also the analysis of micro-sleep architecture (e.g., sleep spindles, slow oscillation, theta activity), can eventually corroborate and extend the current findings. Also, in our sample the depressive symptoms were exclusively evaluated using a single questionnaire (the BDI-II) administered once, and the inclusion criteria for the minimal depression group were less severe, in contrast to the more comprehensive sample selection of Harrington and colleagues (Harrington et al., 2018a,b). Lastly, we cannot exclude that using a different paradigm (e.g., a recall task instead of a recognition task) and/or a different type of stimuli (e.g., stories, video clips) would result in different outcomes.

## CONCLUSION

In conclusion, we showed that while the self-reported valence and arousal changed as a function of the re-exposure to the emotional stimuli over time, emotional memories became resistant to forgetting, particularly when sleep was disrupted, and they were not affected by non-clinical levels of depression.

## DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

## AUTHOR CONTRIBUTIONS

NC and MS developed the study concept and contributed to the study design. NC and MM performed the testing, data collection, and data analysis. All authors interpreted the data, drafted the manuscript, provided critical revisions, and approved the final version of the manuscript for submission.

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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.2019.00481/full#supplementary-material

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# Emotional Memory Moderates the Relationship Between Sigma Activity and Sleep-Related Improvement in Affect

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Sleep is essential for regulating mood and affect, and it also consolidates emotional memories. The mechanisms underlying these effects may overlap. Here, we investigated whether the influence of sleep on affect may be moderated by emotional memory consolidation. Young adults viewed 45 negative and 45 neutral pictures before taking an afternoon nap measured with polysomnography. Following the nap period, participants viewed the same pictures intermixed with novel ones and indicated whether they remembered each picture. Affect was measured with the Positive and Negative Affect Schedule (PANAS) at baseline before the initial picture viewing task, immediately following the initial picture viewing task, and following the nap. The ratio of positive to negative affect declined over the task period and recovered over the nap period. When controlling for pre-nap affect, NREM sigma activity significantly predicted post-nap affect. Memory for negative pictures moderated this relationship such that a positive association between sigma activity and affect occurred when memory was low but not when memory was high. These results indicate that emotional memory consolidation influences the relationship between nap physiology and mood.

**Keywords: sleep, emotional memory, affect, sigma, mood**

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## INTRODUCTION

Sleep is important for multiple domains of emotional functioning. One such domain is the regulation of mood and affect. It is well known that sleep loss leads to impaired mood; both total sleep deprivation and sleep restriction have been linked to mood deficits (Pilcher and Huffcutt, 1996; Watling et al., 2017). Further, sleep disturbances and alterations are prevalent among those with mood disorders and may contribute to the development of these disorders (Meerlo et al., 2015; Murphy and Peterson, 2015). For example, major depressive disorder is marked by increased sleep latency and awakenings, decreased rapid eye movement (REM) sleep latency, increased REM density and REM sleep duration, and declines in slow wave sleep (SWS).

The mechanisms underlying the contribution of sleep to daily mood/affect in healthy individuals are not well understood, but REM sleep and SWS are both implicated by prior work. In healthy male adults who underwent two nights of normal sleep and two nights of sleep restriction, reduced REM sleep was associated with reduced functional connectivity between the medial prefrontal cortex and

amygdala, which was in turn related to increased anxiety (Motomura et al., 2017). Collecting dream reports from healthy adults upon awakening from REM sleep indicated a decline in negative dream emotion throughout the night, which corresponded to an overnight reduction in negative mood (Cartwright et al., 1998). Slow wave sleep has also been linked to mood in healthy individuals. Compared to those undergoing restricted sleep, individuals undergoing forced awakenings had reduced SWS and positive mood, with the reduction in SWS mediating the reduction in positive mood (Finan et al., 2015). To our knowledge, no links between sleep spindles and mood have been reported in non-clinical samples. However, lower sleep spindle activity has been observed in individuals with anxiety and depression (Lopez et al., 2010; Wilhelm et al., 2017), suggesting that spindle activity may also be important for regulating mood.

In addition to regulating mood, sleep consolidates emotional memories (Tempesta et al., 2018). Compared to those who remain awake, participants who sleep perform better at emotional memory tasks. For example, participants who slept for 3 h immediately after reading negative text performed better on a memory test 4 years later compared to participants who stayed awake immediately after reading the texts (Wagner et al., 2006). Moreover, the consolidation of emotional memory by sleep has been linked to mechanisms also implicated in the effects of sleep on mood. Negative memory consolidation has been associated with REM sleep (Wagner et al., 2001; Nishida et al., 2009; Cairney et al., 2014), slow wave sleep (Groch et al., 2011; Cairney et al., 2014; Payne et al., 2015; Alger et al., 2018), and spindle activity (Kaestner et al., 2013; Alger et al., 2018). The shared mechanisms by which sleep influences mood and emotional memory may result in interactions between these influences. For example, sleep-related emotional memory consolidation induces plasticity within the ventromedial prefrontal cortex, a key mood-regulatory center (Nieuwenhuis and Takashima, 2011). Such plasticity may contribute to or impact the effect of sleep on mood.

Indeed, previous research suggests that emotional memory consolidation may influence the relationship between sleep and mood. We observed that when controlling for pre-sleep affect, percent of time spent in SWS during the night predicts morning affect (Jones et al., 2016). Specifically, more SWS was related to worse morning affect in young adults. This relationship was moderated by negative memory performance such that better post-sleep recognition for negative pictures was associated with a stronger negative relationship between SWS and morning affect.

The objective of the current study is to further investigate the influence of emotional memory consolidation on sleep-related change in affect. Here, we sought to determine the relationship between sleep physiology during a daytime nap and change in affect over the nap period. We further sought to determine whether negative memory performance would moderate any such relationship. Based on our previous findings, we hypothesized that SWS would be associated with worse affect upon wake and that higher negative memory performance would be associated with a stronger negative relationship between sleep and affect.

# MATERIALS AND METHODS

## Participants

Data were collected from 50 young adults between 18 and 28 years of age ($M$ = 20.94; $SD$ = 2.29; 35 females). Participants had normal or corrected-to-normal vision and no history of neurological disease, sleep disorders, head injury, or use of medications known to affect sleep or cognitive function. Participants were instructed to refrain from alcohol, sleep at least 6 h the night before the experiment, wake up no later than 8:00 AM the morning of the experiment, and limit caffeine intake the day of the experiment. All participants were compensated with payment or course credit. Experimental procedures were approved by the University of Massachusetts, Amherst Institutional Review Board and written informed consent was obtained before the experiment.

Seven participants were excluded from all analyses for sleeping less than 45 min (half of a typical sleep cycle), and 1 participant was excluded due to multiple awakenings due to construction noise near the sleep lab. Thus, analyses of affect are based on 42 participants. Due to data loss, sleep stage scoring was not possible for 13 participants. Thus, sleep stage analyses are based on 29 participants. Four additional participants were excluded from sigma and delta activity analyses due to poor recording quality at electrode site F3 and/or F4 (where these measures were calculated), leaving 25 participants for these analyses. Finally, 2 multivariate outliers were excluded from moderation analyses, leaving 23 participants (see Data Analysis for outlier detection). Demographic information and variables of interest showed similar characteristics across these four subsamples (see **Supplementary Table 1**).

## Materials

Stimuli were 90 emotionally negative and 90 emotionally neutral pictures. The majority of stimuli were obtained from the International Affective Picture System (IAPS; Lang et al., 2005). The rest were from an in-house set and were chosen to match the IAPS pictures in content and emotionality (Baran et al., 2012). Based on normative data and previous work in our lab (Jones et al., 2016), negative pictures were moderate to high in arousal, and neutral pictures were low in arousal.

## Procedure

Participants arrived for the Encoding session between 12:30 and 1:00 PM. Following Encoding, an electrode cap was applied and a 2-h nap opportunity was given. Following the nap opportunity, the electrode cap was removed and participants completed the Recognition session. Affect was measured at three time points: immediately before Encoding (pre-Encoding), immediately after Encoding (post-Encoding), and immediately before Recognition (post-nap; **Figure 1A**). Approximately 30 min passed between waking and Recognition to allow for dissipation of sleep inertia.

During Encoding, participants viewed 90 target stimuli (45 negative, 45 neutral) in random order (**Figure 1B**). Each picture appeared on the computer screen for 2 s, followed by a black screen for 6 s. After this black screen, participants were first

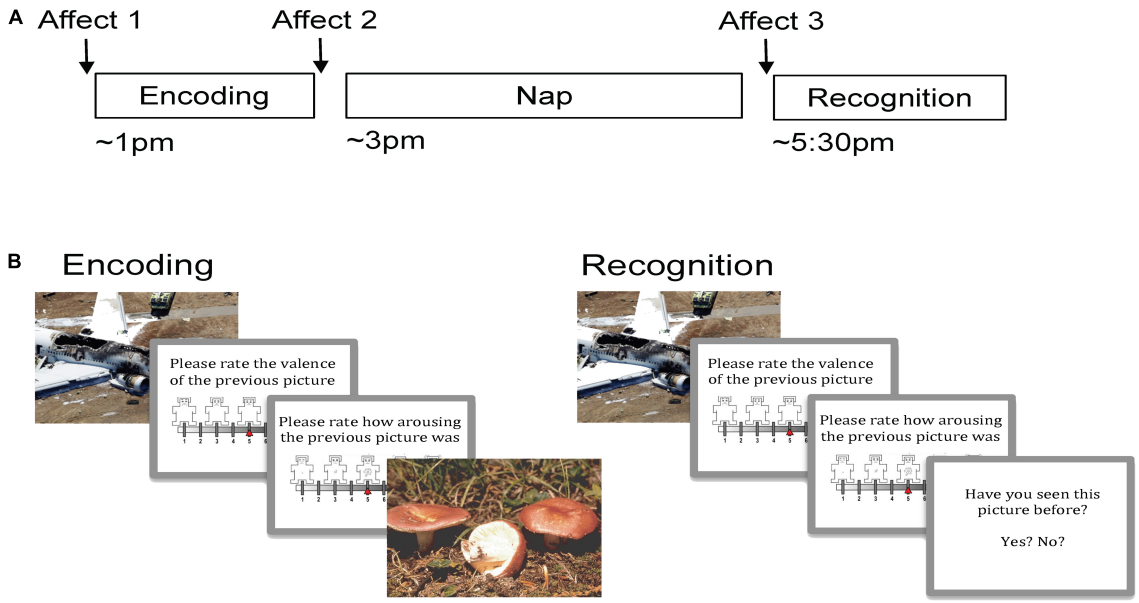


**FIGURE 1 |** Experimental procedure and task. **(A)** Encoding took place in the early afternoon followed by a 2 h nap opportunity and then Recognition. Affect was measured prior to Encoding, just following Encoding, and then following the nap prior to Recognition. **(B)** During Encoding participants viewed 90 pictures (targets) and rated the valence and arousal of each on 9-point self-assessment manikin scales. During Recognition, participants viewed 180 pictures, a mixture of target and novel foil pictures, and rated each one on valence and arousal. Participants indicated whether or not they recognized the picture by responding yes/no.

prompted to rate the valence of the picture on a nine-item self-assessment manikin (SAM) valence scale (1 = negative, 5 = neutral, 9 = positive), and then prompted to rate its arousability on a nine-item SAM arousal scale (1 = no arousal, 9 = highly arousing; Bradley and Lang, 1994). Ratings were entered using numbers on a keyboard without any time limit. Following the rating scales, another black screen appeared for 10–14 s before the next picture. A long inter-stimulus interval was used in order to collect emotion physiology data (including skin conductance response), which are not presented here. Participants were not informed that their memory for the pictures would be tested later.

During Recognition, participants were shown 180 pictures: the same 90 targets seen during Encoding intermixed with 90 novel pictures (foils; 45 neutral and 45 negative). The stimulus presentation procedure was identical to Encoding with the following exceptions: (1) following valence and arousal ratings, participants were prompted to indicate whether they had seen each picture before by pressing "y" for yes and "n" for no, and (2) a 1-s inter-stimulus interval was used during the second half of the session in order to prevent fatigue.

## Polysomnography

Polysomnography (PSG) was recorded in the sleep laboratory using the Comet Plus PSG system (Grass Technologies) combined with a 32-electrode cap (EasyCap GmbH, Germany) that included two electrooculography (EOG; right and left ocular canthi), two chin electromyography (EMG), and 27 electroencephalography (EEG) leads (Fz, F3, F4, F7, F8, FCz, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, POz, O1, O2, M1, M2). PSG data were collected at a sampling rate of 200 Hz with a bandpass of 0.1–100 Hz. EOG and EEG channels were referenced to Cz during recording and re-referenced to the contralateral mastoid for scoring. Recordings were obtained and scored according to the specifications provided by the American Academy of Sleep Medicine (Iber et al., 2007).

## Data Analysis

Participants' individual valence ratings of the pictures were used to categorize stimuli for analyses (as in St. Jacques et al., 2009). Due to individual differences in emotional response, individualized categorization may provide the most accurate measures. Targets were categorized based on ratings during the Encoding session, and foils were categorized based on ratings during the Recognition session. Negative and neutral pictures were defined as those rated 1–3 and 4–6 on valence, respectively. Hence, the analyzed picture sets were unique for each participant. On average, 36.92 $\pm$ 8.55 target pictures were rated as negative (valence: $M$ = 1.83, $SD$ = 0.53; arousal: $M$ = 5.89, $SD$ = 1.92) and 43.05 $\pm$ 11.60 target pictures were rated as neutral (valence: $M$ = 5.02, $SD$ = 0.13; arousal: $M$ = 2.13, $SD$ = 1.36). Hit rate, defined as the percentage of target pictures correctly identified as previously seen, was chosen as the memory measure based on our previous findings (Baran et al., 2012; Jones et al., 2016).

Affect was measured using the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). The PANAS consists of 10 positive and 10 negative attributes that participants rate on a scale from 1 to 5 according to their current feelings, resulting in a possible score of 10–50 for each valence. Higher scores indicate

higher affect. Affect Ratio was calculated as an adjusted ratio of positive to negative affect for each of the three time points. Because a simple affect ratio (positive affect divided by negative affect) would range from 1 to 5 when positive affect is equal to or higher than negative, but would only range from 0.20 to 0.98 when negative affect is higher than positive, we calculated an adjusted ratio to keep negative and positive affect on the same scale. The adjusted ratio was calculated by dividing the higher valence score by the lower valence score, multiplying by −1 if negative affect was higher, and then subtracting 1 from positive values and adding 1 to negative values. This transformation resulted in a linearly spaced composite measure with a possible range of −4 to 4. Thus, positive scores indicate that positive affect was higher than negative affect, and negative scores indicate that negative affect was higher than positive affect.

EEG amplitude density was measured in the delta (0.5–4 Hz) and sigma (12–16 Hz) bands over frontal scalp regions (F3, F4) by extracting the amplitude envelope of bandpass-filtered EEG, summing it within identified sleep stages, and normalizing by time. The use of the Hilbert-transformation-derived amplitude envelope to quantify signal dynamics is a common method in engineering that has been previously applied to EEG analysis in multiple contexts, including sleep (Clochon et al., 1996; Freeman, 2004; Díaz et al., 2018). We opt to use this approach over the potentially more familiar short-time Fourier transform or wavelet decomposition methods of signal dynamics quantification because it is more computationally efficient, and because recent evidence suggests that Hilbert-transformation-derived envelopes may more accurately capture arrhythmic elements of the EEG (Díaz et al., 2018).

EEG data were first re-referenced offline to the averaged mastoid recording, then filtered separately into delta activity using a Butterworth infinite-impulse response filter (order = 2) that did not remove mean recording bias, and sigma activity using a forward impulse response filter (order = 164) that did remove mean recording bias. Regions of continuous filtered EEG exceeding frequency-band specific thresholds (delta: ±250 μV, sigma: ±75 μV) within a moving 500 ms window were marked as artifact. Delta and sigma amplitude envelopes were then calculated for each electrode as the magnitude (absolute value) of the analytic signal (z) of the filtered EEG, where the analytic signal is the sum of the filtered EEG and its discrete Hilbert transformation multiplied by the imaginary unit: z(EEG) = EEG + $i$ * Hilbert(EEG). Amplitude envelopes were then averaged across electrodes. Samples not previously marked as artifact at either electrode were then summed across stage 2 non-rapid eye movement (NREM2) sleep and SWS epochs, and divided by the combined number of artifact-free seconds spent in NREM2 sleep and SWS. Less than 0.04 and 0.02% of samples were marked as artifact for any participant for delta and sigma, respectively. EEG analyses were conducted in MATLAB using a combination of EEGLAB (Delorme and Makeig, 2004), ERPLAB (Lopez-Calderon and Luck, 2014), and custom in-house functions (available upon request).

Within-subject comparisons of means were conducted using repeated-measures analyses of variance (ANOVAs), and *post hoc* pairwise comparisons were made using Student's paired-sample *t*-tests. Pearson's *r* was used to assess bivariate linear relationships. Hierarchical multiple linear regression was used to conduct moderation analyses. Independent variables were mean-centered before being entered into regression models. Significant interactions were decomposed according to the guidelines of Aiken and West (1991), with fitted regression lines plotted at high (+1 *SD*) and low (−1 *SD*) levels of the moderating variable using estimates obtained from the final model. Simple slopes testing was conducted to assess relationships at high and low levels of the moderator. Multivariate outliers were detected and removed based on a studentized residual greater than 2.5 (1 data point removed) or a Cook's Distance greater than 3 *SD* from the mean Cook's Distance (1 data point removed). Significance levels were set to $p < 0.05$. A "marginal" effect was defined as having a $p$-value $\geq$0.05 and <0.075. Statistical analyses were conducted in SPSS, and interaction plots were created using open-source tools[1].

# RESULTS

## Change in Affect Over the Encoding and Nap Periods

Mean positive affect and negative affect scores measured at the three time points are reported in **Table 1**. A repeated-measures ANOVA with Time (pre-Encoding, post-Encoding, post-nap) as the within-subjects factor was conducted on Affect Ratio. There was a main effect of Time [$F_{(1.7,70.3)} = 21.676$, $p < 0.001$, Huynh-Feldt correction]. Follow-up paired-sample *t*-tests indicated that

[1]www.jeremydawson.co.uk/slopes.htm

**TABLE 1 |** Affect [mean (*SE*)].

| | Pre-Encoding | Post-Encoding | Post-Nap |
|---|---|---|---|
| Positive | 25.24 (1.09) | 18.07 (1.00) | 21.90 (1.22) |
| Negative | 12.19 (0.37) | 12.36 (0.39) | 11.12 (0.35) |

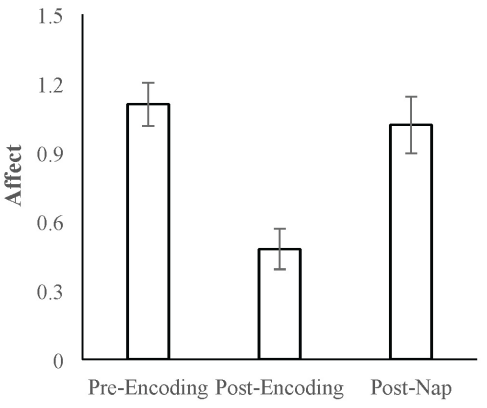


**FIGURE 2 |** Mean Affect Ratio (adjusted ratio of positive to negative affect) at the pre-Encoding, post-Encoding, and post-nap time-points. Error bars represent standard errors of means.

**TABLE 2 |** Nap characteristics [mean (*SE*)].

| TST (min) | SL (min) | SE (%) | RL (min) | NREM1 (%) | NREM2 (%) | SWS (%) | REM (%) |
|---|---|---|---|---|---|---|---|
| 93.34 (4.11) | 12.40 (2.30) | 80.68 (2.95) | 63.61 (3.45) | 11.66 (1.65) | 50.01 (3.11) | 25.59 (3.84) | 12.75 (2.43) |

*TST, total sleep time, SL, sleep latency, SE, sleep efficiency, RL, REM latency.*

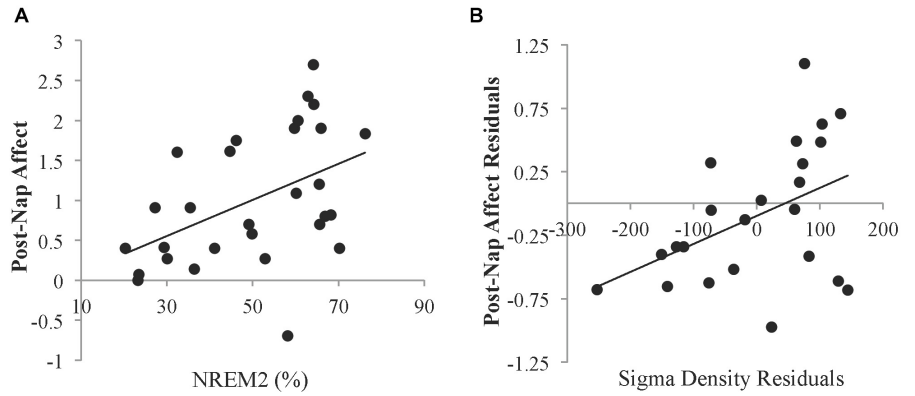


**FIGURE 3 |** Relationships between sleep and affect. **(A)** Relationship between the percent of time spent in NREM2 sleep and the Affect Ratio (adjusted ratio of positive to negative affect) after the nap. **(B)** Partial correlation between sigma density and post-nap Affect Ratio when controlling for post-Encoding Affect Ratio. Residuals were obtained by regressing sigma density and post-nap Affect Ratio against the post-Encoding Affect Ratio. Sigma density values are reported in arbitrary amplitude envelope units summed per second. These values can be converted to mean amplitude envelope units (comparable to microvolts) by dividing by the sampling rate (200 Hz).

affect decreased over the encoding task period ($t$ = 7.258, $p < 0.001$) and increased/recovered between the post-Encoding and post-nap time points ($t = -5.670$, $p < 0.001$; **Figure 2**).

We next analyzed positive and negative affect separately. For positive affect, there was a main effect of Time [$F_{(1.8,74.7)}$ = 28.719, $p < 0.001$, Huynh-Feldt correction]. Follow-up comparisons indicated that positive affect decreased over the encoding task period ($t$ = 8.717, $p < 0.001$) and increased/recovered over the nap period ($t = -4.333$, $p < 0.001$). For negative affect, there was also a main effect of Time [$F(2,82)$ = 5.659, $p$ = 0.005], with follow-up comparisons indicating that negative affect did not significantly change over the encoding task period ($t = -0.382$, $p = 0.704$) but did decrease over the nap period ($t$ = 3.812, $p < 0.001$). Given that both positive and negative affect change over the nap period, we use Affect Ratio for subsequent analyses in order to capture overall affect while limiting the number of comparisons/tests.

## Relationships Between Nap Physiology and Affect

Average nap parameters are reported in **Table 2**. Of the 29 participants for whom sleep stage scoring was possible, 26 obtained SWS, and 16 obtained REM sleep. Nineteen participants were in NREM2 when they woke from the nap, 6 were in SWS, and 4 were in REM sleep.

To investigate whether specific sleep stages were associated with the recovery in affect, correlation analyses were conducted. Neither percent time spent in SWS ($r = -0.187$, $p$ = 0.331) nor REM sleep ($r = -0.222$, $p$ = 0.247) was significantly related to post-nap affect. However, percent time spent in NREM2 sleep was positively related to post-nap affect ($r$ = 0.459, $p$ = 0.012; **Figure 3A**). Since sleep measures may be related to trait characteristics of affect, we next controlled for pre-nap (post-Encoding) affect to identify relationships with change in affect over the nap period. When controlling for post-Encoding affect, the relationship with percent time in NREM2 sleep remained marginally significant (partial $r$ = 0.344, $p$ = 0.073), suggesting that NREM2 sleep during the nap may be associated with improvement in affect. Neither SWS nor REM sleep was significantly related to post-nap affect when controlling for post-Encoding affect ($p$'s > 0.16). Furthermore, neither total sleep time nor sleep efficiency was significantly related to post-nap affect ($p$'s > 0.52). Post-nap affect also did not significantly vary according to the sleep stage from which participants awoke ($p$'s > 0.43), suggesting that individual differences in sleep inertia was not a factor in these results.

Given the relationship with NREM2 sleep, we investigated whether sigma activity (a hallmark of NREM2 sleep) was associated with improvement in affect. Controlling for post-Encoding affect, greater NREM sigma density was associated with higher post-nap affect (partial $r$ = 0.439, $p$ = 0.036; **Figure 3B**). To determine whether this relationship was specific to the sigma band, we also calculated delta density during NREM sleep. There was no significant relationship with delta activity during NREM sleep (partial $r = -0.175$, $p$ = 0.414).

## Moderation by Memory

We next asked whether emotional memory consolidation influenced the relationship between sleep physiology and affect. Memory performance and relationships between memory and

affect are reported in **Supplementary Tables 1** and **2**, respectively. A moderation analysis was conducted using hierarchical linear regression with post-Encoding affect entered in level 1 as the control variable, NREM sigma density and memory performance (hit rate for negative pictures) entered in level 2 as the predictor variable and moderator variable, respectively, and the NREM sigma density X memory performance interaction term entered in level 3. Sigma density (β = 0.259, $p$ = 0.045) and memory performance (β = −0.289, $p$ = 0.028) each predicted change in affect. Adding the interaction term significantly increased model fit, indicating that memory moderated the relationship between sigma density and improvement in affect (**Table 3**). Specifically, simple slopes testing indicated there was a positive relationship between NREM sigma density and change in affect at low (−1 *SD*) memory levels (β = 0.592, $p$ = 0.003) but not high (+1 *SD*) memory levels (β = −0.090, $p$ = 0.631; **Figure 4**). The moderation effect remained when we included false alarm rate as an additional control variable in the level 1 model ($R^2$ change = 0.071, $p$ = 0.024), suggesting that the effect is not driven by response bias. Additionally, the moderation was not significant using hit rate of neutral pictures ($R^2$ change = 0.009, $p$ = 0.445), indicating it is specific to negative memory.

**TABLE 3 |** Multiple regression analysis.

| | Post-Nap Affect | | |
|---|---|---|---|
| **Predictor** | **Model 1 – *B* (*SE*)** | **Model 2 – *B* (*SE*)** | **Model 3 – *B* (*SE*)** |
| (Constant) | 0.977 (0.117)*** | 0.962 (0.098)*** | 0.962 (0.087)*** |
| Post-Encoding affect | 1.023 (0.201)*** | 1.071 (0.170)*** | 1.201 (0.160)*** |
| Sigma density | | 0.002 (0.001)* | 0.002 (0.001)* |
| Negative hit rate | | −2.692 (1.103)* | −2.503 (0.979)* |
| Interaction term | | | −0.027 (0.011)* |
| $R^2$ | 0.563*** | 0.727*** | 0.798*** |
| $\Delta R^2$ | | 0.163* | 0.072* |

*B, unstandardized regression coefficient; SE, standard error; $R^2$, model fit; $\Delta R^2$, change in model fit, *p < 0.05, ***p < 0.001.*

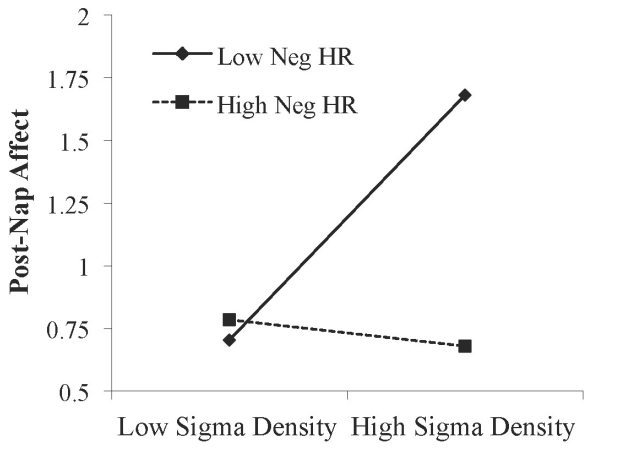


**FIGURE 4 |** Interaction between NREM sigma density and negative memory in predicting the post-nap Affect Ratio (adjusted ratio of positive to negative affect), while controlling for the post-Encoding Affect Ratio. Neg HR, negative hit rate.

## DISCUSSION

Here we show that percent time spent in NREM2 sleep as well as NREM sigma density during an afternoon nap predict recovery of affect over the nap period following a decline related to viewing negative pictures. The relationship between sigma density and affect was moderated by memory performance for negative pictures. Specifically, this relationship was present for those with low memory performance but not for those with high memory performance. Further, this effect was specific to negative memory, as memory performance for neutral pictures did not moderate the relationship between sigma density and affect. These results may suggest that processing of emotional memories during sleep contributes to the impact of sleep on subsequent affect.

Based on our previous study of overnight sleep (Jones et al., 2016), we hypothesized that higher percent time in SWS would predict less improvement in affect over the nap. Instead, we did not find any significant relationship between SWS during a nap and affect. However, we did see that percent time in NREM2 sleep, as well as sigma activity [which is most prevalent in NREM2 sleep (De Gennaro and Ferrara, 2003)], were positively related to change in affect over the nap. Since percent time in NREM2 sleep and SWS are often inversely related, these findings may simply reflect this inverse relationship. Alternatively, there may be separate mechanisms acting on affect during NREM2 sleep and SWS, with a longer sleep period needed to uncover the relationship with SWS.

Sigma activity predominately reflects sleep spindles, though it should be kept in mind that they are not necessarily the same. While previous studies have more often linked REM sleep (Cartwright et al., 1998; Palagini et al., 2013; Motomura et al., 2017) and SWS/slow wave activity (Landsness et al., 2011; Cheng et al., 2015; Finan et al., 2015) to mood, some recent studies have implicated sleep spindles in relation to mood. Reduced spindle activity has been seen in children and adolescents with social anxiety, with greater fast spindle activity (13–16 Hz) related to less severe symptoms (Wilhelm et al., 2017). A reduction in spindle activity was also observed in children and adolescents with or at risk for depression (Lopez et al., 2010). In adults, reduced spindles have been reported in depressed individuals compared to controls (de Maertelaer et al., 1987), though there have also been reports of no difference between groups (Ferrarelli et al., 2007) or increased spindle activity in depressed individuals (Plante et al., 2013). Sleep spindles reflect synchronization between cortical and subcortical structures and promote synaptic plasticity, which may be integral to regulating structural and functional connectivity and effective communication among brain regions regulating mood and affect (Meerlo et al., 2015; Ulrich, 2016). Thus, sigma activity during sleep may generally benefit and restore mood. Lower trait-level sigma activity may predispose individuals to anxiety and mood disorders due to a reduction in the capacity of sleep to restore mood. Future

research could investigate whether experimentally manipulating spindles could influence mood regulation.

In the current study negative (but not neutral) memory performance influenced the relationship between sigma activity and affect. Sigma density predicted improvement in affect only when memory performance was low and not when memory performance was high. These results are in some ways consistent with our prior findings. We previously observed a negative relationship between the percent time spent in SWS overnight and next morning affect (ratio of positive to negative affect; Jones et al., 2016). However, negative memory performance moderated this relationship. There was a significant negative relationship between SWS and affect only when negative memory was high, and not when it was low. Thus, in both the previous and current study, high negative memory was associated with worse affect than low negative memory. Since high memory performance suggests strong consolidation during sleep, these results may suggest that negative memory consolidation hinders the extent to which sleep benefits and restores mood.

Together, these current and past findings may suggest a multi-step process during sleep with regard to affect: sigma activity, most prevalent during NREM2 sleep, may benefit affect, but if subsequent mechanisms (particularly during SWS) lead to strong consolidation of negative memory (and thus high memory performance), affect is diminished. Thus, more sigma activity predicts better affect when negative memory is low, and more SWS predicts worse affect when negative memory is high. Additionally, we previously observed that high (but not low) *positive* memory performance was associated with a significant positive relationship between percent time spent in overnight SWS and morning affect in older adults (Jones et al., 2016). Thus, while consolidation of negative memories may adversely affect sleep-related restoration of mood, consolidation of positive memories may have the opposite effect. Since emotional memory consolidation involves mood-regulating circuitry, such as the ventromedial prefrontal cortex (Nieuwenhuis and Takashima, 2011), it may lead to functional changes within this circuitry that impact mood. More research manipulating memory valence and consolidation mechanisms such as slow wave activity is needed to investigate these possibilities.

This study provides evidence that emotional memory consolidation may impact the influence of sleep on mood. However, limitations of this research should be considered. First, these findings are associative in nature, and further research is needed to establish a causal relationship and determine the underlying mechanisms. Furthermore, though post-sleep memory performance is expected to reflect sleep-dependent memory consolidation to some extent, future studies should use over-sleep change in memory performance, as this change may be a more accurate representation of sleep-dependent consolidation. Finally, although fairly standard in the sleep and memory field, the sample sizes used in our sleep analyses ($n$ = 23–29) are still relatively low, particularly for moderation analyses, and thus future studies with larger sample sizes are warranted.

## DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available to a qualified researcher upon reasonable request.

## AUTHOR CONTRIBUTIONS

BJ designed the experiments and collected the data. BJ and AF analyzed the data and wrote the manuscript. RS supervised the entire project.

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## SUPPLEMENTARY MATERIAL

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# Preferential Consolidation of Emotional Memory During Sleep: A Meta-Analysis

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It is uncertain whether sleep preferentially consolidates emotional over neutral material. Some studies suggest that sleep enhances emotional memory (i.e., that there are large differences in strength of memory for valenced material compared to neutral material after a sleep-filled interval, but that this difference is smaller after a wake-filled interval). Others find no such effect. We attempted to resolve this uncertainty by conducting a meta-analysis that compared valenced to neutral material after both sleep- and wake-filled delays. Standard search strategies identified 31 studies (containing 36 separate datasets) that met our inclusion criteria. Using random effects modeling, we conducted separate analyses for datasets comparing (a) negative vs. neutral material, (b) positive vs. neutral material, or (c) combined negative and positive vs. neutral material. We then specified several subgroup analyses to investigate potential moderators of the relationship between sleep and emotional memory consolidation. Results showed no overall effect for preferential sleep-dependent consolidation of emotional over neutral material. However, moderation analyses provided evidence for stronger effects when (a) studies used free recall rather than recognition outcome measures, or (b) delayed recall or recognition outcomes were controlled for initial learning. Those analyses also suggested that other methodological features (e.g., whether participants experience a full night of sleep and a regular daytime waking control condition rather than a nap and a night-time sleep deprivation control condition) and sample characteristics (e.g. all-male or not, young adult or not) should be carefully addressed in future research in this field. These findings suggest that sleep does enhance emotional memory, but that in the laboratory the effect is only observed under particular methodological conditions. The conditions we identify as being critical to consider are consistent with general theories guiding scientific understanding of memory consolidation during sleep.

**Keywords: consolidation, emotional memory, meta-analysis, review, sleep**

Across species, sleep plays a critical role in many physiological systems, from immune to metabolic to neurobiological (Cirelli and Tononi, 2008; Rasch and Born, 2013). One strand of human neuroscientific research has focused on the active role that sleep plays in the consolidation of newly-acquired information (Diekelmann and Born, 2010). Numerous studies suggest that healthy sleep is associated with enhanced preservation of multiple types of memory, from declarative (e.g., memory for highly complex episodes) to non-declarative (e.g., conditioning of simple stimulus-response associations). Recently, there has been an increased focus within this sleep-memory literature on ways in which sleep directs preferential processing and storage of memories that may be relevant for guiding future behavior (i.e., emotional memories; van der Helm and Walker, 2011).

A number of seminal studies (e.g., Wagner et al., 2001; Hu et al., 2006; Payne et al., 2008) suggest that emotional memory is enhanced by sleep. They report that differences in strength of memory for valenced material compared to neutral material are larger after a sleep-filled delay than after a comparable wake-filled delay. A standard interpretation of this result is that, during sleep, emotional memories are preferentially consolidated so that they are relatively easily accessible for retrieval, whereas neutral memories tend to fade away.

Many studies, most focusing on emotional episodic memory, have attempted to replicate this result, investigating how preferential consolidation might work and whether it might be moderated by various study-design and individual-difference factors. Although the preferential preservation of emotional compared to neutral episodes is demonstrated in some studies (Wagner et al., 2001, 2006; Hu et al., 2006; Sterpenich et al., 2007; Payne et al., 2008; Nishida et al., 2009; Prehn-Kristensen et al., 2009, 2017; Chambers and Payne, 2014), it is not in others (Wagner et al., 2007; Atienza and Cantero, 2008; Sterpenich et al., 2009; Baran et al., 2012; Cunningham et al., 2014a; Morgenthaler et al., 2014; Tempesta et al., 2015, 2017; Cellini et al., 2016; Jones et al., 2016, 2018; Alger et al., 2018; Bolinger et al., 2018). A central problem in this literature is vast cross-study differences in methodology, and consequent difficulties in accounting for sources of discrepancy in results. These methodological variations include the timing and duration of the sleep condition, the type of waking control used, the primary outcome measure, nature of encoding encouraged by the study protocol, gender composition of the sample, and age range studied. Hence, the aggregate literature has not answered the questions of (a) whether there are large differences in strength of memory for valenced material compared to neutral material after a sleep-filled interval, but smaller differences after a wake-filled interval, and (b) if sleep does enhance emotional memory, under which experimental conditions is the effect observed.

We took a meta-analytic approach to answering these questions. We reviewed 31 studies that reported memory for emotionally 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).

A series of initial analyses assessed strength of memory for (i) valenced compared to neutral material after a sleep-filled interval, and (ii) valenced compared to neutral material after a wake-filled interval. Secondary analyses examined potential moderators of the enhancement effect.

# METHODS

## Study Selection

Two authors (GL and EB) searched the Academic Search Premier, MedLine, PubMed, PsycARTICLES, and PsycINFO databases using the following terms: *sleep* AND *affect* memory*; *sleep* AND *emotion* memory*. The search was limited to articles published in English, and the search terms were determined a priori by the research team. The same two authors then combed the reference lists of pertinent reviews (both quantitative and narrative) for other articles that met the search criteria. This search process began in April 2018 and continued through September 2018.

Two authors (EB and GL) reviewed titles and abstracts of the articles retrieved via the above-described searches ($n = 2{,}029$). They selected for further evaluation only those articles that included: (1) healthy human participants, and (2) comparison of a sleep condition (e.g., a nap, or a full night's sleep) to a waking control condition (e.g., sleep deprivation, or a full day's waking activity).

We obtained a full-text copy of each article meeting these criteria ($n = 47$), and then split that set among the team for detailed review. This review ensured that the studies described in the articles met the above-listed, as well as the following three additional, criteria: (3) a basic screen (self-report was permitted) for psychiatric, medical, neurological, or other conditions with the potential to affect study outcomes, (4) at least one primary outcome measure focused on memory for emotional stimuli (e.g., recognition or free recall of valenced stimuli compared to neutral stimuli), and (5) presentation of extractable data (i.e., *M* and *SD* or *SEM*, or figures from which data could be extracted). We permitted inclusion of data from studies that featured a psychiatric comparison group only if data from healthy participants were presented separately. Similarly, we permitted inclusion of data from intervention studies (e.g., those using sleep consolidation techniques via drug or sensory cue activation) only if data from intervention-free participants were presented separately. We did, however, exclude studies (Hu et al., 2006) that grouped emotional stimuli by arousal (high, low) and matched valence within those groups. We did so because the convention in this literature is to group emotional stimuli by valence (negative, positive) rather than by arousal. We placed no restrictions on publication date, participant age range, study design, or duration of the sleep condition.

A total of 31 articles remained in our pool after full-text screening (see **Figure 1**). For 23 of those, we could extract data either directly from the tables or from text contained in the paper. For the remaining 8, we requested the relevant data from the corresponding author. Five authors (representing six datasets) responded positively, but three did not. For these three, figures contained within the paper allowed us to estimate *M* and *SD* using the WebPlotDigitizer program (version 4.1; Rohatgi, 2018).

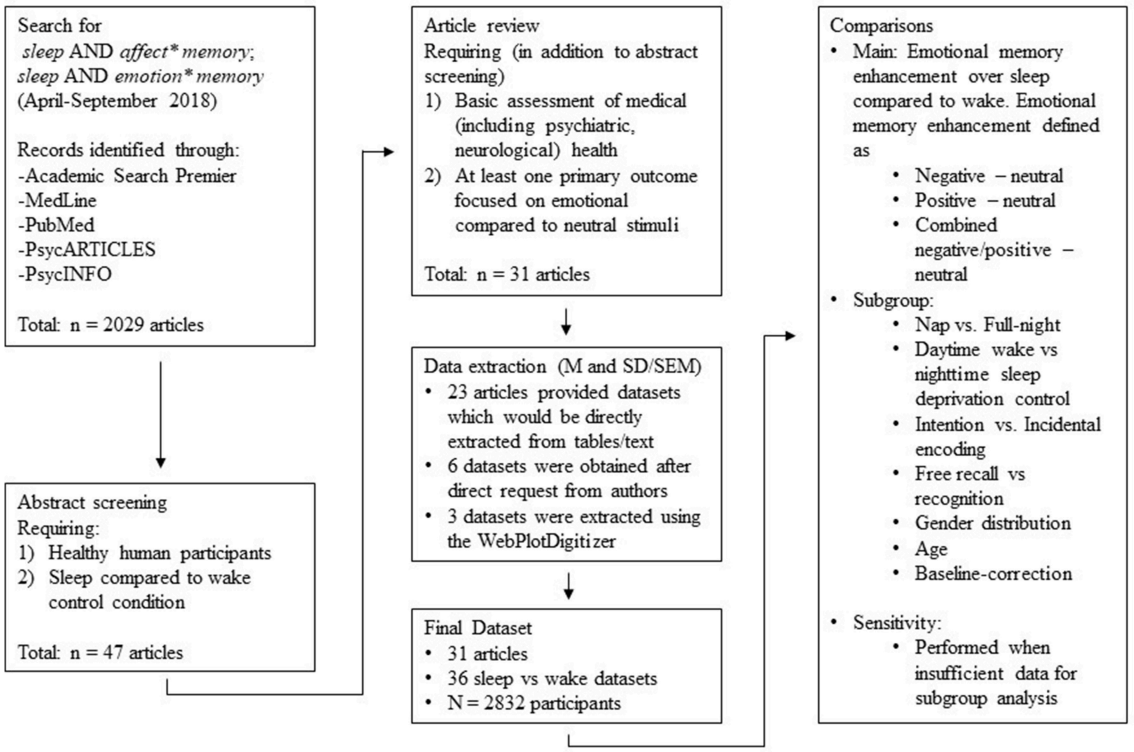


**FIGURE 1 |** Flowchart describing the process underlying study selection.

Hence, the final sample for data analysis consisted of data from 31 articles, with 36 separate datasets represented ($N = 2{,}832$ participants; see **Table 1**).

## Data Extraction and Coding

Three authors (GL, KGFT, and EB) extracted the following data from the 31 studies that comprised the final sample: sample size (number of participants enrolled as well as number of participants who completed the protocol), age (*M*, *SD*) and sex distribution of participants in each of the sleep and control conditions, study design, number and type of control conditions, type of sleep condition (nap or full night), and type of encoding (incidental or intentional). We also extracted data related to the outcome measures: type of primary outcome (recognition accuracy, as estimated by *d'*, [hit rate – false alarm rate], or hit rate; and/or free recall accuracy, as estimated by the number of correctly recalled items), and the relevant statistics (*M* and *SD* for each valence category (negative, positive, neutral) within both the sleep and control conditions) for each outcome variable. Where studies reported *SE* rather than *SD*, we estimated the latter using the formula $SD = SE \times \sqrt{n}$.

In cases where a study used more than one sleep condition, we only extracted data from the sleep condition that most closely matched the control condition (e.g., if the control was a full day's waking activity, we extracted data from the sleep condition that featured a full night's sleep, rather than from one that featured a nap). Moreover, we maintained independence of studies by using a unique control condition for each sleep condition.

We coded the extracted data into an MSExcel spreadsheet, and for each study also coded risk of bias (high, low, or uncertain) along the following dimensions: (a) clarity regarding definition of study sample; (b) clarity regarding definition and implementation of eligibility criteria; (c) clarity regarding definition of sampling strategy; (d) demographic or other matching of groups; (e) control for potential confounds (e.g., caffeine, adaptation night, daytime nap); (f) quality and validity of outcome measures; (g) percentage of participants who completed the study protocols; (h) amount of missing data; (i) adjustment of results for confounds; and (j) other.

## Risk of Bias in Included Studies

At least two members of the research team evaluated, for each study individually, features relating to sources of potential bias across 10 domains. Inter-rater disparities in evaluation were resolved by consensus.

Overall, the risk of bias analysis revealed that no studies should be considered as 'high risk' (i.e., no study carried a high-risk profile over all or most of the bias domains). Indeed, most studies had either a low or unclear risk of bias across most domains.

### Definition of Study Sample

All studies were judged to have a low or uncertain risk of study sample bias.

**TABLE 1 |** Datasets included in the meta-analysis.

| | Sleep condition | | Waking control condition | | Sample characteristics | | Stimulus characteristics | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study/dataset** | **Type** | ***n*** | **Type** | ***n*** | **Age (years)** | **Gender** | **Type** | **Valence[a]** | **Outcome** |
| 1. Ackermann et al., 2015 | Full night | 27 | Full day | 28 | ∼25 | Mixed | Pictures | -/+ | FR[§] |
| 2. Alger et al., 2018, dataset 1 | 90-min nap | 15 | 90-min waking | 15 | 18–39 | Mixed | Foreground pictures | – | Recog. Acc.[§] |
| 3. Alger et al., 2018, dataset 2 | 90-min nap | 12 | 90-min waking | 11 | 40–64 | Mixed | Foreground pictures | – | Recog. Acc.[§] |
| 4. Atienza and Cantero, 2008 | Full night | 14 | Sleep deprivation | 14 | 19–28 | Mixed | Pictures | C | Recognition d′ |
| 5. Baran et al., 2012 | Full night | 54 | Full day | 28 | 18–30 | Mixed | Pictures | – | HR |
| 6. Bennion et al., 2015 | Full night | 25 | Full day | 17 | 18–34 | Mixed | Pictures | – | Recog. Acc. |
| 7. Bennion et al., 2016 | 120-min nap | 24 | 120-min waking | 24 | 18–27 | Mixed | Foreground pictures | C | Recog. Acc. |
| 8. Bolinger et al., 2018 | Full night | 16 | Full day | 16 | 8–11 | Mixed | Pictures | – | Recog. Acc. |
| 9. Cellini et al., 2016 | 90-min nap | 16 | 90-min waking | 16 | 20–30 | Mixed | Pictures | -/+ | d′ |
| 10. Chambers and Payne, 2014 | Full night | 15 | Full day | 15 | ∼20 | Mixed | Cartoon narratives | + | FR % |
| 11. Cunningham et al., 2014a | Full night | 18 | Full day | 21 | University age | Mixed | Foreground pictures | – | Recog. Acc. |
| 12. Cunningham et al., 2014b | Full night | 21 | Full day | 20 | University age | Mixed | Foreground pictures | – | Recog. Acc. |
| 13. Göder et al., 2015 | Full night | 18 | Full day | 18 | ∼28 | Mixed | Pictures | – | Recog. Acc. |
| 14. Harrington et al., 2018 | Full night | 14 | Sleep deprivation | 14 | 18–25 | Mixed | Pictures | -/+ | d′ [§†] |
| 15. Jones et al., 2016, dataset 1 | Full night | 23 | Full day | 19 | 50–80 | Mixed | Pictures | – | d′ |
| 16. Jones et al., 2016, dataset 2 | Full night | 24 | Full day | 24 | 50–80 | Mixed | Pictures | + | d′ |
| 17. Jones et al., 2016, dataset 3 | Full night | 52 | Full day | 34 | 18–30 | Mixed | Pictures | + | d′ |
| 18. Jones et al., 2018 | Full night | 20 | Full day | 20 | 35–50 | Mixed | Pictures | – | d′ |
| 19. Mantua et al., 2017 | Full night | 19 | Full day | 20 | 18–30 | Mixed | Pictures | – | d′ |
| 20. Morgenthaler et al., 2014 | Full night | 14 | Full day | 14 | ∼23 | Mixed | Pictures | – | Recog. Acc. |
| 21. Nishida et al., 2009 | 90-min nap | 15 | 90-min waking | 16 | ∼23.5 | Mixed | Pictures | – | d′ |
| 22. Payne et al., 2008 | Full night | 24 | Full day | 24 | University age | NR | Foreground pictures | – | HR |
| 23. Payne and Kensinger, 2011 | Full night | 21 | Full day | 21 | 18–29 | Mixed | Foreground pictures | – | Recog. Acc. |
| 24. Payne et al., 2015 | 90-min nap | 23 | 90-min waking | 34 | 18–26 | Mixed | Foreground pictures | – | Recog. Acc. |
| 25. Prehn-Kristensen et al., 2009 | Full night | 20 | Full day | 20 | 10–13 | All male | Pictures | – | Recog. Acc. |
| 26. Prehn-Kristensen et al., 2011 | Full night | 12 | Full day | 12 | 11–14 | All male | Pictures | – | Recog. Acc. |
| 27. Prehn-Kristensen et al., 2013, dataset 1 | Full night | 20 | Full day | 20 | 20–28 | All male | Pictures | – | Recog. Acc.[§] |
| 28. Prehn-Kristensen et al., 2013, dataset 2 | Full night | 16 | Full day | 16 | 9–12 | All male | Pictures | – | Recog. Acc.[§] |
| 29. Prehn-Kristensen et al., 2017 | Full night | 16 | Full day | 16 | 9–11 | All male | Faces | –/+[b] | d′ [§] |
| 30. Schoch et al., 2017, dataset 1 | Full night | 30 | Full day | 28 | 18–35 | Mixed | Pictures | C | FR % |
| 31. Schoch et al., 2017, dataset 2 | Full night | 29 | Full day | 28 | 18–35 | Mixed | Pictures | C | FR % |
| 32. Sterpenich et al., 2007 | Full night | 21 | Sleep deprivation | 21 | ∼22 | Mixed | Pictures | -/+ | HR[†] |
| 33. Tempesta et al., 2015 | Full night | 31 | Sleep-deprivation | 23 | ∼24 | Mixed | Pictures | -/+ | d′ [§] |
| 34. Tempesta et al., 2017 | Full night | 24 | Sleep-deprivation | 24 | 20–28 | Mixed | Pictures from films | -/+ | d′ |
| 35. Wagner et al., 2001 | Late-night[c] | 12 | Late-night[c] | 11 | 20–30 | All male | Text | – | FR[§] |
| 36. Wagner et al., 2007 | Full night | 12 | Sleep deprivation | 12 | 19–30 | Mixed | Faces | –/+[d] | Recog. Acc. |

*Most studies used a between-subjects design. The exceptions were the following, which used a crossover design: Bolinger et al. (2018), Göder et al. (2015), Morgenthaler et al. (2014), Prehn-Kristensen et al. (2009, 2011, 2013, 2017), and Wagner et al. (2001). FR, Free Recall; Recog. Acc., Recognition Accuracy (calculated as hit rate minus false alarm rate); HR, hit rate; NR, not reported.*

[§] *Retention measure used.*

[†] *Data taken from the remember condition of a remember/know paradigm.*

[a] *Studies presented the following variations of valence-based analyses: -/+, negative and positive stimuli presented and analyzed separately; –, negative stimuli only; +, positive stimuli only; C, combined (i.e., negative and positive stimuli presented and collapsed together to form "emotional" variable).*

[b] *Fearful (negative) and happy (positive) stimuli only; presented in separate blocks or trials.*

[c] *03h00–06h00.*

[d] *Angry (negative) and happy (positive) stimuli only; presented in separate blocks or trials.*

## Stipulation of Eligibility Criteria

Many studies were judged as having an uncertain level of bias (e.g., Atienza and Cantero, 2008; Payne et al., 2008; Baran et al., 2012; Ackermann et al., 2015; Bennion et al., 2016; Alger et al., 2018). A single study was considered to have a high risk of bias (Schoch et al., 2017) as it provided no details of eligibility criteria

other than describing participants as "healthy." The remaining studies were judged to be at low or uncertain risk of bias in this domain.

### Group Assignment and Randomization

Many studies were judged to be at low risk in this domain (e.g., Sterpenich et al., 2007; Prehn-Kristensen et al., 2013; Chambers and Payne, 2014; Harrington et al., 2018). Because details provided in other reports (e.g., Cunningham et al., 2014b; Göder et al., 2015; Jones et al., 2016; Mantua et al., 2017) were insufficient to allow clear judgements, those studies were judged to have an uncertain level of bias.

### Matching of Study Groups

One study (Baran et al., 2012) was judged to have a high risk of bias in this domain because the gender distribution differed between the two groups and was not controlled for in the analyses. Other studies were judged to be at a low or uncertain risk of bias.

### Methodological Attempts to Control for Potential Confounding Factors

Risk of bias was judged uncertain in four studies, due to uncertainties about (a) the location of sleep (Ackermann et al., 2015), (b) whether participants were asked not to consume alcohol- or caffeine-containing drinks prior to participation (Morgenthaler et al., 2014), or (c) whether participants were allowed naps or caffeine-containing drinks prior to participation (Payne et al., 2008; Prehn-Kristensen et al., 2013).

### Quality and Validity of Outcome Measures

Most studies were considered at low risk of bias in this domain.

### Participant Attrition

Two studies had high levels of participant attrition. Chambers and Payne (2014) excluded data from 46% of enrolled participants from the dataset that form part of this analysis because those individuals had prior exposure to the study materials. Morgenthaler et al. (2014) excluded data from 8 of 37 randomized participants (21.6%) from further analysis. Other studies were judged to be at low or uncertain risk of bias in this domain.

### Other Missing Data

All studies were considered at low or uncertain risk of bias in this domain.

### Statistical Adjustment for Potential Confounding Effects

We considered no study to be at high risk of bias in this domain. However, in four studies (Wagner et al., 2001, 2007; Atienza and

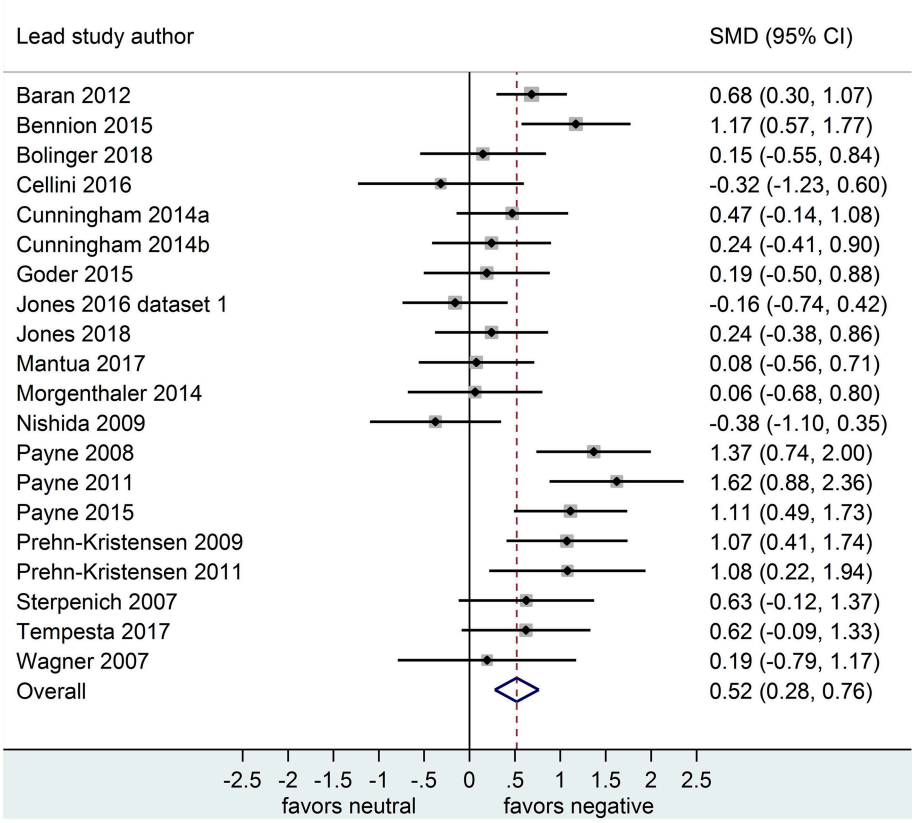


**FIGURE 2 |** Memory for negative vs. neutral information after a sleep-filled delay ($k = 20$, $n = 785$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 0.52$. Heterogeneity is reported as $I^2 = 62.1$ %, $p_Q < 0.001$. SMD, standardized mean difference; CI, confidence interval.

Cantero, 2008; Ackermann et al., 2015) there was no explicit adjustment for the influence of potential confounding factors.

## Meta-Analytic Procedure

Due to anticipated between-study heterogeneity, we made the a priori decision to pool studies using a generic inverse variance random effects model for meta-analysis. This analysis was performed in Stata v14 with the metan command which produced the overall pooled estimate and forest plots for all comparisons. Because studies used different scales to report the same outcome measure, we have reported standardized mean differences with 95% confidence intervals. Heterogeneity is reported using the $I^2$ statistic. The standardized effect size produced by the meta-analysis can be interpreted as per Cohen's *d* (Bradburn et al., 1998). An overall effect size of 0.2–0.5 was regarded as small, 0.5–0.8 as moderate, and more than 0.8 as large (Cohen, 1988).

We conducted separate analyses for datasets comparing (a) negative vs. neutral material, (b) positive vs. neutral material, and (c) combined negative and positive vs. neutral material. In studies reporting memory performance for both positive and negative material, we split the neutral control condition over the two comparisons to avoid unit of analysis errors (Higgins and Green, 2011).

We adopted this general analytic approach because our primary interest was the difference between memory for valenced vs. neutral stimuli. This interest is informed by the overall thrust of the literature, which claims that sleep preferentially consolidates valenced over neutral information. An alternative approach would have been to compare memory performance in response to sleep vs. waking conditions, with results from each type of stimulus computed separately. Adopting that approach, however, would mean we would not have been able to directly compare memory performance for valenced vs. neutral stimuli.

### Subgroup Analyses

We pre-specified a number of subgroup analyses to investigate potential moderators of the relationship between sleep and emotional memory consolidation. These potential moderators included timing and duration of the sleep condition (nap vs. full-night); type of waking control condition (regular daytime waking vs. night-time sleep deprivation); type of memory encoding (intentional vs. incidental); type of outcome measure (free recall vs. recognition); gender distribution of sample (all male vs. mixed); age range of sample (young adult vs. older adult vs. children); and, finally, whether memory measures were baseline-controlled or not.

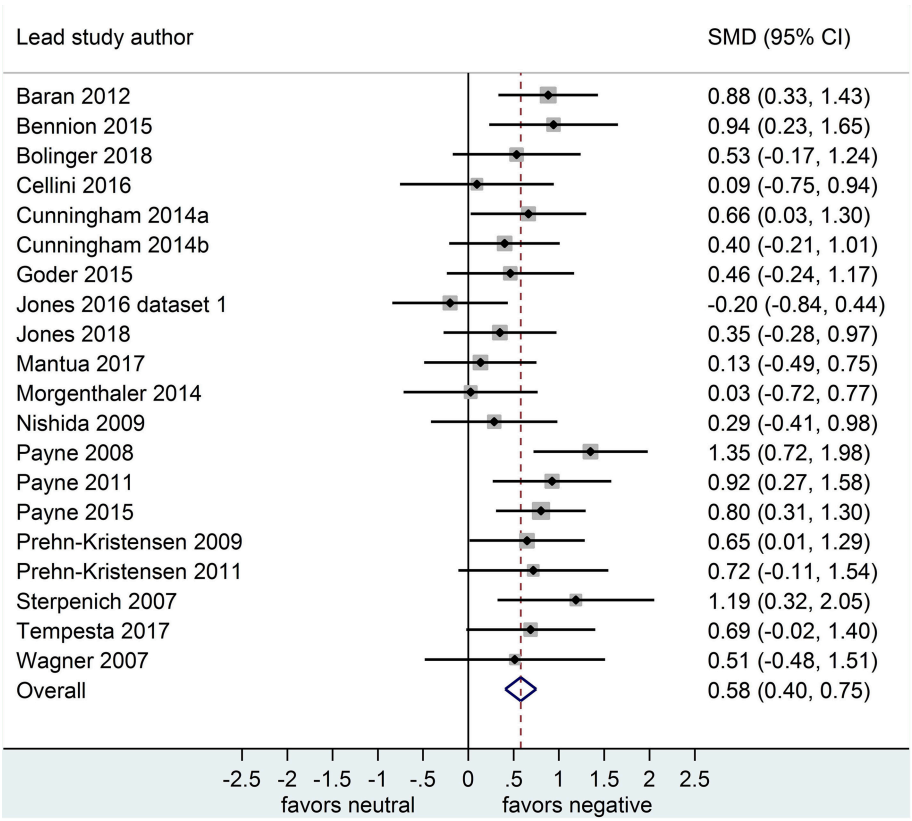


**FIGURE 3 |** Memory for negative vs. neutral information after a wake-filled delay ($k = 20$, $n = 739$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 0.58$. Heterogeneity is reported as $I^2 = 23.3\ \%$, $p_Q = 0.17$. SMD, standardized mean difference; CI, confidence interval.

Where the chi-squared value of the test for heterogeneity indicated statistically significant differences in effect sizes between subgroups, we report effect sizes separately for each predefined subgroup. Where the results of the chi-squared test are not statistically significant, subgroup effects are not reported.

### Sensitivity Analyses

Where there was insufficient data for a subgroup analysis (e.g., in cases where a subgroup contained only one study), we performed a sensitivity analysis instead and report the results excluding that study.

For studies where results were only displayed graphically, we extracted the data using the WebPlotDigitizer program and planned a sensitivity analysis excluding these studies to determine whether this method of data extraction had an influence on the results.

## RESULTS

## Strength of Memory for Valenced vs. Neutral Material After Sleep, and After Waking

### Negative vs. Neutral Material

Separate analyses of data shown in **Figure 2** ($k = 20$ datasets, $n = 785$ participants) and in **Figure 3** ($k = 20$, $n = 739$) suggested that, after both sleep-filled and wake-filled delays (daytime waking and sleep-deprivation conditions, combined), participants recalled or recognized negative stimuli more readily than neutral stimuli. The effect size associated with the sleep-filled delay was similar to that associated with the waking control condition (Cohen's $d = 0.52$ and 0.58, respectively) and the confidence intervals overlapped, suggesting there is no sleep benefit for negative over neutral information.

### Positive vs. Neutral Material

Separate analyses of data shown in **Figure 4** ($k = 7$, $n = 289$) and in **Figure 5** ($k = 7$, $n = 251$) suggested that, after both sleep-filled and wake-filled delays (daytime waking and sleep-deprivation conditions, combined), participants did not recall or recognize positive stimuli more readily than neutral stimuli. The effect size associated with the sleep-filled delay ($d = 0.22$) was slightly larger than that associated with the waking control condition ($d = 0.12$), but in both cases the confidence intervals were quite wide and included a zero value. Moreover, the confidence intervals overlapped. Together, these data suggest there is no sleep benefit for positive over neutral information.

### Combined Negative and Positive vs. Neutral Material

Separate analyses of data shown in **Figure 6** ($k = 4$, $n = 213$) and in **Figure 7** ($k = 4$, $n = 208$) suggested that, after both sleep-filled and wake-filled delays (daytime waking and sleep-deprivation conditions, combined), participants recalled or

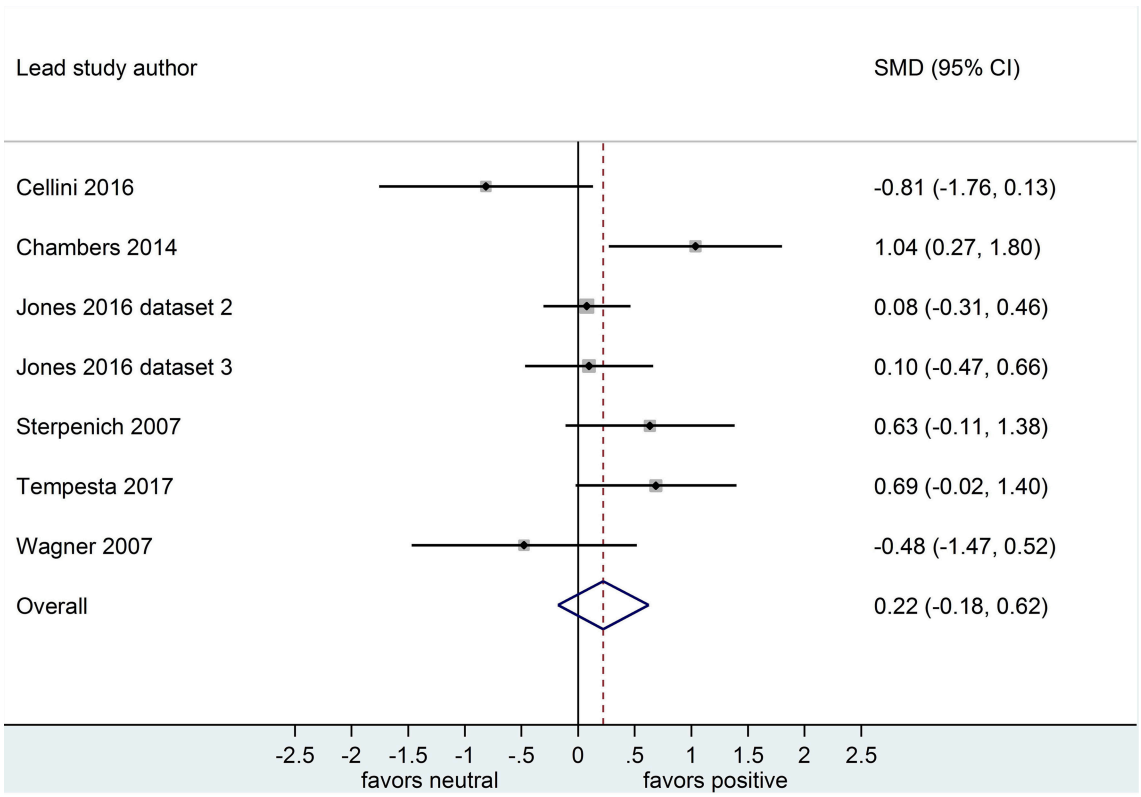


**FIGURE 4 |** Memory for positive vs. neutral information after a sleep-filled delay ($k = 7$, $n = 289$). The $x$-axis represents effect size (Cohen's $d$). The dashed red line indicates the overall effect size, $d = 0.22$. Heterogeneity is reported as $I^2 = 58.3\%$, $p_Q = 0.03$. SMD, standardized mean difference; CI, confidence interval.

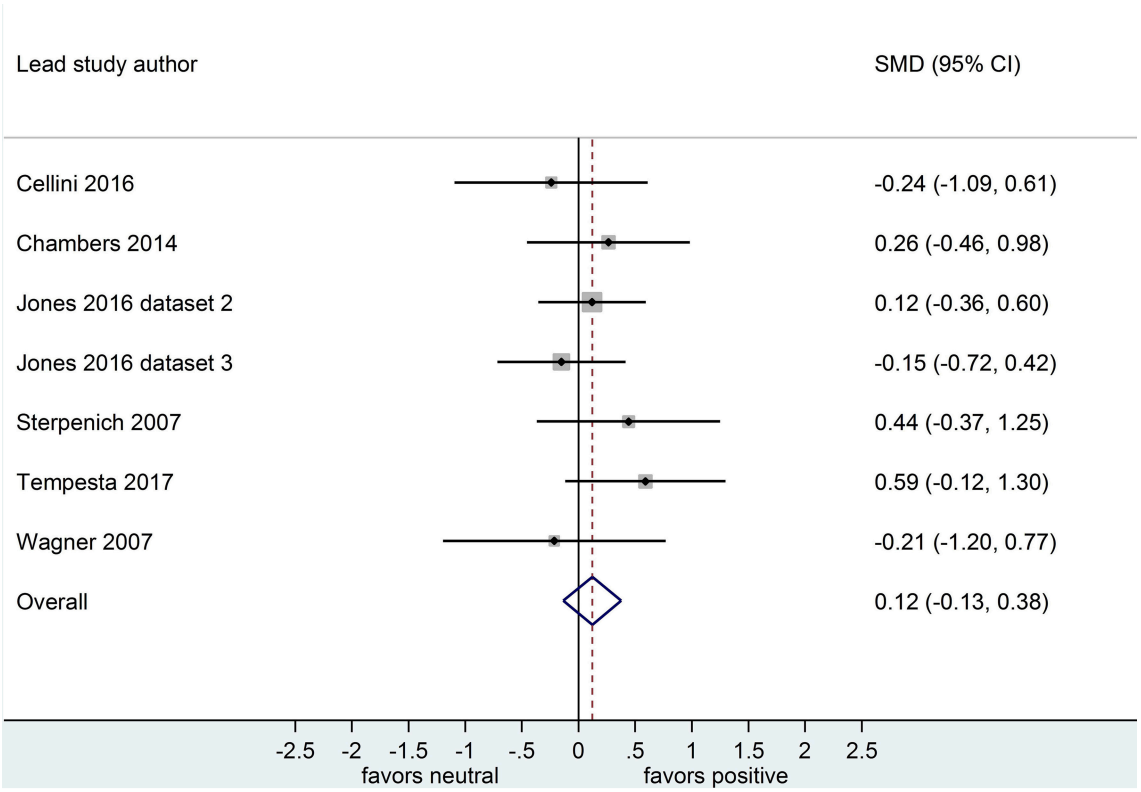


**FIGURE 5 |** Memory for positive vs. neutral information after a wake-filled delay ($k = 7$, $n = 251$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 0.12$. Heterogeneity is reported as $I^2 = 0\%$, $p_Q = 0.62$. SMD, standardized mean difference; CI, confidence interval.

recognized valenced stimuli more readily than neutral stimuli. The effect sizes associated with the sleep- and wake-filled delays were similarly large ($d = 1.35$ and 1.33, respectively), and they overlapped, suggesting there is no sleep benefit for valenced over neutral information.

## Potential Moderators of Sleep-Enhanced Memory for Valenced Material

### Timing and Duration of Sleep Condition

This set of analyses indicated that memory performance (emotional vs. neutral) after a sleep-filled delay might be influenced by whether participants experienced a nap or a full night of sleep.

Of the 20 datasets comparing memory performance for negative vs. neutral stimuli (see **Figures 2**, **3**), three (Nishida et al., 2009; Payne et al., 2015; Cellini et al., 2016) made the performance comparison after either a nap or a matched waking delay, whereas 17 ($n = 1{,}303$) made the comparison after either a full night of sleep or a matched waking delay. Subgroup analyses detected no significant effect for either the nap vs. full-night comparison, $p = 0.250$, or for the short- vs. long-duration control comparison, $p = 0.756$.

Because only 1 nap study compared positive to neutral memory performance (Cellini et al., 2016), we undertook no subgroup analysis in this regard. Results of sensitivity analyses indicated that, after removing this study from the group, the effect size for both the post-sleep and post-waking comparisons increased slightly (see **Table 2**). However, the associated confidence intervals remained similar. Together, these results suggest that including or excluding the nap study from this overall pool of datasets makes little difference to the observed effect.

Similarly, only 1 nap study compared combined negative and positive to neutral memory performance after either a sleep-filled or wake-filled delay (regular day-time waking or night-time sleep deprivation; Bennion et al., 2016). Sensitivity analyses indicated that the magnitude of the difference in effect size estimates for the two comparisons becomes larger when excluding the nap study (see **Table 2**). This finding suggests that the preferential consolidation of emotional over neutral material is observed more strongly after a full night of sleep than after a nap. A caveat here, though, is that the confidence intervals presented above overlap quite markedly, and hence this finding should be explored with a larger pool of datasets, particularly in the nap condition.

### Type of Waking Control Condition

There were some suggestions from this set of analyses that memory performance (especially negative vs. neutral) after a wake-filled delay might be significantly influenced by whether participants experienced (as a control condition) regular daytime waking or night-time sleep deprivation.

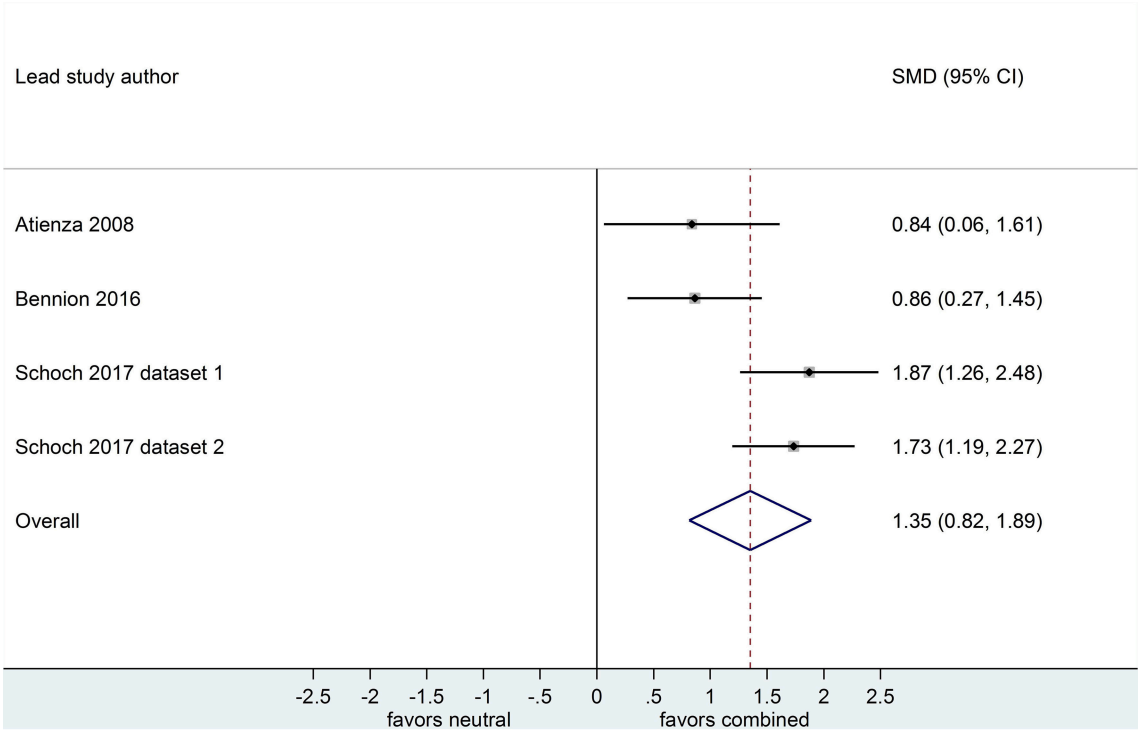


**FIGURE 6 |** Memory for combined negative and positive vs. neutral information after a sleep-filled delay ($k = 4$, $n = 213$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 1.35$. Heterogeneity is reported as $I^2 = 66.6$ %, $p_Q = 0.03$. SMD, standardized mean difference; CI, confidence interval.

Of the 20 datasets comparing memory performance for negative vs. neutral stimuli (see **Figures 2**, **3**), three (n = 167; Sterpenich et al., 2007; Wagner et al., 2007; Tempesta et al., 2017) made the performance comparison after a period of night-time sleep deprivation $d = 0.80$, 95% CI [0.32, 1.28]. The other 17 ($n = 1{,}357$) made the comparison after a regular daytime waking delay, $d = 0.56$, 95% CI [0.37, 0.76]. Subgroup analysis detected a significant effect, $p = 0.03$, suggesting that although in both control conditions negative material is remembered more readily than neutral material, this effect is more pronounced in studies using sleep deprivation paradigms.

Of the 7 datasets comparing memory performance for positive vs. neutral stimuli (see **Figures 4**, **5**), three ($n = 54$; Sterpenich et al., 2007; Wagner et al., 2007; Tempesta et al., 2017) made the performance comparison after a period of night-time sleep deprivation, $d = 0.36$, 95% CI [−0.11, 0.83]. The other four ($n = 89$) made the performance comparison after regular daytime waking delay, $d = 0.02$, 95% CI [−0.28, 0.33]. Subgroup analysis detected a significant effect, $p < 0.001$. Of note here, however, is that both confidence intervals are relatively wide, and both cross the zero midline. Hence, one might draw two conclusions: (a) this effect is more pronounced in studies using sleep deprivation paradigms, and (b) this is an unreliable finding that requires exploration in larger samples of studies.

Because only one sleep deprivation study compared combined negative and positive to neutral memory performance (Atienza and Cantero, 2008), we undertook no subgroup analysis in that regard. However, sensitivity analyses indicated that including or excluding the sleep deprivation study from this overall pool of datasets made little difference to the observed effect (see **Table 2**).

## Type of Memory Encoding

This set of analyses indicated that memory for emotional vs. neutral material after a sleep- or wake-filled delay was not significantly influenced by whether participants' pre-delay encoding of the to-be-remembered material was intentional or incidental.

Of the 20 datasets comparing memory performance for negative vs. neutral stimuli (see **Figures 2**, **3**), 8 ($n = 492$; Wagner et al., 2007; Nishida et al., 2009; Prehn-Kristensen et al., 2009, 2011; Cunningham et al., 2014a; Morgenthaler et al., 2014; Göder et al., 2015; Bolinger et al., 2018) used intentional encoding, whereas 12 [$n = 1{,}032$; Sterpenich et al., 2007; Payne et al., 2008, 2015; Payne and Kensinger, 2011; Baran et al., 2012; Cunningham et al., 2014b; Bennion et al., 2015; Cellini et al., 2016; Jones et al., 2016 [Dataset 1], 2018; (Mantua et al., 2017; Tempesta et al., 2017)] used incidental encoding. Subgroup analyses detected no significant effect for either the sleep condition, $p = 0.087$, or for the waking control condition, $p = 0.361$.

Because only 1 study used intentional encoding when comparing positive to neutral memory performance (Wagner et al., 2007), we undertook no subgroup analysis in that regard. However, sensitivity analyses indicated that including or

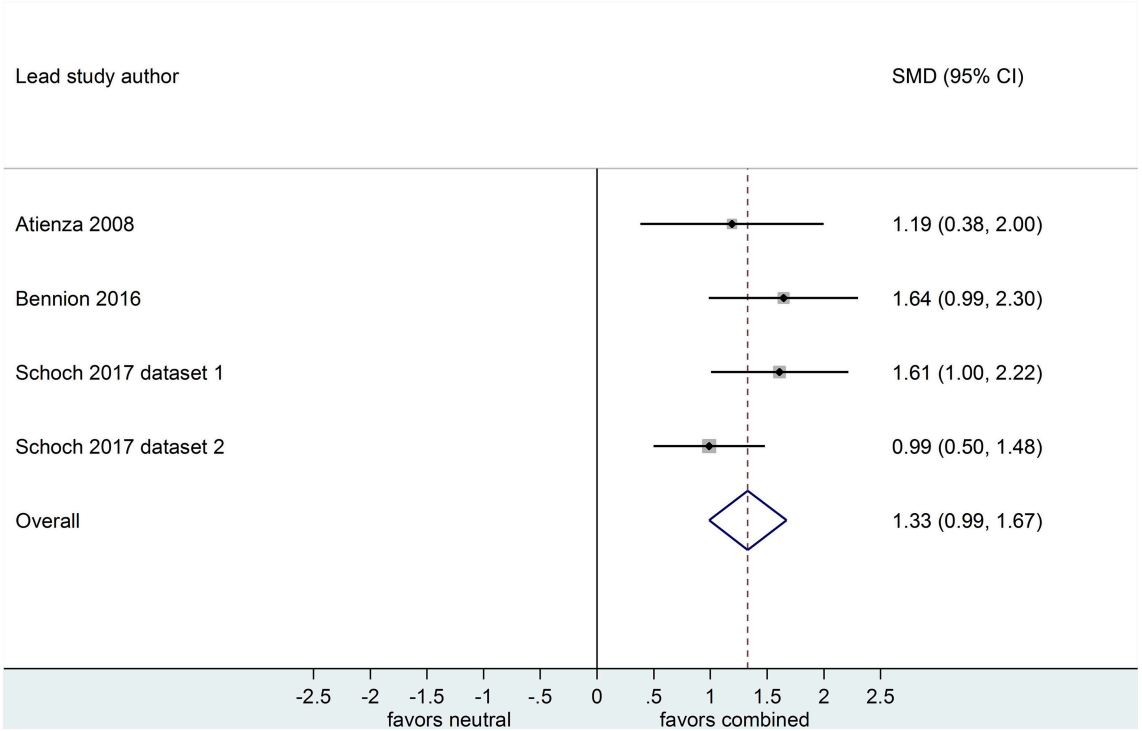


**FIGURE 7 |** Memory performance for combined negative and positive vs. neutral information after a wake-filled delay ($k = 4$, $n = 208$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 1.33$. Heterogeneity is reported as $I^2 = 17.7\%$, $p_Q = 0.30$. SMD, standardized mean difference; CI, confidence interval.

excluding the sleep deprivation study from this overall pool of datasets made little difference to the observed effect (see **Table 2**).

Only 1 study (Bennion et al., 2016) used intentional encoding and then compared combined negative and positive to neutral memory performance. Hence, we undertook no subgroup analysis in this regard. Sensitivity analyses indicated that the magnitude of the difference in effect size estimates for the two comparisons becomes larger when excluding the dataset reporting intentional encoding study (see **Table 2**). Although this finding suggests that the preferential consolidation of emotional over neutral material is observed more strongly after incidental rather than intentional encoding of information, this sensitivity analysis is identical to the one performed for the timing and duration of sleep. Therefore, it is impossible to determine which of these moderator variables (timing and duration of sleep condition, or type of encoding) drives this effect.

## Type of Outcome Measure

This set of analyses indicated that sleep-dependent preferential consolidation of emotional over neutral material was more likely to be demonstrated in studies using free recall than recognition outcome measures.

While no studies compared free recall outcome measures for negative vs. neutral material, only 1 study (Chambers and Payne, 2014) reported these outcomes for a comparison of positive vs. neutral information, after either a sleep- or wake-filled delay. Hence, we undertook no subgroup analysis in this regard. However, sensitivity analyses for positive-neutral comparison indicated that including or excluding the dataset from the pool of studies made little difference to the observed effect (see **Table 2**).

Of the 4 datasets comparing memory performance for combined negative and positive vs. neutral stimuli after a sleep-filled delay (see **Figures 6**, **7**), two ($n = 269$; (Schoch et al., 2017) [Dataset 1 and Dataset 2]) used a free recall outcome measure, $d = 1.79$, 95% CI [1.39, 2.19]. The other two ($n = 152$) made the performance comparison using a recognition outcome measure, $d = 0.85$, 95% CI [0.38, 1.32]. Subgroup analysis detected a significant difference, $p = 0.003$. This result suggests that, although emotional material is remembered significantly more readily than neutral material after a sleep-filled delay, this effect is particularly pronounced when participants are asked to recall the material spontaneously, without re-exposure to the stimulus.

When a similar subgroup analysis was applied to data from waking conditions, it detected no significant difference, $p = 0.495$. Taken together, these results suggest that the probability of observing preferential sleep-dependent consolidation of emotional over neutral material is higher in studies using free recall outcome measures than in those using recognition measures. This interpretation is tempered somewhat by the finding that the confidence intervals are wide and do overlap to some extent.

**TABLE 2 |** Comparison of effect sizes: original full-sample analyses vs. sensitivity analyses.

| Potential moderator/comparison | Dataset removed | Original | | Sensitivity | |
|---|---|---|---|---|---|
| | | *d* | 95% CI | *d* | 95% CI |
| Timing and duration of sleep condition[a] | | | | | |
| Positive vs. neutral | Cellini et al., 2016 | | | | |
| Post-sleep | | 0.19 | −0.15, 0.54 | 0.28 | 0.03, 0.53 |
| Post-waking | | 0.12 | −0.12, 0.36 | 0.15 | −0.11, 0.42 |
| Combined negative-positive vs. neutral | Bennion et al., 2016 | | | | |
| Post-sleep | | 1.32 | 0.90, 1.74 | 1.59 | 1.23, 1.95 |
| Post-waking | | 1.24 | 0.94, 1.55 | 1.23 | 0.88, 1.57 |
| Type of waking control condition[b] | | | | | |
| Combined negative-positive vs. neutral | Atienza and Cantero, 2008 | | | | |
| Post-waking | | 1.24 | 0.94, 1.55 | 1.37 | 0.93, 1.82 |
| Type of memory encoding[c] | Wagner et al., 2007 | | | | |
| Positive vs. neutral | | | | | |
| Post-sleep | | 0.22 | −0.18, 0.62 | 0.25 | 0.01, 0.50 |
| Post-waking | | 0.12 | −0.13, 0.38 | 0.15 | −0.12, 0.41 |
| Combined negative-positive vs. neutral | Bennion et al., 2016 | | | | |
| Post-sleep | | 1.32 | 0.90, 1.74 | 1.59 | 1.23, 1.95 |
| Post-waking | | 1.24 | 0.94, 1.55 | 1.23 | 0.88, 1.57 |
| Type of outcome measure[d] | | | | | |
| Positive vs. neutral | Chambers and Payne, 2014 | | | | |
| Post-sleep | | 0.19 | −0.15, 0.54 | 0.21 | −0.13, 0.37 |
| Post-waking | | 0.12 | −0.12, 0.36 | 0.10 | −0.14, 0.37 |
| Age distribution of sample[e] | | | | | |
| Positive vs. neutral | Jones et al., 2016, dataset 2 | | | | |
| Post-sleep | | 0.19 | −0.15, 0.54 | 0.21 | 0.13, 0.55 |
| Post-waking | | 0.12 | −0.12, 0.36 | 0.02 | −0.32, 0.35 |
| Method of data extraction[f] | | | | | |
| Negative vs. neutral | Atienza and Cantero, 2008; Payne et al., | | | | |
| Post-sleep | 2008; Bennion et al., 2016 | 0.55 | 0.31, 0.79 | 0.55 | 0.31, 0.80 |
| Post-waking | | 0.55 | 0.38, 0.73 | 0.51 | 0.36, 0.66 |

*Sensitivity analyses removed:*
[a] *Datasets from studies using a nap paradigm;*
[b] *Dataset from study using a sleep deprivation paradigm;*
[c] *Dataset from a study using intentional encoding during learning phase;*
[d] *Datasets from studies using free recall outcome measures;*
[e] *Dataset from a study using an older adult sample;*
[f] *Datasets that were extracted graphically.*

## Gender Distribution of Sample

Of the 21 datasets comparing memory performance for negative vs. neutral stimuli after a sleep-filled delay (see **Figure 2**), two datasets [$n = 128$; (Prehn-Kristensen et al., 2009, 2011)] recruited only male participants, $d = 1.08$, 95% CI [0.55, 1.60]. The other 18 ($n = 1,396$) made the comparison using a mixed sample of male and female participants, $d = 0.50$, 95% CI [0.34, 0.65]. Subgroup analysis detected a significant effect, $p = 0.039$ suggesting that although both men and women remember negative material more readily than neutral material after a period of sleep, the effect is more pronounced in studies using male-only samples.

Of note here is that when a similar subgroup analysis was applied to data from waking conditions, it detected no significant difference, $p = 0.709$. These findings suggest that the probability of observing preferential sleep-dependent consolidation of emotional over neutral material is higher in all-male than in mixed-genders samples.

All datasets comparing memory performance for positive vs. neutral material, and combined negative and positive vs. neutral material, used mixed-gender samples.

## Age Range of Sample

Among the set of 20 datasets comparing memory performance for negative vs. neutral material after either a sleep- or wake filled delay (see **Figures 2**, **3**), 1 ($n = 84$; Jones et al., 2016 [Dataset 1]) used a sample of older adults aged >50 years, 3 (n = 192; Prehn-Kristensen et al., 2009, 2011; Bolinger et al., 2018) used samples of children aged < 18 years, and the remaining 16 ($n = 1,248$) used samples of young/middle aged adults aged 18-50 years. Analyses detected no significant subgroup effect after either a sleep- or a wake-filled delay, $p = 0.522$ and 0.926, respectively.

Only 1 study (Jones et al., 2016 [Dataset 2]) used a sample of older adults in comparing memory performance for positive vs. neutral material after either a sleep- or wake-filled delay. All other datasets making that comparison used samples of young/middle-aged adults. A sensitivity analysis indicated that removing this older-adult dataset from the overall pool resulted in a larger effect size difference between the sleep and the waking condition (see **Table 2**). This result suggests that, for the comparison of these types of material, sleep-dependent preferential consolidation of emotional over neutral material may be present for younger adults (18-45 years) but not older adults (>45 years).

All datasets comparing memory performance for combined negative and positive vs. neutral material used samples of adults.

## Baseline Learning Control for Memory Outcome Measures

This set of analyses indicated that sleep-dependent preferential consolidation of emotional over neutral material was more likely to be demonstrated in studies that used baseline-controlled outcome measures (i.e., that used, as a primary outcome, a measure of retention, calculated as the score at delayed retrieval minus the score at pre-delay encoding) than in those studies that did not (i.e., that used post-delay recall or recognition scores as their outcomes).

Nine datasets recorded retention memory outcome measures (i.e. baseline-corrected measures) rather than post-delay means only. Statistically, it is not possible to include these retention values alongside uncontrolled post-delay mean scores in the same meta-analysis reporting standardized mean differences (Higgins and Green, 2011). Hence, we report here on separate analyses of datasets using retention scores. Given the small number of datasets, we did not undertake further subgroup or sensitivity analyses of the afore-described potential moderator variables.

Nine datasets compared retention for negative vs. neutral stimuli after a sleep-filled delay ($n = 297$), $d = 0.64$, 95% CI [0.22, 1.07] or after a wake-filled delay ($n = 280$), $d = 0.18$, 95% CI [-0.06, 0.43]. This pattern of results suggests that sleep-dependent enhancement of emotional over neutral memory is observed clearly in studies reporting retention memory outcome measures (see **Figures 8**, **9**).

Four datasets compared retention for positive vs. neutral stimuli after a sleep-filled delay ($n = 147$), $d = 0.21$, 95% CI [-0.15, 0.58] or after a wake-filled delay ($n = 134$), $d = 0.11$, 95% CI [-0.26, 0.49]. Although the confidence intervals for these two analyses included a zero value and largely overlap, the difference between effect sizes is consistent with the pattern described for memory performance comparing negative vs. neutral material, albeit with a smaller sample of studies (see **Figures 10**, **11**).

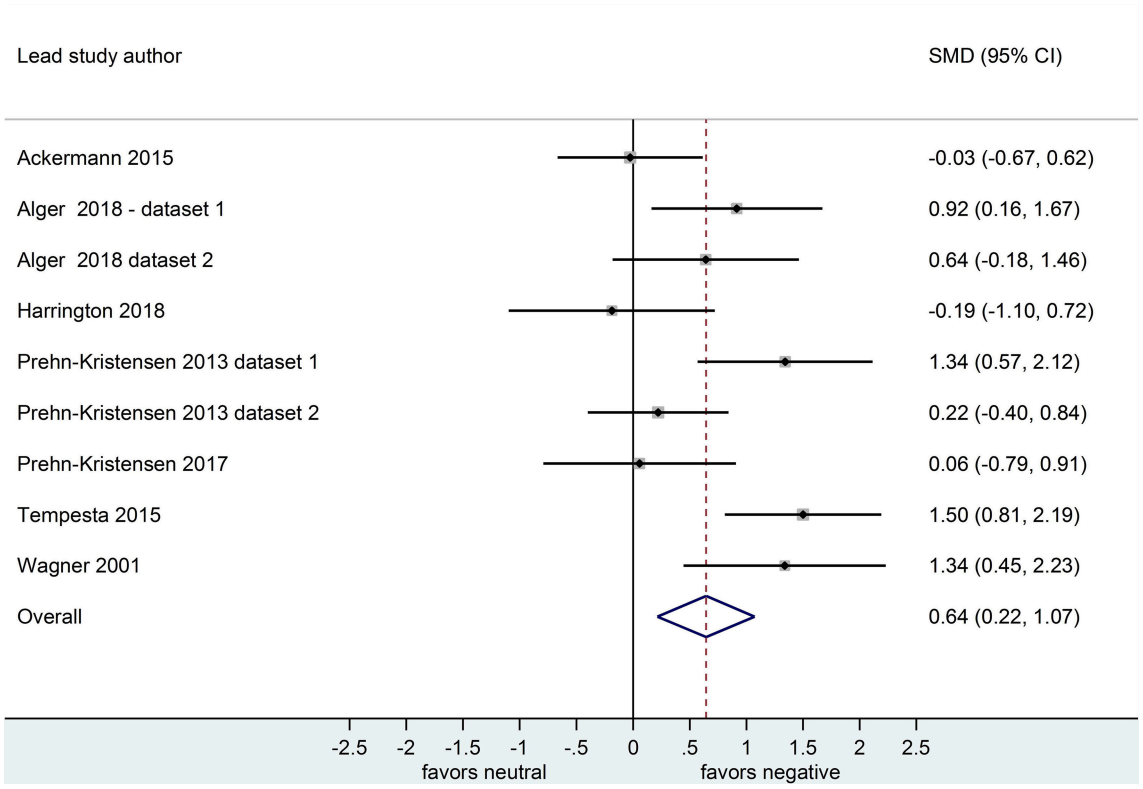


**FIGURE 8 |** Memory performance for negative vs. neutral information after a sleep-filled delay in datasets using retention memory outcome measures ($k = 9$, $n = 297$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 0.64$. Heterogeneity is reported as $I^2 = 65.0\%$, $p_Q < 0.01$. SMD, standardized mean difference; CI, confidence interval.

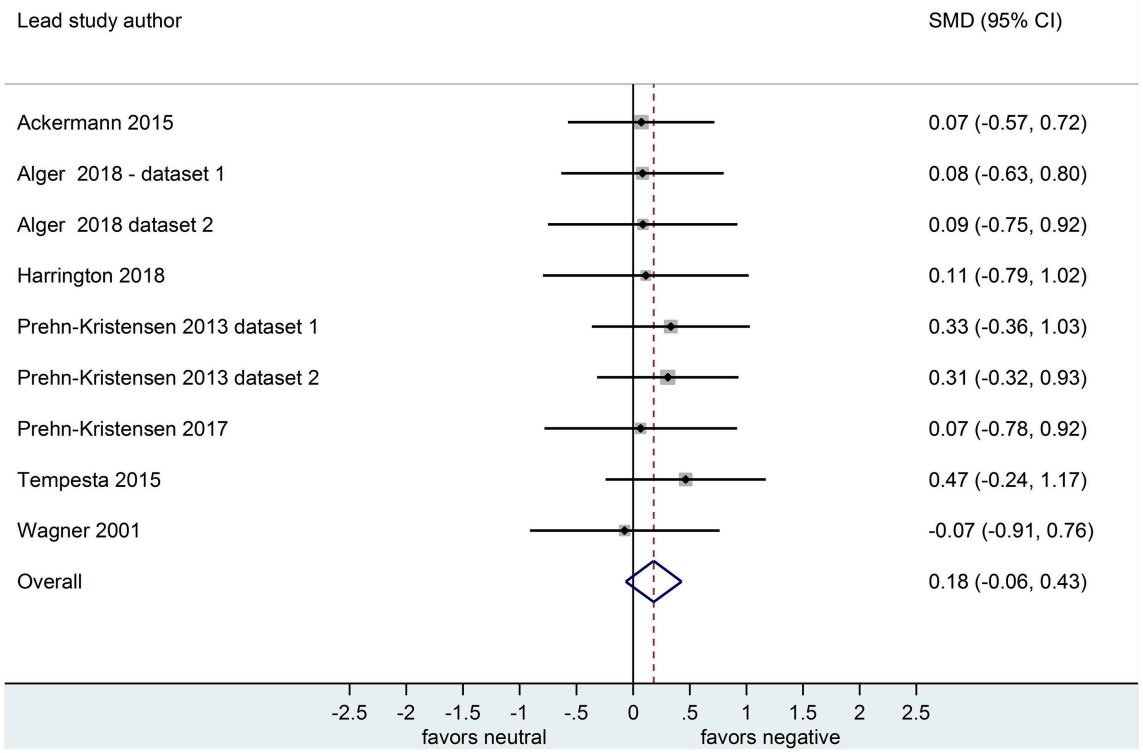


**FIGURE 9 |** Memory performance for negative vs. neutral information after a wake-filled delay in datasets using baseline-controlled memory outcome measures ($k = 9$, $n = 280$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 0.18$. Heterogeneity is reported as $I^2 = 0\%$, $p_Q = 0.99$. SMD, standardized mean difference; CI, confidence interval.

There were no datasets examining retention outcome measures in the combined negative and positive compared to neutral memory performance comparison.

### Method of Data Extraction

For three datasets ($n = 124$; Atienza and Cantero, 2008; Payne et al., 2008; Bennion et al., 2016), all of which compared negative to neutral memory performance, we had to extract data using the WebPlotDigitizer program. Sensitivity analyses indicated that including or excluding this data from the overall pool of datasets made little difference to the observed effect (see **Table 2**).

## DISCUSSION

Numerous studies suggest that whereas neutral memories tend to fade away over time, emotional memories are preferentially consolidated during sleep so that they remain stronger for longer (Wagner et al., 2001; Hu et al., 2006; Payne et al., 2008). However, not all studies replicate this result. The aim of this quantitative review was to evaluate the totality of evidence and to explore potential sources of inconsistency.

Our initial set of analyses assessed strength of memory for (i) valenced compared to neutral material after a sleep-filled interval, and (ii) valenced compared to neutral material after a wake-filled interval. The results showed that, after both sleep-filled and wake-filled delays, emotional material was remembered better than neutral material. Of primary importance here, then, was that there was no sleep-specific effect on memory for emotionally valenced (negative, positive, or combined negative-positive) material over neutral material.

Despite this negative result, further exploration of potential moderators suggested that two methodological conditions, in particular, might provide a better context for exploring whether sleep might provide a neurobiological environment that preferentially consolidates emotional over neutral material more strongly than waking does.

The first of these conditions involves the type of outcome measure used. We found that, in studies reporting free recall outcome measures, the magnitude of difference between strength of memory for emotional (specifically, combined negative-positive stimuli) vs. neutral material after a sleep-filled delay was significantly larger than that in studies reporting recognition measures. This subgroup difference was not significant when participants experienced a wake-filled delay between encoding and retrieval.

Few empirical studies in this literature make a direct comparison between memory performance on different outcome measures. Notably, however, Schoch et al. (2017) reported a pattern of data consistent with aggregate analyses within our review: They observed an enhancing influence of sleep on emotional memory when participants were asked to report images they remembered, but not when they were asked

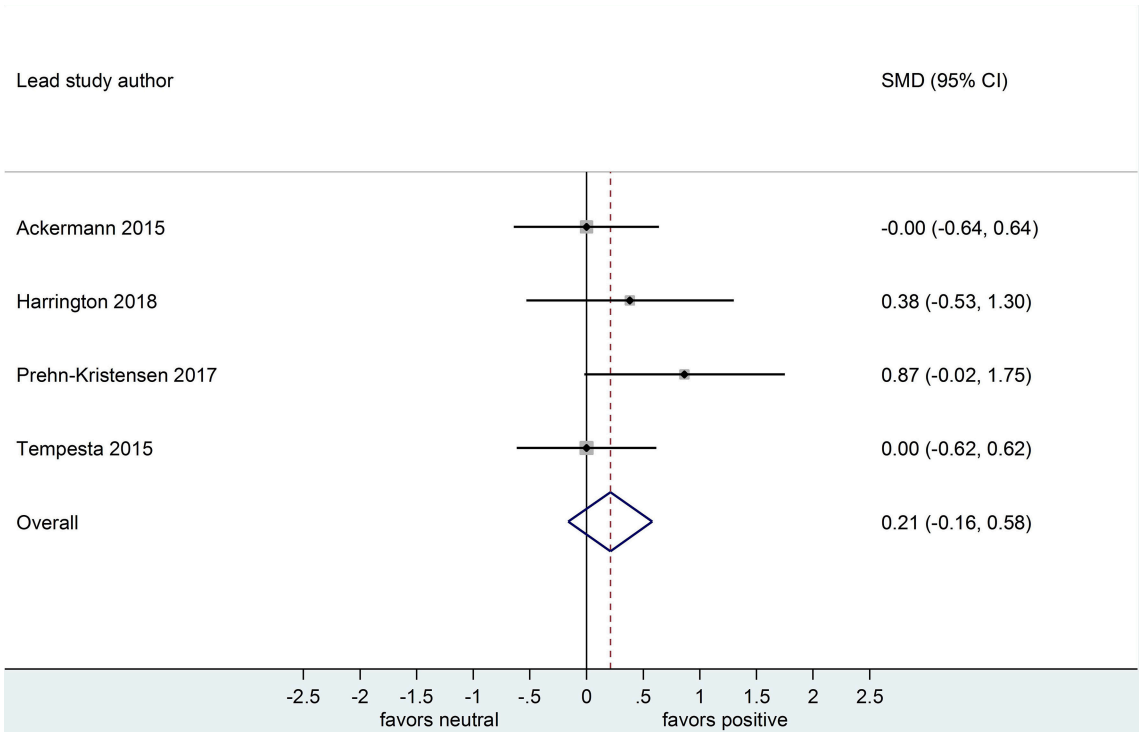


**FIGURE 10 |** Memory performance for positive vs. neutral information after a sleep-filled delay in datasets using retention memory outcome measures ($k$ =4, $n$ = 147). The $x$-axis represents effect size (Cohen's $d$). The dashed red line indicates the overall effect size, $d = 0.21$. Heterogeneity is reported as $I^2 = 3.2\%$, $p_Q = 0.62$. SMD, standardized mean difference; CI, confidence interval.

to complete a forced-choice recognition task. Moreover, a sizable literature suggests that two key memory processes under consideration here (retrieval during free recall tasks and consolidation during sleep) are reliant on hippocampal structure and activity (Girardeau et al., 2017; Miyamoto et al., 2017). Recognition-based retrieval, in contrast, relies more heavily on frontal-subcortical circuitry (Squire and Dede, 2015). An important consideration here, however, is the fact that free recall tasks tend to be more cognitively demanding than cued recall or recognition tasks. Hence, variation in task difficulty may be a confounding factor when attempting to describe whether, and how, differences in task type (free recall vs. recognition) might influence the ways in preferential consolidation of valenced over neutral material might be captured in the laboratory.

A second methodological condition that our review suggests may be important to uncovering sleep-dependent enhancement of emotional information is whether the post-delay memory outcome measure factors in a pre-delay control for initial learning. Specifically, our analyses suggested that, in studies subtracting performance on a pre-delay recall or recognition trial from performance on post-delay memory testing (i.e., studies reporting performance on what is commonly referred to as a measure of retention), there was post-sleep evidence of preferential consolidation of emotional over neutral material. In studies that did not control for initial learning, there was no evidence of this enhancing effect. This finding is consistent with the understanding that, in sleep research, baseline-controlled memory measures (i.e., of the amount of information retained after the delay, often reported as retention) are the best behavioral representations of memory consolidation (Antony and Paller, 2018).

Of note here is that this finding held in the relatively large group of studies ($k = 6$) comparing memory performance of negative vs. neutral material. Only two studies compared memory performance of positive vs. neutral material; no study compared memory performance of combined negative and positive vs. neutral material.

There are at least two plausible interpretations of this finding. One is that for sleep-dependent consolidation to occur, new learning may need to be actively brought to mind (i.e., reactivated) to 'tag' it as relevant for consolidation during sleep (Antony and Paller, 2018). A second, and perhaps more prosaic, interpretation is that statistical differences, which are obscured by noise in the data, only become apparent after controlling for initial learning (for example, individual differences in learning capacity may obscure between-condition differences in memory consolidation). One way to test the strength of these two interpretations is to examine whether the exact same material recalled after initial learning is recalled again after the sleep- or wake-filled delay. This test is easy to apply in studies using free recall memory outcomes. However, recognition studies often use different subsets of the initial pool of learned material at immediate and post-delay recognition, and so in that context it is impossible to tease apart the merit of each interpretation.

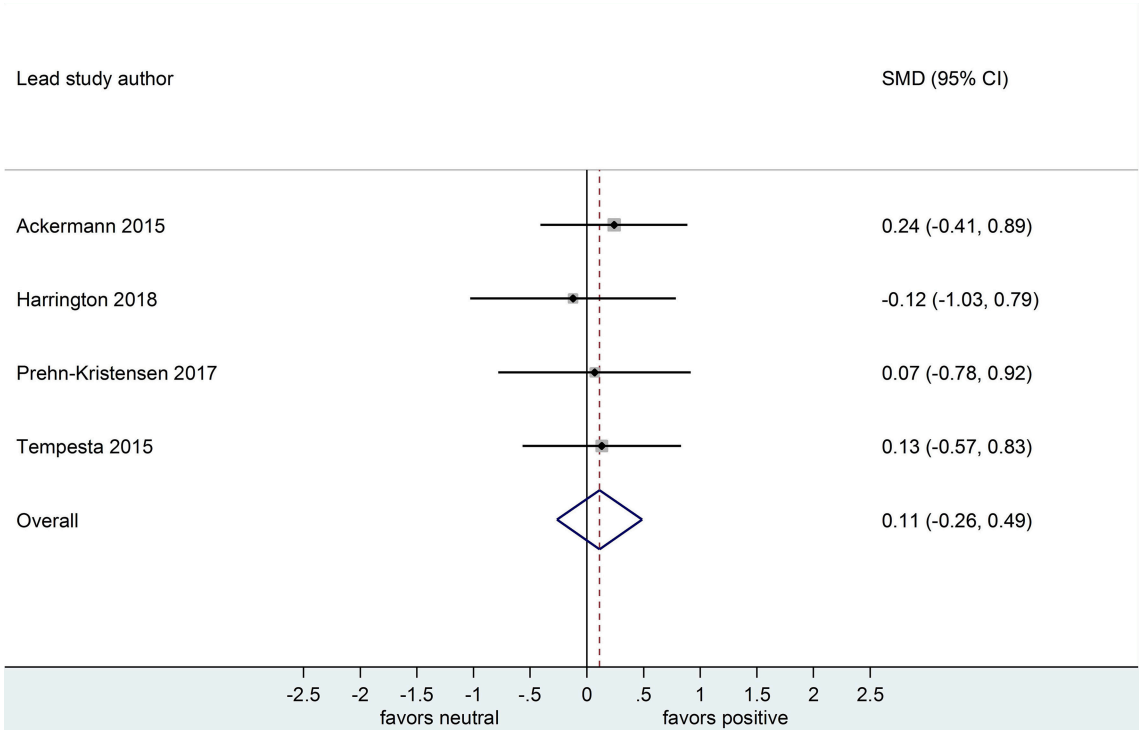


**FIGURE 11 |** Memory performance for positive vs. neutral information after a wake-filled delay in datasets using retention memory outcome measures ($k = 4$, $n = 134$). The *x*-axis represents effect size (Cohen's *d*). The dashed red line indicates the overall effect size, $d = 0.11$. Heterogeneity is reported as $I^2 = 0\ \%$, $p_Q = 0.94$. SMD, standardized mean difference; CI, confidence interval.

Analyses of these two moderating variables (free recall vs. recognition as the type of outcome measure, and baseline-controlled or not as a feature of the memory measure) provide perhaps the most persuasive (and relevant, from the perspective of the sleep-memory literature) results from our secondary analyses. Analyses of the other moderating variables add methodological guidance for future research in this field.

First, our analyses suggested that future studies should carefully consider whether to use a nap or full-night paradigm. Specifically, excluding a nap study from the pool of studies comparing memory performance for combined negative-positive material to neutral material resulted in a larger post-sleep emotional-neutral memory difference. Two notes of caution here are that (a) this finding was only demonstrated for one of the three memory comparison conditions, and (b) the same dataset (Bennion et al., 2016) was removed as part of the sensitivity analyses for another moderator variable (type of memory encoding; it was the only study within this pool that used intentional encoding), and so we cannot be certain whether it was exclusion of the nap or exclusion of the intentional encoding that drove the change in effect. Given that only one of these accounts (the nap) drives the effect in the predicted direction, we favor this interpretation.

Second, studies that used sleep deprivation as a control for night-time sleep rather than regular day-time waking, showed a more pronounced emotional memory effect. That is participants experiencing sleep deprivation tended to remember both negative and positive information more readily than neutral information. This result is consistent with literature that demonstrates that sleep deprivation results in increased emotional reactivity both in reaction to negative (Yoo et al., 2007; van der Helm and Walker, 2011) and positive (Gujar et al., 2011; Krause et al., 2017) stimuli. Stronger emotional responses may result in stronger emotional memory for this category of stimuli. Methodologically studies should consider which kind of control condition they choose, because using the sleep deprivation paradigm may paradoxically result in participants remembering more emotional information after sleep deprivation rather than after sleep.

Third, our analyses revealed that studies that compared memory outcomes for combined negative-positive information with neutral information showed a stronger emotional memory effect than studies that compared a single valanced category to the neutral category. That is, the difference in memory strength for emotional material vs. neutral material was much larger in studies that combined positive and negative information into a single emotional category. Research findings consistently show that the strength of emotional response at encoding is highly correlated with the strength of memory recall or recognition after a delay (Sharot et al., 2004; Phelps, 2006). Studies that presented participants with both negative and positive emotional material may have achieved higher levels of emotion elicitation, whereas studies that presented either negative or positive information only may have dampened the strength of participants emotional

experiences through desensitization (i.e. through repetitive presentation of material of the same valence; van den Hout et al., 2014; Ratneswaran et al., 2016).

Finally, our analyses indicated particular effects of sociodemographic variables on sleep-dependent consolidation of emotional memory. Specifically, both sample gender distribution (i.e., whether it was all male or mixed) and age (i.e., whether children, adults or older adults were studied) appeared to affect the size of effects.

Regarding gender, several previous studies (e.g., Debarnot et al., 2013; McDevitt et al., 2014; Sattari et al., 2017) have reported that, in women, sleep-dependent memory consolidation is affected by variations in female sex hormones (i.e., at some points in the menstrual cycle, effects are weaker than at others). Hence, studies recruiting male-only samples are more likely to observe consistent effects. However, no published study has specifically examined gender differences, or effects of menstrual cycle phase, on sleep-dependent consolidation of emotional material.

Regarding age, there are well-documented age-related differences in sleep architecture, memory processing, and sleep-dependent memory consolidation. Relative to young adults, older adults sleep more poorly, process learned material differently, and do not consolidate that material as effectively (Gui et al., 2017). Sensitivity analyses for positive vs. neutral material generated results consistent with this pattern: When the study containing an older-adult sample was removed, we observed preferential sleep-dependent consolidation of positive over neutral material. We did not, however, observe the same age-related effect within our largest subgroup analysis (for negative vs. neutral material). This inconsistency may be attributed to (a) the relatively small pool of studies we examined, and/or (b) the fact that we defined older adults here as those aged >45 years (rather than the more conventional >65 years).

## LIMITATIONS

The strength of our findings must be weighed against the following limitations. Primarily, as with any systematic review, the quality of our findings are constrained by the quality of the data we analyzed. Although we regard the included studies as being of sound design and without high risk of bias, there was substantial variability in their methodology. Hence, we had to conduct several subgroup and sensitivity analyses, and in most cases those analyses featured small numbers of studies and data derived from relatively low numbers of participants. Together, these factors constrain our ability to make strong inferences based on our moderator analyses.

Furthermore, we were unable to perform a direct statistical comparison of the sleep and waking conditions in addition to our primary comparison of memory for emotional vs. neutral stimuli. To compute the sleep-waking comparison, we would first need to calculate the difference between emotional and neutral memory for each condition separately and then compare those values meta-analytically. Although the difference of the means for emotional and neutral memory performance can be calculated reliably, the difference of the standard deviations (where standard deviations are a requirement of meta-analysis) cannot be computed in the same way.

We also note that although our analyses investigated quantitative influences on emotional memory, we did not explore whether sleep might induce qualitative/transformational changes in emotional memories. For example, a large body of work has demonstrated that sleep induces an "emotional trade-off," wherein core emotional aspects of a memory episode are retained at the cost of forgetting non-emotional details (Payne et al., 2008, 2015; Cunningham et al., 2014a,b; Alger et al., 2018).

## SUMMARY AND CONCLUSION

Our first major finding was that the extant literature does not conclusively demonstrate that sleep preferentially consolidates emotional over neutral memories. However, our secondary analyses demonstrated that specific methodological features allowed such preferential consolidation to be observed. Most persuasive are the analyses suggesting that studies using free recall rather than recognition outcome measures, and baseline-controlled rather than uncontrolled post-sleep outcome measures, are more likely to demonstrate the effect.

Much attention has been paid to research investigating the functional value of sleep for cognitive processes, and especially for various forms of memory. There is widespread agreement that sleep plays a vital role in consolidating previously-learned information, and that the associated emotional valence may play an organizing role in how that information is processed during sleep. Neuroscientists will acknowledge, however, that there is much work to be done on the mechanisms underlying sleep-dependent emotional memory consolidation. We hope the current findings, and especially our proposition that particular aspects of study design (e.g., the types of sleep and waking control conditions, the categories of stimuli to which participants are exposed, and the outcome measures used) are critical, will guide future research in this field.

## AUTHOR CONTRIBUTIONS

GL and EB conceptualized the meta-analysis and first-screened the papers. GL, EB, KT, and DB second-screened the papers. GL, EB, and KT performed data extraction. BS conducted the data analysis and all authors were involved in manuscript preparation.

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**Conflict of Interest Statement:** DB would nevertheless like to declare that he is Chair of the Psychopharmacology Committee of the Royal College of Psychiatrists, Clinical Advisor to the National Clinical Audit of Anxiety and Depression, and a Medical Patron of Anxiety UK.

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# Facial Emotion Recognition and Executive Functions in Insomnia Disorder: An Exploratory Study

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**Background:** Clinical and experimental findings suggest that insomnia is associated with changes in emotional processing and impairments in cognitive functioning. In the present study, we investigate the relationship between facial emotion recognition and executive functioning among individuals with insomnia as well as healthy controls.

**Method:** A total of 11 individuals (mean age 31.3 ± 9.4) diagnosed with insomnia disorder and 15 control participants (mean age 24.8 ± 4.6) took part in the study. Participants responded to a facial emotion recognition task which presented them with static and dynamic stimuli, and were evaluated with regard to cognition, sleep, and mood.

**Results:** Compared to controls, we found that participants with insomnia performed worse in the recognition of the facial emotion of fear ($p = 0.001$;$\eta_p^2 = 0.549$; $\beta = 0.999$) and had lower scores in tests of verbal comprehension and perceptual organization (104.00 vs. 115.00, $U = 135.5$; $p = 0.004$; Cohen's, 2013 $d = 1.281$). We also found a relationship between facial emotion recognition and performance in cognitive tests, such as those related to perceptual organization, cognitive flexibility, and working memory.

**Conclusion:** Results suggest that participants with insomnia may present some impairment in executive functions as well as in the recognition of facial emotions with negative valences (fear and sadness).

**Keywords: insomnia, facial emotional recognition, sleep deprivation, cognition, executive functions**

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## INTRODUCTION

Insomnia disorder (ID) is considered the most prevalent sleep disorder and constitutes a significant burden on health care, causing societal costs (e.g., absenteeism at work, accident risks, a decrease in productivity), functional and cognitive impairment, and increased risk of mental disorders, such as depression (Hillman et al., 2006; Morin et al., 2009; Baglioni et al., 2011; Waters and Bucks, 2011; Suh et al., 2012; Morin et al., 2015; Hertenstein et al., 2018). Some epidemiological studies have shown that 30–50% of the general population complains of some insomnia symptoms (difficulty initiating sleep, difficulty maintaining sleep, waking up too early in the morning). The diagnostic evaluation of insomnia

in the general population is uncommon, but a few studies reported 10–15% of individuals meet the criteria for the diagnosis of ID diagnosis (Morin and Benca, 2012; American Psychiatric Association [APA], 2013; American Academy of Sleep Medicine [AASM], 2014; Chaput et al., 2018). According to operational diagnostic criteria, ID is defined as a main complaint of dissatisfaction with sleep quantity or quality, along with difficulty initiating or maintaining sleep, or waking up earlier than expected, not being able to get back to sleep, and followed by a perception of non-restoring sleep (American Psychiatric Association [APA], 2013; American Academy of Sleep Medicine [AASM], 2014). Furthermore, the significant clinical distress and impairment in important areas of daytime functioning must be present.

Clinical and experimental findings have suggested that sleep loss and insomnia is associated with altered emotional processing, such as facial emotion recognition (Tempesta et al., 2018; Zhang et al., 2019). Accurate facial emotion recognition is an important predictor of successful social interactions as it helps to recognize different individuals in their social interactions, to perform accurate interpretations of human faces, and to correctly identify an individual's current emotional state. Functional deficits in emotion processing have been associated with poor social functioning (Almondes et al., 2016b).

Facial emotion recognition alterations in insomnia patients have recently been presented by a number of studies (Kyle et al., 2014; Crönlein et al., 2016). Some results have shown that ID is associated with a lower accuracy of facial emotion recognition and a reduced rating of emotion intensity for face expressions, as compared to control groups (Kyle et al., 2014; Crönlein et al., 2016). On the other hand, some studies have not found this association between insomnia or sleep disorders and recognition of facial emotions, suggesting that the data are inconclusive (Sheth et al., 2009; Almondes et al., 2016b; Brand et al., 2016, 2019).

In ID, some studies have reported functional and metabolic changes in brain regions associated with emotional processing. For example, Nofzinger et al. (2004), in a functional brain imaging study using $^{18}$F-fluorodeoxyglucose Positron emission tomography (PET), reported that patients with ID presented, from wakefulness to non-rapid eye movement (NREM) sleep states, relative hypometabolism in brain structures related to emotion and cognitive functioning, including the amygdala, hippocampus, anterior cingulate cortex, and bilateral medial prefrontal cortex (PFC), and in wake-promoting structures including the hypothalamus, thalamus, and ascending reticular activating system. While awake, patients with ID showed smaller decline in relative glucose metabolism in the PFC bilaterally and in other associative areas, and in the thalamus, hypothalamus, and brainstem reticular formation. However, considering the whole brain metabolism, when compared to normal control subjects, ID patients showed greater global metabolism during sleep and while awake (Nofzinger et al., 2004). More pronounced hypoactivation of prefrontal regions and its connections (frontosubcortical and frontoparietal networks) in patients with insomnia was reported by some studies (Altena et al., 2008; Drummond et al., 2013; Stoffers et al., 2014). Overall, it seems that there are interacting neural networks with relative hypometabolism and hypermetabolism, including a general arousal system (ascending reticular formation and hypothalamus), an emotion regulating system (hippocampus, amygdala, and anterior cingulate cortex), and a cognitive system (frontosubcortical and frontoparietal networks). Furthermore, evidence from resting-state functional magnetic resonance imaging (fMRI) indicated that ID appears to alter the functional connectivity in the frontoparietal network (Li et al., 2014).

This data taken together indicates that insomniacs appear to be in a sleep deprivation condition and that this sleep loss seems to be associated with the deterioration of the coding of emotional information, processes of emotional memory consolidation, and the achievement of related cognitive processes of the executive functions (EFs). The EFs are related to emotional and motivational aspects, as well as cost and benefit analysis.

The underlying brain mechanisms of ID are not fully understood, and there is a lack of consensus on how differences in brain activity relate to cognitive and emotional functioning in ID (Kay and Buysse, 2017). However, some neuroimaging studies aggregate relevant findings, especially those showing discrepancies in patterns of brain alterations or activation in emotional contexts. Under sleep deprivation, the amygdala increases responses to negative emotional stimuli, and its connectivity with the PFC is diminished (Motomura et al., 2017). In other lines of evidence with ID, in a sample with a wide range of insomnia severity, restless REM sleep impairs emotional processing in relation to amygdala reactivity (i.e., continued amygdala reactivity). Amygdala reactivity decreased overnight if REM sleep was undisturbed, and individual differences in the reactivity decreasing were proportional to the total duration of REM episodes (Wassing et al., 2019). Patients with ID showed abnormally increased activation in the amygdala from stimuli with insomnia-related content (Baglioni et al., 2014). Also, self-perceived sleep quality modulates the amygdala resting-state functional connectivity in individuals with and without clinical anxiety or depression disorders (Klumpp et al., 2018). Albeit with discrepant findings, most evidence cited so far shows a pattern of amygdala overactivation in the context of emotional stimulus. The PFC top–down connection activity over the limbic region, especially the amygdala and insula, may be disrupted in insomnia and sleep deprivation conditions, leading to emotional dysregulation and alterations, which includes facial expressions. However, it should be noted that brain alterations in ID may be more complex and involve other connections. For example, resting-state fMRI studies show that there are functional disruptions in ID patients, such as disruptions in global and regional topological organization of the brain functional connectome, including the dorsal attention, default mode, and sensory-motor networks (Li et al., 2018).

Evidence also suggests PFC subregions, such as ventromedial and dorsomedial prefrontal areas along with the amygdala and temporal lobe (i.e., inferior and fusiform areas) connections are necessary for a complex executive control of facial recognition and emotional attribution (Vuilleumier and Pourtois, 2007; Heberlein et al., 2008; Todorov, 2012). Beyond emotion association, this relation is important owing to the

frontosubcortical and frontoparietal roles in so-called EFs, which refers to an umbrella term denoting a branch of top–down and higher-order cognitive processes involved in the coordination and control of goal-directed behavior, such as inhibitory control, working memory, and cognitive flexibility (Miyake et al., 2000; Chan et al., 2008; Diamond, 2013). Working memory involves holding information temporarily in the mind and mentally working with it to perform a task (Baddeley and Hitch, 1994). Inhibitory control involves being able to control one's attention, behavior, thoughts, and/or emotions to do what is more appropriate or needed and adaptive (Diamond, 2013). Cognitive flexibility is the ability to change the course of an action or thought and to adjust quickly in favor of the demands and priorities of the environment (Miyake et al., 2000).

Although findings about executive functioning in patients with ID still appear non-consensual, there are findings that indicate that these individuals may present mild to moderate deficits in processes such as working memory, selective attention, problem solving, and inhibitory control (Fernandez-Mendoza et al., 2010; Shekleton et al., 2010; Fortier-Brochu et al., 2012; Suh et al., 2012; Fortier-Brochu and Morin, 2014), which suggests that ID patients can have a reduced ability to engage task-related frontosubcortical and frontoparietal networks. Moreover, there is a discussion that the contradictory literature on the association between insomnia and EFs is essentially due to insomnia phenotypes. Fernandez-Mendoza et al. (2010) and Vgontzas et al. (2013) concluded that only individuals with insomnia with shortened sleep duration, measured objectively through polysomnography, present impairment in EFs.

The current study sought to investigate whether (1) patients with ID would perform differently relative to normal controls on tasks involving facial emotion recognition (happiness, sadness, anger, and fear), whether (2) tasks performance would relate to EF and (3) whether both groups would differ in EF performance. It is hypothesized that patients with ID will present alterations in recognition of facial emotions, that such alterations will be related to EF, and that ID patients will exhibit a lower EF performance when compared to normal controls individuals.

# MATERIALS AND METHODS

## Participants and Design

A cross-sectional study was conducted. The Insomnia Disorder Group (IDG) comprises participants recruited in the Sleep Clinic AMBSONO of the Federal University of Rio Grande do Norte. Inclusion criteria for participants with ID were as follows: diagnosis of insomnia according to the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) (American Psychiatric Association [APA], 2013), normal or corrected visual acuity, and aged between 20 and 45 years. Exclusion criteria included diagnosis of depression and other psychiatric and neurological disorders, current psychiatric medication use, and dependence on drugs or alcohol.

Normal control group (NCG) participants were recruited through several channels at local universities and public places: online, print, and broadcast media announcements or advertisements for comparative purposes. The inclusion criteria comprised: (a) no sleep disorder; (b) between 20 and 45 years old; (c) normal or corrected visual acuity; (d) not presenting psychiatric disorders; (e) no present dependence on drugs or alcohol.

The total sample ($n$ = 26) was composed of 11 participants (four males and seven females; mean age 31.3 $\pm$ 9.4 years old) in the IDG and 15 participants (5 male and 10 female; mean age 24.8 $\pm$ 4.6 years old) in NCG.

Participants from both groups were submitted sequentially to a sleep and mood evaluation, a cognitive assessment, and emotional face recognition tasks (**Figure 1**). This study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte (registration number 10843713.2.0000.5537). All participants gave written informed consent for participation. The study was conducted in conformity with the ethical standards proposed in the World Medical Association Declaration of Helsinki.

## Assessments and Procedure

Participants will not receive reimbursement for their participation, since the research was voluntary. The procedures were applied at the laboratory of researchers located at the Federal University of Rio Grande do Norte, between 10 am and 4 pm, in line with participants' free schedule of activities.

### Sleep and Mood Evaluation

A structured interview based on clinical diagnostic criteria for insomnia contained in the DSM-5 (American Psychiatric Association [APA], 2013) was conducted. The interview investigated factors such as sleep habits and daytime impairment. The main objective was to answer the inclusion and exclusion criteria, confirming the diagnosis of insomnia participants. This interview was conducted as the first stage of the study (**Figure 1**).

Participants from both groups completed a number of self-administrated standardized questionnaires commonly used to evaluate sleep, mood, and stress. The severity of insomnia was estimated using the Athens Insomnia Scale (AIS). This is a self-assessment questionnaire consisting of eight items. The total score ranges from 0 (absence of any sleep-related problem) to 24 (the most severe degree of insomnia) (Soldatos et al., 2000). The Insomnia Gravity Index (IGI) was used to assess the severity, nature, and impact of both nighttime and daytime components of insomnia. It is a seven-item self-report questionnaire with a five-point Likert scale to rate each item (e.g., 0 = no problem; 4 = very severe problem), generating a score that ranges from 0 to 28 (Bastien et al., 2001).

The Pittsburgh Quality Sleep Index (PSQI) is a self-report questionnaire that was used to assess sleep quality and quantity over a 1-month period. The global PSQI score represents the sum of the seven subscales (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) and ranges from 0 to 21. Higher scores indicate worse sleep quality (Buysse et al., 1989; Bertolazi et al., 2011). A sleep diary was designed to gather information about an individual's daily sleep pattern, over a period of 2 weeks. It yielded information about the

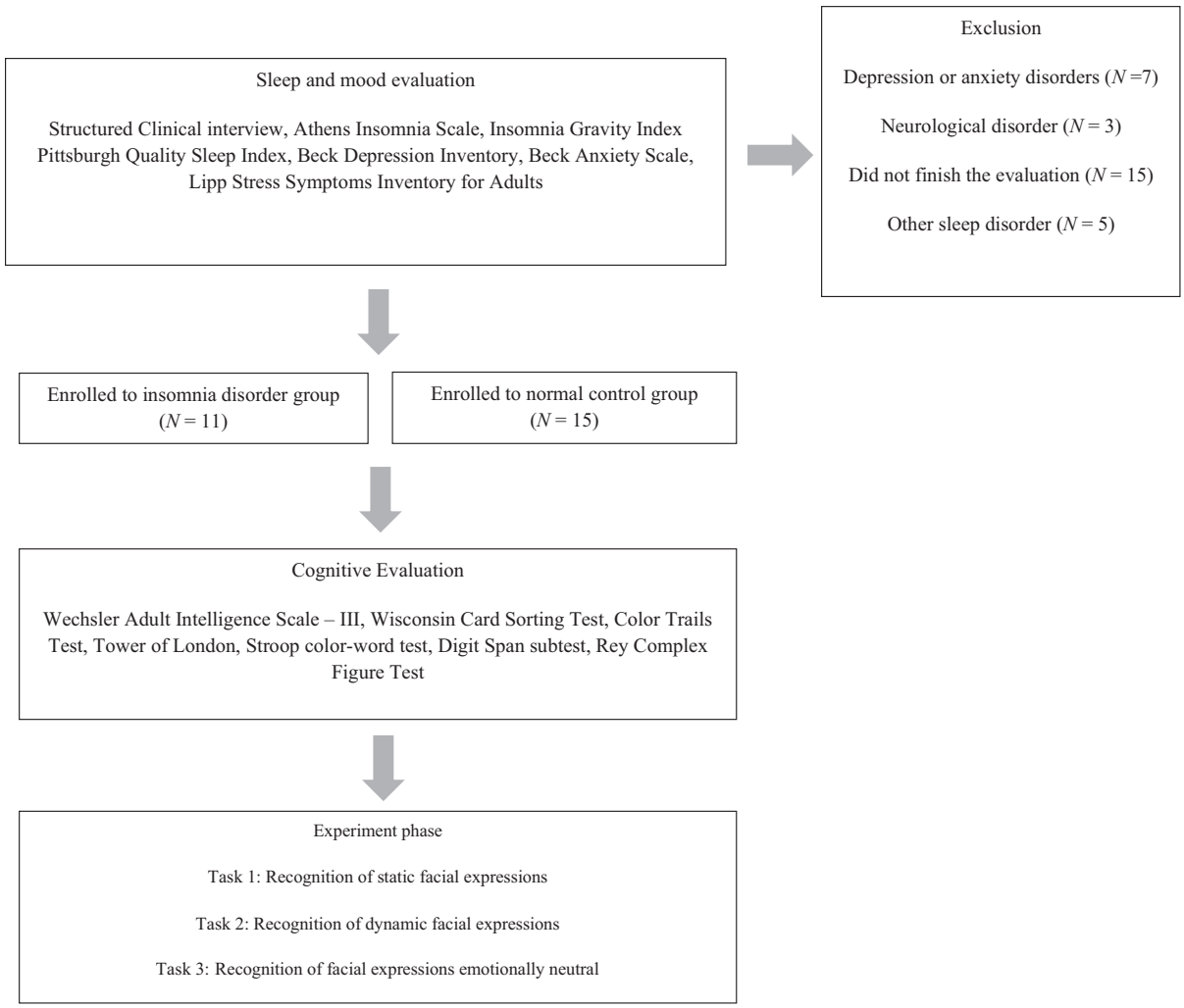


**FIGURE 1 |** Flowchart of design and procedures of the study.

following measures: sleep fragmentation (SF), total sleep time (TST), sleep efficiency (SE), and restorative sleep perception (RSP) (Carney et al., 2012).

Depressive symptoms were evaluated using the Beck Depression Inventory (BDI). This is a 21-items, self-report rating inventory that assesses the severity of symptoms of depression. The total score ranges from 0 to 63 (Beck et al., 1988b; Cunha, 2001). The Beck Anxiety Scale (BAS) was used to assess the severity of anxiety symptoms. The total score ranges from 0 to 63 (Beck et al., 1988a; Cunha, 2001). The Lipp Stress Symptoms Inventory for Adults (LSSIA) was used to identify and classify stress symptoms (i.e., psychological and physical) among adults according to the four stages of stress: alarm, resistance, quasi-exhaustion, and exhaustion (Lipp, 2000).

## Cognitive Assessment

Cognitive performance was assessed with a series of widely used neuropsychological tests. The Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III) provides a measure of general intellectual function. The four-factor indices were used for cognitive evaluation: Verbal Comprehension, Perceptual Organization, Working Memory, and Processing Speed (Wechsler, 2004). Executive functioning was specifically assessed with the following tests: The Wisconsin Card Sorting Test (WCST) was used to measure the ability to develop abstract concepts (abstract reasoning) and shift between sets (cognitive flexibility and problem solving). The participants have received a set of four reference cards, each differing from the others in terms of three categories: color (red, blue, green, or yellow), shape (triangle, circle, square, or cross), or number (1, 2, 3, or 4). The task is to match the stimuli card to one of four key cards, but the participant is not told how to match the cards, only whether a match is right or wrong. The matching rules change as the test progresses, and participants must adapt their strategy based on feedback from the administrator. The 128-cards version was used. Completed categories, perseverative errors and perseverative responses were used as dependent measures (Heaton et al., 2005).

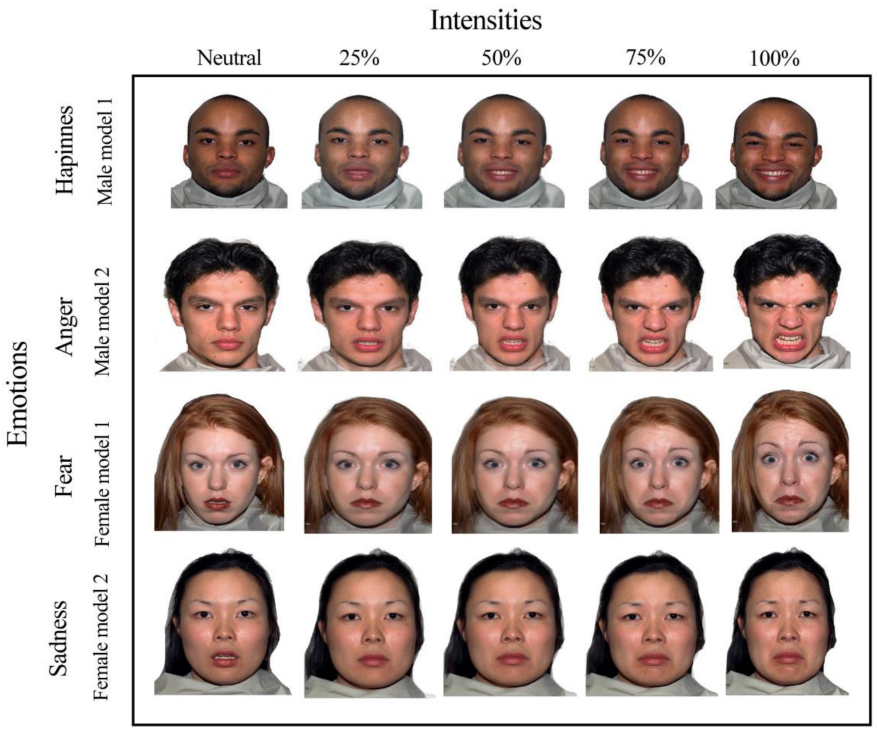


**FIGURE 2 |** Facial stimuli for the emotions of happiness, sadness, fear, and anger with emotional intensities of 25, 50, 75, 100% and "neutral faces" of two male and female models.

The Color Trails Test (CTT) was used as a measure of attention (i.e., sustained and divided), processing speed, and cognitive flexibility. It consists of two parts — CTT 1 and CTT 2. For CTT 1, the participant uses a pencil to rapidly connect colored circles numbered 1–25 in sequence. It evaluates perception tracking and sustained attention. For CTT 2, the participant rapidly connects numbered circles in sequence (the numbers 2–25 are presented twice), but alternates between pink and yellow. The CTT 2 evaluates the same functions and introduces a divided attention and cognitive flexibility components because it demands sequential alternations of colors and numbers. The test was scored based on the time, in seconds, to complete the task. An additional score, the interference index, was used for comparison of the participant's performance on the CTT 1 relative to CTT 2 (D'Elia et al., 2010). Planning capacity and problem solving were evaluated using the Tower of London (ToL). The test comprises three vertical pegs of different lengths and three blocks of different colors (red, blue and green). The blocks must be moved in a certain sequence, peg to peg, from a standard configuration to produce a set pattern (reflected by the examiner's model) within a specified number of moves. The total score is the sum of obtained points in each sequence problem (Krikorian et al., 1994).

The Stroop color-word test (Victoria Version) is a timed test that evaluates processing speed, attention, and response inhibition. It consists of three separate subtests that involve naming the color of dots (C), of neutral words (W), and of color words printed in incongruent colors (C/W). Each condition contains 24 items. The Color (C) and Word (W) cards were assessed as a first measure of processing speed and sustained attention. The Color/Word (C/W) card was used as a measure of response inhibition. The time needed to finish the cards was recorded (Strauss et al., 2006). The Digit Span Subtest (WAIS-III) is a test that consists of two conditions: digits forward and digits backward, which measures auditory attention and working memory respectively. In both conditions, the examiner reads aloud up to eight (forward) or seven (backward) pairs of random digits, then the participant is asked to repeat the digits in order (Wechsler, 2004). The cognitive assessment also included a measure of visuoconstructive skill and visual episodic memory taken by the Rey Complex Figure Test (RCFT). It comprises a copy trial of the complex figure followed by one more recall trial after 30 min (Rey, 2010).

## Facial Expressions Tasks

The experimental stimuli were comprised of photographs extracted from the NimStim Face Stimuli Set (Tottenham et al., 2009). The facial expressions of two male and female models showing happiness, anger, fear, sadness, and neutrality were used (**Figure 2**).

Three tasks to evaluate facial emotion recognition were designed as follows: recognition of static facial expressions (Task 1), recognition of dynamic facial expressions (videos) (Task 2), and emotional attribution to neutral and emotional faces (Task 3) (**Figure 3**). The software SuperLab 5.0 was used in the stimuli presentation.

In the individual session participants were instructed, for all tasks, to indicate the most appropriate emotional expression for each presented image, using the numeric keypad on their computer. They could observe each picture for the time stipulated by the system. Response options were given on the screen after each stimulus presentation, with a free response time for the participant.

### Task 1: Accuracy and Response Time in Recognition of Static Facial Expressions

The Software Morpheus 4.0 was used to produce faces varying in emotional intensity, from a neutral face (0%) to full emotional expression (100%). In this task, we used faces with emotional intensities corresponding to 25, 50, 75, and 100%, which were presented for the times of 1, 2, 3, and 4 s, respectively. We maintained such presentation times to static stimuli in order to follow the presentation pattern of the dynamic stimuli as described in Task 2. In each session, 64 stimuli were presented, composed of 4 expressions (fear, anger, sadness, and happiness) vs. 4 intensities (25, 50, 75, and 100%) vs. 4 models (two males and two females). After the stimulus presentation, participants had to press the corresponding option to the emotion on the keyboard.

### Task 2: Accuracy and Response Time in Recognition of Dynamic Facial Expressions

The Software Adobe Premiere Pro CS3 was used to produce dynamic facial expressions. The process of creating videos of facial expressions involves the ordering of photos (morphings) with a time criterion of transition from one image to other. Videos began with 1% and increased progressively by steps of 1% to the values of 25, 50, 75, and 100% of emotional intensity. We used the rate of 25 frames per second (FPS). Therefore, dynamic stimuli with 25, 50, 75, and 100% of emotional intensity lasted 1, 2, 3, and 4 s, respectively. A screen with emotional labels was presented after each dynamic stimulus, and the participant had free time to respond by pressing the corresponding key to the emotion on the keyboard.

### Task 3: Emotional Attribution to Neutral Faces

In this task, we used the same 64 static faces presented in Task 1, with addition to 8 neutral faces, totaling 72 stimuli. We set the presentation time to 1 s for all stimuli in order to increase the difficulty level of the emotional identification task. After observing the facial expressions, including 'neutral faces,' the participant should indicate the most appropriate emotional expression. There was not a 'neutral face' in the alternative responses and it was not mentioned to the participants that neutral faces would also be presented. Therefore, as they were to choose the emotion corresponding to each face presented, they were forced to assign an emotion to the neutral faces.

## Statistical Analysis

The software SPSS (Statistical Package for the Social Sciences) 21.0 was used for data analysis. In all statistical tests, we assigned the alfa of 0.05 (5%) as the statistical significance criterion. The Shapiro–Wilk (SW) test was used to verify normality. For demographic and sleep variables, the SW test indicated that data does not follow a normal distribution. For this reason, we used the Mann–Whitney test (U) and Chi-square test ($X^2$) to compare IDG and NCG groups with regard to these variables. The relationship among sleep measures, cognition, and recognition were evaluated using the Spearman test ($r_s$) in case of a non-parametric distribution and using the Pearson test (r) in case of a normal distribution according to the results obtained from the SW test.

The SW test indicated a normal distribution to other variables investigated in the study: (a) accuracy and response time in facial emotion recognition in Tasks 1 and 2; (b) attribution of emotions to neutral faces in Task 3; (3) accuracy and response time in facial emotion recognition in Task 3; and (4) Cognitive measures. In Tasks 1 and 2, variables were submitted to an ANOVA between-within of repeated measures of model 2 groups (insomniacs and controls) x [2 conditions (static and dynamic) x 4 emotions (happiness, fear, anger, and sadness)]. In Task 3, the variable attribution of emotion was submitted to an ANOVA between-within of repeated measures of model 2 groups (insomniacs and controls) x [4 emotions (happiness, fear, anger, and sadness)]. In Task 3, the variable response time and accuracy in emotional recognition were submitted to an ANOVA between-within of repeated measures of model 2 groups (insomniacs and controls) x [4 emotions (happiness, fear, anger, and sadness x 4 emotional intensities (25, 50, 75, and 100%)]. In the ANOVAs, the variable "groups" was taken as a between-subject factor and the variables "conditions," "emotions," and "intensities" were taken as within-subject factors. Statistically significant interactions between factors were analyzed with *post hoc* tests using the Bonferroni's alfa correction. In the ANOVAs, we also calculated effect size ($\eta_p^2$) and observed power (β) for main factors and interactions between them.

# RESULTS

These groups were compared in terms of sociodemographic variables, sleep measures, mood, and cognition (**Table 1**). Groups did not differ with regard to age ($U$ = 53.50; $t$ = 1.51; $p$ = 0.134; $r$ = 0.30) or number of male and female participants [$X^2(1) = 0.26$; $p = 0.598$].

Severity and clinical impact of insomnia was statistically higher in IDG when compared to the NCG [$Mdn_{IDG}$ = 16.0, $IQR_{IDG}$ = 5.0 vs. $Mdn_{NCG}$ = 5.0, $IQR_{NCG}$ = 6.0; $U$ = 3.0; $p$ = 0.001). Further, IDG presented worse sleep quality ($Mdn_{IDG}$ = 13.00, $IQR_{IDG}$ = 6.0 vs. $Mdn_{NCG}$ = 6.00, $IQR_{NCG}$ = 3.0; $U$ = 9.5; $p$ = 0.001) (PSQI > 6). Fourteen-days of sleep diaries confirmed subjective sleep complaints in the IDG. As expected, this group presented greater levels of sleep fragmentation ($Mdn_{IDG}$ = 8.00, $IQR_{IDG}$ = 8.0 vs. $Mdn_{NCG}$ = 1.00, $IQR_{NCG}$ = 2.0; $U$ = 14.00; $p$ = 0.01), poorer sleep efficiency ($Mdn_{IDG}$ = 83%, $IQR_{IDG}$ = 26.0 vs. $Mdn_{NCG}$ = 99%, $IQR_{NCG}$ = 4.0; $U$ = 157.00; $p < 0.01$), fewer hours of sleep ($Mdn_{IDG}$ = 330.00, $IQR_{IDG}$ = 140.0 vs. $Mdn_{NCG}$ = 466.00 min, $IQR_{NCG}$ = 63.0; $U$ = 154.5; $p < 0.01$) and less perception of restorative sleep [6.7 (tired) vs. 90.9% (tired and very tired);

**TABLE 1 |** Descriptive statistics of demographic data, sleep evaluation, mood and cognitive assessment for Insomnia Disorder Group and Normal Control Group.

| Groups | Insomnia Disorder Group (*N* = 11) | Normal Control Group (*N* = 15) | *p* |
|---|---|---|---|
| **Demographic characteristics** | ***N* (%)** | ***N* (%)** | 0.59[1] |
| **Gender** | | | |
| Male | 4 (36.4) | 5 (33.3) | |
| Female | 7 (63.6) | 10 (66.7) | |
| **Age (years)** | **Mean *(SD)*** | **Mean *(SD)*** | 0.13[2] |
| | 31.3 (9.4) | 24.8 (4.6) | |
| **Education** | ***N (%)*** | ***N (%)*** | 0.95[2] |
| Primary School | 1 (9.1) | 1 (6.7) | |
| High School | 7 (63.6) | 10 (66.7) | |
| College | 3 (27.3) | 4 (26.7) | |
| **Sleep and mood evaluation** | **Mdn (IQR)** | **Mdn (IQR)** | |
| AIS | 14.0 (5.0) | 5.0 (6.0) | *<0.01*[2] |
| IGI | 16.0 (5.0) | 5.0 (7.0) | *<0.01*[2] |
| PSQI | 13.0 (6.0) | 6.0 (3.0) | *<0.01*[2] |
| *Sleep diary measures* | **Mdn (IQR)** | **Mdn (IQR)** | |
| *Sleep fragmentation* | 8.0 (8.0) | 1.0 (2.0) | *<0.01*[2] |
| *Total sleep time* (min) | 330.0 (140) | 466.0 (63.0) | *<0.01*[2] |
| *Sleep efficiency* (%) | 83.0 (26) | 99.0 (4.0) | *<0.01*[2] |
| *Restorative sleep perception* | ***n* (%)** | ***n* (%)** | *<0.01*[2] |
| Rested | 1 (9.1) | 14 (93.3) | |
| Tired | 7 (63.6) | 1 (6.7) | |
| Very tired | 3 (27.3) | 0 (0) | |
| BDI | 11.0 (5.97) | 6.0 (2.93) | *<0.01*[2] |
| BAS | 17.0 (8.44) | 7.0 (4.78) | *0.01*[2] |
| **LSSIA** | ***n* (%)** | ***n* (%)** | <0.01[2] |
| No stress | 1 (9.1) | 10 (66.7) | |
| Alarm | 0 (0) | 1 (6.7) | |
| Resistance | 6 (54.5) | 4 (26.7) | |
| Quasi-exhaustion | 0 (0) | 0 (0) | |
| Exhaustion | 4 (36.4) | 0 (0) | |
| **Cognitive assessment** | **Mdn (IQR)** | **Mdn (IQR)** | |
| *WAIS* | | | |
| Verbal comprehension | 118.0 (6.0) | 125.0 (12.0) | 0.06[2] |
| Perceptual organization | 104.0 (11.0) | 115.0 (10.0) | *<0.01*[2] |
| Working memory | 113.0 (12.0) | 117.0 (18.0) | 0.38[2] |
| Processing speed | 117.0 (22.0) | 113.0 (6.0) | 0.64[2] |
| WCST – Perseverative responses | 20.0 (24.0) | 12.0 (13.0) | 0.13[2] |
| WCST – Perseverative errors | 11.0 (19.0) | 11.0 (10.0) | 0.22[2] |
| WCST – Completed categories | 5.0 (2.0) | 6.0 (0.0) | 0.07[2] |
| CTT 1 | 50.0 (22.0) | 50.0 (22.0) | 0.64[2] |
| CTT 2 | 93.0 (41.0) | 89.0 (39.0) | 0.95[2] |
| CTT – Measure interference | 1.0 (0.0) | 1.0 (0.0) | 0.76[2] |
| ToL | 33.0 (2.0) | 34.0 (2.0) | 0.33[2] |
| Stroop test (C) – time | 14.0 (9.0) | 15.0 (7.0) | 0.44[2] |
| Stroop test (W) – time | 17.0 (9.0) | 16.0 (4.0) | 0.76[2] |
| Stroop test (C/W) – time | 26.0 (13.0) | 22.0 (5.0) | 0.44[2] |
| Digits span forward | 9.0 (3.0) | 11.0 (3.0) | 0.10[2] |
| Digits span backward | 8.0 (2.0) | 8.0 (4.0) | 0.14[2] |
| RCFT – Copy | 35.0 (1.0) | 36.0 (2.0) | 0.19[2] |
| RCFT – Memory | 19.0 (6.0) | 24.0 (7.0) | 0.06[2] |

*Data are presented as a function of Means (M), Medians (Mdn), and Interquatile Range (IQR). [1]p-Value refers to chi-square test and generalized Fisher test. [2]p Refers to Mann–Whitney Test. AIS, Athens Insomnia Scale; IGI, Insomnia Gravity Index; PSQI, Pittsburgh Quality Sleep Index; BDI, Beck Depression Inventory; BAS, Beck Anxiety Scale; LSSIA, Lipp Stress Symptoms Inventory for Adults; WCST, Wisconsin Card Sorting Test; CTT, Color Trails Test; ToL, Tower of London; RCFT, Rey Complex Figure Test. The italicized p-values are significant at p < 0.05. Significant p-values are presented in italic.*

$U = 11.50$; $p = 0.01$] than the NCG. Taken together these findings validate the composition of the groups.

The mood evaluation revealed that depressive ($Mdn_{IDG}$ = 11.00, $IQR_{IDG}$ = 10.0 vs. $Mdn_{NCG}$ = 6.00, $IQR_{NCG}$ = 6.0; $U$ = 9.5; $p$ = 0.01), anxiety ($Mdn_{IDG}$ = 17.00, $IQR_{IDG}$ = 8.0 vs. $Mdn_{NCG}$ = 7.00, $IQR_{NCG}$ = 5.0; $U$ = 20.5; $p$ = 0.001) and stress symptoms (54.5 vs. 26.7%; $U$ = 22.0; $p$ = 0.01) were statistically significantly more present in the IDG than the NCG, although participants from the IDG did not present mood and anxiety disorders.

Regarding cognitive assessment, the Perceptual Organization Index (WAIS III) (POI) was found to be statistically significantly lower in the IDG ($Mdn_{IDG}$ = 104.00, $IQR_{IDG}$ = 11.0 vs. $Mdn_{NCG}$ = 115.00, $IQR_{NCG}$ = 10,0; $U$ = 135.5; $p$ = 0.004) than in the NCG. The other cognitive domains evaluated did not show any significant differences (**Table 1**), suggesting that the NCG had a better performance only in non-verbal reasoning and visuospatial integration, which are processes that compose the POI.

## Tasks 1 and 2: Accuracy in Facial Emotion Recognition

The ANOVA showed a statistically significant effect on the main factors "groups" ($F_{1,24}$ = 9,454; $p$ = 0.005; $\eta_p^2$ = 0.283; β = 0.839), "conditions" ($F_{1,24}$ = 20,548; $p$ = 0.001; $\eta_p^2$ = 0.461; β = 0.991), and "emotions" ($F_{3,22}$ = 12,084; $p$ = 0.001;$\eta_p^2$ = 0.335; β = 0.991), as well as statistically significant interactions between the factors "emotions" and "groups" ($F_{3,22}$ = 3.149; $p$ = 0,030;$\eta_p^2$ = 0.116; β = 0.708), and "conditions" and "emotions" ($F_{3,22}$ = 5.362; $p$ = 0.006;$\eta_p^2$ = 0.183; β = 0.848). We found no statistically significant effects for the interactions between "conditions" x "groups" ($F_{1,24}$ = 0.14; $p$ = 0.908; $\eta_p^2$ = 0.001; β = 0.051), and "groups," "conditions," and "emotions" ($F_{3,22}$ = 0.609; $p$ = 0.564; $\eta_p^2$ = 0.025; β = 0.151) (**Table 2**).

The analysis of the interaction between "emotions" and "groups," carried out with the Bonferroni's correction (**Table 2**), showed that individuals with insomnia presented a lower recognition of facial expressions of fear ($p$ = 0.001; $\eta_p^2$ = 0.549; β = 0.999) and sadness ($p$ = 0.026; $\eta_p^2$ = 0.191; β = 0.627) in comparison to control volunteers. Both groups had a similar performance in the identification of happiness ($p$ = 0.972;

$\eta_p^2 = 0.001$; $\beta = 0.050$) and anger ($p = 0.540$; $\eta_p^2 = 0.191$; $\beta = 0.627$) (**Figure 4**). For the interaction between "conditions" and "emotions," a *post hoc* test indicated an advantage in recognizing dynamic, compared to static, expressions of happiness in both groups of participants ($p = 0.001$; $\eta_p^2 = 0.628$; $\beta = 1.000$). For other emotions, there were no differences between the dynamic and static conditions. The analysis of the main factor "emotion" showed a lower recognition for sadness compared to happiness ($p = 0.001$; $\eta_p^2 = 0.588$; $\beta = 0.995$) and fear ($p = 0.001$; $\eta_p^2 = 0.588$; $\beta = 0.995$) (**Table 2**).

## Tasks 1 and 2: Response Time in Facial Emotion Recognition

The ANOVA showed statistically significant effects on the main factors "conditions" ($F_{1,24} = 756.790$; $p = 0.001$; $\eta_p^2 = 0.969$; $\beta = 1.000$) and "emotions" ($F_{3,22} = 4.245$; $p = 0.014$; $\eta_p^2 = 0.150$; $\beta = 0.779$) (**Table 2**). Groups of participants (IDG and NGC) presented similar response times in evaluation of facial emotions ($F_{1,24} = 2.928$; $p = 0.100$; $\eta_p^2 = 0.109$; $\beta = 0.376$).

We also found an interaction between the factors "conditions" and "emotions" ($F_{3,22} = 4.211$; $p = 0.017$; $\eta_p^2 = 0.150$; $\beta = 0.779$). *Post hoc* analysis showed no differences between emotions in the static condition. However, in the dynamic condition, more time was needed to evaluate the face of sadness compared to the faces of fear ($p = 0.013$) and happiness ($p = 0.003$) (**Figure 4**). Other interactions in ANOVA were not significant: "conditions" x "groups" ($F_{3,22} = 0.296$; $p = 0.591$;$\eta_p^2 = 0.012$; $\beta = 0.082$); "emotions" x "groups" ($F_{3,22} = 0.270$; $p = 0.806$; $\eta_p^2 = 0.011$; $\beta = 0.094$), "conditions" x "emotions" x "groups" ($F_{3,22} = 0.313$; $p = 0.755$; $\eta_p^2 = 0.013$; $\beta = 0.99$) (**Table 2**).

## Task 3: Emotional Attribution to Neutral Faces

In Task 3, we used a forced choice procedure, in which participants had to attribute an emotion to both emotional and neutral faces. In data analysis, we carried out separate ANOVAs for the judgment of neutral and emotional faces (**Table 2**).

### Response Time in Emotion Recognition in Task 3

For recognition accuracy, the ANOVA indicated a statistically significant effect on the main factors "groups" ($F_{1,24} = 5.106$; $p = 0.033$; $\eta_p^2 = 0.175$; $\beta = 0.583$), "emotions" ($F_{3,22} = 6{,}744$; $p = 0.001$; $\eta_p^2 = 0.219$; $\beta = 0.934$), and "intensities" ($F_{3,22} = 65.676$; $p = 0.001$; $\eta_p^2 = 0.732$; $\beta = 1.000$) as well as the interactions "emotions" x "group" ($F_{3,22} = 3.086$; $p = 0.045$;$\eta_p^2 = 0.114$; $\beta = 0.620$) and "intensities" and "emotions" ($F_{9,16} = 2{,}697$; $p = 0.033$;$\eta_p^2 = 0.101$; $\beta = 0.743$) (**Table 2**). We found no statistically significant effect for other interactions: "intensities" x "groups" ($F_{3,22} = 0.338$; $p = 0.684$; $\eta_p^2 = 0.014$; $\beta = 0.097$), "intensities" x "emotions" x "groups" ($F_{9,16} = 1.099$; $p = 0.362$; $\eta_p^2 = 0.044$; $\beta = 0.343$). The analysis of the interaction between "emotions" and "groups" showed that participants of IDG had a lower accuracy in the recognition of the expression of fear ($F_{1,24} = 9.423$; $p = 0.005$; = 0.283; $\beta = 0.839$) compared to the control group. However, groups did not differ with regard to the

**TABLE 2** | Summary of data analysis carried out with variables related to facial emotion recognition.

| Variable | Task | Main factors | | | | Interactions | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Groups | Conditions | Emotions | Intensities | Groups vs. (Conditions or Intensities) | Groups vs. Emotions | Emotions vs. (Conditions or Intensities) | Groups vs. Emotions vs. (Conditions or Intensities) |
| Accuracy | 1 and 2 | $p = 0.005$ | $p = 0.001$ | $p = 0.001$ | not | ns | $p = 0.030$ INT1 | $p = 0.006$ INT2 | ns |
| Response time | 1 and 2 | $p = 0.100$ | $p = 0.001$ | $p = 0.014$ | not | ns | ns | p = 0.017 INT3 | ns |
| Emotional attribution to neutral faces | 3 | $p = 0.395$ | not | $p = 0.003$ | not | ns | ns | ns | ns |
| Accuracy | 3 | $p = 0.033$ | not | $p = 0.001$ | $p = 0.001$ | ns | $p = 0.045$ INT4 | $p = 0.033$ INT5 | ns |
| Response time | 3 | $p = 0.006$ | not | $p = 0.001$ | $p = 0.018$ | ns | $p = 0.001$ INT6 | ns | ns |

*Here, we present results for main factors and interactions in the ANOVAs. Interactions were analyzed with post hoc tests using Bonferroni's alpha correction. INT1: Insomnia group presented a lower recognition of fear and sadness compared to control volunteers. INT2: Dynamic faces of happiness were recognized better than static faces of happiness. INT3: In the dynamic condition, more time was needed to evaluate sadness compared to fear and happiness. INT4: Insomnia group had a lower recognition of fear compared to control group. INT5: Differences between intensities were found more frequently for happiness than for other emotions. INT6: Insomnia group needed more time to recognize fear and sadness compared to the control group. not: factor not included in the ANOVA model. ns: non-statistically significant.*

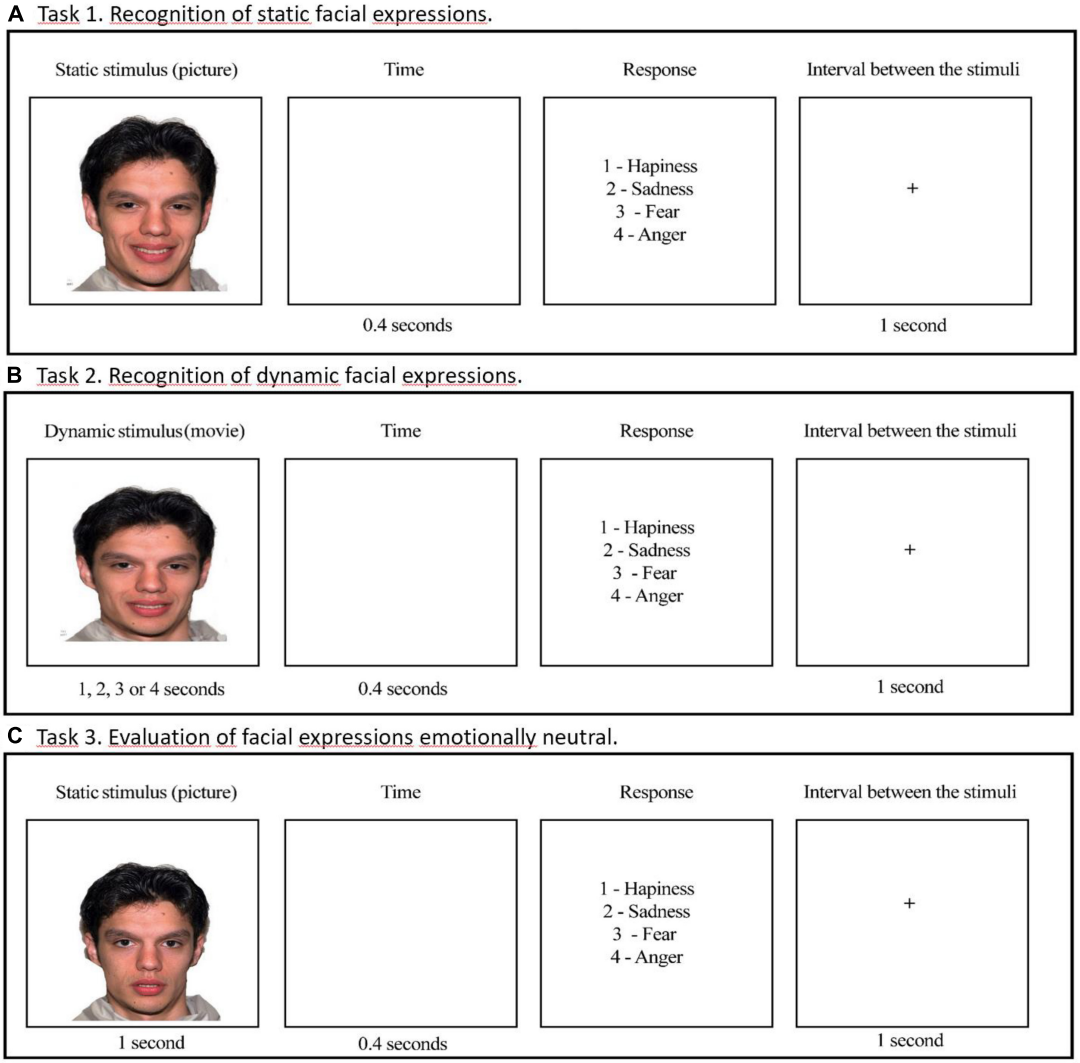


**FIGURE 3 |** Examples of stimuli presentation in the tasks. **(A)** Task 1: Recognition of static facial expressions. **(B)** Task 2: Recognition of dynamic facial expressions. **(C)** Task 3: Evaluation of facial expressions emotionally neutral.

expression of happiness ($F_{1,24}$ = 0.007; $p$ = 0.933; $\eta_p^2$ = 0.001; β = 0.051), anger ($F_{1,24}$ = 0.643; $p$ = 0.430; $\eta_p^2$ = 0.026; β = 0.120) and sadness ($F_{1,24}$ = 3.042; $p$ = 0.094;$\eta_p^2$ = 0.112; β = 0.388) (**Figure 5**).

## Attribution of Emotions to Neutral Faces in Task 3

For the variable attribution of emotions to neutral faces, we found a statistically significant effect on the main factor "emotions" ($F_{3,22}$ = 6.643; $p$ = 0.003; $\eta_p^2$ = 0.217; β = 0.884), but not "groups" ($F_{1,24}$ = 0,750; $p$ = 0.395; $\eta_p^2$ = 0.030; β = 0.132). The interaction between "groups" and "emotions" was not statistically significant ($F_{3,22}$ = 1.421; $p$ = 0.692; $\eta_p^2$ = 0.007; β = 0.067). Bonferroni's *post hoc* indicated a lower attribution of the emotion of happiness to the neutral faces compared to fear ($p$ = 0.001), anger ($p$ = 0.010), and sadness ($p$ = 0.024) (**Figure 5**).

For response times, the ANOVA indicated a statistically significant main effect of the variables "emotions" ($F_{3,22}$ = 11.655; $p$ = 0.001; $\eta_p^2$ = 0.614; β = 0.998) and "intensities" ($F_{3,22}$ = 4.041; $p$ = 0.018;$\eta_p^2$ = 0.360; β = 0.778), "groups" ($F_{1,24}$ = 9.138; $p$ = 0.006; $\eta_p^2$ = 0.276; β = 0.826) and a statistically significant interaction between the variables "emotions" and "groups" ($F_{3,22}$ = 2.231; $p$ = 0.001;$\eta_p^2$ = 0.542; β = 0.984). Other interactions were not significant: "intensities" and "groups" ($F_{3,22}$ = 0.201; $p$ = 0.895; $\eta_p^2$ = 0.027; β = 0.082), "intensities" x "emotions" ($F_{3,22}$ = 2.151; $p$ = 0.087; $\eta_p^2$ = 0.547; β = 0.669), and "intensities" x "emotions" x "groups" ($F_{9,16}$ = 1.220; $p$ = 0.349;$\eta_p^2$ = 0.407; β = 0.397). The analysis of the interaction between "emotions" and "groups" showed that participants of IDG groups need more time to recognize the expressions of fear ($F_{1,24}$ = 18.829; $p$ = 0.001; $\eta_p^2$ = 0.440; β = 0.986) and sadness ($F_{1,24}$ = 6.030; $p$ = 0.022;$\eta_p^2$ = 0.201; β = 0.654) compared to the control

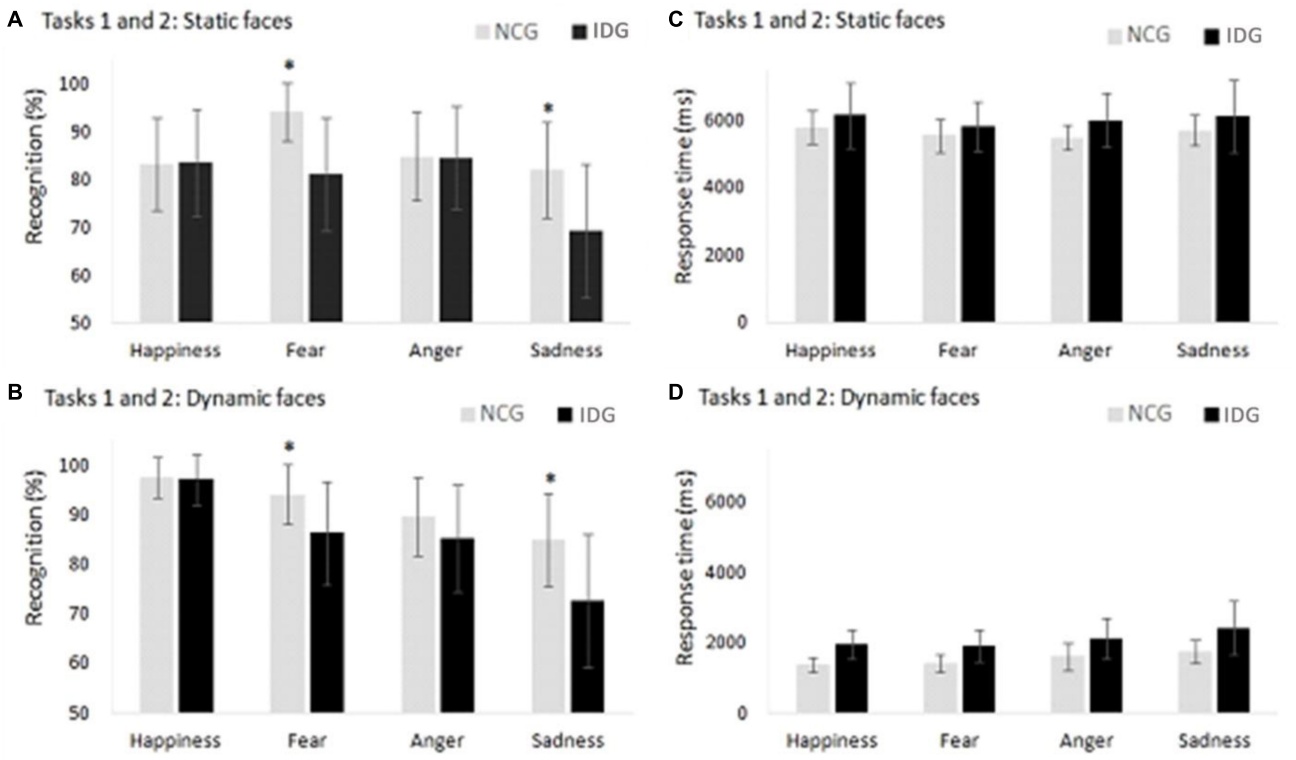


**FIGURE 4 | (A,B)** Control Group (NCG) performed better in the recognition of facial emotions of fear and sadness compared to the Insomnia Disorder Group (IDG). **(C,D)** We found no statistically significant differences between groups with regard to response times in facial emotion recognition in the static and dynamic conditions. Data are presented as a function of means and standard errors. Statistically significant interactions between factors were analyzed with *post hoc* tests using the Bonferroni's alfa correction (*$p < 0.05$).

group. However, groups did not differ with regard to happiness ($F_{1,24} = 4.108$; $p = 0.054$; $\eta_p^2 = 0.146$; $\beta = 0.494$), and anger ($F_{1,24} = 3.825$; $p = 0.062$; $\eta_p^2 = 0.137$; $\beta = 0.467$) (**Figure 5** and **Table 2**).

## Relationships Between Sleep, Cognition, and Recognition of Dynamic and Static Expressions

We carried out two types of correlational analysis: (1) with all participants and (2) for each group (IDG and NCG) (**Table 3**).

For correlations with all participants, we found that recognition of the static expression of fear was statistically significantly interrelated to the WCST measures: generated categories ($r = 0.583$; $p < 0.01$), perseverative responses ($r = -0.506$; $p < 0.01$), perseverative errors ($r = -0.473$; $p = 0.01$). Furthermore, the same expression was also associated with the Perceptual Organization – WAIS III ($r = 0.439$; $p = 0.02$), Verbal Comprehension Index – WAIS III ($r = 0.436$; $p = 0.02$), response time from the Stroop Test C/W ($r = -0.438$; $p = 0.02$), SE ($r = 0.402$; $p = 0.04$) and TST ($r = 0.586$; $p < 0.01$).

Accuracy of recognition of the dynamic sadness expression was negatively associated with response time from the Stroop Test W ($r = -0.483$; $p = 0.01$), C/W ($r = -0.625$; $p < 0.01$) and positively associated to the Verbal Comprehension Index – WAIS III ($r = 0.503$; $p < 0.01$). Additionally, recognition of the static expression of sadness was associated with CTT 1 ($r = -0.411$; $p = 0.03$). We found a statistically significant correlation between recognition of sadness and TST ($r = 0.586$; $p < 0.01$). Finally, the recognition of happiness was correlated to the performance in the tests: RFCT – copy ($r = -0.448$; $p = 0.02$), Working Memory Index (WMI) – WAIS III ($r = -0.395$; $p = 0.04$), ToL ($r = 0.429$; $p = 0.01$); CTT 2 ($r = -0.406$; $p = 0.03$), response time from the Stroop Test W ($r = -0.412$; $p = 0.03$) and C/W ($r = -0.457$; $p = 0.01$).

For the IDG, there was a statistically significant negative association between the recognition of the static expressions of anger and happiness and the working memory measures – WAIS III ($r_s = -0.629$; $p = 0.03$; $r_s = -0.604$; $p = 0.03$), and between the dynamic expression of anger, the digits span backward ($r_s = -0.634$; $p = 0.03$) and working memory measures – WAIS III ($r_s = -0.650$; $p = 0.03$). Recognition of the dynamic sadness expression was negatively associated with response time in the Stroop Test C ($r_s = -0.606$; $p = 0.04$), W ($r_s = -0.684$; $p = 0.02$), and C/W ($r_s = -0.688$; $p = 0.01$). Lastly, perseverative and response errors from WCST were negatively associated with recognition of the static fear expression ($r_s = -0.671$; $p = 0.02$; $r_s = -0.607$; $p = 0.04$). We also found a positive correlation between the recognition of the static face of fear and ToL scores ($r_s = 0.632$;

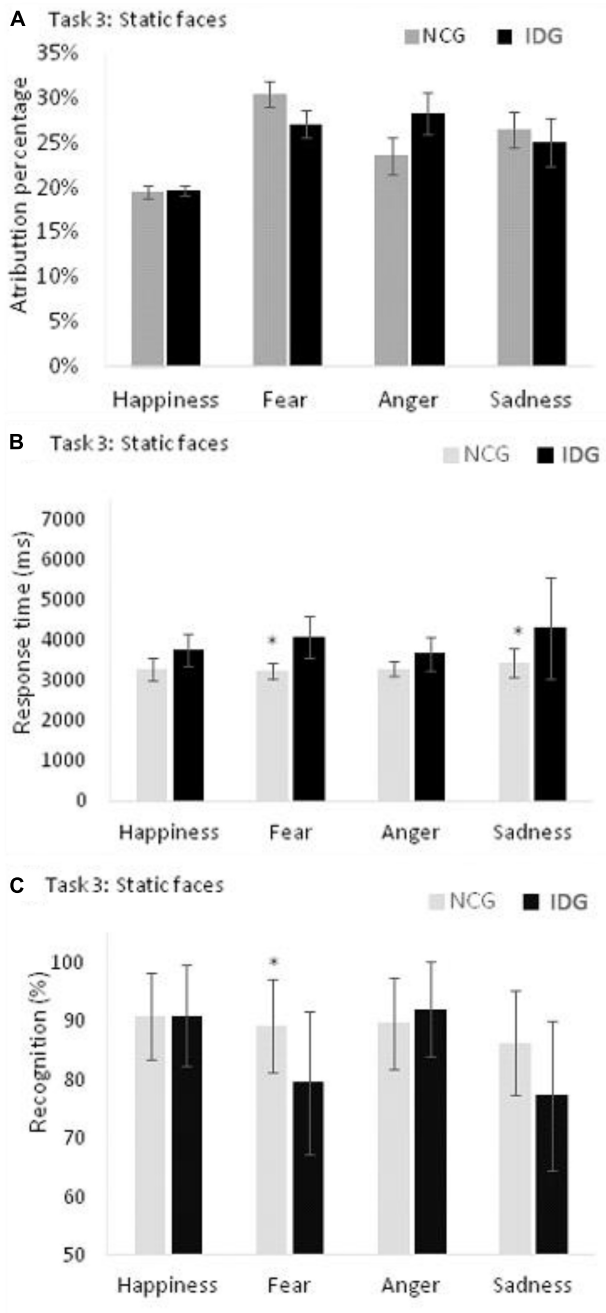


**FIGURE 5 | (A)** Control Group (NCG) and Insomnia Disorder Group (IDG) did not differ in attribution of emotions to neutral faces. **(B)** IDG showed higher response times, when compared to NCG, in recognition of fear and sadness. **(C)** We found statistically significant differences between groups (NCG and IDG) only for fear. Data are presented as a function of means and standard errors. Statistically significant interactions between factors were analyzed with *post hoc* tests using the Bonferroni's alfa correction (*$p < 0.05$).

$p = 0.03$). Examples of data plotting of the correlations between cognitive measures and facial emotion recognition are presented in **Figure 6**.

For the NCG, the accuracy of the recognition of static happiness and anger expressions were positively associated with the Verbal Comprehension Index – WAIS – III ($r_s = 0.645$; $p < 0.01$; $r_s = 0.600$; $p = 0.01$). The recognition of static and dynamic sadness expressions was identified to have a statistically significant negative association with CTT 1 ($r_s = -0.606$; $p = 0.01$; $r_s = -0.528$; $p = 0.04$), and recognition of the dynamic face of sadness was positively associated with Processing Speed (WAIS III) ($r_s = 0.540$; $p = 0.03$), which suggests that a better accuracy in recognition of these emotions is related to the ability of processing speed and sustained attention in NCG. Additionally, perseverative errors in WCST were negatively related to accuracy of the static happiness expression ($r_s = -0.518$; $p = 0.04$). For sleep measures, TST was positively associated with the recognition of the static expression of fear ($r_s = 0.567$; $p = 0.02$), which indicated that a high amount of sleep time is related to better accuracy in the recognition of fear.

## DISCUSSION

The present study investigated whether patients with ID had impairments in the ability to recognize facial emotion as well as their relationship to executive functioning. Findings suggest that patients with insomnia have a lower recognition of the facial emotions of fear and sadness, and lower perceptual organization. Insomniacs with impairment in facial emotion recognition had a lower performance in neuropsychological tests related to inhibitory control, planning capacity, problem solving, and cognitive flexibility.

Insomniac individuals reported poor sleep quality, poor sleep efficiency, sleep fragmentation, and perception of non-restoring sleep through their 14-day filled sleep diaries. These findings are consistent with the definition and classification of ID based on subjective complaints (The International Classification of Sleep Disorders – ICSD-3). Groups were balanced with regard to age and sex. The research questions formulated are now discussed.

### Association Between Facial Emotion Recognition and Subjective Symptoms of Insomnia

Overall, the data showed that insomnia may affect the reaction time and accuracy of facial recognition of fear and sadness in static and dynamic conditions. The IDG showed more incorrect responses and needed more time to recognize facial emotions when compared to control individuals. These data are compatible with studies which show that a shorter sleep duration, in the case of insomnia patients, is associated with a lower performance in facial emotion recognition (Cote et al., 2014; Motomura et al., 2014; Almondes et al., 2016b).

Kyle et al. (2014) analyzed emotional categorization and intensity ratings related to the emotions of anger, fear, happiness and sadness. They found that groups did not differ on emotion categorization (i.e., matching the facial expression to the emotion category), but patients with insomnia tended to rate facial expressions of fear and sadness as less emotionally intense than healthy control individuals. Therefore, their findings

**TABLE 3 |** Correlations among measures of sleep, cognition and recognition of dynamic and static expressions.

| **Overall (*N = 26*)** | **Dynamic facial expressions** | | | | **Static facial expressions** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Happiness** | **Fear** | **Anger** | **Sadness** | **Happiness** | **Fear** | **Anger** | **Sadness** |
| RCFT – Copy | 0.079 | 0.034 | −0.296 | 0.206 | −0.448* | 0.336 | −0.208 | −0.041 |
| RCFT – Memory | −0.026 | 0.049 | 0.216 | 0.256 | −0.121 | 0.086 | 0.196 | 0.278 |
| WAIS – Verbal comprehension | 0.255 | 0.114 | 0.077 | 0.503** | 0.110 | 0.436* | 0.277 | 0.041 |
| WAIS – Perceptual organization | 0.288 | 0.254 | 0.064 | 0.305 | −0.100 | 0.439* | −0.040 | −0.059 |
| WAIS – Working memory | 0.099 | −0.012 | −0.313 | 0.292 | −0.395* | 0.144 | −0.121 | 0.070 |
| WAIS – Processing speed | 0.223 | −0.260 | −0.018 | 0.023 | −0.022 | −0.145 | −0.097 | 0.095 |
| Digits span forward | 0.078 | 0.235 | −0.278 | 0.149 | −0.235 | 0.083 | −0.166 | 0.222 |
| Digits span backward | 0.706 | 0.247 | 0.170 | 0.469 | 0.247 | 0.687 | 0.419 | 0.279 |
| Tower of London | 0.429* | 0.203 | 0.160 | 0.285 | 0.110 | 0.311 | 0.025 | −0.143 |
| WCST – Generated categories | −0.075 | 0.217 | −0.012 | 0.186 | 0.092 | 0.583** | −0.257 | 0.126 |
| WCST – Perseverative responses | −0.021 | 0.034 | 0.046 | −0.281 | −0.094 | 0.506** | 0.019 | −0.014 |
| WCST – Perseverative errors | −0.045 | 0.024 | 0.002 | −0.238 | −0.127 | −0.473* | 0.026 | −0.005 |
| CTT 1 | −0.278 | −0.040 | 0.154 | −0.216 | 0.092 | 0.001 | 0.228 | −0.411* |
| CTT 2 | −0.406* | 0.114 | −0.098 | −0.033 | −0.199 | −0.140 | 0.009 | −0.058 |
| CTT – Measure interference | −0.102 | 0.105 | −0.180 | 0.240 | −0.288 | −0.191 | −0.205 | 0.312 |
| Stroop test (C) – time | −0.359 | −0.252 | 0.313 | −0.268 | 0.052 | −0.136 | 0.312 | −0.099 |
| Stroop test (W) – time | −0.412* | −0.199 | 0.056 | −0.483* | 0.036 | −0.303 | 0.041 | −0.049 |
| Stroop test (C/W) – time | −0.457* | −0.233 | 0.029 | −0.625** | 0.221 | −0.438* | 0.034 | −0.203 |
| **Insomnia disorder group (N = 11)** | | | | | | | | |
| RCFT – Copy | −0.249 | −0.563 | −0.349 | 0.032 | −0.384 | 0.372 | −0.157 | −0.434 |
| RCFT – Memory | 0.088 | −0.392 | 0.368 | 0.119 | −0.314 | −0.061 | 0.299 | −0.079 |
| WAIS – Verbal comprehension | 0.203 | 0.529 | −0.337 | 0.594 | −0.209 | 0.284 | 0.061 | −0.181 |
| WAIS – Perceptual organization | 0.290 | 0.279 | −0.152 | 0.289 | 0.169 | 0.492 | −0.078 | −0.284 |
| WAIS – Working memory | 0.116 | −0.220 | −0.650* | 0.419 | −0.604* | 0.218 | −0.629* | 0.201 |
| WAIS – Processing speed | 0.493 | −0.136 | 0.344 | −0.155 | 0.067 | 0.146 | 0.061 | 0.161 |
| Digits span forward | 0.059 | −0.017 | −0.488 | 0.393 | −0.506 | −0.082 | −0.628* | 0.444 |
| Digits span backward | −0.030 | 0.323 | −0.634* | 0.364 | −0.301 | −0.218 | −0.461 | 0.423 |
| Tower of London | 0.595 | 0.543 | −0.129 | 0.531 | 0.140 | + 0.632* | −0.295 | 0.148 |
| WCST – Generated categories | −0.092 | 0.085 | −0.208 | 0.071 | −0.054 | 0.541 | −0.473 | −0.206 |
| WCST – Perseverative responses | < 0.001 | 0.005 | 0.354 | −0.506 | 0.194 | −0.671* | 0.403 | 0.046 |
| WCST – Perseverative errors | −0.087 | 0.034 | 0.231 | −0.318 | 0.039 | −0.607* | 0.385 | −0.133 |
| CTT 1 | −0.467 | 0.017 | −0.134 | 0.133 | −0.040 | −0.161 | 0.284 | −0.328 |
| CTT 2 | −0.231 | −0.348 | 0.051 | 0.101 | −0.189 | −0.295 | 0.380 | 0.027 |
| CTT – Measure interference | 0.289 | −0.372 | 0.205 | 0.051 | −0.356 | −0.212 | 0.052 | 0.402 |
| Stroop test (C) – time | −0.556 | −0.423 | 0.387 | −0.606* | 0.225 | −0.455 | 0.582 | −0.259 |
| Stroop test (W) – time | −0.521 | −0.443 | 0.226 | −0.684* | 0.137 | −0.329 | 0.277 | −0.181 |
| Stroop test (C/W) – time | −0.580 | −0.403 | 0.152 | −0.688* | 0.049 | −0.441 | 0.254 | −0.200 |
| **Normal control group (N = 15)** | | | | | | | | |
| RCFT – Copy | 0.263 | 0.017 | −0.334 | 0.121 | −0.490 | −0.047 | −0.333 | 0.335 |
| RCFT – Memory | −0.145 | −0.054 | 0.017 | 0.112 | −0.045 | −0.468 | 0.137 | 0.090 |
| WAIS – Verbal comprehension | 0.129 | −0.386 | 0.275 | 0.122 | 0.645** | 0.232 | 0.600* | −0.380 |
| WAIS – Perceptual organization | 0.292 | −0.251 | 0.075 | −0.028 | −0.056 | −0.335 | −0.033 | −0.035 |
| WAIS – Working memory | −0.070 | −0.148 | −0.310 | −0.037 | −0.176 | −0.166 | −0.158 | 0.138 |
| WAIS – Processing speed | 0.128 | −0.445 | −0.245 | 0.540* | −0.103 | −0.362 | 0.034 | 0.325 |
| Digits span forward | 0.102 | −0.180 | −0.204 | −0.41 | −0.151 | 0.104 | −0.097 | −0.168 |
| Digits span backward | −0.035 | −0.002 | −0.253 | 0.211 | −0.259 | −0.218 | −0.196 | 0.161 |
| Tower of London | 0.226 | 0.072 | 0.438 | −0.126 | 0.174 | −0.68 | 0.395 | −0.501 |
| WCST – Generated categories | −0.314 | 0.145 | 0.006 | −0.223 | 0.428 | 0.103 | −0.009 | 0.015 |
| WCST – Perseverative responses | 0.075 | 0.150 | −0.064 | 0.133 | −0.485 | −0.084 | −0.238 | 0.260 |
| WCST – Perseverative errors | 0.008 | 0.138 | −0.084 | 0.103 | −0.518* | −0.044 | −0.278 | 0.292 |
| CTT 1 | −0.186 | −0.11 | 0.280 | −0.518* | 0.326 | 0.046 | 0.199 | −0.606* |

*(Continued)*

**TABLE 3 |** Continued

| Overall (*N = 26*) | Dynamic facial expressions | | | | Static facial expressions | | | |
|---|---|---|---|---|---|---|---|---|
| | **Happiness** | **Fear** | **Anger** | **Sadness** | **Happiness** | **Fear** | **Anger** | **Sadness** |
| CTT 2 | −0.333 | 0.505 | −0.102 | −0.046 | −0.102 | −0.067 | −0.184 | −0.114 |
| CTT – Measure interference | −0.283 | 0.248 | −0.513 | 0.411 | −0.319 | −0.167 | −0.511 | −0.440 |
| Stroop test (C) – time | −0.050 | −0.009 | 0.366 | 0.172 | −0.096 | −0.345 | 0.209 | 0.119 |
| Stroop test (W) – time | −0.025 | 0.278 | 0.168 | −0.006 | −0.018 | −0.233 | 0.041 | 0.284 |
| Stroop test (C/W) – time | −0.180 | 0.277 | 0.009 | −0.085 | 0.416 | 0.068 | 0.150 | 0.099 |
| **Whole group (N = 26)** | | | | | | | | |
| SF | 0.134 | −0.252 | −0.353 | −0.024 | 0.088 | −0.372 | −0.023 | −0.111 |
| SE | −0.054 | 0.175 | −0.084 | 0.312 | −0.338 | 0.402* | −0.125 | 0.203 |
| TST | 0.208 | 0.135 | 0.203 | 0.568** | −0.129 | 0.586** | 0.077 | 0.379 |
| **Insomnia disorder group (N = 11)** | | | | | | | | |
| SF | 0.319 | 0.228 | −0.421 | 0.552 | 0.151 | 0.264 | −0.233 | 0.248 |
| SE | −0.405 | −0.230 | −0.478 | −0.035 | −0.803** | −0.310 | −0.371 | −0.087 |
| TST | 0.115 | −0.599 | 0.074 | 0.336 | −0.527 | 0.290 | −0.019 | −0.059 |
| **Normal control group (N = 15)** | | | | | | | | |
| SF | 0.423 | −0.125 | 0.232 | 0.238 | 0.294 | 0.322 | 0.326 | 0.236 |
| SE | 0.191 | −0.266 | 0.091 | 0.050 | 0.351 | −0.230 | 0.143 | 0.172 |
| TST | 0.333 | −0.402 | 0.143 | 0.567* | 0.342 | −0.169 | 0.282 | 0.373 |

**p-Values refers to $p < 0.05$; **p values refer to $p < 0.01$; SF, sleep fragmentation; TST, total sleep time; SE, sleep efficiency; WCST, Wisconsin Card Sorting Test; CTT, Color Trails Test; RCFT, Rey Complex Figure Test.*

indicate that people with insomnia may present changes in the evaluation of facial emotions of sadness and fear, in a partial agreement with our results. Furthermore, Maccari et al. (2014) investigated the impact of reduced vigilance due to moderate sleep deprivation on the ability to recognize emotional expressions of faces and the emotional content of words, and they found that positive faces were more resistant than negative faces to the detrimental effect of sleep deprivation. However, there are divergent results about the specific emotions affected by sleep loss. Crönlein et al. (2016) demonstrated that insomnia patients performed worse in recognition of facial emotions of happiness and sadness compared to controls. Killgore et al. (2017) showed that one night of sleep deprivation affects the facial recognition of happiness and sadness. Van der Helm et al. (2010) found that sleep deprivation selectively impairs detection of angry and happy facial emotions. Cote et al. (2014) investigated the impact of sleep deprivation on neural responses to facial emotions as well as on the accuracy and speed of categorization of faces, and found that sleep deprivation preferentially impacted the processing of sadness. Differently, Holding et al. (2017) found that sleep deprivation had no influence on emotional recognition. More recently, Sack et al. (2019) presented videos clips of female senders communicating the emotions of anger, fear, disgust, and sadness to their romantic partner. They found that sleep-deprived participants performed better at recognizing emotion in the videos with a longer presentation time (8–10 s), compared to controls. Considering this literature, it is important to highlight that there are few studies analyzing the association between insomnia and facial emotion recognition.

It is not clear why studies differ with regard to the affected emotions, including our findings. One of the hypotheses may be related to the modality chosen to present the stimulus. In our study, individuals with insomnia and controls had to recognize facial emotions in both static and dynamic conditions. Static conditions may produce more accuracy when used in experiments evaluating the recognition (identity) of unfamiliar faces (Roark et al., 2003). However, dynamic conditions can reflect real-life conditions more deeply. It is important to note that we do not use real dynamic facial expressions as stimuli, here defined as the video recording of a facial expression occurring in an individual in real time. Real dynamic expressions can be expected to have more ecological validity compared to "morphed" dynamic expressions. However, in the literature, we found similar results in studies containing both types of stimuli, with an advantage among the recognition of dynamic expressions compared to static ones (for a review, see Alves, 2013). In the case of our study, the use of dynamic stimuli composed of morphed faces was important to control the exposition time and emotional intensity (25, 50, 75, and 100%) of each stimulus.

Hoffmann et al. (2013) showed that only two emotions (fear and surprise) were easily recognized in dynamic stimuli. Although neuroimaging studies have shown that static and dynamic facial stimuli activate the fusiform gyrus, there are sub-regions close to this region that respond separately to static and dynamic stimuli (Kawasaki et al., 2012). In our study, we found that fear and sadness expressions were judged less accurately by patients with insomnia in both dynamic and static conditions, evidencing the association between insomnia and the recognition of those particular facial emotions.

One of the main findings in literature concerning sleep deprivation and insomnia is the increase of negative moods (anger, depression, fear, and fatigue), which can be associated with depression and anxiety in adults and older adults (Babson

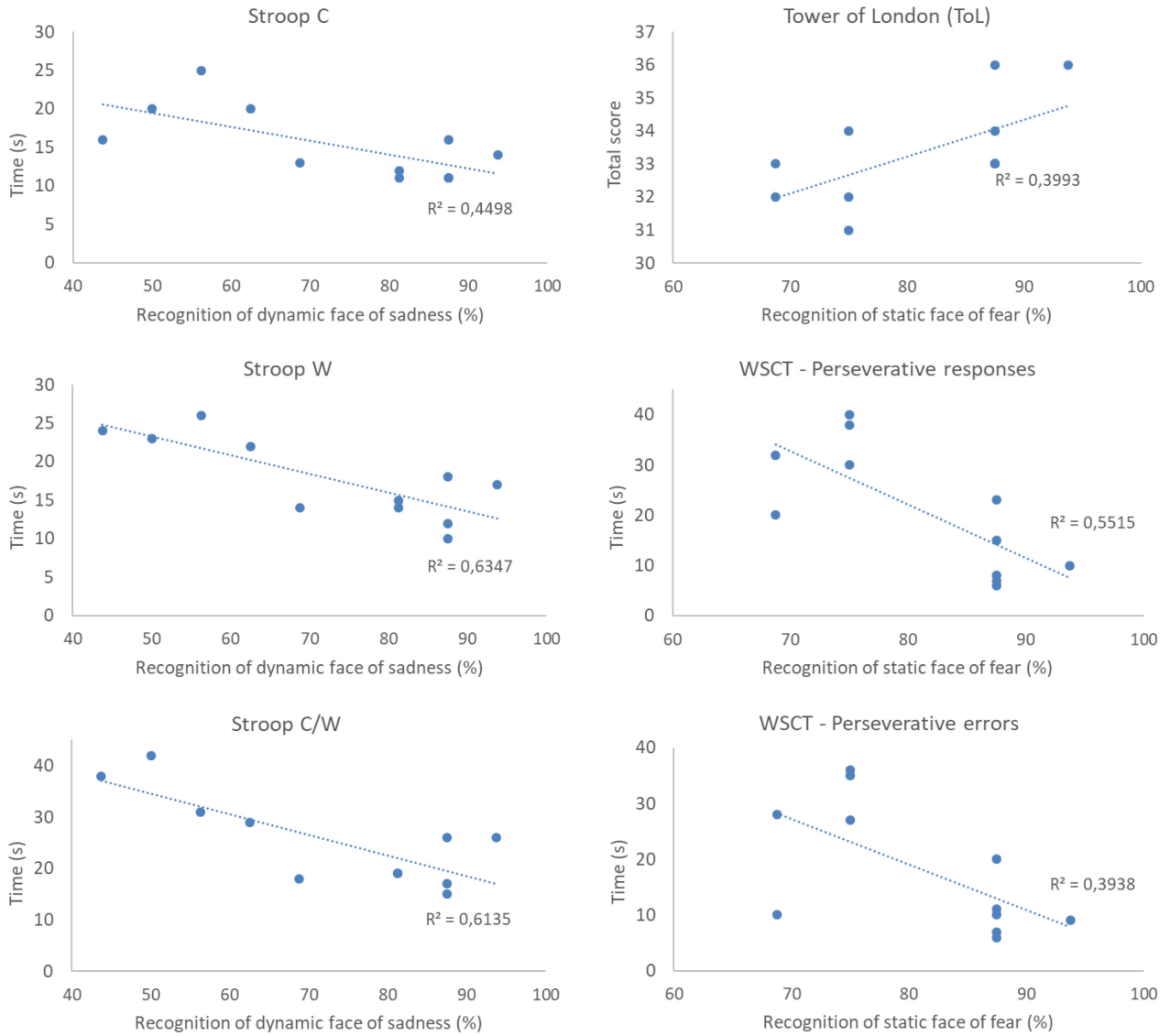


**FIGURE 6 |** Example of data plotting of correlations between cognitive measures and recognition of the expressions of sadness and fear in participants with insomnia disorder (IDG group). All correlations were significant at the level of 5% ($p < 0.05$). $r_s^2$ represents effect sizes of correlations. As a general result, we see that the performance in the cognitive measures is positively correlated to facial emotion recognition.

et al., 2010; Baglioni et al., 2010; Paterson et al., 2011; Almondes et al., 2016a). For dynamic expressions, we found a positive correlation between the recognition of sadness and TST (Total Sleep Time) indicating that the lower recognition of sadness was associated with less hours of sleep. For static expressions, we found positives correlations between the recognition of fear and the measurement of TST (Total Sleep Time) and SE (sleep efficiency). Kyle et al. (2014) and Holding et al. (2017) did not observe significant associations between markers of sleep deprivation (parameters of sleep diary) and specific emotions. However, Visted et al. (2018) showed in their systematic review and meta-analysis that individuals with a history of depressive episodes (current or remission) reported more difficulties in emotional regulation.

Although insomniac individuals were psychologically healthy, they presented indications of anxiety, stress, and depression. This data may reflect the daytime consequences of perceived sleep loss. Besides, insomnia increases the risk of psychopathology (Hertenstein et al., 2018). Whether impairment in the processing of emotions is due to psychological distress mediated by the fatigue of insomnia, or whether chronic sleep disorder has a direct impact on the processing of emotions, is a field of research for the future.

Threat-related signals and facial expressions of fear are processed mainly by the amygdala structure (Adolphs, 2008; Méndez-Bértolo et al., 2016). Greater activation in the amygdala to threat-related signals and fear expressions has been shown in individuals with chronic insomnia and in sleep deprived subjects,

while prefrontal networks exhibit hypoactivation (Huang et al., 2012; Motomura et al., 2013; Baglioni et al., 2014). Maybe the frontal-amygdala route could be disrupted in insomnia, affecting emotional regulation and functioning, which are necessary for recognition of the facial emotion of fear.

## Executive Functions Performance in Insomnia Individuals

There were no statistically significant differences between groups in almost all measures of EFs, with the exception of the Perceptual Organization Index (POI), in which the IDG had a lower performance compared to the NCG. POI is a multi-process measure of non-verbal fluid reasoning, visual perception and integration, and visual-spatial problem-solving. Fluid reasoning and problem-solving are considered more complex components of EFs (Diamond, 2013), and their visual modality (e.g., non-verbal fluid reasoning and visual-spatial problem-solving) relies mainly on frontoparietal networks (Watson and Chatterjee, 2012). Recent investigation has pointed to a disrupted connectivity between the superior frontal gyrus and the superior parietal lobe in patients with insomnia (Li et al., 2014), which would explain the current findings from the IDG.

This data indicates that insomniac individuals can present visual alterations in perception. Chee et al. (2008), Chuah and Chee (2008), and Chee and Tan (2010) have shown that during sleep deprivation there is a decline in visual sensory processing, which could be due to an attenuation of a normal top–down attention biasing system that supports the recognition of familiar faces through the evaluation of stimuli and information processing. Zhang et al. (2019) showed that the impaired perception of facial expressions after sleep loss is associated with a diminishment in the visual attention control and emotional functioning.

## Association Between Executive Functions and Facial Emotion Recognition in Insomnia

Taken together, correlation analysis indicates that individuals with insomnia who had lower recognition of fear presented a worse performance in inhibitory control, planning ability, problem solving, and cognitive flexibility. By this turn, individuals with insomnia who had a lower recognition of sadness presented impairment in inhibitory control.

We found that insomniacs with low recognition of static fear expressions had less ability to plan and solve problems, and more perseverative responses and errors (measured by the Wisconsin Card Sorting Test – the EF test). This result indicates that a low recognition of facial emotions may be associated with a difficulty in identifying the most appropriate strategies in response to a situation of choice or difficulties with problem solving which requires flexibility of reasoning. Facial emotion recognition requires cognitive ability, because there are multiple face details to be identified and differentiated (Calcutt et al., 2017). In addition, the occurrence of a large number of persevering errors can be considered an important behavioral marker for PFC-related dysfunctions (Strauss et al., 2006). The insomniacs also presented non-perseverative errors (errors response), which suggests the adoption of an incorrect classification logic when performing the test. Such performance suggests a state of inattention characterized by a difficulty in focusing attention on the execution of a task.

Executive functions, in general, are superior cognitive processes that allow the maintenance of proper mental functioning to achieve a future goal, being partly responsible for the ability to initiate actions, plan and predict ways of solving problems, anticipate consequences and modify strategies flexibly (Lezak et al., 2004). These functions allow the individual to perform, independently and autonomously, activities aimed at a specific goal which involve complex processes and behaviors. These actions depend on the integrity of various cognitive, emotional, motivational, and volitional processes, which are closely associated with the functioning of the frontal lobes.

Another hypothesis to explain this data is that there is an interaction between PFC subregions, such as ventromedial and dorsomedial prefrontal areas with the amygdala and temporal lobe connections required for complex emotional control and allocation, as well as an adequate functioning of complex order processes such as EFs (Vuilleumier and Pourtois, 2007; Heberlein et al., 2008; Todorov, 2012). Thus, insomnia, a state of sleep deprivation in relation to hypermetabolism relationship at night and hypometabolism during wakefulness (Nofzinger et al., 2004), would lead to an impact on the emotional regulation system as well as in the cognitive processing system.

We found a negative correlation between the recognition of dynamic expressions of sadness and the performance in the Stroop Test, which evaluates sustained attention, processing speed, and inhibition of response. In such a case, participants who had a worse performance in the recognition of the dynamic expressions of sadness also performed worse in the Stroop test (greater response times). Killgore et al. (2017) evaluated the effects of one night of sleep deprivation and one night of subsequent recovery sleep on the ability to identify the six basic emotion categories (happiness, surprise, fear, sadness, disgust, anger). They found that sleep deprivation negatively affected the recognition of facial cues of happiness and sadness, but did not affect the recognition of fear. They argued that survival would be most assured if an individual was able to sustain accurate or enhanced recognition of cues reflecting potential danger (e.g., the face expressing anger, fear, surprise, or disgust), and that sleep deprivation increases the general tendency to perceive facial expressions as "threatening" in appearance. Similar data was found by Cote et al. (2014), in which sleep deprivation led to greater neural reactivity for threat-related negative emotions and a lower performance in the processing of sad faces. This hypothesis seems to be substantiated by the association found in our study between the recognition of static and dynamic expressions of anger and working memory. The insomniacs recognized this facial emotion that is necessary for survival, regardless of their difficulty with working memory. On the other hand, we found that the insomniacs in our research also had low recognition of the expression of fear, which may have been influenced by the data on depression and anxiety symptoms found in this sample.

The cognitive processes most affected in the insomnia group were related to perceptual organization (non-verbal fluid reasoning, visual-motor integration, and visual-spatial problem-solving) and marginally to verbal comprehension; visuospatial organization; and to the ability of developing abstract concepts and cognitive flexibility. Contradictory findings are reported in the literature regarding the presence of EFs impairments in insomnia (Fernandez-Mendoza et al., 2010; Shekleton et al., 2010, 2014; Vgontzas et al., 2013; Ferreira and Almondes, 2014; Fortier-Brochu and Morin, 2014). It might be explained due the use of neuropsychological tests primarily designed to detect neurological lesions (Lezak et al., 2004). Considering that insomnia is not necessarily correlated to neurological lesions, it would be difficult to detect the cognitive changes in insomnia with such tests. Another discussion for conflicting results is that cognitive processes present different outcomes throughout the day, and neuropsychological tests cannot be applied more than once a day because the tests would facilitate adaptation and learning. Our cognitive evaluation data shows impairments in perceptual organization processes, which are considered components of EFs. We use a battery of extensive tests to measure only components of EFs. In addition, when we analyze data in association with facial emotion recognition, the different cognitive processes that are components of EFs are impaired. Thus, our hypothesis is that there is a connection between emotional and cognitive systems, and in insomnia there would be a decreased functional connectivity between the amygdala and the PFC.

An important piece of data for discussion is that there is evidence that age is a factor in altering the ability to recognize expressions of emotion in the face (Dalgleish, 2004). Older people need less environmental/contextual information to properly recognize facial expressions of emotions, and younger people need contextual details to be able to correctly process expressions. Older individuals have a better ability to distribute attentional resources to facial expressions in relation to contextual information (Leitzke and Pollak, 2016). Other studies have found that older people may have a lower hit rate on face recognition tasks compared to younger people because of age-related cognitive impairment (Leime et al., 2013). Considering the results of cognitive impairment is age-related in the case of older people, in our study, our sample of insomniacs was composed of adult individuals who would not have their results influenced by age, so that impairment in EFs and impairment in facial emotions recognition were associated with insomnia.

### Limitations

To the best of our knowledge, this is the first study that investigates the relationship between EFs and facial emotional recognition in insomnia patients. Despite the novelty of the findings, several limitations do not allow for broad generalizations.

First, we rely on self-reports, which, by its own definition, might be biased. We did not employ objective measures of sleep (e.g., polysomnography and actigraphy) to provide a more robust assessment protocol, or to assess sleep stages and sleep-wake parameters related to emotional processing. On the other hand, we rely on the diagnostic evaluation of insomnia according to the International Classification of Sleep Disorders (ICSD-3).

Moreover, the study was designed for participants to report their subjective symptoms of insomnia, reflecting their real-life conditions. We did not perform sleep deprivation research and did not conduct research on all study variables in a laboratory.

Another limitation concerns the small number of participants. This diminished our capacity to detect more statistically significant interaction effects. A great number of people (100 people) had shown interest in the research, but only 56 individuals agreed to participate. However, due to its voluntary nature and lengthy protocol, it became impossible for many to participate. Despite this, in most ANOVA comparisons of main effects and interactions, we found partials eta squared of large size, varying between 0.20 and 0.80. Considering the present work as an exploratory one, we suggest the need for replication and for caution in the interpretation of the results.

Finally, another limitation of the study is that we did not have information and did not assess whether there was a difference between the groups regarding what time the tests were run.

## CONCLUSION

Insomnia disorder seems to be associated with a lower performance in the recognition of the facial emotions of fear and sadness. Insomniacs with impairment of facial emotion recognition had a lower performance in neuropsychological tests related to inhibitory control, planning capacity, problem solving, and cognitive flexibility. Furthermore, patients with ID may present alterations in perceptual organization.

## ETHICS STATEMENT

This study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte (registration number 10843713.2.0000.5537).

## AUTHOR CONTRIBUTIONS

KA, FJ, ML, and NA: author contribution study design, writing the draft, and integration of the authors' comments. FJ and ML: data gathering. KA and NA: interpretation of the data and final manuscript.

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