How Cognitions Affect Sleep

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The cumulative dissertation includes the following three studies:

Study 1

Beck, J., Loretz, E., & Rasch, B. (2021). Exposure to relaxing words during sleep promotes slow-wave sleep and subjective sleep quality. *Sleep*, zsab148. DOI: https://doi.org/10.1093/sleep/zsab148

Study 2

Beck, J., Loretz, E., & Rasch, B. (2021). *Stress dynamically reduces sleep depth: Temporal proximity to the stressor is crucial* [Unpublished manuscript]. Department of Psychology, University of Fribourg.

Study 3

Beck, J., Cordi, M. J., & Rasch, B. (2021). Hypnotic suggestions increase slow-wave parameters but decrease slow-wave spindle coupling. *Nature and Science of Sleep, 13*, 1383-1393. DOI: https://doi.org/10.2147/NSS.S316997

Abstract

Our thoughts and cognitions can affect sleep. The present dissertation aims to provide a better understanding of the mechanisms underlying how cognitions affect sleep. The empirical part of the dissertation includes three studies that examine the effect of positive and negative cognitions before and during sleep on sleep physiology. The theoretical part of the dissertation reviews mechanisms suggested by insomnia models and by the "Memories-of-Sleep" hypothesis, which assumes that mental concepts that are active during sleep affect sleep regulatory systems. The first study suggests that inducing positive cognitions during sleep by activating the mental concept of relaxation improves sleep depth. The second study showed that negative cognitions before sleep deteriorate sleep quality during early and during late sleep. The third study showed that positive cognitions before sleep enhance slow-waves but not memory consolidation processes. Thus, the empirical evidence of this dissertation suggests that positive and negative cognitions before as well as during sleep can affect sleep physiology. The findings are explained best by the theoretical framework of the "Memories-of-Sleep" hypothesis and provide a basis for future research and theory-driven interventions to improve sleep.

Contents

List of Abbreviations

AASM	American Academy of Sleep Medicine
ACTH	Adrenocorticotropic hormone / Adrenocorticotropin
ARAS	Ascending reticular activating system
CRH	Corticotropin-releasing hormone
DMN	Default mode network
ECG	Electrocardiogram / Electrocardiography
EEG	Electroencephalogram / Electroencephalography
EMG	Electromyogram / Electromyography
EOG	Electrooculogram / Electrooculography
ERP	Event-related potential
GABA	γ-aminobutyric acid
HGSHS	Harvard Group Scale of Hypnotic Susceptibility
HPA axis	Hypothalamic pituitary adrenal axis
IQR	Interquartile range
MDBF	Multidimensional mood questionnaire
NREM sleep	Non-rapid eye movement sleep
PAL	Paired-associate learning task
PNS	Parasympathetic nervous system
PSAS-C	Cognitive arousal subscale of the pre-sleep arousal scale
PSAS-S	Somatic arousal subscale of the pre-sleep arousal scale
REM	Rapid eye movement
RMS	Root mean square
SEM	Standard error of the mean
SF-A/R	Schlaffragebogen A, revised
SNS	Sympathetic nervous system
SOL	Sleep onset latency
SPT	Sleep period time
SWA	Slow-wave activity
SWS	Slow-wave sleep
SW/SP coupling	Slow-wave/spindle coupling
TST	Total sleep time
WASO	Wake after sleep onset
VLPO	Ventrolateral preoptic area

Introduction

Most people have experienced nights with little, poor or no sleep at all. When tiredness and exhaustion kicks in the next day, it becomes evident how important sleep is for regenerating physical and mental capacities. However, in our chronically stressed and performance-oriented society, sleep disturbances play an increasingly important role and lead to short- and long-term consequences that come with high costs for the individual and the society (Bjorøy et al., 2020; Geoffroy et al., 2020; Hillman et al., 2018; S. Hu et al., 2021; Jalali et al., 2021; Li et al., 2021; McArdle et al., 2020; Wallace et al., 2021). Psychosocial stress causes negative cognitions such as repeatedly thinking about past and future stressful events (e.g., a past bad job interview or an exam the next day), and worsens our sleep quality (Åkerstedt, 2006; Clancy et al., 2020; Lemyre et al., 2020). Moreover, positive cognitions, enhanced by hypnosis, mindfulness exercises or relaxing music before sleep, have been shown to improve sleep (Cordi et al., 2014; Cordi et al., 2019; Rusch et al., 2019). Thus, our thoughts and cognitions are a powerful and decisive factor influencing how we fall asleep and maintain sleep overnight. It is therefore important to understand underlying mechanisms of how our thoughts and cognitions affect our sleep in order to provide the basis for theory-based interventions to improve sleep.

After providing a brief background on sleep, the present dissertation describes the close link between sleep and cognitions as well as memory. Subsequently, a short theoretical background on stress is provided, followed by recent empirical evidence on the negative effects of stress and dysfunctional cognitions on sleep. The next chapter will discuss theories and models from insomnia research with regard to their proposed mechanism of how negative cognitions affect sleep. More specifically, the models will be investigated concerning predictions of whether cognitions before sleep, during awakenings and/or during sleep itself influence sleep. Next, research will be presented showing that positive thoughts and cognitions are able to improve sleep. Since current theories and models from the insomnia literature run short in explaining such effects, our recent theory will be presented, which proposes a memory-based mechanism for how positive as well as negative cognitions can influence sleep in the pre-sleep period and throughout the whole night. Lastly, the aim of this dissertation will be presented comprising three projects which studied (1) the core mechanism of our proposed theory, (2) the relevance of the timing of a psychosocial stressor for its effect on sleep (3) the effect of positive pre-sleep cognitions on sleep parameters linked to memory processes.

Theoretical Background on Sleep

On a behavioral level, sleep is defined as a reversible state of reduced conscious awareness and characterized by reduced mobility, closed eyes, a distinctive posture, quiescence, a reduced response to external stimuli, an increased arousal threshold and reaction time and impaired cognitive function (Chokroverty, 2017). On a physiological level, sleep in humans is defined based on brain activity measured by the electroencephalogram (EEG), ocular activity measured by the electrooculogram (EOG) and muscle activity measured by the electromyogram (EMG). Based on these signals, sleep is categorized into the sleep stages N1, N2 and N3 and rapid-eye movement sleep (REM; Iber et al., 2007). The transition from wake to sleep is usually accomplished by the light sleep stage N1, characterized by less than 50% alpha activity (8-11 Hz) and slowly rolling eye movements. Sleep stage N2 is the most predominant sleep stage and occupies about 50% of the total sleep time (TST) and is characterized by K-complexes (i.e., steep negative peaks followed by a positive peak and a minimum duration of 0.5 s) and sleep spindles (i.e., short bursts of oscillatory activity with 9 – 16 Hz) with a waxing and waning shape in the surface sleep EEG and a duration between 0.5 – 3 s; see Figure 1). Deep sleep, also called slow-wave sleep (SWS) or sleep stage N3, is characterized by a slow oscillatory rhythm (<1 Hz), which synchronizes the brain activity in excitatory up- and inhibitory down-states, by high-amplitude slow-waves in the scalp EEG (0.5 – 4.5 Hz) and is characterized by an increased power in the slow-wave activity band (SWA; 0.5 – 4.5 Hz). REM sleep is distinguished by the lowest muscle tone compared with other sleep stages, mixed frequency EEG around the theta frequency band (4.5 – 8 Hz) and sharp-peaked eye-movements. Throughout the night, these sleep stages occur in roughly 90-minute cycles, with the end of each cycle marked by a REM sleep episode (Feinberg & Floyd, 1979). Moreover, the first half of the night is usually characterized by an increased amount of SWS, while during the second half of the night the amount and duration of REM sleep episodes increases (see Figure 1).

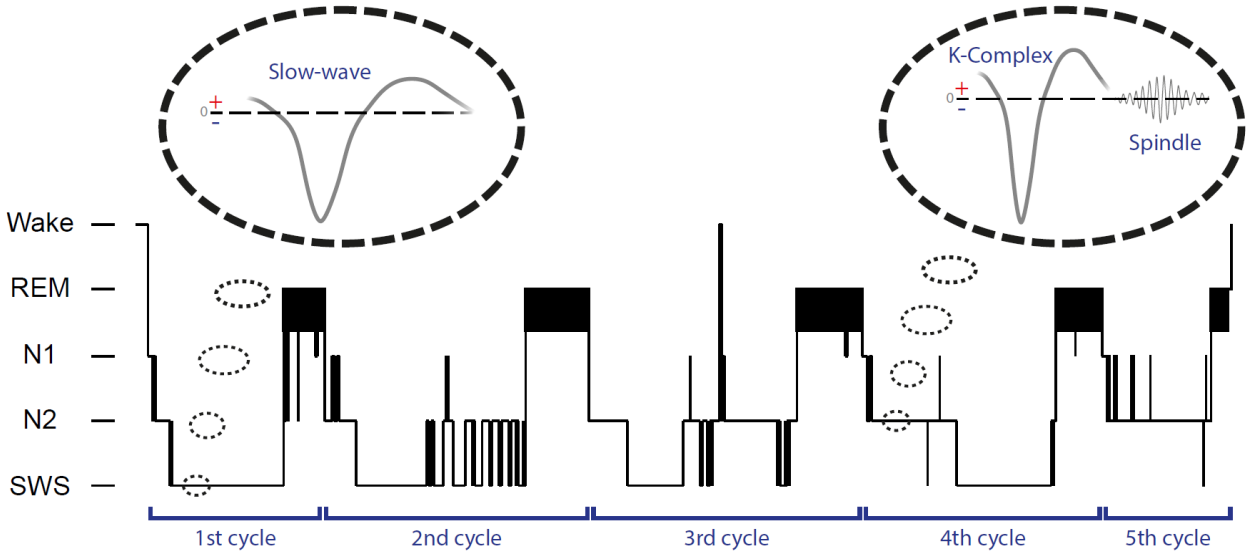

Figure 1. Sleep architecture of a healthy young subject. Adapted from Beck, Cordi, and Rasch (2021) and Beck, Loretz, and Rasch (2021).

Regarding sleep regulation, the seminal two-process model (Borbély, 1982; Borbély et al., 2016) states that the sleep-wake rhythm is regulated by two processes: a circadian process (C) and a homeostatic process (S; Figure 2). The circadian process describes a 24h variation of intrinsic activity following a sinusoidal curve. This activity is orchestrated by a circadian pacemaker and internal clock, the suprachiasmatic nuclei, and synchronizes to the time of day according to external cues, especially via the light-dark cycle (Riemann et al., 2015). Markers to measure this circadian process are for example core body temperature, melatonin, and cortisol levels. The homeostatic process reflects sleep pressure (i.e., our need for sleep) and increases continuously during wakefulness and declines during sleep.

The principal marker for this homeostatic sleep pressure is SWA measured during non-rapid eye movement sleep (NREM sleep, sleep stage N2 and SWS) and theta activity during wake (Borbély & Achermann, 1999). Early lesion studies in animals indicate that both processes are regulated separately from each other (Tobler et al., 1983; Trachsel et al., 1992). However, newer evidence on energy metabolism suggests that both processes C and S are continuously interacting with each other (Borbély et al., 2016). The model has been applied on healthy as well as on disturbed sleep and accurately predicts the timing and intensity of sleep in various different experiments (Borbély et al., 2016). In clinical research, the model promoted the development of

circadian therapy methods by manipulating the circadian phase, sleep and light exposure (Borbély et al., 2016).

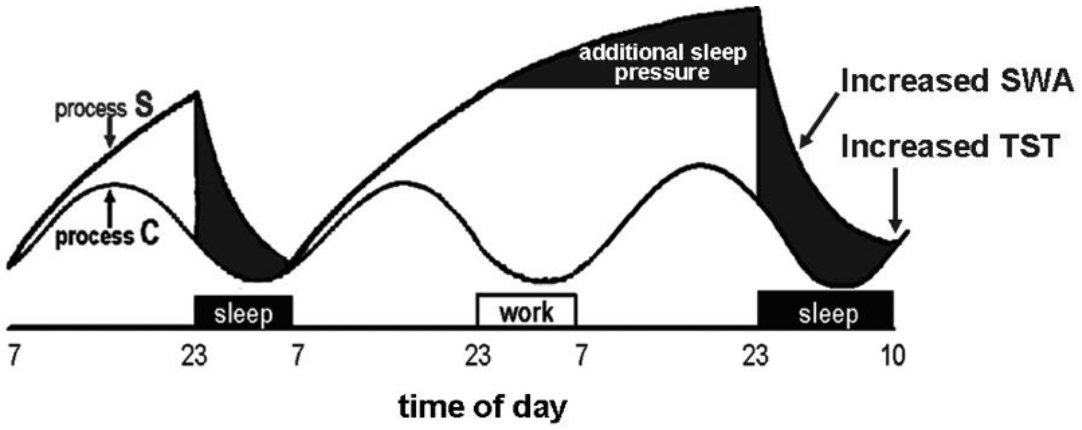

Figure 2. Two-process model of sleep regulation. Adapted from Borbély (1982).

The research and debate about the core functions of sleep has certainly not come to an end. Some of the most prominent functions have been discussed (Chokroverty, 2017; Krueger et al., 2016) such as sleep conserving energy (Zepelin & Rechtschaffen, 1974), restoring the brain and body tissue (Adam & Oswald, 1977), serving an immune function (Besedovsky et al., 2012), removing toxic byproducts of waking activity via the glymphatic system (Xie et al., 2013), restoring cognitive and behavioral performance (Belenky et al., 2003; van Dongen et al., 2003), and supporting brain connectivity and plasticity (Diekelmann & Born, 2010; Tononi & Cirelli, 2014). Overall, sleep is closely linked to and important for our mental and physical health. A prospective study on over 350.000 participants showed that healthy sleep is associated with a reduced risk for cardiovascular disease and for coronary heart disease (Fan et al., 2020), which are two of the most common causes of death worldwide (Naghavi et al., 2017; World Health Organisation, 2021).

However, with an increasing prevalence of sleep disorders (Gulia & Kumar, 2018) with up to 40% in younger (McArdle et al., 2020), 49 % in older adults (Jalali et al., 2021) and up to 60% in a Norwegian sample (Bjorøy et al., 2020), they are one of the most common disorders in our society. Sleep disturbances are usually categorized into difficulties initiating sleep, difficulties maintaining sleep, and early morning awakening insomnia (Bjorøy et al., 2020; Yokoyama et al., 2010) and have been associated with poorer cognitive performance

(Gharzeddine et al., 2021), increased depressive symptoms (Yokoyama et al., 2010), an increased risk for cardiocerebral vascular diseases and hypertension (S. Hu et al., 2021; Li et al., 2021), higher levels of inflammation markers like C-reactive protein and interleukin-6 (Irwin et al., 2016), and with an increased suicide rate (Geoffroy et al., 2020). In addition, sleep disorders cause yearly costs of $45.21 billion in Australia (Hillman et al., 2018) and are linked to a generally increased mortality (Altevogt & Colten, 2006; Wallace et al., 2021). Therefore, healthy sleep is essential for the individual and our society (Hale et al., 2020) and it is crucial to gain a better understanding of the factors that promote and maintain sleep health and sleep disturbances in order to develop more targeted interventions to improve sleep.

Arousal	State of increased activation level of the central nervous system, characterized by increased alertness, vigilance, increased attention and responsiveness. Can occur on a cognitive, physiological, cortical and/or emotional level.
Hyperarousal	Condition of a persistently increased activation level, also referred to as overexcitation.
Cognitive arousal	Aspects of arousal manifested in increased cognitive activity like worrying, rumination or racing thoughts.
Cortical arousal	Increased high frequencies in the electroencephalogram (EEG) in the beta (14–32 Hz) and gamma range (>32 Hz). Assumed to be a physiological measure of brain activity and cognitive processes.
Physiological arousal	Aspects of arousal manifested in physiological responses like increases in heart rate, blood pressure, respiration rate and an inhibition of growth, reproduction, digestion and immune response systems. Also referred to as somatic arousal.
Stress	The response in order to adapt to psychological, environmental or physiological threats. Physiological responses to stress include the activation of the autonomic nervous system and the HPA-axis.
HPA-axis	An endocrinological regulatory circuit involving the hypothalamus, pituitary gland and adrenal cortex, which affects numerous bodily functions and reactions, including the stress response.

Box 1. Central terms related to arousal.

Cognition	Broad term that includes all mental/cognitive processes involved in knowing, awareness, acquiring and processing information. Cognitions or cognitive activity can vary e.g., in the level, thought content and emotional tone.
Mental/cognitive processes	Processes involved in cognition, such as memory, perception, reasoning, comprehension, language, attention, judgement and problem solving
Mental/cognitive representation	A hypothetical mental entity that is assumed to stand for a memory, a perception, a thought, etc. during cognitive operations
(Mental) Concept	Mental grouping of similar classes of objects, persons, events or their properties.
Semantic concept	A concept that groups the meaning of objects, persons and events.
Embodied cognition	The theory that the body and its interactions with the environment are involved in cognition and sensory experiences. Also referred to as embodiment.
Sensorimotor	Concerning the sensorimotor system, which describes the interplay between sensory and motor systems.
Perseverative Cognition	Repetitive negative thinking about past and future events that means it includes rumination and worry.
Rumination	Repetitive negative thoughts about past events.
Worry	Repetitive negative thoughts about future events.

Box 2. Central terms related to cognition.

Sleep is Closely Linked to Memory and Cognition

Sleep is important for a variety of cognitive functions, including executive functions, regulations of inhibitory control, attentional processes like selective attention and vigilance, working memory, memory transformations (e.g., gist extraction or insight) and declarative as well as procedural memory consolidation (Roshchupkina & Peigneux, 2020). For the purposes of this dissertation, this chapter focuses on the beneficial effect of sleep on memory consolidation.

According to the synaptic down-selection theory, the beneficial effect of sleep on memory consolidation occurs passively (Tononi & Cirelli, 2014). During wakefulness, synaptic potentiation increases and during SWS, slow oscillations are thought to globally downscale this synaptic strength. In addition, weak connections are eliminated and thereby relatively strengthen

remaining connections. However, recent findings support the notion of sleep actively contributing to brain plasticity rather than being a period of reduced interference, by restoring task performance, which is correlated with the amount of NREM sleep and SWA (Nissen et al., 2021).

This notion of sleep actively contributing to memory consolidation during sleep is addressed by the active system consolidation hypothesis (Diekelmann & Born, 2010; Figure 3). It is based on the two-stage model of memory consolidation (McClelland et al., 1995) assuming a slow-learning long-term memory store located in the neocortex, and a fast learning temporary store located in the hippocampus (Figure 3A). Memory is gradually transferred from the temporary to the long-term store by repeated reactivation of memories during offline periods that means during sleep. This system consolidation process leads to a strengthening and integration of the new memories into existing memory representations. This active reactivation process of declarative memories is thought to occur especially during SWS. More specifically, the depolarizing up-states of cortical slow oscillations (<1 Hz) are thought to drive hippocampal memory reactivation by synchronizing spindle-ripple events, where sharp-wave ripples (transient network oscillations with 80-200 Hz) are nested into succeeding troughs of a spindle (Figure 3B).

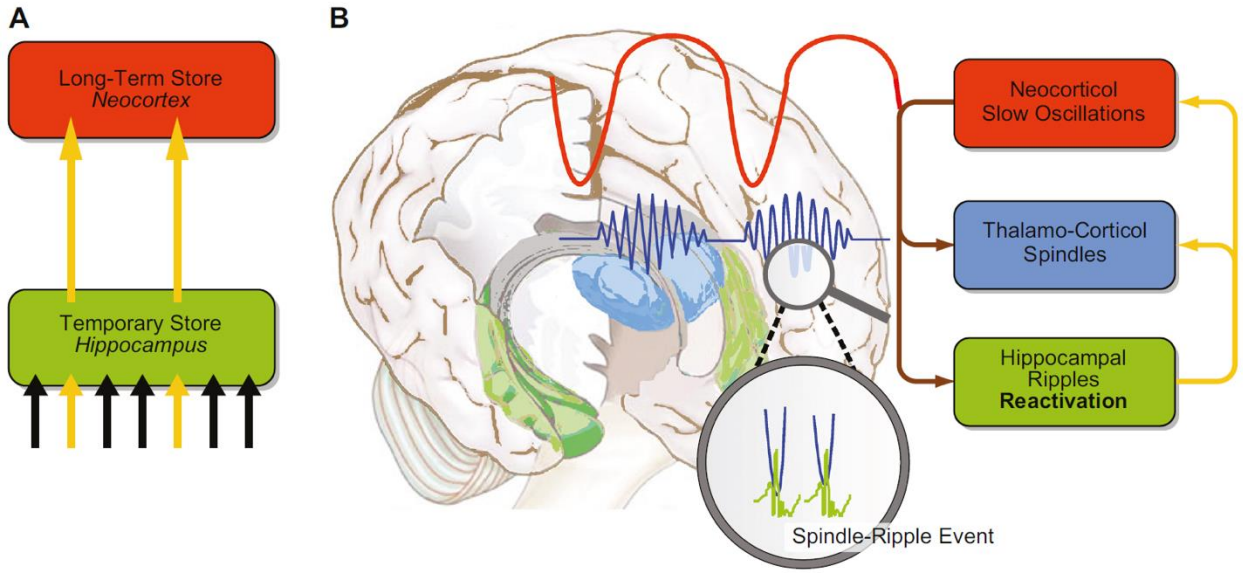

Figure 3. Active system consolidation hypothesis. (A) Newly encoded memories are temporarily stored in the hippocampus and gradually transferred to the neocortex for long-term storage. (B) This transfer of memory is orchestrated by neocortical slow oscillations, which drive

hippocampal memory reactivations by synchronizing spindle-ripple events. Adapted from Rasch and Born (2013), p.691.

Several studies have provided evidence that daytime memories are indeed reactivated during sleep. Spiking patterns of hippocampal place cells in rats during the exploration of a maze have been shown to be replayed during sharp-wave ripples in SWS (O'Neill et al., 2010). Similar replay of learning-related neural patterns emerged for rule-learning in the pre-frontal cortex during sharp-wave ripples during SWS (Peyrache et al., 2009). In humans, an EEG study using multivariate pattern classification successfully decoded EEG activity patterns related to previous learning during subsequent REM and NREM sleep (Schönauer et al., 2017). In addition, a magnetoencephalography (MEG) study showed that brain synchronization patterns of oscillatory activity during a visuomotor learning task reappeared during subsequent delta (1–4 Hz) power fluctuations (Piantoni et al., 2015). Moreover, a study using intracranial recordings from epilepsy patients confirmed the results from animal research by showing that stimulus-specific gamma activity (30–90 Hz) is spontaneously reactivated during NREM sharp-wave ripples and related to post-sleep memory recall (Zhang et al., 2018). This is in line with the active system consolidation hypothesis, assuming a central role of memory reactivations during sleep, however the synaptic down-selection theory does not assume memories to be reactivated during sleep.

A large body of research has provided evidence for the fact that memory reactivations during sleep are functionally and behaviorally relevant for the beneficial effect of sleep on memory. These studies used targeted memory reactivation (TMR) paradigms to improve memory consolidation during sleep (Rasch & Born, 2007). In this approach, a memory representation (e.g., the location of a card pair in a grid) is associated with a cue (e.g., a pleasant odor) during wake. During subsequent sleep, the cue is presented again and thought to reactivate the memory representation and thereby facilitate the stabilization, strengthening and integration of the memory. A recent meta-analysis on 91 experiments and over 2000 participants concluded that TMR during NREM and SWS is effective with a small to medium effect size (Hedges' $g = 0.29$) and is not effective during REM sleep or wakefulness. TMR has been successfully used to improve performance in declarative memory task such as spatial location, word pair learning, emotional memory, creative solution, lecture learning, directed forgetting and false memory tasks (e.g., Cairney et al., 2014; Cousins, 2014; Gao et al., 2019; Rasch & Born, 2007; Ritter et al.,

2012; Schreiner & Rasch, 2015; Simon et al., 2018). In addition, TMR has been shown to improve performance in procedural memory tasks including finger sequence tapping, target throwing, serial reaction time, and melody production tasks (e.g., Antony et al., 2012; Cheng et al., 2019; Cousins et al., 2016; Johnson et al., 2018; Schönauer et al., 2014b), as well as improving performance in other types of memory such as counter social bias learning (X. Hu et al., 2015), auction decision making (Ai et al., 2018), trust learning (Strachan et al., 2020) and body perception (Honma et al., 2016). In addition, TMR of declarative memory seems to occur locally in the cued hemisphere, when the odor is presented in only one nostril (Bar et al., 2020) and seems to work best when cues are presented during the up-state of a slow oscillations (Göldi et al., 2019). Moreover, TMR seems to require a silent undisturbed period after one TMR cue to achieve the gain in memory consolidation (Farthouat et al., 2017; Schreiner et al., 2015). As the presentation of words during sleep has been linked to an increase in the spindle frequency band (Schreiner & Rasch, 2017), this period could be linked to the spindle refractory period reported in recent research (Antony, Schönauer, et al., 2018).

However, the effects of TMR are limited, as several studies reported no or even negative effects of TMR on memory consolidation (e.g., Antony, Cheng, et al., 2018; Ashton et al., 2018; Hennies et al., 2017; Humiston & Wamsley, 2019; Pereira et al., 2017) questioning the effect size of TMR paradigms, especially concerning a publication bias with less published non-significant results. In addition, TMR might be not as effective in younger and older adults (Cordi et al., 2018; Wilhelm et al., 2020). Nonetheless, TMR remains a promising method to examine the beneficial effect of sleep on memory consolidation. In addition, the TMR literature supports a functional and behavioral relevant role of repeated memory reactivations during sleep for memory consolidation during sleep. This is in line with the assumptions of the active systems consolidation hypothesis and highlights the link between sleep and human memory functions.

Both the synaptic down-selection theory and the active system consolidation hypothesis assign an important role to cortical slow oscillations in memory consolidation, which is supported by research showing that externally enhancing slow-waves improves memory consolidation of hippocampus dependent declarative memory (Marshall et al., 2006; Ngo et al., 2013). In addition to slow oscillations, sleep spindles, which occur during N2 sleep and SWS, have also been related to memory consolidation during sleep. Based on their topography and core frequency, sleep spindles are further divided into frontal slow (~ 9 – 12 Hz) and parietal fast

spindles (~ 12 – 16 Hz, Mölle et al., 2011). Parietal fast spindles occur more frequently during early sleep while frontal slow spindles are more likely during later sleep (Siclari et al., 2014), with a continuous change of spindle frequency from the parietal to the frontal cortex (Piantoni et al., 2017). They facilitate synaptic plasticity (Niethard et al., 2018; Seibt et al., 2017) and pharmacologically increasing the amount of sleep spindles has been shown to improve declarative memory (Mednick et al., 2013). It has been proposed that spindle events represent the reinstatement of a memory trace, which is processed in a refractory period 3-6 s after the occurrence of a spindle (Antony, Schönauer, et al., 2018). Such local refractory periods are thought to protect memory reprocessing from interference and to optimize interactions between neural oscillations. In line with the active system consolidation hypothesis, hippocampal ripples have also been linked to memory replay during sleep (Dupret et al., 2010; O'Neill et al., 2010) and suppression of ripples has been shown to impair memory performance (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009).

Recent research highlights that it is not the single sleep oscillations per se that support memory consolidation but rather the interplay and precise timing of them (Fernandez & Lüthi, 2020; Peyrache & Seibt, 2020; Schreiner & Staudigl, 2020). Experimentally increasing the coupling between slow oscillations and spindles using the GABAergic (γ-aminobutyric acid) drug Zolpidem in humans (Niknazar et al., 2015) and optogenetically inducing thalamic spindles phase locked to the slow oscillation up-state in mice (Latchoumane et al., 2017) has been shown to promote hippocampus dependent memory consolidation. In addition, the precision of slow oscillation and spindle coupling has been shown to predict memory consolidation across the lifespan and is considered to be crucial for the timing of endogenous memory reactivations (Helfrich et al., 2018; Muehlroth et al., 2019; Schreiner et al., 2021). This strengthens the assumption that the interplay between sleep oscillations, especially the coupling between spindles and slow oscillations, is crucial for memory consolidation during sleep.

In this section, literature is reviewed showing that sleep is involved in memory processing and cognition and that memory is reactivated during sleep. Results from targeted memory reactivation studies support the notion that memory reactivations during sleep are essential for the beneficial effect of sleep on memory consolidation. Thereby, the interplay between slow-waves and sleep spindles in particular has been shown to be crucial for memory

processes during sleep. The next chapter focuses on the opposite direction and presents literature showing how negative cognitions such as stress can affect sleep itself.

Negative Cognitions and Stress Impact Sleep

A large area of research has studied the effects of stress and negative cognitions on sleep. Stress is a response allowing to adapt to a psychological, environmental or physiologic stressor that threatens a homeostatic state (Chrousos & Gold, 1992; Peterson et al., 1991). A meta-analysis differentiates between two fundamental types of stressors (Kogler et al., 2015): Physiological stress that means unpleasant sensory, emotional and subjective experiences endangering bodily integrity and activating brain areas associated with a motoric fight-or-flight reaction, and psychosocial stress, which is triggered by situations with social judgement, social exclusion and performance situations that demand goal-directed performance and activates brain areas involved in emotion regulation and goal-directed behavior.

Physiological Responses

Physiological responses to a stressor comprise activation of the autonomic nervous system, which includes the sympathetic (SNS) and the parasympathetic nervous system (PNS) and the hypothalamic pituitary adrenal (HPA-) axis. Activation of the HPA-axis starts with the release of corticotropin-releasing hormone (CRH) and vasopressin in hypothalamic neurons, followed by the secretion of adrenocorticotropin (ACTH), which lead to the secretion of cortisol (Dresler et al., 2014). In response to the increased metabolic demands of acute stress, the heart rate, blood pressure, respiration and gluconeogenesis are increased and growth, reproduction, digestion and immune response systems are inhibited (Black, 2002; Charmandari et al., 2005; Dickerson & Kemeny, 2004; Drake et al., 2017).

Increased levels of CRH have been associated with HPA-axis activation and have been shown to impair sleep and enhance vigilance (Steiger, 2002). The injection of CRH directly into the cerebrospinal fluid in ventricles in rats and rabbits reduces the amount of SWS up to 72 hours later (Ehlers et al., 1986; Opp et al., 1989) and prolongs sleep onset latency and REM sleep (Marrosu et al., 1990). In healthy young men, four hourly intravenous injections (10 p.m. – 1 a.m.) of CRH around sleep onset and during early sleep led to an increase in cortisol and a decreased surge of growth hormone during early sleep, followed by a decrease of SWS and REM sleep in the second half of the night (Holsboer et al., 1988). In women, the same CRH injection

protocol led to an increase of REM sleep and lighter sleep stages (N1, N2) and a decrease of SWS during early sleep (Schüssler et al., 2016). In addition, lower doses of CRH have shown to decrease SWS and increase wakefulness in middle-aged men (Vgontzas et al., 2001). Such CRH induced changes in sleep architecture are quite similar to the changes of sleep in depressive patients (Waters et al., 2015). Moreover, insomnia patients display higher pre-sleep salivary cortisol levels (Roehrs & Roth, 2019), which have been associated with an increased beta power during sleep (Pesonen et al., 2021).

However, several studies provided evidence for the fact that acute administration of HPA-axis-related hormones like cortisol and ACTH over a longer period (e.g., 5 p.m. – 7 a.m.) stimulates the release of growth hormone and prolongs the time spent in SWS, increases SWA and reduces REM sleep in healthy young male subjects (Born et al., 1989; Friess et al., 1994; Friess et al., 2004), in elderly (Bohlhalter et al., 1997) and in depressive patients (Schmid et al., 2008). It has been argued that this sleep promoting effect occurs due to a negative feedback inhibition of endogenous CRH secretion that means experimentally increased levels of cortisol lead to a reduced CRH secretion during sleep. Moreover, similar effects have been shown in interaction with the appetite enhancing hormone ghrelin (Kluge et al., 2008). The growth hormone and ghrelin are part of the hypothalamo-pituitary-somatotrophic system and it has been proposed that this system affects sleep in a reciprocal relationship with the HPA axis and with a central role of the growth hormone-releasing hormone and CRH (Dresler et al., 2014; Ehlers & Kupfer, 1987; Steiger, 2007).

Prolonged Stress Response by Cognitive Processes

Cognitive responses to acute stress contain an increased cognitive arousal, alertness, vigilance, analgesia and a suppression of appetite (Charmandari et al., 2005; Dickerson & Kemeny, 2004). Moreover, early stress models like the transactional model of stress (Lazarus & Folkman, 1984) and the allostatic load concept (McEwen & Stellar, 1993) emphasize the importance of reappraisal, cognitive evaluation and subjective perception in the stress response.

It has been highlighted that the stress response needs to be sustained or prolonged to explain the detrimental effect on health (Brosschot et al., 2016, 2017, 2018). Acute stress or the stressful event itself, which is only present for a short time, only accounts for a small part of the daily stress response and therefore cannot explain the detrimental effects of stress on health (Chandola et al., 2008; Chandola et al., 2010; Dimsdale, 2008; Landsbergis et al., 2013; Orth-

Gomér et al., 2000). For example, stressful encounters with the superior at work or disputes with one's spouse result in a prolonged or chronic stress response, while the stressor itself is comparably short enduring (e.g., only several minutes). But how is the stress-related physiological activity prolonged?

A prolonged activation of stress is achieved by repeatedly thinking about a past or upcoming stressor, which has been labeled as perseverative cognition (Brosschot et al., 2006), repetitive negative thinking (Watkins et al., 2005) or more generally cognitive arousal. It includes worry (i.e., repetitive thoughts about anticipated future events) and rumination (i.e., repetitive negative thoughts about past events). Cognitive arousal is associated with a physiological stress response like an altered activity of cardiovascular (e.g., increased heart rate, blood pressure), endocrine (e.g., elevated cortisol levels), immune (e.g., decreased amount of natural killer cells), and neurovisceral activity (e.g., impairment of inhibitory cortical-subcortical neural circuits; Brosschot et al., 2006). Mental representations of the stressful events are thought to be created and activated long before and after the events happen, and are thereby responsible for anticipatory effects, slow recovery and also recurrent activity of stressors (Brosschot et al., 2006; Brosschot et al., 2018; Verkuil et al., 2010). Brosschot and colleagues argue that the mental representation of these events are leading to the "fight-or-flight" action tendency, which causes the brain to induce a peripheral stress response (e.g., increasing heart rate, blood pressure, stress hormones like cortisol; Brosschot et al., 2010).

In addition to consciously thinking about the stressors, a main assumption of their extended perseverative cognition hypothesis is that we are not aware of a large part of these cognitive representations (Brosschot et al., 2010; Figure 4). This assumption is based on both the notion that the majority of cognitive processing is unconscious and operates automatically (Bargh & Morsella, 2008; Dijksterhuis & Nordgren, 2006; Kihlstrom, 1987), as well as on results showing a prolonged cardiac response to a stressor up to two hours after consciously worrying about the event (Pieper et al., 2010). In addition, the authors support their idea of unconscious cognitive representations of stress by referring to literature showing that increased daytime physiological activation in response to stress and perseverative cognition is maintained during unconscious, subsequent sleep (Brosschot et al., 2007; Hall et al., 2004; Yoshino & Matsuoka, 2009). Within this framework, researchers attribute unconscious cognitive representations of the stressor an even greater role for the prolonged physiological activity in

response to a stressor compared with conscious perseverative cognition (Brosschot et al., 2010, 2018). They assume that unconscious cognitive representations of stressors or stressful events are active during sleep and thereby induce a physiological response, such as increases in heart rate. However, they do not provide a mechanistic explanation on how such unconscious representations might affect sleep. In sum and similar to previous models (Lazarus & Folkman, 1984; McEwen & Stellar, 1993), the physiological response to a stressor is assumed to result from an interaction with conscious and unconscious cognitive responses to the stressor.

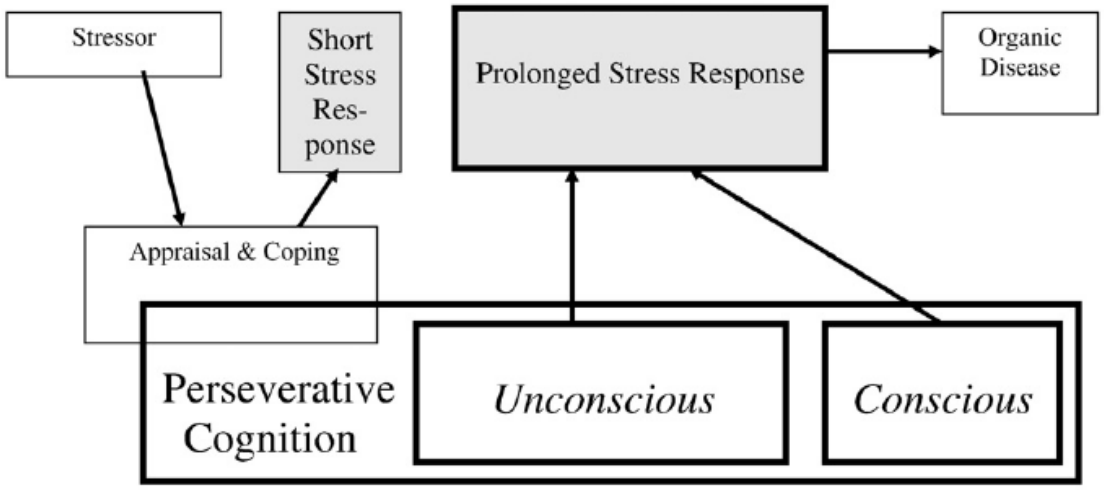

Figure 4. The extended perseverative cognition hypothesis. Conscious and unconscious forms of perseverative cognitions are mediating the effect of stress on organic disease. Adapted from Brosschot (2010) p. 411.

Regarding the effect of stress on sleep, especially a prolonged activation of stress has been shown to have detrimental effects on sleep (Åkerstedt, 2006; Åkerstedt et al., 2015; Cui et al., 2008; Drake et al., 2017; Eskildsen et al., 2017; Garde et al., 2011; Lin et al., 2014). In addition, research suggests that psychosocial stress in particular is a major factor in the development and maintenance of sleep disturbances (Åkerstedt, 2006; Drake et al., 2017; Harvey, 2002; Kalmbach et al., 2018; E.-J. Kim & Dimsdale, 2007; Riemann et al., 2010). Psychosocial stress has been defined as the response to situations with social exclusion, social judgement and performance situations that demand goal-directed performance and has been

shown to activate brain areas involved in emotion regulation and goal-directed behavior (Kogler et al., 2015).

As previously mentioned, short lasting (i.e., acute) stress episodes cause a strong physiological response but are insufficient to affect our health. Interestingly, in sleep research, studies assessing the effect of acute stress before sleep has been shown to affect early sleep especially by delaying the onset of sleep and SWS (Ackermann et al., 2019; Vandekerckhove et al., 2011; Wuyts et al., 2012). It has also been shown that acute stress before sleep may produce no effect on sleep physiology at all, in particular when an intense psychosocial stressor is followed by an additional memory task before sleep that means when the time interval between the acute stressor and sleep is increased (S. Y. Kim et al., 2019). Such effects could be explained by the physiological response to the stressor or in the latter case by an already declined physiological response before subjects go to bed.

To have a larger and maintaining effect on sleep, stress has to be active for a longer time period that means also during sleep or become chronic. As mentioned in the previous section, conscious as well as unconscious cognitive arousal, for example perseverative cognition, is thought to play a crucial role in the prolonged effect of stress on physiology. Such cognitive arousal has been suggested to mediate the negative effect of stress on sleep (Tousignant et al., 2019) and can be differentiated between general and sleep-related cognitive arousal (Spiegelhalder et al., 2012). One example for a situation with increased cognitive arousal would be sleeping in an unfamiliar environment, which might be perceived as unsafe or threatening, also known as the first night effect. It has been shown that sleeping in an unfamiliar environment reduces the amount of SWS and decreases SWA specifically over the left brain hemisphere (Le Bon et al., 2000; Tamaki et al., 2016). Sleep-related cognitive arousal will be discussed in detail in the following chapter on insomnia models.

Moreover, a large body of research provides evidence that cognitive arousal is a main factor for sleep disturbances in insomnia patients as well as in healthy sleepers (Ballesio et al., 2020; Clancy et al., 2020; Kalmbach et al., 2020; Lemyre et al., 2020). Importantly, cognitive arousal is thought to affect sleep consciously during the pre-sleep period as well as unconsciously during sleep itself (Brosschot et al., 2007; Brosschot, 2010; Hall et al., 2004; Hall et al., 2007). In addition, cognitive arousal is increased in insomnia patients compared with healthy controls (Spiegelhalder et al., 2012), especially while falling asleep (Hantsoo et al., 2013;

Harvey, 2000; Jansson-Fröjmark & Norell-Clarke, 2012; Kalmbach et al., 2020). Moreover, cognitive arousal has been associated with objective sleep disturbances and physiological hyperarousal during day and night and has been suggested as a promising target for severe sleep disturbances (Kalmbach et al., 2020). In line with these results, reducing cognitive arousal with cognitive behavioral therapy for insomnia has been linked to decreased post-treatment depression and anxiety symptoms (Ballesio et al., 2020).

Taken together, research has shown that stress and negative cognitions can have a large effect on sleep on a physiological and on a cognitive level. But how are cognitions able to affect sleep? In the next chapter, past and current theories from the insomnia literature will be presented and investigated regarding their explanation on how cognitions before and during sleep are able to affect sleep.

Cognitive Models of Insomnia

As described in the previous section, negative cognitions such as cognitive arousal in response to stress have a detrimental effect on sleep. Both past and recent insomnia models assume an important role of cognitions in the development and maintenance of sleep disturbances. This section will describe several insomnia models by focusing on two main aspects: Does the model provide a mechanism explaining how cognitions affect sleep? Are cognitive processes active and do they affect sleep before sleep, during awakenings and/or also during sleep itself?

In early research, insomnia has been seen as a disorder of physiological hyperarousal (Bonnet & Arand, 1997). This led to the development of early behavioral treatments which focus on decreasing physiological arousal directly, using techniques such as biofeedback (Hauri, 1981) or progressive muscle relaxation (Jacobson, 1938). In addition, indirect approaches evolved aiming to reduce physiological arousal by targeting cognitive arousal. For instance, stimulus control reduces arousal induced by the conditioned response to sleep-related stimuli (Bootzin, 1972), paradoxical intention targets the arousal induced by performance anxiety that means the inability to fall asleep (Ascher & Efran, 1978), and sleep restriction limits the time in bed and thereby increases the homeostatic sleep pressure to surpass physiological wake promoting arousal (Spielman, Saskin, & Thorpy, 1987). Recent guidelines for cognitive behavioral therapy

of insomnia still recommend most of these therapeutic approaches as they have been shown to be successful in the treatment of sleep disorders (Ferini-Strambi et al., 2021; Riemann et al., 2017).

The hyperarousal concept and behavioral treatments of insomnia have been integrated in an early diathesis-stress-response model which describes acute insomnia and how it becomes chronic (Spielman, Caruso, & Glovinsky, 1987). It is referred to as the '3P' model (Figure 5) and assumes the following three factors to be responsible for acute and chronic insomnia symptoms (Perlis et al., 2011): predisposing factors, including biological (e.g., increased basal metabolic rate), psychological (e.g., excessive worrying) and social factors (e.g., social pressure to sleep with a non-preferred sleep schedule), and precipitating factors such as stressful life events. In interacting with perpetuating factors like practice of non-sleep activities in the bedroom, staying in bed while awake and generally spending a large amount of time in bed, acute insomnia symptoms are maintained and cause the onset of early and chronic insomnia.

The model assumes that cognitions affect sleep mainly in the form of pre-sleep worries or as precipitating factors like a stressful life event by increasing pre-sleep physiological arousal. This physiological arousal is then thought to prolong sleep onset latency. The model does not consider a direct effect of cognitions on sleep and an effect of cognitions during sleep on sleep itself. In addition, the model highlights the importance of stimulus control and sleep restriction to target perpetuating factors and it lacks a clear definition of hyperarousal.

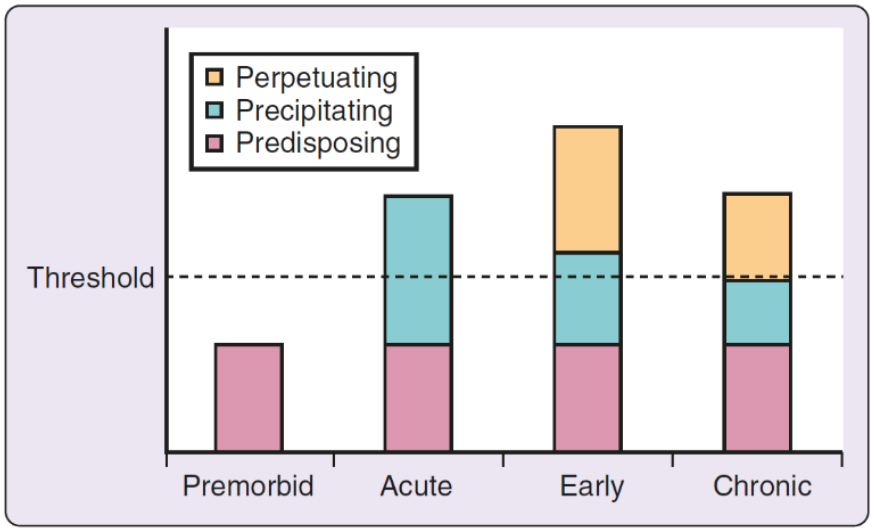

Figure 5. The '3P' model by Spielman, Saskin, and Thorpy (1987). Adapted from Perlis et al. (2011), p.852.

In an early cognitive-behavioral model of insomnia focusing on sleep-related cognitions, Morin (1993) presented a vicious cycle on how insomnia is perpetuated containing four domains: arousal, dysfunctional beliefs and attitudes, maladaptive habits and consequences (see Figure 6). The model is based on the '3P' model and assumes sleep disturbances to occur in response to a stressor (precipitating event), such as separation or medical illness, and should resolve when the stressor has faded or the person has adapted to its presence. To become chronic, the four presented domains maintain the sleep disturbances and lead to a functional independence of the sleep disturbances from the original stressful event.

The cognitive-behavioral model of insomnia assumes a close relationship between emotional, cognitive and physiological arousal and makes no further assumptions about differences in their contribution to sleep disorders. It levels arousal on a similar level with the purely cognitive domain of dysfunctional beliefs and attitudes, like worry and rumination. Thus, Morin's model emphasizes the influence of cognitive mechanisms and assumes a direct effect of them on the maintenance of sleep disorders. In addition to existing behavioral treatments at that time such as progressive muscle relaxation, biofeedback, stimulus control or sleep restriction, Morin therefore suggested to include cognitive therapy strategies to target dysfunctional cognitions, which are directly related with increases in arousal and sleep disturbances. However, the model does not provide a mechanism on how cognitions are able to directly affect sleep. Because it is based on the '3P' model and no other mechanism is provided, it implicitly suggests that cognitive and emotional arousal increases physiological arousal and thereby affects sleep. Moreover, it assumes that cognitive processes such as worrying affect sleep (via physiological arousal) in the pre-sleep period and during awakenings but does not address cognitions during sleep itself.

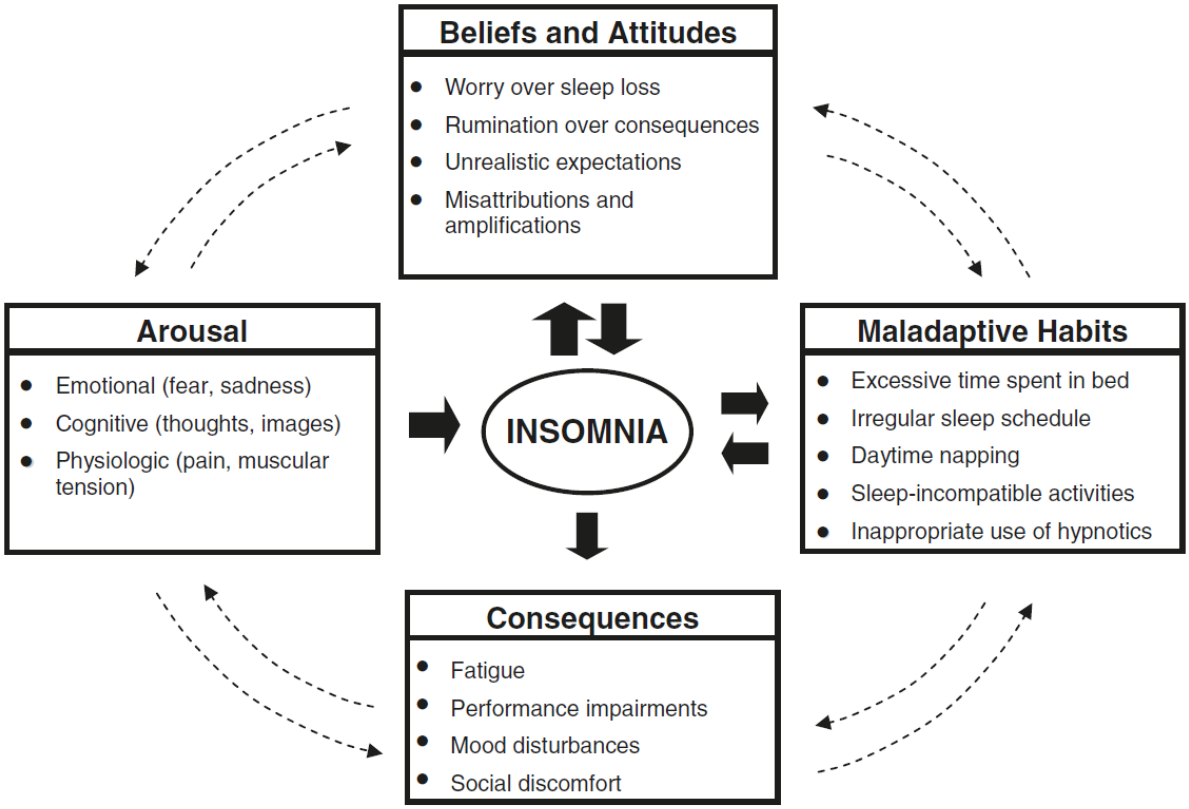

Figure 6. Cognitive-behavioral model of chronic insomnia (Morin, 1993). The model depicts how arousal, dysfunctional beliefs and attitudes and maladaptive habits can maintain insomnia symptoms. Adapted from Bélanger et al. (2012), p.103.

Based on cognitive models of anxiety disorders and empirical studies on cognitive processes in insomnia, Harvey (2002) developed a cognitive model of insomnia describing the maintenance (i.e., perpetuating factors of insomnia) during the day and in bed (Figure 7). People suffering from insomnia are thought to exhibit excessive negatively toned cognitive activity in bed and during the day, such as intrusive thoughts, worrying, or rumination about the consequences of insufficient sleep on health and daytime functioning. Such cognitive activity is thought to induce emotional distress and to activate the sympathetic nervous system (SNS) leading to an increased autonomic arousal and leaving the individual in an anxious state. Similar to an attentional bias towards possible threatening stimuli in anxiety disorder (Dalgleish & Watts, 1990), the author assumes that this anxious state shifts the attention to sleep-related cues threatening a good night of sleep. Shifted attentional processes to sleep-related stimuli create a

distorted perception of an increased sleep deficit and an overestimated worsening of their daytime performance. This distorted perception, as well as internal and external monitoring for sleep-related threats, are assumed to be automatic (i.e., occur unconsciously) and assumed to increase negatively toned cognitive activity like worrying and thus further perpetuate sleep disturbances. In addition, strategies/safety behaviors to avoid the feared outcome of sleep disturbances like “trying to stop all thinking” during the day and erroneous beliefs about sleep like “controlling my thoughts helps to get rid of them and helps me sleep” are thought to further exacerbate negative cognitive activity.

The cognitive model of insomnia assumes a central role of day- and night-time cognitive processes such as negative cognitive activity, selective attention and monitoring, distorted perception, erroneous beliefs, and safety behaviors on sleep in the maintenance of insomnia. Moreover, the author suggests that cognitive and physiological arousal have a reciprocal and exacerbating relationship. If someone is cognitively aroused (e.g., worries about something), they will also be physiologically aroused and if someone detects that they are physiologically aroused (e.g., sweating, heart beating), they will search for an explanation and thereby increasing cognitive arousal. Therefore, the author suggests that cognitive activity like increased worrying, physiological arousal and emotional distress are conditions that facilitate sleep disturbances and decreased daytime functioning.

Thus, the cognitive model of insomnia assumes that an interaction between cognitive and physiological arousal maintains sleep disturbances, but it also states that increases in both types of arousal are the direct result of cognitive processes. Such an increased arousal is assumed to be incompatible with sleep, but the model fails to provide an explanation of other possible underlying mechanisms. In addition, the model emphasizes that cognitive processes during awakenings are as important as during the pre-sleep period for sleep disturbances, but it does not consider cognitive processes during sleep itself.

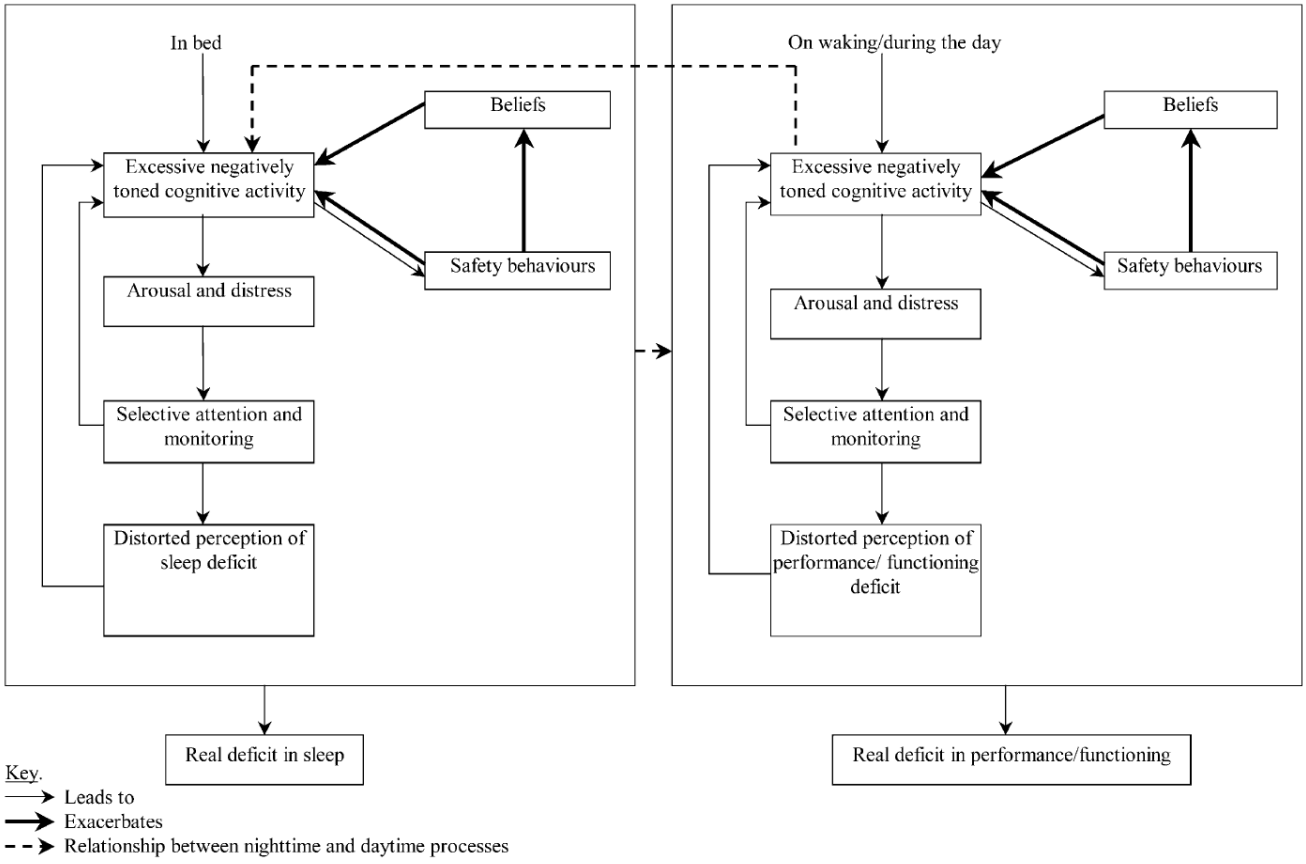

Figure 7. Cognitive model of insomnia (Harvey, 2002). The model describes how day and nighttime cognitive processes perpetuate insomnia symptoms. Adapted from Harvey (2002), p.874.

A first psychobiological inhibition model of good sleep (Espie, 2002) explains the transition from good sleep to acute insomnia (Figure 8), and in an updated version the development from acute to chronic insomnia by including an attention-intention-effort pathway (Espie et al., 2006; Figure 9). The first inhibition model stands out from other models as it uses good sleep as a starting point. The authors describe the core of good sleep as an involuntary and harmonious interaction between homeostatic and circadian mechanisms and the subjective perception of good sleep quality (Espie, 2002). These processes are thought to be protected by plasticity (i.e., the flexibility of the sleep-wake system to adjusts to challenges) and automaticity (i.e., the notion that sleep comes passively and effortlessly). This center of good sleep is influenced by four interdependent component processes: sleep-related stimulus control, daytime

facilitation of night-time sleep and sleep-related physiological as well as cognitive de-arousal. They assume that in healthy sleep, physiological and cognitive arousal are actively reduced in interaction with affect regulation. In insomnia, high affect inhibits such de-arousal due to the intention to sleep well and an increased effort to sleep, which further inhibits automaticity and plasticity. Another example of how one of the component processes may inhibit automaticity and plasticity in insomnia could be a low stimulus control, like irregular sleep habits or conditioning of waking activities (e.g., eating, problem-solving) within the sleep environment.

The psychobiological inhibition model starts with cognitive and physiological mechanisms of good and healthy sleep and assumes an active process of inhibition and de-arousal (i.e., wakefulness) in the evening as essential for the development of sleep disturbances (Espie, 2002). Physiological and cognitive arousal are assumed to occur in parallel and to affect each other and their contribution in affecting sleep is equal. However, a clear definition of arousal and inhibition processes is lacking. In addition, the concept of de-arousal is mainly applied to the pre-sleep period and neither on awakenings during the night nor during sleep itself.

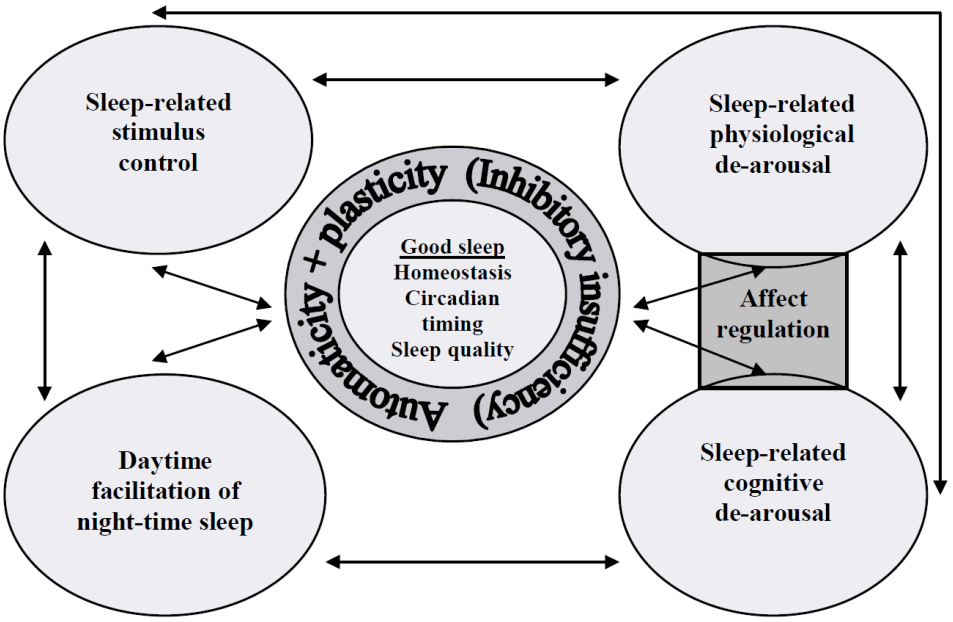

Figure 8. Psychobiological inhibition model of good sleep. The model conceptualizes sleep disturbances as a failure to de-arouse (i.e., inhibit wakefulness) in the evening. Adapted from Espie (2002), p.227.

In their updated attention-intention-effort model (Espie et al., 2006), the authors describe the development from acute/adjustment insomnia (i.e., sleep disturbances occurring in response to a specific stressor) to chronic/persistent psychophysiological insomnia (Figure 9). They pick up on the concept of automaticity that means the idea of a good sleeper as being passive with automated internal and external cues smoothing the way to a good night of sleep. In addition, they introduce three factors with the ability to inhibit this sleep-wake automaticity: selective attention to sleep (attention), explicit intention to sleep (intention), and effort into the sleep engagement process (effort). First, stress is thought to induce psychological and physiological responses, which in turn inhibit the sleep-related de-arousal, and thereby causes insomnia symptoms. During acute/adjustment insomnia, attention is focused on that stressor and the strength of arousal mediates the severity of insomnia symptoms. Likewise, when the stressor resolves, insomnia symptoms are thought to resolve themselves. If the stressor ends but insomnia symptoms persist, the attention might shift from the resolving stressor to any persisting sleep disturbance, first implicitly and later to an explicit and conscious processing bias (Figure 9, A1 A2). This attention shift is thought to perpetuate the insomnia symptoms and create the explicit intention (i.e., the mental response) to get a good amount of sleep. In the context of psychophysiological insomnia, this intention is leading to an actual behavioral effort to actively try to sleep (Figure 9, E1) and to an indirect sleep effort (Figure 9, E2), for example increasing the opportunity to sleep. The authors dedicated a separate model to the sleep effort, which will not be further discussed here.

The core assumption of the attention-intention-effort model that insomnia is explained by a failure to inhibit wakefulness is supported by evidence from studies in humans measuring event-related potentials (ERP; Bastien et al., 2008; Yang & Lo, 2007) and by the rodent model of sleep-wake regulation, proposing that stress-induced sleep disturbances originate from an increased activity in the limbic arousal system, while the sleep system remains active (Cano et al., 2008; Saper et al., 2005). Moreover, the authors supported their choice of defining selective attention as a central concept with similar findings on a wide range of other psychiatric disorders such as panic, eating, generalized anxiety, and post-traumatic stress disorder (Dalgleish & Watts, 1990; Mathews & MacLeod, 1994; Mogg & Bradley, 1998; Williams et al., 1996) and with results showing an attention shift in insomnia patients (Jones et al., 2005; MacMahon et al., 2006).

Within the attention-intention-effort pathway model (Espie et al., 2006), acute sleep disturbances are caused by a similar contribution of cognitive and physiological arousal leading to the failure to inhibit wakefulness. In addition, the model assigns cognitive mechanisms a causal role in the development and maintenance of chronic/psychophysiological insomnia. In this case, a person suffering from chronic insomnia is thought to be awake because he/she is worrying and not due to an increased physiological arousal (Perlis et al., 2011). However, like in their psychobiological inhibition model (Espie, 2002), the authors fail to provide a clear conceptualization of how cognitive and physiological arousal are initially able to affect de-arousal and thereby lead to sleep disturbances. Similarly, the model focuses on the pre-sleep period and neglects cognitive and physiological processes during nocturnal awakenings and during sleep.

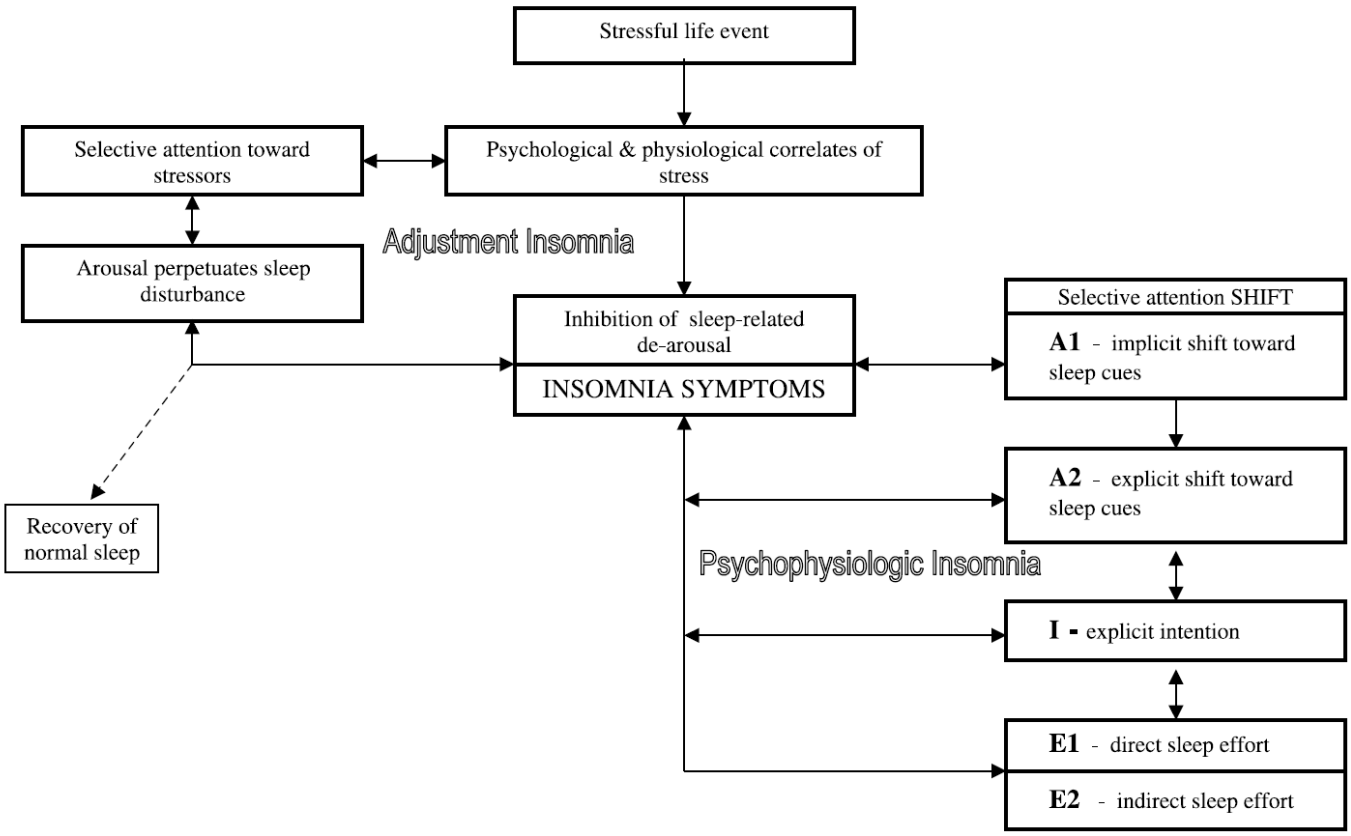

Figure 9. Attention-intention-effort (A–I–E) pathway model. The model describes the development from acute/adjustment insomnia to chronic/psychophysiological insomnia. Adapted from Espie et al. (2006), p.226.

The recent two-level of sleep-related arousal model (Figure 10) focuses on the explanation of two levels of sleep-related cognitive arousal, which are primary and secondary cognitive arousal, and introduces metacognitive processes (Ong et al., 2012). The model does not claim to fully explain insomnia but to complement existing models by an in-depth explanation of sleep-related cognitive arousal. Metacognition is defined as the awareness or knowledge of one's own cognitions (Flavell, 1976). Primary sleep-related arousal refers to cognitions related to the inability to sleep, such as daytime consequences of sleep loss, expectations about sleep or generally an increased mental activity in bed. An example for a thought creating primary arousal would be "I need eight hours of sleep to function well the next day". Secondary arousal stands on a higher cognitive level and in a reciprocal relationship with primary arousal and refers to how one relates to such thoughts about sleep. For instance, a rigid adherence to the previously mentioned thought would impede considerations of other possible outcomes or solutions and thereby enhance the negative affect of this thought leading to a secondary arousal. Factors increasing sleep-related secondary arousal in insomnia are an emotional or attentional bias towards sleep-seeking or sleep-aversive thoughts and behaviors, a rigidity instead of flexibility in sleep-related behaviors and beliefs, attachment in contrast to equanimity about sleep-related needs and expectations, and lastly the absorption in solving problems associated with sleep instead of pursuing a valued living with a variety of thoughts and emotions.

Like previous models, the two-level model of sleep-related cognitive arousal sees sleep-related cognitive hyperarousal and problems to de-arouse as key elements in the development and maintenance of insomnia. The authors state that cognitive treatments based on previous models mostly target primary sleep-related arousal (Ong et al., 2012). Based on the metacognition framework, the authors propose that cognitive therapy of insomnia would profit from targeting metacognitive processes such as observing and noticing thoughts to reduce secondary sleep-related cognitive arousal using mindfulness and acceptance-based approaches. In addition, they argue that previous models also already contain metacognitive processes, for example the loss of automaticity in insomnia (Espie, 2002) and the selective attention shift to sleep-related cues in insomnia (Espie et al., 2006; Harvey, 2002; Riemann et al., 2010), yet not explicitly naming them as such and not introducing them as a separate component.

This model highlights the importance of cognitive arousal and cognitions for perpetuating sleep disturbances and offers a new approach by introducing metacognitive processes. However,

it is the narrowest model by focusing on solely sleep-related cognitive arousal and neglecting other types of cognitive and physiological arousal. By assuming itself to fit into existing models (Espie, 2002; Harvey, 2002; Morin, 1993), it implicitly states that sleep-related cognitive arousal may lead to sleep disturbances via increasing physiological arousal or in interaction with physiological arousal. In addition, they implicitly assume that sleep-related cognitive arousal affects sleep especially during the pre-sleep period, but they do not address possible effects on or during awakenings and sleep itself.

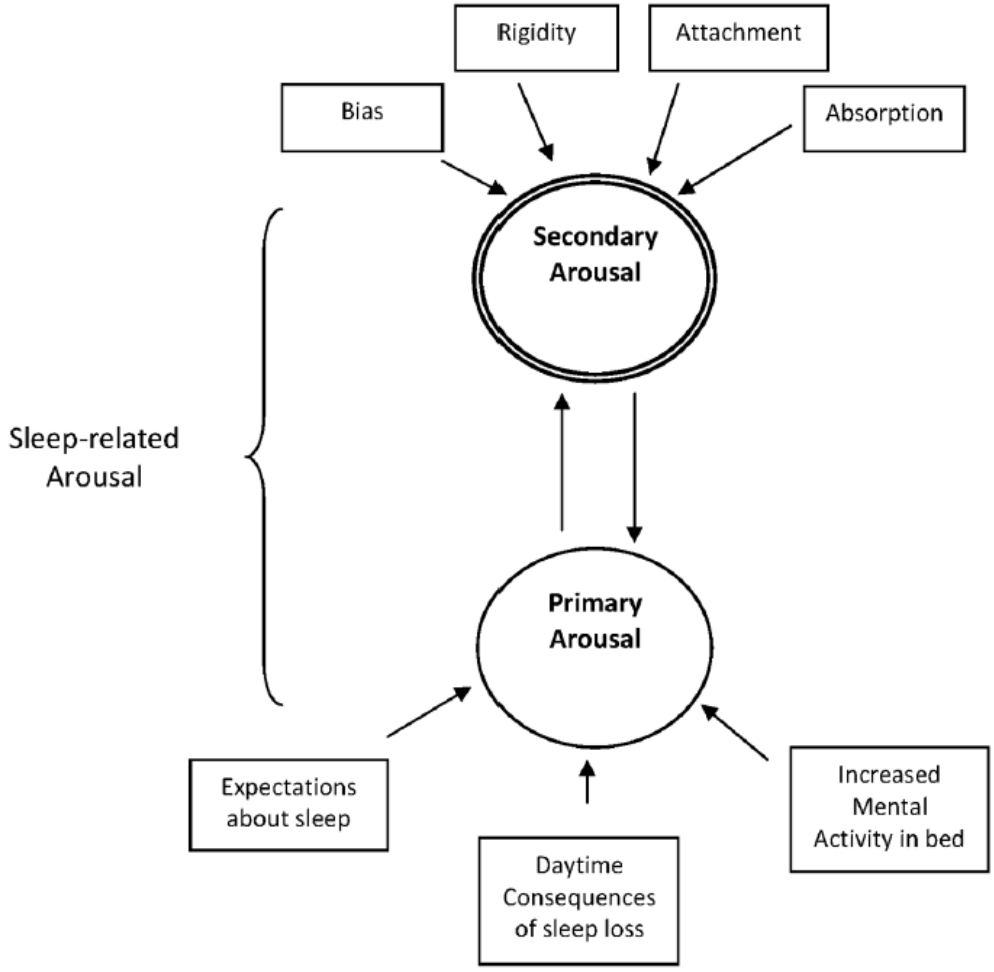

Figure 10. Two-level model of sleep-related cognitive arousal. It complements existing insomnia models by introducing two levels of sleep-related cognitive arousal: primary arousal refers to cognitions related to the inability to sleep; secondary arousal stands on a higher (i.e. metacognitive) level and refers to how one relates to such thoughts about sleep. Adapted from Ong et al. (2012), p.20.

The neurocognitive model of insomnia (Perlis et al., 1997) extended the initially mentioned '3P' model by including classical conditioning as a perpetuating factor and elaborated the view of hyperarousal being of cortical, cognitive and somatic nature (Figure 11). Cortical arousal is defined as an increased amount of high frequency EEG in the beta (14–32 Hz) and gamma range (>32 Hz) and thought to be a physiological measure of brain activity and cognitive processes. The model stresses the role of cortical arousal in the etiology and pathophysiology of insomnia via enhanced sensory processing, information processing, and memory formation around sleep onset and during non-rapid eye movement (NREM) sleep. Learned associations between sleep-related stimuli and arousal or wakefulness are thought to produce increased conditioned cortical arousal at sleep onset and during sleep. Thereby, cortical arousal is thought to be a preliminary stage of cognitive arousal in chronic insomnia. The model provides an explanation for sleep state misperception, as it assumes that enhanced information processing around sleep onset and during NREM sleep blurs the phenomenological differentiation between sleep and wakefulness and that enhanced long-term memory of such experiences further contributes to this effect (Perlis et al., 2011).

The neurocognitive model links somatic and cognitive arousal by introducing cortical arousal as (1) a form of somatic arousal and a measure of brain activity in contrast to mental activity and (2) an analogue of cognitive arousal due to its correlation with cognitive processes. Therefore, the model highlights the relatedness between cognitive and somatic arousal and does not make specific predictions if somatic or cognitive arousal per-se, in the form of worrying or rumination, lead to sleep disturbances. Within this framework, it assigns somatic arousal a comparably small role, except its relation to cortical arousal. Moreover, the definition of hyperarousal remains rather vague, and the model does not clearly explain, how cognitive arousal like rumination and worrying impacts sleep. Because the model is based on the '3P' model, it may implicitly assume that such cognitive arousal leads to an increase in physiological hyperarousal, which in turn causes the sleep disturbances.

However, this model stands out from the other models as it assumes that cognitive processes, which are linked to cortical arousal (i.e. sensory processing, information processing and long-term memory formation) directly affect sleep itself and sleep-related subjective complaints that are characteristic for insomnia. Thereby, this model also states that such

cognitive processes are not only active during the pre-sleep period and during awakenings, but also during NREM sleep.

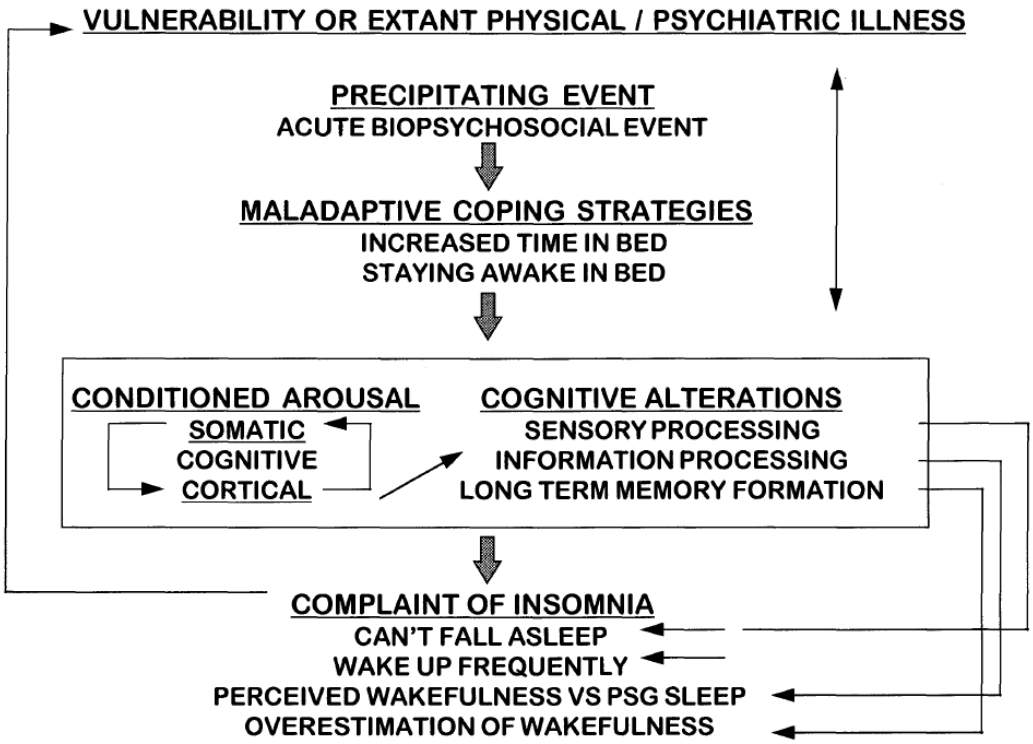

Figure 11. Neurocognitive model of insomnia. The model highlights the importance of cortical arousal in the development and maintenance of insomnia. Adapted from Perlis et al. (1997), p.183.

The most elaborate insomnia model is the hyperarousal model of insomnia (Riemann et al., 2010) and is originally based on the neurocognitive model of insomnia (Perlis et al., 1997). It defines insomnia as a state of increased arousal, which can present itself on multiple levels: physiological, cortical, and cognitive (Figure 12). The model differentiates between acute (1-90 days), subchronic (3-6 months) and chronic insomnia (> 6 months) both on a cognitive-behavioral as well as on a neurobiological level and thereby proposes that insomnia is a psychobiological disorder rather than a pure psychological disorder. In their model, they focus on the explanation of the neurobiological domain, but argue that both domains are highly interdependent and interrelated.

On the cognitive-behavioral level, the hyperarousal model assumes similar to previous models that predisposing and precipitating factors (e.g., psychosocial stressors, worry and rumination) are involved in acute insomnia whereas perpetuating factors (e.g., increased time in bed) are major factors in the development of chronic insomnia. During the acute phase, such precipitating factors lead to an increased sleep onset latency (SOL), a reduced total sleep time and an increased time awake after sleep onset (WASO). The chronification of acute insomnia is then favored by increased worrying about sleep, selective attention towards sleep-related stimuli and an attentional bias towards daytime consequences of insufficient sleep. Subchronic worrying may then lead to an adaptation of the individual's behavior, such as extending the opportunity to sleep or remain in bed awake. Next, and in addition to previously mentioned perpetuating factors, such behavior may lead to conditioning effects, which are thought to perpetuate an increased SOL, WASO and worrying about sleep.

On the neurobiological level, the model assumes an increased secretion of the stress hormone cortisol, the wakefulness promoting hypothalamic neuropeptide orexin and other excitatory monoamines (e.g., noradrenaline) together with a decreased secretion of inhibitory neurotransmitters (e.g., adenosine and serotonin) during acute insomnia. These changes are thought to affect sleep-wake regulatory systems such as the wake promoting ascending reticular activating system (ARAS), which originates in the brainstem, and neurons in the sleep promoting ventrolateral preoptic nucleus (VLPO; Saper et al., 2005).

These neurobiological changes are further thought to induce an acute cortical hyperarousal, which is defined similarly to the neurocognitive model (Perlis et al., 1997). Cortical arousal can be measured as increases in fast (beta and gamma) activity in the EEG and is subjectively experienced as an increased cognitive activity. Cortical arousal is associated with an enhanced sensory processing, information processing and memory formation for events around sleep onset and during awakenings. Moreover, the model assumes that such cognitive processes linked to cortical arousal can directly affect sleep in the pre-sleep period, during awakenings as well as during NREM and possibly REM sleep itself. For example, enhanced sensory processing during sleep might facilitate processing of ambient noise in the sleep environment and thereby lead to sleep disturbances. In addition, enhanced memory formation during sleep might deteriorate the ability to differentiate between sleep and wakefulness. Implicitly, cortical arousal thereby provides a link between the neurobiological and the cognitive

domains, however it is not placed between the domains but within the neurobiological domain, which strengthens the view that cortical arousal is a mainly physiological marker.

To continue on the neurobiological domain, such cortical hyperarousal leads to a homeostatic and circadian dysregulation and a chronification of insomnia. Chronic insomnia is neurobiologically characterized by chronic changes of the ARAS and VLPO, chronic cortical hyperarousal, reduced hippocampal volumes and impaired nocturnal memory consolidation. Such chronic neurobiological changes in turn perpetuate acute changes of the ARAS and VLPO and cortical hyperarousal. Finally, chronic changes in both, the cognitive-behavioral and neurobiological, domains are thought to favor the development of depression, addiction and anxiety disorders, which in turn exacerbate acute sleep disturbances.

In summary, the hyperarousal model is the most comprehensive model including assumptions about cognitive-behavioral and neurobiological changes throughout chronification of insomnia. Sleep is thought to be negatively affected by an increased somatic, cognitive and cortical arousal. Similar to the neurocognitive model, it highlights the importance of cortical hyperarousal and assumes that associated cognitive processes are also active during NREM and REM sleep.

Regarding the questions, how the cognitive-behavioral and the neurobiological domains interact with each other to induce acute sleep disturbances and which type of arousal finally affects sleep, the model refrains from providing a concrete answer. However, on the cognitive-behavioral level, their model suggests a direct effect of pre-sleep cognitive arousal such as psychosocial stress, worrying, and rumination on early sleep in the form of an increased SOL. While this effect on SOL could also explain the assumed effect of cognitive arousal on TST, it cannot explain the assumed direct effect of cognitive arousal on WASO (i.e., wake after sleep onset). Thereby, the model assumes an effect of cognitive arousal on later parts of the night, because an increased WASO requires the subject to have fallen asleep. Thus, they implicitly assume that cognitive arousal is able to affect sleep throughout the night.

However, the model does not further elaborate effects in the cognitive-behavioral domain and how cognitive precipitating events such as increases in psychosocial stress, worry, and rumination lead to increases in SOL and WASO and reduce total sleep time. As the model is based on the neurocognitive model of insomnia and the ‘3P’ model, it may maintain the assumption that cognitive processes fuel and trigger sleep disturbances, but they merely enhance

physiological or cortical hyperarousal, thereby impairing sleep. In this scenario, the model would not predict that psychosocial stress affects sleep without a concomitant increase in physiological arousal.

In addition, hyperarousal in general is thought to affect sleep in the pre-sleep period, during awakenings and during sleep itself. However, which types of arousal are likely to affect which phases is not further specified by the model. Implicitly, all types of arousal are likely to directly or indirectly affect sleep during the pre-sleep period and during awakenings in the form of for example worrying/rumination, increased high frequency EEG power and an increased heart rate. The contribution of physiological and cortical arousal is highlighted also in a more recent publication, which presents empirical studies showing increased cortisol levels (HPA-axis activity), heart rate and heart rate variability (autonomic nervous system), and EEG beta power during NREM sleep (cortical arousal) in insomnia patients (Riemann et al., 2015). In addition, cognitive processes associated with cortical arousal are thought to directly affect sleep during NREM and possibly also during REM sleep. Moreover, as highlighted in the previous paragraph, the model implicitly assumes that also cognitive arousal like psychosocial stress, worrying and rumination might affect sleep during later parts of the night (increased WASO), but it remains open if such cognitive arousal affects sleep only during awakenings or also during sleep itself.

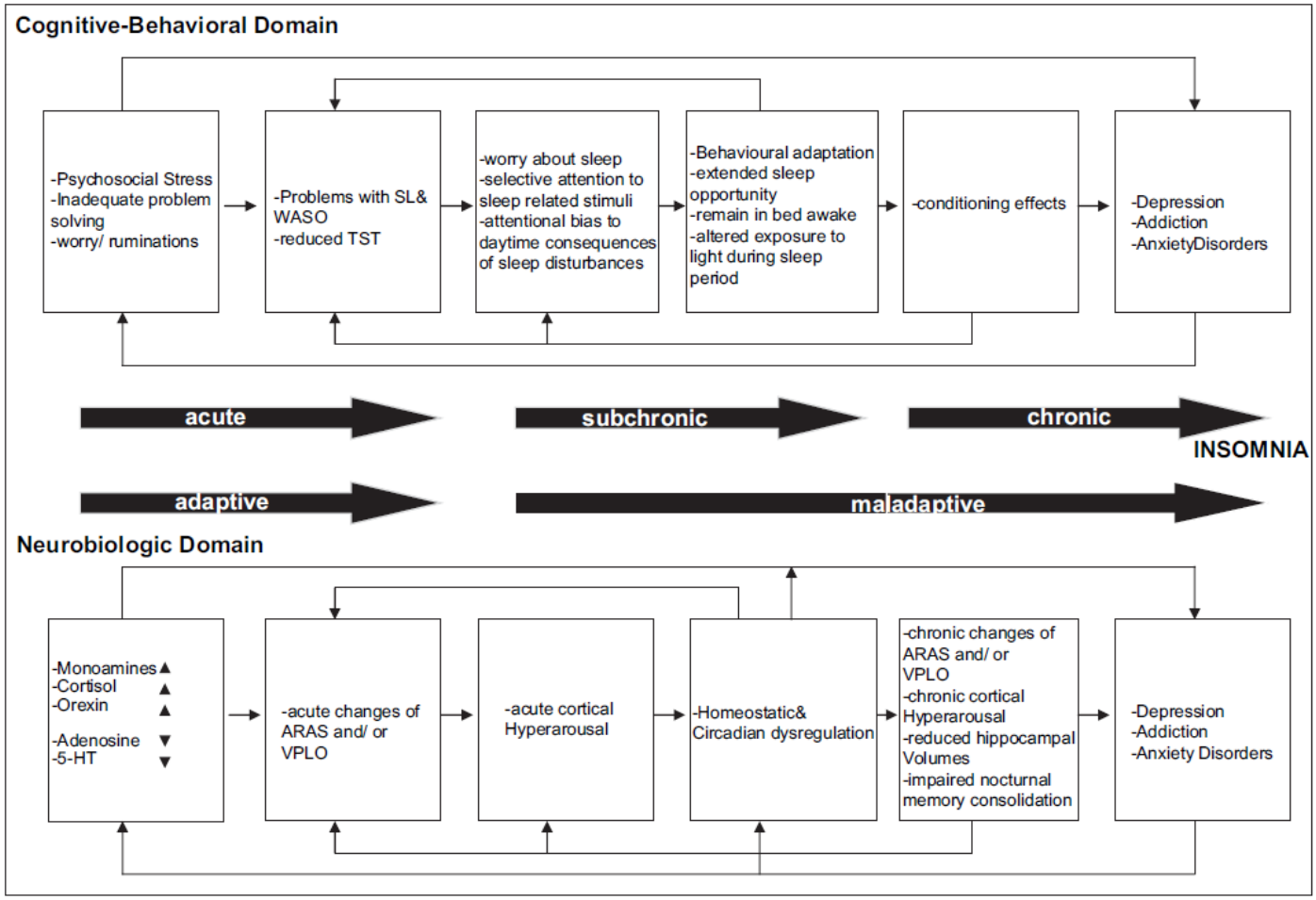

Figure 12. The hyperarousal model of insomnia (updated neurocognitive model of insomnia; Riemann et al., 2010). The most elaborate insomnia model describes the development from acute to chronic insomnia on a cognitive-behavioral and a neurobiological domain. Both domains are assumed to be interdependent and interrelated. 5-HT: Serotonin; ARAS: ascending reticular activating system; SL: sleep latency; TST: total sleep time; VLPO: ventrolateral preoptic area of the hypothalamus; WASO: wake after sleep onset; Acute insomnia: 1–90 days; subchronic: 3–6 months; chronic: > 6 months. Adapted from Riemann et al. (2010), p.21.

Taken together, these models have paved the way for contemporary cognitive-behavioral therapy of insomnia (Ferini-Strambi et al., 2021). They emerged from a view of insomnia as a physiological disorder (Spielman, Caruso, & Glovinsky, 1987) including behavioral treatment recommendations into an increasing importance of cognitive arousal and cognitions (Espie, 2002; Espie et al., 2006; Harvey, 2002; Morin, 1993; Ong et al., 2012; Perlis et al., 1997)

including neurobiological changes throughout chronification of insomnia (Riemann et al., 2010). With the aim of developing new treatment approaches and explaining the efficacy of current treatments, most models focused on factors perpetuating insomnia symptoms (Espie et al., 2006; Harvey, 2002; Morin et al., 1993; Ong et al., 2012; Perlis et al., 1997; Riemann et al., 2010) and the development from acute to chronic insomnia (Espie et al., 2006; Riemann et al., 2010). However, none of the presented models considers varying predisposing factors like aging, pregnancy or a new sleep environment, and only few address effects of circadian systems and sleep-wake homeostasis (Espie, 2002; Riemann et al., 2010). More importantly, only the psychobiological inhibition model broaches the issue on how precipitating factors may lead to a transition from good sleep to acute insomnia by starting the model with the description of good sleep (Espie, 2002).

The models presented in this chapter follow a top-down approach with physiological, cortical and/or cognitive hyperarousal leading to sleep disturbances. For the sake of completeness, bottom up-approaches, which have not been covered in detail here, assume that sleep disturbances are caused by a genetic dysfunction of the sleep-wake regulatory systems in the brainstem and thereby lead to cognitive and emotional disturbances (Cano et al., 2008; Saper et al., 2005). This idea has been integrated in the most recent hyperarousal model of insomnia, which assumes an interaction between bottom-up and top-down processes (Riemann et al., 2010).

The first purpose of this chapter was to explore available insomnia models with regard to their explanation on how cognitions are able to affect sleep. All models assume quite generally that some sort of hyperarousal, consisting of physiological, cortical and/or cognitive hyperarousal or an interaction between them, induces sleep disturbances (Espie, 2002; Espie et al., 2006; Harvey, 2002; Morin, 1993; Ong et al., 2012; Perlis et al., 1997; Riemann et al., 2010; Spielman, Caruso, & Glovinsky, 1987). Overall, the underlying assumption is that an increased arousal level is thought to be incompatible with sleep and occurs due to acute stress, or chronically due to behavioral changes (Perlis et al., 2011). In addition, all models assign cognitive of processes a central role in the perpetuation of sleep disturbances. Within this hyperarousal framework, most models either explicitly or implicitly assume that dysfunctional cognitive processes induce or fuel physiological hyperarousal and thereby lead to sleep disturbances (Morin, 1993; Ong et al., 2012; Perlis et al., 1997; Riemann et al., 2010; Spielman,

Caruso, & Glovinsky, 1987). Some models generally assume an interaction between both types of arousal (Espie, 2002; Espie et al., 2006; Harvey, 2002; Riemann et al., 2010) but they fail to provide a mechanistic explanation on how this interaction between physiological and cognitive arousal is able to affect sleep. Most importantly, the neurocognitive model (Perlis et al., 1997) and the hyperarousal model (Riemann et al., 2010) stand out from other models by assuming a direct effect of cognitive processes linked to cortical arousal (i.e., sensory processing, information processing and memory formation) on sleep itself. Moreover, the hyperarousal model (Riemann et al., 2010) assumes a direct effect of cognitive arousal like psychosocial stress, rumination and worrying on sleep parameters, but lacks to explain this relationship and a possibly assumed mediation by physiological arousal. To further understand and explain the relationship between cognitive and physiologic arousal and their effect on sleep, future studies including a systematic analysis of both measures are required.

The second purpose of this chapter was to explore, whether cognitions are active and affect sleep before sleep, during awakenings and/or during sleep itself. Half of the models assumed that cognitions are only active and affect sleep during the pre-sleep period, via or in interaction with physiological arousal (Espie, 2002; Espie et al., 2006; Ong et al., 2012; Spielman, Caruso, & Glovinsky, 1987). Two models additionally highlight the importance of cognitive processes during nocturnal awakenings (Harvey, 2002; Morin, 1993). In addition, the neurocognitive model (Perlis et al., 1997) and its successor, the hyperarousal model of insomnia (Riemann et al., 2010), assume that cognitive processes, which are associated with cortical arousal, remain active during NREM and possibly also during REM sleep. More importantly, they assume that such enhanced cognitive processes directly affect sleep itself and the subjective experience of sleep. For example, enhanced sensory processing during the pre-sleep period, during awakenings, during NREM and possibly also during REM sleep may directly interfere with sleep initiation and the maintenance of sleep. To affect the maintenance of sleep, such processes have to be active and affect sleep during sleep. In addition, enhanced memory formation of negative events such as arousals in the pre-sleep period, during awakenings and also during sleep itself, are assumed to deteriorate the subjective experience of sleep. Thereby, these models clearly state that cognitive processes that are directly linked to cortical arousal are able to directly affect sleep in the pre-sleep period, during awakenings and also during sleep itself (Perlis et al., 1997; Riemann et al., 2010). Moreover, cognitions linked to cognitive arousal

(i.e., psychosocial stress, worrying and rumination) are assumed to affect sleep throughout the night, but it remains open whether they only act during conscious waking periods or also during sleep itself (Riemann et al., 2010). Given the empirical evidence that cognitions linked to cognitive arousal have a detrimental effect on sleep (see Chapter 3), future studies and theoretical models are needed to investigate and conceptualize if and how such cognitions might also remain active during sleep and can also affect sleep itself.

The models described in this chapter explain the effect of negative cognitions on the development and maintenance of sleep disturbances, with a focus on insomnia. Thereby, the models assume that getting rid of or inhibiting negative cognitions should resolve sleep disturbances and lead to good sleep. This notion is supported for example by a study showing that an image based distraction task before sleep reduced sleep onset latency in insomnia patients by distracting the patients from negative thoughts (Harvey & Payne, 2002). However, as will be outlined in the next section, cumulating evidence suggests that positive cognitions such as hypnosis, meditation or relaxing music are able to improve sleep in healthy subjects. Such effects have not been considered in insomnia models and new approaches are needed to explain such effects.

Effects of Positive Cognitions on Sleep

Regarding positive cognitions, a series of studies from our lab have shown that listening to a hypnotic suggestion to sleep more deeply is able to prolong the amount of SWS during subsequent sleep. This was shown for young and healthy subjects in a nap (Cordi et al., 2014) and in a night design (Cordi et al., 2020), as well as for elderly subjects in a nap design (Cordi et al., 2015). However, the positive effect of the hypnotic suggestion on sleep depth was only observed for subjects, which are generally susceptible to hypnosis. In addition, listening to relaxing music before sleep increased the amount of SWS and increased SWA/beta power ratio during NREM sleep, which is a marker for more restorative sleep and is usually decreased in insomnia (Cordi et al., 2019; Hall et al., 2007; Hogan et al., 2020; Maes et al., 2014). Moreover, regular meditation practices have shown to retain a higher amount of SWS even with increasing age and prolong REM sleep (Sulekha et al., 2006). In addition, a recent meta-analysis including over 1500 subjects of randomized controlled trials of studies yielded a positive effect of a mindfulness meditation on sleep quality compared with an active control group with a medium

effect size (Rusch et al., 2019). Moreover, watching a video to trigger the autonomous sensory meridian response (ASMR) for two weeks has been shown to increase subjective sleep quality (Hardian et al., 2017). Furthermore, listening to relaxing music while falling asleep reduced the time spent in N1 and improved subjective evaluation of sleep quality in all subjects, and even increased the amount of SWS in low hypnotizable subjects (Cordi et al., 2019). In addition, writing down a to-do list for five minutes prior to sleep with tasks that have to be completed the next day has been shown to reduce the sleep onset latency compared with a group, which was journaling about already completed tasks (Scullin et al., 2018). It has also been demonstrated that positive cognitions benefit subjective complaints in insomnia patients. A recent meta-analysis suggest that acceptance and commitment therapy, which attempts to increase mindfulness, motivation, psychological flexibility and self-efficacy in an individual (Jacobsen et al., 2017), increases subjective sleep quality in primary and comorbid insomnia (Salari et al., 2020). Taken together, recent research shows that altering cognitions before sleep can have a positive effect on subsequent objective and subjective sleep using a variety of different and promising approaches.

Current insomnia models do not account for positive effects of cognitions by focusing on negative cognitions in insomnia patients. Therefore, the next chapter discusses our recent "Memories-of-Sleep" (MemoSleep) hypothesis (Rasch, 2016) offering a theoretical framework on how cognitions, positive as well as negative, are able to affect sleep. In addition, the theory offers a mechanistic approach on how cognitions remain active during ongoing sleep and thereby affect sleep throughout the whole night.

The "Memories-of-Sleep" Hypothesis – A New Approach

The MemoSleep hypothesis consists of three core assumptions (Rasch, 2016). First, it is assumed that cognitions related to sleep or wake are embodied. This means that mental representations related to sleep and wake also contain a sensorimotor body representation in addition to the semantic meaning (Figure 13a). This idea is based on theoretical accounts of grounded and embodied cognition research, which assume that semantic meaning is stored in multimodal (e.g., auditory, visual, motor, somatosensory) neuronal networks and thereby posit a mutual link between cognitive processes and body-related functions including sensorimotor systems of the brain (Barsalou, 2008; Gallese & Lakoff, 2005; Shapiro, 2014). Thereby, activation of one part of the network is thought to spread over the whole multimodal neuronal

network. For example, mental processes are thought to include simulations of bodily perceptions and actions. Studies have already shown that processing the semantic meaning of words (e.g., arm-related words like “catch”) activates associated somatosensory brain functions (e.g., cortical activation in the arm motor/premotor region; Boulenger et al., 2012; Dreyer & Pulvermüller, 2018; Moseley et al., 2012). In addition, pre-activation of motor areas has been shown to promote the processing of action words within brain areas involved in language comprehension (Mollo et al., 2016; Pulvermüller et al., 2005). A recent ERP-study from our lab already provided initial evidence that sleep- and wake-related words are associated with bodily functions (Hülsemann & Rasch, 2021). Results showed that the processing of sleep-related words was facilitated when the subjects were lying down (i.e., in a position congruent to the semantic concept of sleep) compared with standing upright (i.e., an incongruent body position to the semantic concept of sleep). Thus, similarly to pre-activation of motor networks facilitating semantic processing of action words (Mollo et al., 2016), pre-activation of a typical sleeping position that is lying down, facilitated semantic processing of sleep-related words (Hülsemann & Rasch, 2021). These results support the assumption that mental representations linked to sleep also contain related sensorimotor body representations. In addition, the model assumes that such sensorimotor bodily functions include sleep depth and wake regulatory systems.

Second, the MemoSleep hypothesis assumes that if such embodied sleep or wake memories are activated before sleep, the chance for a reactivation during sleep is increased (Figure 13b). This assumption is based on previously described memory research (see Chapter 3) showing that the beneficial effect of sleep on memory consolidation depends on repeated and spontaneous memory reactivations during sleep (Diekelmann & Born, 2010; O'Neill et al., 2010; Oudiette & Paller, 2013a; Peigneux et al., 2004; Rasch & Born, 2013; Schreiner & Staudigl, 2020) and that experimentally enhancing memory reactivations during sleep leads to an increased memory performance after sleep (Oudiette et al., 2013; Rasch & Born, 2007; Rudoy et al., 2009; Schönauer et al., 2014a). Moreover, this assumption is in accordance with stress literature, suggesting that a pertaining effect of stress on physiological activity, including sleep, is achieved via active and unconscious cognitive representations of a stressor or the stressful events (Brosschot et al., 2010, 2018).

Third, the MemoSleep hypothesis assumes that an increased reactivation of embodied sleep or wake memories during sleep will activate associated sensorimotor bodily functions and

thereby affect sleep architecture (Figure 13b). Activating sleep-related memories (e.g., “relaxation”, “calmness”) is thought to also activate associated sensorimotor areas, including sleep regulatory systems and thereby increase sleep depth. In contrast, the activation of wake-related memories (e.g., “running”, “exam”) during sleep is supposed to decrease sleep depth via activation of wake-related sensorimotor areas. The idea that cognitions remain active during sleep and thereby continuously affect sleep physiology has previously been mentioned (Brosschot, 2010). In addition, research on memory consolidation during sleep also shows that memory processes during sleep are closely linked to sleep oscillations (e.g., slow-waves and spindles).

The MemoSleep hypothesis provides a theoretical framework to explain how negative as well as positive pre-sleep cognitions are able to affect sleep in people with and without sleep disturbances: pre-sleep cognitions or more generally preoccupying cognitions are repeatedly reactivated during subsequent sleep. Due to their assumed link to sensorimotor brain areas, they are thought to directly affect sleep depth regulatory systems and thereby alter sleep depth, or even induce awakenings. For example, if someone is expecting an important job interview the next day (embodied wake memory), the model would assume an existing multimodal neuronal network of this interview across respective brain areas including mental representations about semantic, sensory, and somatosensory information as well as links to all of these representations to sensorimotor bodily functions. Semantic information could contain knowledge about previous interviews and inferred expectations about the upcoming situation. Sensory information could include visual information of the imagined situation, auditory information about an imagined voice of the interviewer and motor information about standing or moving the arms during the presentation. Somatosensory information could contain the perception of standing upright with an increased arousal, heart rate and breathing. Links of semantic, sensory, and somatosensory information to sensorimotor bodily functions could contain connections to stress regulatory systems including the autonomic nervous system and the HPA-axis.

In contrast to previous models, the MemoSleep hypothesis offers a mechanistic explanation of how cognitions are able to affect sleep during the sleep onset period but also minutes to hours after already having fallen asleep. Repeated activations of sleep- or wake-related multimodal networks including sensorimotor associations to bodily functions are thought to affect sleep regulatory systems throughout the whole night. In addition, the model is

applicable to healthy and disturbed sleep and is not restricted to effects of negative cognitions and stress on sleep but also explains effects of positive cognitions on sleep.

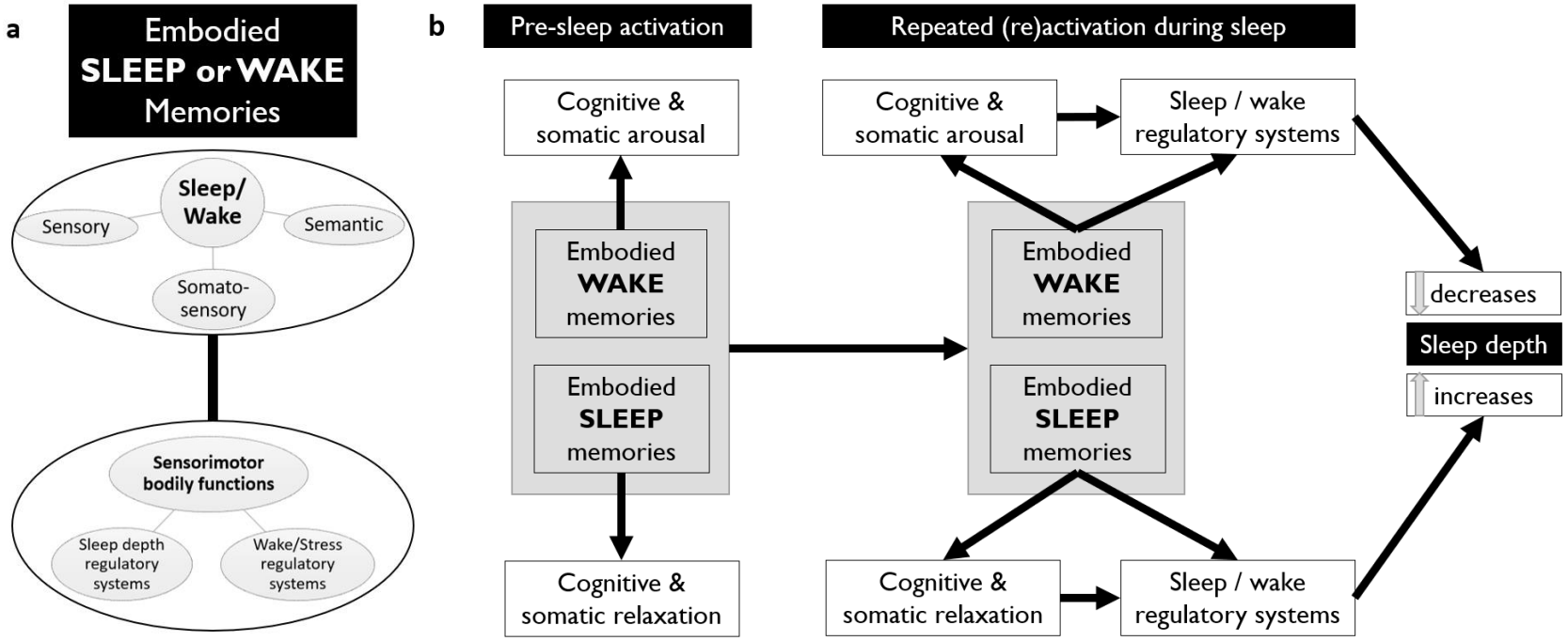

Figure 13. "Memories-of-Sleep" hypothesis. (**a**) The hypothesis assumes that sleep and wake memories are embodied that means linked to sensorimotor bodily functions including sleep depth and wake/stress regulatory systems. (**b**) The hypothesis assumes that activation of embodied wake memories leads to an increased cognitive and somatic arousal, while activation of embodied sleep memories leads to cognitive and somatic relaxation. In addition, pre-sleep activation is thought to increase the chance of reactivation of embodied sleep or wake memories during subsequent sleep. Activation of embodied wake memories during sleep leads to an increase in cognitive and somatic arousal and affect sleep/wake regulatory systems and thereby decrease sleep depth. Activation of embodied sleep memories during sleep increases cognitive and somatic relaxation and affects sleep/wake regulatory systems and thereby increases sleep depth.

Aim

As presented in the Introduction, sleep is closely linked to and affected by our thoughts and cognitions. However, more research is needed to further study the mechanisms underlying how cognitions are able to affect sleep. Understanding these mechanisms is crucial for the development of theory-driven preventive measures and treatment methods for sleep disturbances. The MemoSleep hypothesis offers a new and promising theoretical framework to explain the relationship between cognitions and sleep. Therefore, the present dissertation aims at investigating assumptions and predictions of this hypothesis to contribute to a better understanding of the underlying mechanisms of how cognitions can influence sleep.

Study 1 investigates the core mechanism of the MemoSleep hypothesis that cognitions affect sleep physiology by a repeated activation of these cognitions during sleep. With the aim to increase sleep depth, we repeatedly played relaxation-related words during NREM sleep and compared sleep to a within-subject control night, where control words were presented. Based on the MemoSleep hypothesis, we assumed that the presentation of relaxing words during sleep activates a pre-existing relaxation concept and related sensorimotor bodily functions and thereby affects sleep physiology. Therefore, we hypothesized that the presentation of relaxing words during sleep would increase SWS, SWA, slow-wave density and event-related SWA.

Study 2 of the present dissertation investigates the effect of anticipating a psychosocial stressor after sleep (i.e., pre-sleep worries), in comparison with experiencing the same psychosocial stressor before sleep. In accordance with the extended perseverative cognition hypothesis (Figure 3) and the MemoSleep hypothesis (Figure 13), we hypothesized that anticipating a stressor would create unconscious representations of the stressor, which are repeatedly activated during sleep and affect sleep physiology by their association to sensorimotor bodily functions. In a first step, we therefore aimed to replicate the negative effects of an anticipated stressor on sleep physiology and expected similar effects in comparison with another group experiencing the same psychosocial stressor before sleep. Second, we hypothesized that, based on previous findings, experiencing a stressor before sleep mainly affects early sleep. Moreover, anticipating the stressor to occur after sleep was assumed to affect sleep also during late sleep that means close to the stressor. To examine such dynamic changes, we analyzed the progression of EEG power and sleep oscillations (slow-waves, spindles) across sleep.

Study 3 examines the sleep depth promoting effect of a positive pre-sleep cognition on sleep physiology. Previous results showed that listening to a hypnotic suggestion to sleep more deeply before sleep increases the amount of SWS in high hypnotizable subjects. Despite literature suggesting an important role of SWS in memory consolidation, these increases in SWS left memory performance unaffected. Therefore, we performed a fine-grained analysis of sleep oscillations (slow-waves, spindles and their coupling) related to memory processes during sleep. Based on literature suggesting that it is not the sleep oscillations per se but rather their interplay and precise timing of them supports memory consolidation, we expected to find that the hypnotic suggestion promotes slow-waves, leaves spindles unaffected and decreases coupling between slow-waves and spindles.

Study 1:
Exposure to Relaxing Words During Sleep Promotes Slow-wave Sleep and Subjective Sleep Quality

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Abstract

Our thoughts alter our sleep, but the underlying mechanisms are still unknown. We propose that mental processes are active to a greater or lesser extent during sleep and that this degree of activation affects our sleep depth. We examined this notion by activating the concept of "relaxation" during sleep using relaxation-related words in 50 healthy participants. In support of our hypothesis, playing relaxing words during non-rapid eye movement sleep extended the time spent in slow-wave sleep, increased power in the slow-wave activity band after the word cue, and abolished an asymmetrical sleep depth during the word presentation period. In addition, participants reported a higher sleep quality and elevated subjective alertness. Our results support the notion that the activation of mental concepts during sleep can influence sleep depth. They provide a basis for interventions using targeted activations to promote sleep depth and sleep quality to foster well-being and health.

Keywords: SWS, sleep quality, relaxation, cognition, slow-waves, auditory, asymmetry

Statement of Significance

Sleep, in particular slow-wave sleep (SWS), is important for our physical and mental health. Therefore, theories and interventions on how to non-pharmacologically extend SWS are highly requested. Here, we propose and test the theory that mental concepts activated during sleep can modulate sleep depth. In support of our theory, presentation of words related to the concept of relaxation during sleep significantly extended the time spent in SWS and increased subjective sleep quality. Our results show that the semantic meaning of words presented during sleep is capable of affecting sleep physiology, SWS maintenance and the subjective evaluation of sleep quality. Additionally, our results set the stage for the development of theory-driven, non-pharmacological interventions to improve sleep in people with sleeping difficulties.

Introduction

Sleep, in particular deep sleep, is important for our mental (Hita-Yañez et al., 2013) and physical health (Javaheri et al., 2018) as well as numerous vital functions such as the immune (Besedovsky et al., 2012) and cardiovascular systems (van Cauter et al., 2008). The amount of deep sleep, referred to as slow-wave sleep (SWS), depends on prior wakefulness (Borbély et al., 2016) and declines with age (Leirer et al., 2011). The depth of sleep is also characterized via slow-wave activity (SWA; EEG power in the 0.5–4.5 Hz band), which has been shown to be a valid marker of global sleep pressure (Borbély et al., 2016) as well as local sleep need, possibly linked to synaptic downscaling (Huber et al., 2004; Siclari & Tononi, 2017; Tononi & Cirelli, 2006).

In addition to neurophysiological mechanisms, cognitive processes can also modulate the depth of sleep. For example, the perception of an unfamiliar sleep environment (known as the "first night effect") typically reduces the amount of SWS (Le Bon et al., 2000). Moreover, unfamiliar environments are suspected to decrease SWA specifically in the left brain hemisphere, resulting in higher hemispheric differences (Tamaki et al., 2016). Similarly, ruminating about a failure experience and bedtime worries about a difficult next day or about an early awakening, negatively affected SWS and SWS latency (Kecklund & Akerstedt, 2004; Vandekerckhove et al., 2011). Conversely, inducing positive thoughts and relaxation using music or hypnotic suggestions increases the amount of SWS and SWA during daytime naps and nighttime sleep (Cordi et al., 2014; Cordi et al., 2019; Cordi et al., 2020). However, it is still unknown how cognitive processes which are typically initiated before sleep affect sleep depth, minutes to hours after having fallen asleep.

Here, we propose a mechanism that is based on the activation of embodied concepts during sleep: we assume that the degree of activation of specific cognitive concepts varies during sleep, and that activated concepts are capable of influencing sleep depth depending on their semantic meaning. For example, if the concept of a new and potentially dangerous sleep environment is activated, it remains active during ongoing sleep and thereby decreases sleep depth. Conversely, activation of mental concepts related to "relaxation" and "sleep" are thought to promote sleep depth. This prediction assumes that mental concepts are closely linked to their related bodily functions. According to the theoretical accounts of embodied or grounded cognition, semantic meaning is stored in multimodal (e.g., auditory, visual, motor,

somatosensory) neuronal networks (Barsalou, 2008; Shapiro, 2014). For instance, processing concrete words (e.g., arm-related words like ‘catch’) led to cortical activation in the arm motor/premotor region (Boulenger et al., 2012). Similar results were found for processing words related to abstract emotion (e.g., ‘love’) and abstract cognition (e.g., ‘thought’) involving hand and face motor cortices (Dreyer & Pulvermüller, 2018; Moseley et al., 2012). Thus, the processing of words directly activates associated somatosensory brain functions.

The current study provides an initial empirical test for the previously explained mechanism. We predicted that the activation of concepts related to “relaxation” during sleep would increase the amount of deep sleep. To activate concepts of “relaxation” during sleep, we repeatedly presented words related to relaxation during non-rapid eye movement sleep (NREM, sleep stage N2 and SWS). Previous research suggests that our brain can process the meaning of words and activate multimodal representations during sleep (Blume et al., 2018; Kouider et al., 2014; Paller et al., 2020; Schreiner & Rasch, 2017). In our study, 50 healthy participants slept in the sleep lab for two experimental nights, in a counterbalanced order (see Figure 1a for an overview of the procedure). In one night, we repeatedly presented relaxing words such as “relax” and “easy” during NREM sleep. In the other experimental night, neutral words were presented (e.g., “produce,” “materials”). Based on the proposed mechanisms explaining how cognitive processes may affect sleep depth, we predicted that the presentation of relaxing words would extend SWS and increase SWA as well as slow-wave density during the time window of word presentation, compared with the control condition. In addition, we hypothesized that event-related responses to the presentation of relaxing words would induce more event-related power in the slow-wave band compared with control words. To control for possible differences in auditory properties between relaxing and control words, a subset of relaxing and control words was also played in reverse during sleep (see Figure 1a; Parise et al., 2011; Strand et al., 2008). Therefore, the main research question comprised increases in SWS, SWA, slow-wave density and event-related SWA when relaxing words were presented. We further explored possible effects on other sleep stages, hemispheric differences, subjective sleep quality, mood, vigilance and memory consolidation.

In line with our hypotheses, we found an increased amount of SWS in the period of relaxing word presentation during sleep compared with the period of control word presentation. Furthermore, the increase in SWS induced by relaxing words translated into an increase in

subjective sleep quality and alertness reported by the participants. While global SWA and slow-wave density were not altered, we observed a decreased asymmetry of SWA and slow-wave density during the presentation of relaxing words. Finally, event-related processing of relaxing words showed a significantly higher power increase in the SWA band at about 2–3.5 s after stimulus onset.

Materials and Methods

Participants

The experiment followed a within-subject cross-over design to compare the effects of the presentation of relaxing or control words during sleep on sleep depth. Fifty-five healthy German-speaking subjects participated in the experiment. Five participants had to be excluded due to insufficient sleep in at least one of the experimental nights (2) or insufficient data quality (3). The final sample consisted of 50 young participants (39 females, mean age = 22.20 ± 3.53 y [M±SD], age range 18–33 y).

None of the subjects were shift workers nor had they been on any intercontinental flights six weeks prior to the experiment. They neither took any sleep influencing medication nor reported any neurological, psychiatric or sleep-related disorders. Subjects confirmed that no surgical interventions had been performed within the three months prior to the experiment, and they did not suffer from impaired hearing. All participants were briefed to wake up at 08.00 h, to refrain from a midday nap as well as to avoid drinking alcohol or caffeine on experimental days. Subjects were paid 130 CHF for participating in all three sessions. The study was approved by the ethics committee of the Canton Vaud (115/15). Participants signed an informed consent after an experimenter explained the study procedure and possible consequences.

Design and Procedure

Subjects participated in three sleep sessions. After an adaptation night, participants slept in the laboratory for two sessions, while polysomnographic data (electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG)) were recorded. Participants arrived between 08.30 p.m. and 09.00 p.m. in the sleep laboratory. Both experimental sessions took place on the same weekday, spaced one week apart and participants filled out questionnaires and performed in memory tasks in both sessions. During one experimental session, relaxing words were presented during non-rapid eye movement sleep (NREM sleep, sleep stage N2 and SWS).

During the other experimental session, control words were presented during NREM sleep. The order of condition was balanced across participants according to a within-subject cross-over design. The word presentation protocol was conducted by an experimenter who was blind to the experimental condition. After sleep, psychomotor vigilance, sleep quality and memory recall were assessed.

In addition to the within-subject comparison between relaxing words and control words presented during sleep, the familiarity of the words was varied between subjects. One group of participants (n = 37) listened to two texts before sleep. One included the relaxing words, and the other the control words. The participants listened to both texts before both nights. Another group of subjects (n = 13) did not listen to the two texts before sleep in any of the two nights. As the effects did not differ between the two groups, we decided to merge the results of both groups.

Subjects completed a paired-associate learning task and two verbal fluency tasks before and after sleep. After waking up, subjects performed a psychomotor vigilance test for 10 min to overcome sleep inertia and assess alertness (see supplementary materials and methods for a detailed description of the three memory tasks and the vigilance test).

Selection of Words

Words were selected and clipped from two texts that we previously used to test the effect of pre-sleep listening on later SWS (Cordi et al., 2014; Cordi et al., 2015; Cordi et al., 2020), and they are available on our homepage (https://www3.unifr.ch/psycho/en/research/biopsy/). Both texts were spoken by the same reader. The text including the relaxing words was spoken in a soft, slow and calm voice, while the control text was spoken in a normal voice and speed. The relaxing text includes a metaphor of a fish swimming deeper and deeper into the sea. It contains many relaxing and reassuring words. The control text comprises a documentation about natural mineral deposits. We selected 40 representative words (see supplementary Table S3, for a complete list of words) from both texts and clipped them from the relaxing text (e.g., to sleep, safe, to relax, fish) and the control text (e.g., surface, deposits, strong, to produce). In a separate study, we assessed whether the words from the two semantic categories (relax vs. control) were directly associated with phonetic differences (independent of their semantic content and spoken in a neutral voice) in non-native German speakers. Twenty-four French-speaking young participants took part in this additional study. Subjects rated all relaxing and control words on their level of relaxation on a nine-point Likert scale from 1 = “stimulating” to 9 = “relaxing”.

They further indicated their level of German language skill, again on a nine-point Likert scale from 1 = “no knowledge” to 9 = “native speaker”. Relaxing and control words were rated comparably relaxing after controlling for the level of German language skill ($F_{1,22} = 0.21$, $p > .60$, $\eta_p = .01$), indicating that our two semantic word categories were not confounded by phonetic differences.

Word Presentation During Sleep

As the amount of SWS usually peaks within the first sleep cycle, we started the presentation of the words in the second sleep cycle to ensure sufficient space for a reliable SWS enhancement. An experimenter started to determine sleep stages according to the criteria of the America Academy of Sleep Medicine (Iber et al., 2007) with an online sleep scoring setup. Prior to the first experimental night, sleep data of the adaptation night were scanned for each participant to obtain an overview of individual sleep oscillations and architecture. The first sleep cycle was considered complete when a REM episode occurred, and finished, between 60-120 minutes after sleep onset. After the first sleep cycle, words were presented with E-Prime (2.0 SP2, Psychology Software Tools, Pittsburgh, PA) during NREM sleep via loudspeakers placed on a nightstand (distance between speaker and mid of pillow: 85 cm) with an average duration of 1.03 ± 0.27 s ($M \pm SD$), and a sound pressure level of 51.34 ± 2.75 dB (see supplementary Table S4 for cue characteristics). The presentations of the cues were separated by a random interstimulus interval between 7–9 s. If no REM episode was detected, cueing was started no later than 120 min after sleep onset. An experimenter monitored, and manually interrupted, stimulation whenever online polysomnography indicated wake, REM sleep, arousals or movements.

In addition to the main effect of playing cues during sleep on SWS, we aimed to examine event-related responses in the time and frequency domain of the cues. To control for basic auditory properties of words (i.e., power spectrum, volume level etc.), we reversed four relaxing words (easy, to relax, dolphin, sea) and four control words (to produce, magmas, lead, phase; Parise et al., 2011; Strand et al., 2008). In German, these words consist of different numbers of syllables, which were balanced between conditions (one syllable: “Meer” vs. “Blei”; two syllables: “Delphin” and “einfach” vs. “Magmen” and “Phase”; three syllables: “ausruhen” vs. “erzeugen”). In each night, either relaxing or control words were presented combined with all eight reverse cues leading to a total number of 48 different cues. Cues were presented in blocks

of six words containing five randomly selected relaxing or control words and one reversed cue at a random position. This procedure was repeated eight times until all cues had been played once and subsequently started from the beginning. Overall, all cues were presented 15 times in each night resulting in a total number of 720 cues. Blocks were presented subsequently without an additional time interval. This led to an overall cueing time of 110.3 min in the relax night and 106.2 min in the control night.

Questionnaires

Subjective sleep quality was measured in the morning with the sleep quality subscale of the SF-A/R (Görtelmeyer, 2011). The value of Cronbach's alpha related to the subscale is .89 in healthy subjects. The scale includes four indices indicating difficulties initiating sleep (1 item), difficulty maintaining sleep (2 items), early awakening with inability to return to sleep (1 item), and general sleep characteristics (6 items). Values between 1–5 indicate if characteristics of good sleep quality are absent (1) or strongly distinct (5). We further analyzed the following items (from 1 = not at all to 5 = very much) of the question "*How did you sleep last night?*": deep, good, ample, relaxed, uniformly, undisturbed and restless. Values are reported as change in % in the relax night relative to the control night (set to 100%).

Mood was assessed before and after sleep using the Multidimensional Mood Questionnaire (MDBF, short form A) (Steyer et al., 1997). Subjects rated their mood state on 12 items of the question "*In this moment I feel …*" on a five-point Likert scale (1 = not at all, 5 = very much). A total score, and three bipolar mood scales, were calculated (good – bad mood, alertness – tiredness, calmness – restlessness). Cronbach's alpha of the three scales ranges between 0.78–0.86, and is 0.92 for the total score (Hinz et al., 2012). Given are the morning ratings relative to the evening ratings (set to 100%). Similar to the SF-A/R analysis, we analyzed the change in % in the relax night relative to the control night (set to 100%).

At the end of the experiment, subjects were asked about the aim of the study in an open question format. In addition, subjects rated the four relaxing and four control words, which were also played in reverse, on their association to "sleep" on a five-point Likert scale (1 = not at all, 5 = very much).

Polysomnographic Recording

Electroencephalographic (EEG) data were recorded using a 32-channel Easycap Net (Easycap GmbH, Herrsching) with a BrainAmp amplifier (Brain Products, Gilching, Germany),

at a sampling rate of 500 Hz, FCz as a physical reference and AF3 as a ground electrode. Two additional electrodes were placed laterally to the outer canthi of the left and right eye to collect electrooculographic (EOG) data. Three bipolar chin electrodes collected electromyogram (EMG) data, and two bipolar electrodes collected electrocardiogram data. Impedances were kept below 10 kΩ for EEG, EOG and EMG electrodes.

For sleep scoring, data were re-referenced against contralateral mastoids, and standard filter settings suggested by the AASM (Iber et al., 2007) were applied (e.g., EEG 0.3–35Hz) with an additional notch filter (50 Hz) to reduce noise if necessary. All scorers were blind to the experimental condition. Sleep was scored manually according to the rules provided by the AASM as well as by a central scoring facility (Anderer et al., 2010), which used a validated scoring algorithm with visual quality control. The overall agreement between the two scorings was of 72.97%. A third expert compared both scorings and determined the sleep stage in the case of a disagreement.

Preprocessing and Artifact Rejection

EEG data preprocessing was conducted using BrainVision Analyzer software (2.2; Brain Products, Gilching, Germany). Data were filtered using a high- (0.1 Hz) and low-pass (40 Hz) filter with an additional notch filter at 50 Hz and re-referenced to averaged mastoids.

Power Analysis

For the power analysis, data were segmented in 30 s epochs of NREM sleep based on sleep scoring results. Afterwards, data were segmented into equally sized segments of 2048 data points (4s) with 102 points overlapping. Artifacts were rejected automatically(Ackermann et al., 2015) and segments had to pass the following three criteria to be kept: (1) the maximum difference in EMG activity < 150 µV in both EMG channels, (2) maximum voltage step in all EEG channels < 50 µV/ms, (3) maximum difference in EEG activity < 500 µV in all EEG channels. The number of removed segments were manually checked for each artifact rejection step. Based on the number of removed segments, artifact heavy EMG and EEG channels were identified and dropped (EMG) or interpolated (EEG) if necessary.

We used a fast Fourier transformation (10% Hanning Window, 0.25 Hz resolution) to investigate power differences during sleep. Mean power values (μV^2) of each channel were exported for SWA (0.5–4.5 Hz) during SWS. Data were further analysed using Rstudio version 1.1.456 (R Core Team, 2018). Power values exceeding mean activity of all channels by 4

standard deviations were replaced by the mean power separately for each subject. Next, power was averaged over six regions of interest based on topography (see supplementary Figure S1).

Slow-wave Detection

Slow-wave detection was applied on artifact rejected data from the power analyses in NREM sleep and utilizing a Matlab-based slow-wave-analysis toolbox (Mensen et al., 2016). Detection followed 4 key stages: first, four reference waves were computed over four regions arranged in a square by calculating the mean activity over 4 electrodes in the same clusters used for power analysis (frontal LR, parietal LR, see supplementary Figure S1). Reference waves were filtered between 0.2 and 4 Hz (2^{nd} order Chebyshev). Second, slow-waves were detected utilizing a local minima approach. As the absolute amplitude of the EEG is influenced by several factors, a relative amplitude criterion (5 standard deviations from the mean negativity) was used to detect local minima. The nearest local maxima served as start and end points of the slow-wave. Only slow-waves with a duration between 0.25–1.25 s were kept for further analyses. Each of the 4 reference waves were initially examined independently. Afterwards, potential slow-waves were analyzed if a slow-wave was also found within the wavelength of another reference wave. Now, unique slow-waves were found in each reference wave of the four regions. The following parameters were calculated for all detected slow-waves: amplitude (peak-to-peak amplitude in μV), negative slope (between local minima and prior local maxima in μV/s) and positive slope (between local minima and subsequent local maxima in μV/s). In addition, slow-wave density was computed as the number of slow-waves per minute. For further analyses, we focused on slow-waves detected in SWS, which were found only in either the left or the right frontal reference wave.

Event-related Analyses

For analyses of event-related potentials (ERP) and changes in event-related oscillatory power (time-frequency analyses), data were segmented into trials of 14 s based on cue markers starting 7 s before the stimulus onset and followed by the same automatic artifact rejection procedure used in the power analysis. In the night where relaxing words were played, event-related responses to the four relaxing words (easy, to relax, dolphin, sea), as well as their counterparts played in reverse, were extracted. In the night where the control words were played, responses to the four control words (to produce, magmas, lead, phase) and their reverse counterparts were analyzed. We used the Fieldtrip toolbox (Oostenveld et al., 2011) to compute

event-related potentials and time-frequency analysis. Baseline normalization was applied with a baseline period of –1 to 0 s before the stimulus onset. Next, data were averaged per subject and per condition, and grand averages of all conditions were computed. For the time-frequency analysis, a continuous wavelet transformation (complex Morlet wavelets, 5 cycles) was performed on single trials to obtain oscillatory power of frequencies between 0.5–20 Hz in steps of 0.5 Hz and 10 ms.

In the first analysis, we compared relaxing words with reverse relaxing words. Second, we compared control words with reverse control words. Lastly, we computed the interaction by contrasting relax (– reverse relax) with control (– reverse control) words. As we were interested in differences in sleep depth after the cue onset, we focused our analysis on slow-wave activity and averaged over the SWA band (1–4.5 Hz) in the time window 0 to 4.5 s after cue onset across all channels.

Statistical Analysis

Statistical analyses were performed using Rstudio version 1.1.456 (R Core Team, 2018). Data are presented as means ± standard error. We analyzed sleep data (SWS, SWA, slow-waves) using a repeated-measures analysis of variance (ANOVA) containing the within-subject factors cueing (control, relax) and time (before cueing, during cueing). To explore hemispheric differences, we added the within-subject factor hemisphere (left, right) if applicable. Post-hoc tests for significant interactions and main effects comprised uncorrected paired and unpaired Student's *t*-tests. Exploratory analysis on other sleep stages, differences between hemispheres, subjective sleep quality, mood, vigilance and memory consolidation were not corrected for multiple comparisons. In case of statistically significant results, effect sizes are reported with partial eta squared (η_p) for main effects and interactions and Cohen's *d* for t-tests. Associations were explored using Pearson product-moment correlations. The level of significance was set at $p < .05$.

Results of event-related potentials and time-frequency analysis were compared using cluster-based permutation tests for dependent samples as implemented in the FieldTrip toolbox (Oostenveld et al., 2011). The maximum sum of t-values within every cluster served as the cluster-level statistic. Cluster-level alpha was set to .05. To consider the multiple comparisons problem, the cluster-level statistic was calculated for each of 1000 randomly drawn data partitions. The proportion of random partitions exceeding the actually observed test statistic is

calculated, resulting in a Monte Carlo *p*-value. The alpha level was set to .05 and corrected for two-sided testing. Alpha level was distributed over both tails by multiplying the probability with a factor of two, prior to thresholding it with the alpha level.

Results

After an adaptation night, 50 healthy subjects slept in the sleep laboratory for two experimental nights (8 h time-in-bed) according to a within-subject cross-over design (see Figure 1a, for an overview of the procedure). Both nights occurred on the same weekday and were spaced one week apart. During one experimental night, relaxing words (e.g., "relax", "easy") were presented during NREM sleep (sleep stage N2 and SWS) to promote SWS. During the other experimental night, control words were presented (e.g., "produce," "materials"). Additionally, relaxing and control words played in reverse were included to control for basic auditory properties of the words (i.e., power spectrum and volume level). Words were presented during NREM sleep starting with the second sleep cycle (at the latest 120 min after sleep onset), as the amount of SWS peaks within the first sleep cycle. Before and after sleep, subjects completed a mood questionnaire. In the morning, a sleep quality questionnaire was conducted.

Playing Relaxing Words During Sleep Promotes SWS and Subjective Sleep Quality

As predicted, playing relaxing words during NREM sleep increased the duration of slow-wave sleep (SWS) compared with the night with control words (see Table 1). This increase was restricted to the time window of word presentation (cueing period). During this cueing period, the duration of SWS was significantly higher in the night with relaxing words (54.81 ± 3.02 min) compared with the night with control words (48.32 ± 3.57 min; $t_{49} = –2.19$, $p = .033$, $d = 0.31$; Figure 1b). The duration of the cueing period did not differ between both nights (relax: 172.73 ± 3.71 min vs. control: 178.68 ± 6.58 min, respectively, $t_{49} = 1.01$, $p > .30$). In the before-cueing period (i.e., the first sleep cycle where no words were played), participants showed comparable amounts of SWS (relax: 48.58 ± 2.91 min, control: 47.92 ± 2.25 min, $t_{49} = –0.28$, $p > .70$). When controlling for the amount of SWS in the before-cueing period (SWS in min set to 100%), playing relaxing words changed the amount of SWS up to 132.49 ± 12.23% relative to the before-cueing period, whereas this change was significantly lower for control words (107.28 ± 9.03%; $t_{48} = –2.18$, $p = .034$, $d = 0.31$; Figure 1c). Note that sleep time in the before-cueing period was shorter than in the cueing period, resulting in slightly higher SWS durations (in

minutes) during the cueing period. One subject had to be excluded in this analysis due to an increase in SWS larger than 3 SD of the mean (1480.00 %) in the night where relaxing words were played. Descriptively, in the relax condition participants spent less time awake and less time in stages N1, N2 and REM sleep during the cueing period than in the control condition (see Table 1). However, none of these changes in sleep architecture were altered significantly (all $p > .14$).

The effect size related to playing relaxing words on increasing SWS duration, was in the small to medium range and restricted to the cueing period. The total amount of SWS during the entire night was also comparable between both nights (relax: 136.21 ± 6.68 min vs. control 130.99 ± 7.39 min, $t_{49} = –1.24$, $p > .20$, see supplementary Table S1 for sleep architecture across the entire night). However, listening to relaxing words significantly improved subjective sleep quality: participants reported an increased sleep quality the morning after having listened to relaxing words (110.01 ± 4.78%) relative to the night presenting control words (set to 100%; $t_{48} = 2.10$, $p = .041$, $d = 0.30$, Figure 1d). Furthermore, participants reported sleeping significantly deeper (121.53 ± 8.83%), better (113.10 ± 6.05%) and having an ample amount of sleep (118.20 ± 7.07%) in the night with relaxing words compared with the control night (all $p < .035$, all $d > 0.31$, see Table 2). At the end of the experiment, subjects were asked about the aim of the study. Only one participant noted a difference between the nights, i.e. that no words were played in one night (which was not the case). None of the participants mentioned that different word types were played during sleep which could be related to the aim of the study. We therefore assume that subjects were not aware that different types of words were presented during sleep. Interestingly, the change in subjective sleep quality from the control to the relax night positively correlated with the change in SWS during cueing from the control to the relax night, although the coefficient only reached a statistical trend ($r_{47} = .26$, $p = .070$). A significant and positive correlation of these differences was found for the subjective rating of sleeping an ample amount of time ($r_{47} = .32$, $p = .025$), while no associations were found between the change in SWS and the change in ratings of sleeping deeper and better ($p > .70$). Yet, these correlations are only exploratory and would not survive a correction for multiple comparisons. Finally, participants reported feeling more alert in the morning compared with the prior evening in the relax night relative to the control night (115.31 ± 6.39%; $t_{49} = 2.40$, $p = .020$, $d = 0.34$, Figure 1d, see Table 2 for other scales of the mood questionnaire). Moreover, the subjective association strength of

relaxing words with "sleep" was increased (2.82 ± 0.13) compared with the association strength of control words to "sleep" (1.84 ± 0.11; $t_{49} = 8.22$, $p < .001$, $d = 1.16$). Interestingly, the difference in association strength of the relaxing and control words correlated positively with the change in SWS in the during cueing period from the control to the relax night as a statistical trend ($r_{48} = .25$, $p = .082$).

On the behavioral level, the presentation of relaxing words during sleep did neither affect vigilance after sleep (as measured by the psychomotor vigilance test) nor memory consolidation during sleep (as measured by a word-pair associate learning task and two verbal fluency tasks, see supplementary Table S2).

Table 1. Sleep parameters in the before- and during-cueing period

Parameter	Control night before cueing	Relax night before cueing	Control night during cueing	Relax night during cueing
SPT	80.71 ± 2.25	79.13 ± 2.41	178.68 ± 6.58	172.73 ± 3.71
WASO	1.00 ± 0.30	1.22 ± 0.57	6.96 ± 1.75	4.74 ± 0.93
N1	6.84 ± 0.69	6.45 ± 0.73	11.12 ± 1.71	9.01 ± 1.09
N2	20.90 ± 1.34	19.33 ± 1.32	79.63 ± 4.51	75.51 ± 3.57
SWS	47.92 ± 2.36	48.58 ± 2.91	**48.32 ± 3.57**	**54.81 ± 3.02***
REM	4.05 ± 0.74	3.55 ± 0.69	32.65 ± 2.51	28.66 ± 1.71
Sleep efficiency	80.19 ± 2.08	81.39 ± 2.03	96.87 ± 0.61	97.49 ± 0.43

Note. Means in minutes ± SEM. Sleep period time (SPT) including wake after sleep onset (WASO), sleep stage N1 and N2, slow-wave sleep (SWS), rapid eye movement (REM) sleep and sleep efficiency (time asleep / time-in-bed * 100). * indicates significant differences between control and relax night with $p < .05$.

Table 2. Subjective sleep quality and mood ratings

Parameter	Control night	Relax night	% change with control night set to 100%	*p*-values
Sleep quality	3.18 ± 0.12	3.29 ± 0.10	**110.01 ± 4.78***	**.041***
deep	3.27 ± 0.16	3.43 ± 0.13	**121.53 ± 8.83***	**.019***
good	3.43 ± 0.15	3.55 ± 0.12	**113.10 ± 6.05***	**.035***
ample	2.94 ± 0.14	3.20 ± 0.16	**118.20 ± 7.07***	**.013***
relaxed	3.47 ± 0.13	3.57 ± 0.11	110.27 ± 5.29	.06
uniformly	2.98 ± 0.15	3.04 ± 0.14	114.90 ± 8.32	.08
undisturbed	3.53 ± 0.17	3.22 ± 0.15	99.90 ± 5.85	.99
restless	3.55 ± 0.16	3.73 ± 0.14	105.54 ± 8.60	.52
Mood (morning / evening)	96.26 ± 2.53	98.13 ± 2.00	103.91 ± 2.25	.09
good – bad mood	93.61 ± 2.48	94.32 ± 1.89	103.37 ± 2.58	.20
alertness – tiredness	100.45 ± 5.13	106.59 ± 4.64	**115.31 ± 6.39***	**.020***
calmness – restlessness	98.65 ± 2.45	100.07 ± 4.71	103.99 ± 3.36	.24

Note. Sleep quality was assessed with the subscale "sleep quality" and single items from the SF-A/R (Schlaffragebogen A) questionnaire. Here provided are the mean values ± SEM of ratings in the morning from control and relax night. Mood was assessed using the Multidimensional Mood Questionnaire. Given are the morning ratings relative to evening ratings (set to 100%) from the control and relax night. The fourth column displays the change in % of scores in the relax night relative to the control night (set to 100%). Right column displays *p*-values of one sample *t*-tests of these scores against $\mu = 100$ with $p < .05$ (*).

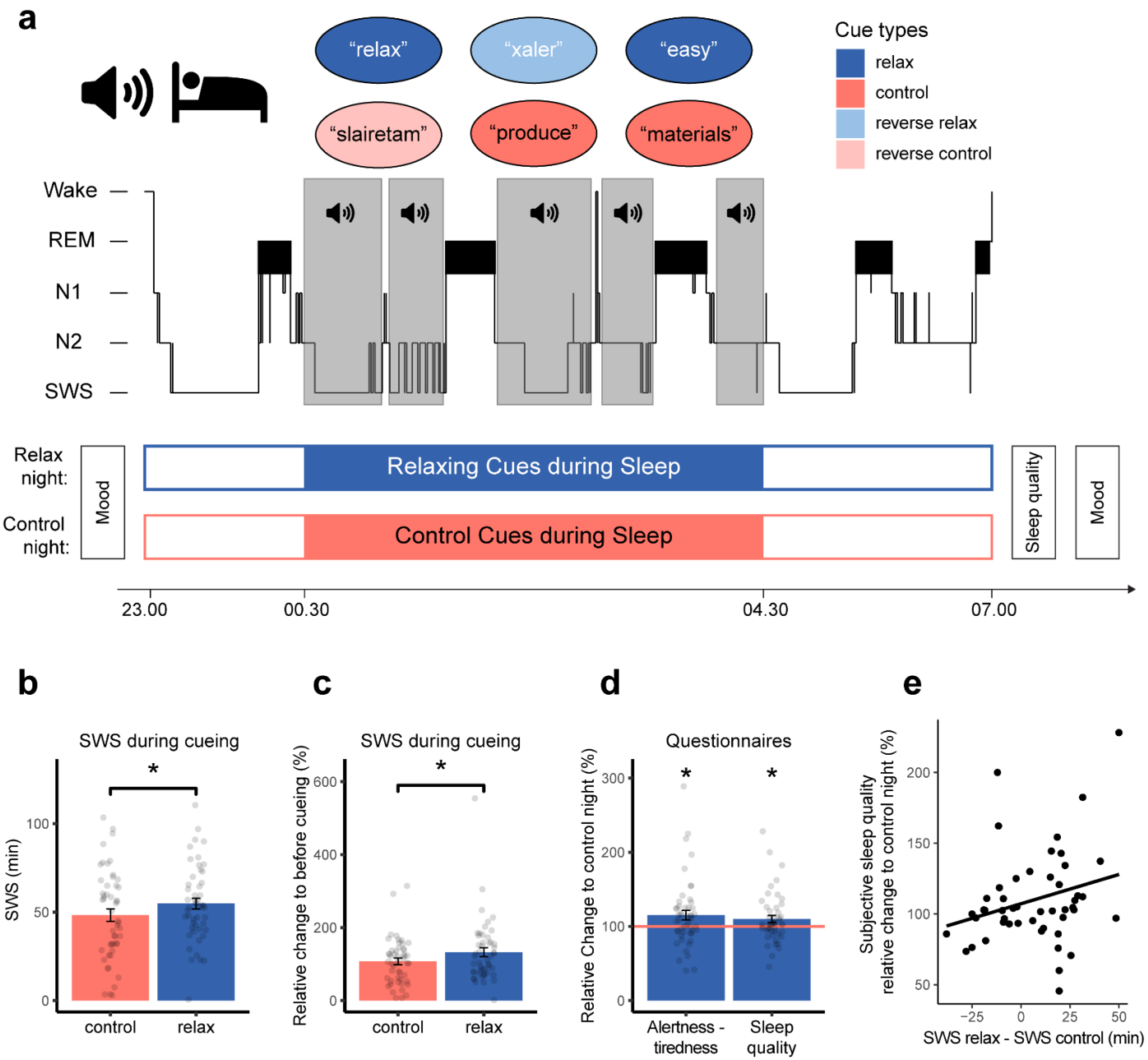

Figure 1. Experimental procedure and sleep results. (**a**) Fifty healthy participants either listened to relaxing words (relax night, blue) or control words (control night, red) during non-rapid eye movement sleep, according to a within-subject cross-over design. During the relax night, 40 different relaxing words (e.g., relax, easy) were played in blocks of six words. Each block contained five randomly selected relaxing words (upper circles, blue) and one reverse word (upper circles, light blue). During the control night, the blocks contained five control words (lower circles, red) plus one reverse word (lower circles, light red). When all words were played

(i.e., after 8 blocks), the procedure was repeated 15 times, resulting in a total number of 720 word presentations per night. An experimenter monitored the word presentations during sleep and started cueing after the first sleep cycle. Before and after sleep, subjects completed a mood questionnaire. In the morning, a sleep quality questionnaire was conducted. (**b**) Playing relaxing words (blue bar) significantly increased the amount of slow-wave sleep (SWS) in the during-curing period compared with the control night (red bar). (**c**) Playing relaxing words significantly increased the change of SWS sleep from the before- to during-cueing period compared with the control night. One participant was excluded due to high values in the relax night. (**d**) Here provided are the scores in the relax night relative to the control night (set to 100%, red horizontal line). Left bar: Subjective alertness scores were computed as the change from before sleep (set to 100%) to after sleep. Playing relaxing words during sleep significantly increased the change in subjective alertness compared with the control night. Right bar: Playing relaxing words during sleep significantly increased subjective sleep quality compared with the control night. One participant was excluded due to missing data. (**e**) The change in SWS from the control to the relax night in the during-cueing period correlated with a statistical trend with the change in subjective sleep quality from the control to the relax night ($r_{47} = .26$, $p = .070$). Values in the bar graphs are displayed as mean ± SEM. * $p < .05$.

Playing Relaxing Words During Sleep Reduces Asymmetry of Frontal SWA and Slow-wave Density

As listening to relaxing words during NREM sleep extended the time spent in SWS, we tested whether relaxing words additionally increased power in the slow-wave activity (SWA) band (0.5–4.5 Hz) during SWS. We analyzed SWA during SWS over the frontal lobe in the cueing period and the before-cueing period. We did not find an increase in SWA during SWS by presenting relaxing words (39.53 ± 1.44 μV^2) compared with control words, in the during-cueing period (39.60 ± 1.65 μV^2, $t_{49} = 0.04$, $p > .90$). SWA during SWS was also comparable between both nights in the before-cueing period (relax: 46.11 ± 2.19 μV^2, control: 46.15 ± 2.08 μV^2, $t_{49} = 0.03$, $p > .90$). Analysis with the factors condition (relax vs. control), time (before- vs. during-cueing period), and hemisphere (left vs. right) revealed no interaction between time and condition ($F_{1,49} = 0.00$, $p > .90$, $\eta_p < .01$). A main effect of time reflected the typical decrease in SWA from the first sleep cycle (before-cueing period) to later sleep cycles (during-cueing period; $F_{1,49} = 13.01$, $p = .001$, $\eta_p = .21$).

Moreover, we observed a significant three-way interaction between condition, time and hemisphere ($F_{1,49} = 10.65$, $p = .002$, $\eta_p = .18$) and an interaction between time and hemisphere ($F_{1,49} = 4.80$, $p = .033$, $\eta_p = .09$). In the before-cueing period, power in the SWA band was decreased over the left frontal hemisphere, whereas higher values were observed in the right hemisphere. This asymmetric SWA was significant ($t_{49} = –2.23$, $p = .030$, $d = 0.32$) and similarly occurred in both nights (Figure 2a, left panel, before-cueing bars). While playing control words, this asymmetry of SWA remained, with higher SWA in the right compared with the left frontal hemisphere ($t_{49} = –2.08$, $p = .043$, $d = 0.29$). However, frontal asymmetry of SWA vanished during the presentation of relaxing words ($t_{49} = 0.25$, $p > .80$). Comparing the degree of asymmetric SWA between the before- and during-cueing period in the night with relaxing words, revealed a significant change from a right dominance in the before-cueing period (left minus right hemisphere: –3.11 ± 1.55 μV^2) to a symmetrical distribution in the during-cueing period (0.37 ± 1.46 μV^2; $t_{49} = –3.57$, $p < .001$, $d = 0.50$; Figure 2a, right panel, relax bar). No change in asymmetric SWA was observed in the night with control words ($t_{49} = 0.43$, $p > .60$). In the during-cueing period, we observed a trend for less asymmetric sleep when participants listened to the relaxing words (0.37 ± 1.46 μV^2) compared with the night in which control words were presented (-2.59 ± 1.25 μV^2, $t_{49} = –1.99$, $p = .053$, $d = 0.28$).

In addition to the general measure of SWA, we analyzed single slow-waves detected in the average wave of either the frontal left (Fp1, F3, F7, FC5) or right clusters (Fp2, F4, F8, FC6, see Figure 1) during SWS. Three participants had to be excluded in this analysis due to an insufficient number of detected slow-waves in the during- or before-cueing period. Consistent with our SWA analysis, we detected a significantly higher density of slow-waves in the before-cueing period over the right frontal cortex (4.55 ± 0.34) compared with the left frontal cortex (4.05 ± 0.26; $t_{46} = –2.25$, $p = .030$, $d = 0.33$) in both nights (see Figure 2b, left panel). When relaxing words were played during the cueing period, the asymmetry of slow-wave density between the left and right hemisphere vanished (left: 2.92 ± 0.21; right: 3.04 ± 0.22; $t_{46} = –0.75$, $p > .40$, $d = 0.11$). The change in asymmetry of frontal slow-wave density, from the before- to the during-cueing period, was significant in the night where relaxing words were presented ($t_{46} = –2.42$, $p = .020$, $d = 0.35$, see Figure 2b, right panel). We observed no significant change in asymmetric slow-wave density in the control night ($p = 0.13$).

When analyzing the negative slope of the detected slow-waves, we also observed steeper negative slopes over the right (–572.20 ± 10.51 μV/s) compared with the left hemisphere (–530.47 ± 11.79 μV/s; $t_{46} = 4.25$, $p < .001$, $d = 0.62$, see Table 3). One additional participant had to be excluded from the analysis of negative slopes due to differences between hemispheres larger than 3 SD of the mean (–1399.47 μV/s) in the relax night during cueing. This asymmetry in the negative slope was stable and occurred in the before- and during-cueing period (all $p < .002$). Importantly, no change (before- to during-cueing period) in the asymmetry of the negative slope was observed in both conditions (both $p > .17$), and asymmetry occurred similarly with both relaxing and control words (see Table 3).

In contrast to slow-wave density and negative slope, the peak-to-peak amplitude of the detected slow-waves was comparable between the right and left hemisphere in the before-cueing period in both nights ($p > .80$) as well as during the presentation of control words ($p > .50$). However, playing relaxing cues during sleep significantly increased the amplitude of slow-waves over the left hemisphere (156.46 ± 4.94 μV) compared with the right (153.95 ± 4.79 μV; $t_{46} = 2.20$, $p = .033$, $d = 0.32$, see Figure 2c, left panel). A statistical trend suggested an increased asymmetry of amplitude in the relax night in the during-cueing period (2.51 ± 1.14 μV) compared with the before-cueing period (0.02 ± 0.97 μV; $t_{46} = –1.72$, $p = .092$, $d = 0.25$, see Figure 2c, right panel). This was driven by an increased amplitude in the left hemisphere in the during-cueing period with relaxing cues (156.46 ± 4.94 μV) compared with the before-cueing period (153.39 ± 5.17 μV; $t_{46} = –2.44$, $p = .019$, $d = 0.36$), while the right hemisphere remained on a similar level ($p > 0.60$). Thus, the change in frontal SWA asymmetry observed in the during-cueing period with relaxing words might be explained by differences in slow-wave density and increases in slow-wave amplitude over the left frontal hemisphere together, but not by changes in negative slope of the slow-waves.

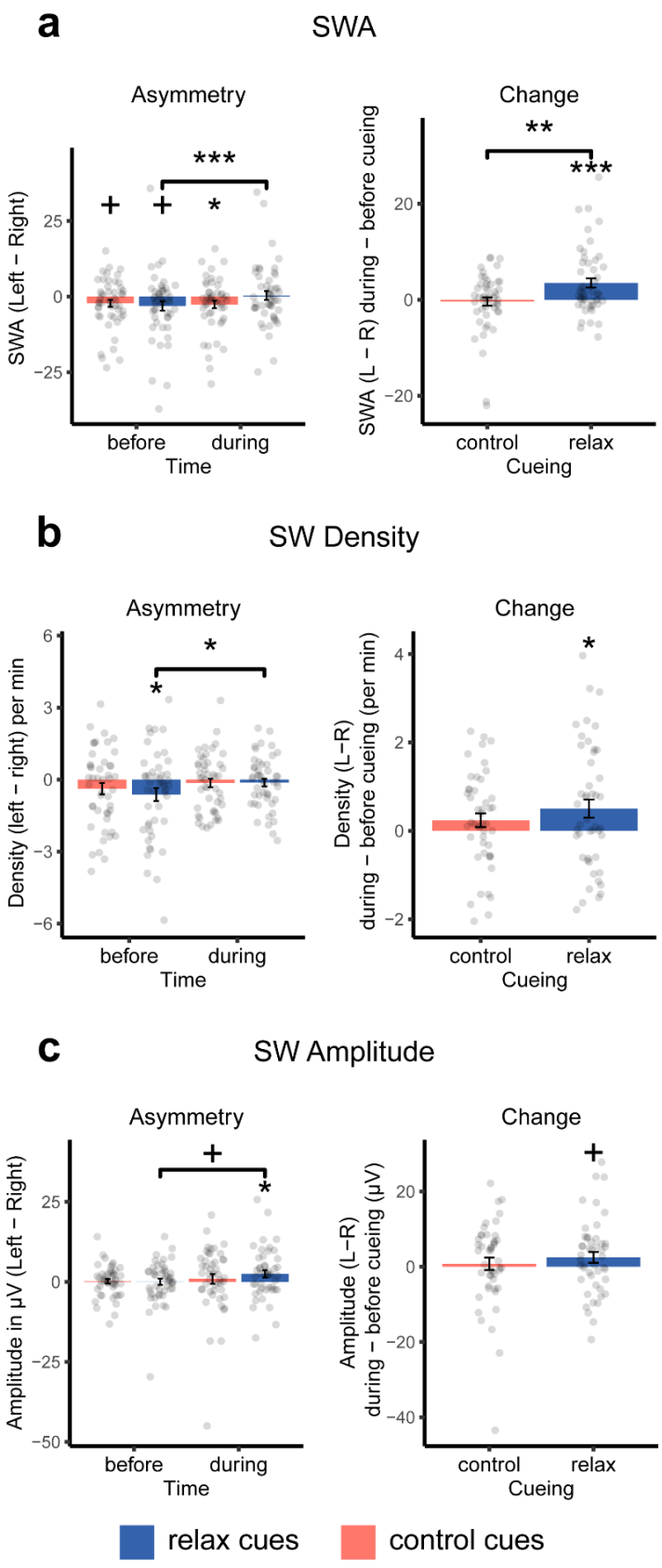
a
SWA
Asymmetry
Change
SWA (Left – Right)
SWA (L – R) during – before cueing
before
during
Time
control
relax
Cueing
b
SW Density
Density (left – right) per min
Density (L–R) during – before cueing (per min)
c
SW Amplitude
Amplitude in µV (Left – Right)
Amplitude (L–R) during – before cueing (µV)
relax cues
control cues

Figure 2. The asymmetry of slow-wave activity (SWA) and slow-waves (SW) during slow-wave sleep (SWS). (**a**) In the before-cueing period, slow wave activity was higher in the right frontal hemisphere compared with the left hemisphere in the relax and control night. The right frontal dominance of SWA persisted during cueing with control cues. In contrast, frontal asymmetry of SWA vanished when relaxing words were played (t_{49} = -3.57, p < .001, d = 0.50). (**b**) For SW density, the asymmetric pattern before cueing in the relax night vanished when relaxing words were played during sleep (t_{46} = -2.42, p = .020, d = 0.35). The asymmetry of SW density was comparable between the before- and during-cueing period in the control night. (**c**) Asymmetry of SW amplitude (left > right) only occurred during cueing with relax cues (p = .033) and increased from the before- to the during-cueing period (p = .092). Values are displayed as mean ± SEM. *** p < .001, ** p < .01, * p < .05, $^{+}$ p < .10.

Table 3. Slow-waves detected in the frontal left or right cluster in SWS

Parameter	Control night before cueing	Relax night before cueing	Control night during cueing	Relax night during cueing
SPT	44.99 ± 2.27	42.94 ± 2.96	45.61 ± 3.32	48.70 ± 2.81
Density	4.20 | 4.57	**3.91 | 4.53***	2.95 | 3.09	2.92 | 3.04[b, (bc)]
Amplitude	151.35 | 151.19	153.39 | 153.37	155.54 | 154.62	**156.46 | 153.95***[, b, (ab)]
Negative slope	**–476.65 | –515.19***	**–488.94 | –530.41***	**–563.08 | –619.10***	**–559.66 | –618.39***[, b, c]
Positive slope	296.37 | 294.571	297.59 | 294.24	309.57 | 313.22	307.90 | 310.01[b]

Note. Means of parameters of slow-waves in the frontal left | right hemisphere. Here provided are sleep period time in min (SPT), slow-wave density per minute (Density), peak-to-peak amplitude in µV (Amplitude) and the negative and positive slope in µV/s. (b) indicates a main effect of time (before, during) and (c) a main effect of hemisphere (left, right). (ab) indicates an interaction between cueing and time. (bc) indicates an interaction between time and hemisphere. Bold values marked with * indicate significant differences between the left and right hemisphere. Effects are reported with p < .05 (*).

Playing Relaxing Words During Sleep Increases Event-related SWA

In addition to the effects of relaxing words on general SWS, SWA and slow-waves, we analyzed event-related responses to the word presentations during sleep in the time and frequency domain. We compared responses to four relaxing and four control words (each word was presented 15 times resulting in 60 stimuli per category). To control for general auditory properties, the responses were also compared to the exact same words played in reverse.

First, we analyzed event-related responses (ERP) of relaxing words (forward vs. reverse) and control words (forward vs. reverse) separately (Parise et al., 2011; Strand et al., 2008). On the ERP level, forward relaxing words evoked a stronger negative response during three time intervals compared with reverse relaxing words: 770–1306 ms, 1814–2246 ms and 2748–3324 ms after stimulus onset (1st cluster, 24 electrodes, $p = .006$, 2nd cluster: 21 electrodes; $p = .036$, 3rd cluster: 21 electrodes $p = .040$, see Figure 3a). No significant difference in the ERP responses were observed between forward and reverse control words (see Figure 3c). When calculating the interaction between condition (relax vs. control) and word type (forward vs. reverse), two clusters in a later period remained significant: A first cluster ($p = .002$) extended from 2662–3346 ms after cue onset, involving 24 electrodes. A second cluster ($p = .018$) extended from 3630–4138 ms after cue onset, involving 22 electrodes (see Figure 3e). An early cluster between 944–1260 ms after cue onset involved 19 electrodes, but did not reach significance ($p = .18$).

In the time frequency domain, we specifically focused on changes in the SWA band (0.5–4.5 Hz) and in the spindle band (11–16 Hz). In a separate analysis of relaxing words (forward vs. reverse), higher power in the SWA band was observed in an earlier time window (30–1400 ms, 29 electrodes, $p = .034$, all electrodes except Fp2 and FPz) and a later time window (1950–3290 ms, 30 electrodes, $p = .034$, all except CP1; see Figure 3b, left panel). The number of concurrent significantly differing electrodes in the second cluster increased until peaking between 2.60–2.65s (30 electrodes), and decreased afterwards (see white line within black bar above Figure 3b, left panel). Mean SWA power within the second cluster was increased after relaxing words (0.48 ± 0.13) compared with reverse relaxing words (0.07 ± 0.14, $t_{49} = 2.81$, $p = .007$, $d = 0.40$, see Figure 3b, right panel). Interestingly, the difference in SWA power within the second cluster correlated positively with the difference in association strength of relaxing and control words, yet non-significantly ($r_{48} = .16$, $p = .26$).

For the contrast between control words vs. reverse control words, no significant clusters were detected (see Figure 3d). Mean SWA power, averaged over the time windows and the electrodes of the significant clusters in the relax condition, were comparable between control and reverse control words in the first ($t_{49} = 0.67$, $p > .50$) and the second cluster ($t_{49} = –1.66$, $p = .10$; see Figure 3d). When calculating the interaction between condition (relax vs. control) and word type (forward vs. reverse), the cluster in the later period remained significant (1880–3410 ms; $p = .012$; 27 electrodes, all except F7, P7, CP1 and CP5; see Figure 3f, left panel and supplementary Movie S1). The number of concurrent significantly differing electrodes increased until peaking between 2530–2640 ms (27 electrodes), and decreased afterwards (see white line within black bar above Fig 3f, left panel). Mean SWA power within the cluster was increased after relaxing words (0.41 ± 0.15) compared with control words (–0.28 ± 0.17; $t_{49} = 2.99$, $p = .004$, $d = 0.42$, see Figure 3f, right panel).

Analysis of the spindle power band revealed no significant clusters in the spindle band for any of the contrasts (relaxing words: $p = .14$; control words: $p > .90$; interaction: $p = .30$), but was strongest for relaxing vs. reverse relaxing words. Analyzing both control and relaxing words together yielded a significant increase in spindle power of forward compared with reverse words (11–16 Hz; 1000–1990 ms; cluster $p = .030$; see supplementary Figure S2, b).

In summary, mean SWA power was increased in an early and late cluster for relaxing vs. reverse words, while no changes in SWA power were observed for control vs. reverse words. In addition, only the later cluster remained significant when contrasting the relaxing (– reverse) words with the control (– reverse) words.

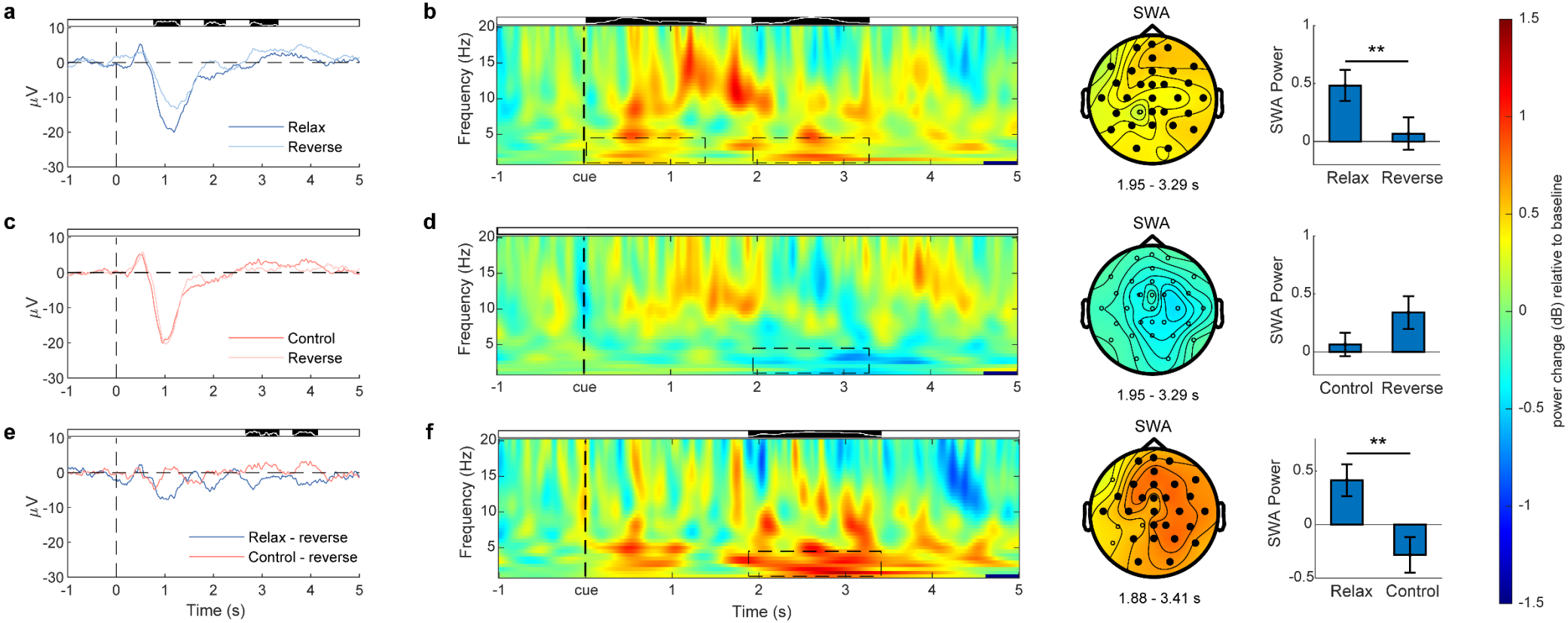

Figure 3. Event-related responses during non-rapid eye movement (NREM) sleep at Fz. The black areas above the plots indicate significant time intervals, while the white line in the black areas displays the number of significant electrodes (full height = 31 electrodes). (**a**): Presentation of relaxing words during NREM sleep elicited a higher negative event-related potential than reverse relaxing words (770–1306 ms, 1814–2246 ms and 2748–3324 ms). (**b**): Presentation of relaxing words during NREM sleep elicited an increase in SWA power (1st: 30–1400 ms and 2nd: 1950–3290 ms; **b**, left). The increase in SWA power in the 2nd time window was most prominent over frontal and right parietal areas (**b**, middle; significant electrodes = filled black dots). Mean SWA power in the significant 2nd cluster averaged over significant electrodes, duration and frequency band of interest was higher for relaxing vs. reverse

relaxing words (**b**, right; $t_{49} = 2.81$, $p = .007$, $d = 0.40$). (**c**): Event-related potentials of control vs. reverse control words were comparable. (**d**): SWA power was comparable for control vs. reverse control words. Mean SWA power averaged over the same time window (2^{nd}) and electrodes as for relaxing words (**b**, right), were comparable between control and reverse control words (**d**, right). (**e**): The interaction between condition (relax vs. control) and word type (forward vs. reverse) indicated a higher negative event-related potential for relaxing (– reverse) words compared with control (– reverse) words (2662–3346 ms and 3630–4138 ms). (**f**): The interaction between condition (relax vs. control) and word type (forward vs. reverse) yielded an increase in SWA power (1950–3290 ms; **f**, left; see also supplementary Movie S1). The increase in SWA power was most prominent over frontal areas and the right hemisphere (**f**, middle, significant electrodes = filled black dots). Mean SWA power in the significant cluster averaged over significant electrodes, duration and frequency band of interest was higher for relaxing (– reverse) vs. control (– reverse) words (**f**, right; $t_{49} = 2.99$, $p = .004$, $d = 0.42$). Values in the bar graphs are displayed as mean ± SEM. ** $p < .01$, * $p < .05$.

Discussion

In the present study, we present empirical support for our hypothesis that active mental concepts during sleep can influence sleep depth: playing relaxing words during sleep promotes SWS in the cueing period compared with a night in which control words are presented. The increased sleep depth by means of relaxing words was accompanied by a reduced interhemispheric asymmetry of SWA and slow-wave density in the during-cueing period as well as an increase in event-related power in the SWA band several seconds after the cue. The changes observed in objective sleep translated into an increase in subjective sleep quality and alertness ratings.

The findings we reported show that it is possible – in principle – to influence sleep depth by presenting relaxing words during NREM sleep. As an underlying mechanism, we propose that semantic concepts are stored in multimodal representations, and that activation of the semantic meaning will automatically modulate the activation of neural networks responsible for processing the associated bodily function. Activation of the semantic concept of relaxation via the presentation of relaxing words is therefore assumed to activate brain regions responsible for relaxation, sleep induction and maintenance, possibly involving the inhibitory GABAergic system or thalamo-cortical loops, generating slow-waves (Chen et al., 2018; Mak-McCully et al., 2017). In addition, activation of meanings related to “relaxation” might also inhibit the activity of arousal- and wake-promoting brain regions in the hypothalamus, brainstem, or basal forebrain (Brown et al., 2012; Xu et al., 2015). Here, we can only speculate on the involved brain regions, as our EEG measures only provide information related to the consequences of the word presentation on the cortical surface.

Still, our event-related analyses revealed distinct increases in power in the SWA band after 2–3.5 seconds, suggesting that the processing of relaxing words during sleep promotes a transient increase in SWA. Importantly, the changes occurred after the typical K-complex-like response to external auditory cues during sleep (Pratt et al., 1999). Previous research showed that the presentation of single ‘click’ tones in phase with the slow-wave rhythm, enhanced slow-waves during sleep (Ngo et al., 2013). However, this effect seems to be limited to the presentation of two consecutive ‘clicks’ (ca. 1s), thus lacking enduring effects as well as changes in sleep architecture (Ngo et al., 2015). Furthermore, the increase in SWA caused by the presentation of relaxing words did not occur for relaxing words played in reverse, thereby

controlling for general effects of the tone spectrum, word length and prosody of the auditory stimulus. The increase in SWA induced by relaxing words must therefore be highly specific to the semantic meaning of the word. Importantly, no late event-related increase in SWA occurred when control words were contrasted against control words played in reverse. These findings support our proposition that the activation of semantic concepts related to relaxation, by means of word presentations during sleep, modulates underlying processes which are responsible for slow-wave generation. A limitation of our study is that we did not include an additional condition using arousing words like “running”, “angry” or “screaming” during sleep, which should decrease SWS and subjective sleep quality. Most studies presenting arousing stimuli during sleep usually presented both negative and positive cues in one single night of sleep, which does not allow any conclusion on the effect of arousing stimuli on sleep itself (Blume et al., 2017; Cairney et al., 2014; Groch et al., 2017; Lehmann et al., 2016). Future studies should systematically compare effects of arousing vs. neutral vs. relaxing words on sleep quality in separate nights.

The promoting effects of relaxing words on deep sleep were specific to the cueing period and did not yield significant changes of SWS in the entire night. Importantly, a systematically increased sleep pressure or rebound of SWS in the relax night cannot explain this effect, as all sleep parameters were comparable in the before-cueing period. In addition, the effects were specific to SWS, as no other sleep stages were significantly affected by our manipulation. However, the descriptive pattern of decreased amounts of N1, N2, WASO, and REM sleep as well as an increased sleep efficiency during the presentation of relax cues, supports an improved objective sleep quality through relaxing words compared with the control night. Remarkably, participants reported having better sleep quality and elevated alertness in the morning after having listened to relaxing words compared with control words during sleep. These results are controlled for individual differences in sleep perception and general sleep quality, as we applied a within-subject design. Furthermore, the change in the amount of SWS in the cueing period, induced by the relaxing words, positively predicted the improved self-reports of sleep quality. Therefore, we assume that the increase in subjective sleep quality is explained by the increase in SWS with relaxing cues in the during cueing period. Yet, presentation of relaxing words during sleep might also directly affect subjective sleep quality independent of objective parameters. Relaxation words could have been consolidated into memory or remain active until subjects filled out the questionnaire directly after waking up. This might also explain the dissociation

between overall comparable objectively measured SWS and vigilance and increased subjective sleep quality and alertness.

Subjective sleep quality is a highly important marker for the individual evaluation of sleep. As the diagnosis of insomnia is solely based on the subjective experience of the patient and not on objective data (American Psychiatric Association, 2013), subjective measures are even considered more important for patients and clinicians to diagnose and assess the severity of sleep disturbances (Riemann et al., 2020). The fact that the presentation of relaxing words during sleep is also capable of improving subjective evaluations of sleep, is therefore highly promising for future applications of such techniques in sleep disturbances like insomnia as well as accompanying affective disorders like depression.

In addition to the effects of SWS and self-reported sleep quality, presentation of relaxing words reduced the typical right-frontal predominance of SWA and slow-wave density during SWS, which was not predicted by our hypothesis. Several previous studies have reported higher frontal SWA in the right compared with the left hemisphere during SWS (Mascetti, 2016; Sekimoto et al., 2000; Tamaki et al., 2016). Recently, it was reported that this asymmetry of SWA is even more pronounced in callotosomized patients (Avvenuti et al., 2020). The authors argue that such frontal asymmetry of sleep SWA is unlikely to occur due to homeostatic regulation (Borbély et al., 2016) or functional specification of hemispheres (Karolis et al., 2019), as extending the time awake leads to a stronger increase of SWA in the left, compared with the right, hemisphere (Achermann et al., 2001; Ferrara et al., 2002). Thus, it has been speculated that the reduction of SWA in the left hemisphere is related to a “monitoring” or “night watch” system, which watches for potential dangers in the environment, with the ability to induce arousal or wakefulness more rapidly due to a reduced sleep depth (Blume et al., 2018; Legendre et al., 2019; Tamaki et al., 2016). In support of this notion, hemispheric differences in SWA mainly occur in unfamiliar environments, such as the first night in a sleep laboratory (Sekimoto et al., 2007; Tamaki et al., 2016; Tamaki & Sasaki, 2019). Moreover, the hemisphere with reduced sleep depth (left) showed an increased evoked brain response to deviant external stimuli while asleep (Tamaki et al., 2016). In line with previous findings, we replicated frontal asymmetry in SWA with reduced SWA in the left, compared with the right, hemisphere in the control night. The same asymmetry occurred in the relax night in the before-cueing period, but vanished when relaxing words were played. A possible explanation is that the activation of the semantic concept

of “relaxation” had a “calming” influence on the night watch system, thereby sparing the need of a reduced sleep depth of the left hemisphere. However, this interpretation needs further experimental support.

In insomnia patients, only few studies investigated asymmetry of EEG power (Provencher et al., 2020). Studies suggest differences in asymmetry patterns between the paradoxical and psychophysiological insomnia subtypes (St-Jean et al., 2012; St-Jean et al., 2013). Paradoxical insomnia patients showed an increased amount of delta activity over the left hemisphere during NREM sleep compared with patients suffering from psychophysiological insomnia (St-Jean et al., 2013). However, asymmetry between hemispheres seems to vary between sleep stages and nights in insomnia patients (Kovrov et al., 2006; St-Jean et al., 2012). In addition, intra hemispheric asymmetry patterns (e.g. fronto-parietal asymmetry) were related to clinical symptoms of insomnia patients (Provencher et al., 2020). Therefore, asymmetry in insomnia patients and their subtypes have to be further studied and modulating asymmetry of EEG power using word presentations during the night might thereby serve as a useful tool.

In a series of previous studies, we have shown that suggestions to relax and to sleep deeper given before sleep, are capable of extending the amount of SWS during a subsequent nap or nighttime sleep (Cordi et al., 2014; Cordi et al., 2015; Cordi et al., 2020). As a possible explanation we suggested that the mental concept of “relaxation”, given by the instruction to relax before sleep, remains active during subsequent sleep, and is capable of increasing sleep depth by its active multimodal representation (Cordi et al., 2020). The current study provides direct support for this notion and offers a potential mechanism for the beneficial effects of cognitive interventions given before sleep on later sleep architecture. However, one could have expected that familiarity of the relaxing material before sleep is a necessary prerequisite for the SWS-extending effect of presenting words during sleep. In our study, a subgroup of the participants listened to a tape in which a suggestion to relax and to sleep deeper was given before sleep. The suggestions were identical to the ones used in our previous studies (Cordi et al., 2014; Cordi et al., 2020). However, we observed no effect of familiarity of the words and therefore decided to combine the data of both groups. Our results suggest that a targeted memory reactivation design is not required to achieve beneficial effects of relaxing word presentations on SWS and subjective sleep quality. We assume that already existing concepts and associations to the selected words, such as “relaxation” and “sleep”, will similarly activate the multimodal

networks related to these concepts, independent of whether these concepts were encountered before sleep or not. To further examine the possibility of targeted memory reactivation of relaxation concepts with verbal cues during sleep, we recommend a learning phase using arbitrary cues, and newly associating them with relaxation-related concepts or experiences (e.g. progressive muscle relaxation or a relaxing virtual reality environment).

Spindle power after a word presentation during sleep has been shown to support the stabilization, strengthening and integration of memories, which have been previously associated with the word (Schreiner & Rasch, 2017; Schreiner & Staudigl, 2020). In our study, we observed an overall increase in spindle power for forward compared with reverse words. This suggests that spindle power increases could also reflect successful processing of semantically meaningful words. Descriptively, the increase in spindle power seemed to be more pronounced for relaxing words. Therefore, relaxing words might have been easier to process or understand during sleep compared with control words. Future studies presenting words during the night should consider such effects of semantic meaning on spindle power during sleep.

A limitation of this study is the choice of words presented during sleep. We presented 40 words from a relaxation text using a metaphor of a fish swimming deeper and deeper into the sea. However, not all of these words might be associated with the same relaxation concept, therefore they might activate other concepts. The associations to one word could also vary interindividually. For instance, “plunge” and “submerge” might even be associated with fear in some people who are afraid of diving for example. Likewise, this should be considered when applying such methods in patients, e.g. with insomnia, where “sleep” might already have negative associations. Moreover, we presented words during NREM sleep, disregarding the phase of the slow-waves. Previous literature suggests that the processing of words is most effective during cortical up states, i.e. at the peaks of slow-waves (Göldi et al., 2019; Navarrete et al., 2020; Züst et al., 2019). A closed-loop setup could benefit word processing by targeting the presentation of words precisely in the up-states of slow-waves. This might even strengthen the effect of relaxing word presentations on the depth of sleep. In addition, the volume of word presentations should be individually adjusted to the hearing threshold during sleep. In our study, we kept the volume of word presentations at the same level for all participants and ensured that the average and peak volumes were comparable between conditions. However, the volume of

single words varied within conditions (see supplementary Table S4), which likely caused some words not to be processed at all during sleep because they were too silent.

Moreover, the increase in SWS during the period of word presentation and subjective sleep quality in the relax night could also be explained by basic auditory properties (e.g. power spectrum, course volume level, tone, style). The semantic categories of words (relax vs. control) were not directly associated with obvious phonetic differences which could have been detected by participants unfamiliar to the German language. However, relaxing words were spoken in a more soft and calm voice. Yet, we argue that differences in basic auditory properties cannot explain the event-related increase in SWA, because the subtracted reversed words contained the same auditory properties. Though, reversing the words might have changed the accentuation and prosody of the words, especially for longer words. Word length has been controlled between the relaxing and control condition by matching the syllable length. However, accentuation and prosody related differences between forward and reversed words could still be more pronounced in the relax night by the calmer tone of speaking the relaxing words. This might also explain the differences in the early ERP peak of forward and reverse relaxing words. In addition, early semantic processing could also explain these differences, but future studies have to further examine ERP components and their relation to prosody and semantic processing during sleep.

Moreover, we only presented words during NREM sleep in this study and can only speculate about possible effects of relaxing word presentations during REM sleep. We would assume, that words and semantically related concepts activated during sleep are incorporated into dreams in all sleep stages. However, during both NREM and REM sleep, dreaming is associated with the activation of multiple concepts and associated emotions. Therefore, processing of associative networks might be facilitated during REM sleep and even show stronger effects on sleep physiology compared with NREM sleep and possibly also induce switches to deeper sleep stages (N2 and N3). Moreover, activating semantic concepts during REM sleep or awakenings during the night might also affect subsequent NREM sleep episodes similarly to pre-sleep cognitions affecting subsequent early NREM sleep.

In conclusion, the present study showed that the semantic meaning of words presented during NREM sleep is capable of affecting sleep physiology, SWS maintenance and the subjective evaluation of sleep quality. We argue that the semantic meaning of words presented during sleep is capable of affecting sleep depth by activation of related semantic concepts during

sleep. In fact, speaking to people while they are asleep to improve their sleep behavior is a common recommendation in the cases of sleep-walking and night terrors (Arnulf, 2018; Leung et al., 2019), and parents frequently use speech to improve and maintain sleep in their children. Therefore, such presentation of individually-chosen words associated with relaxation and sleep promoting concepts might prove an effective intervention to promote sleep depth and increase subjective sleep quality also in people with sleep disturbances.

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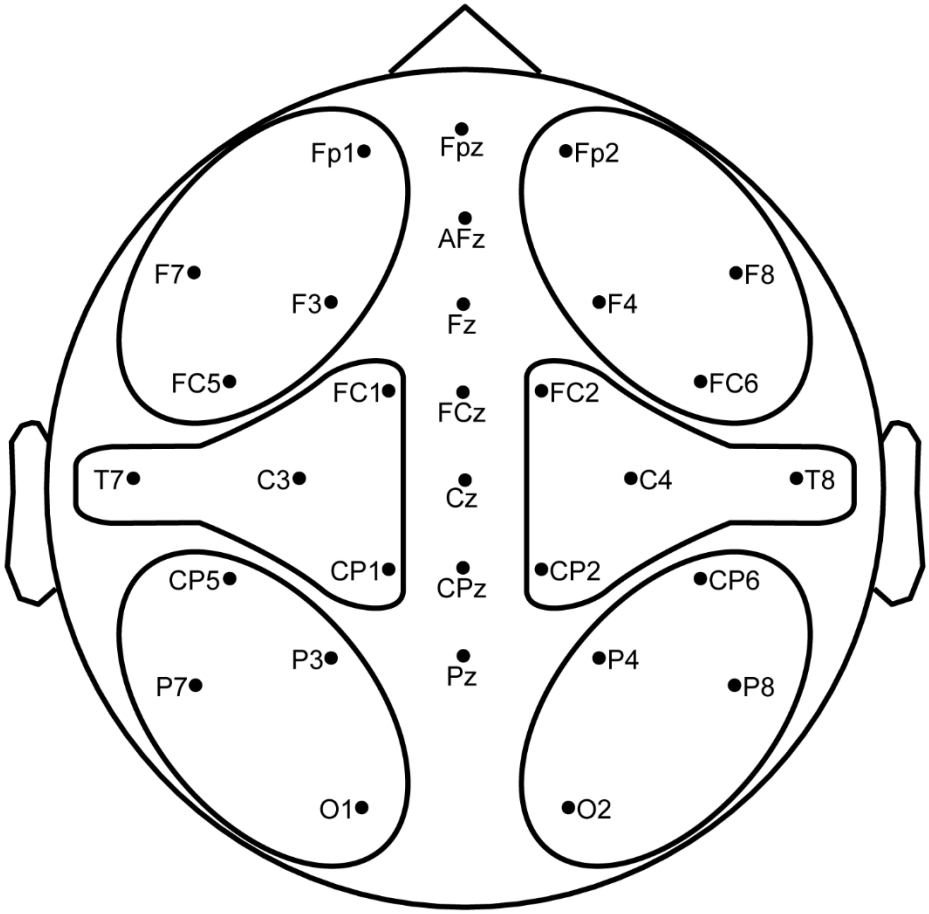
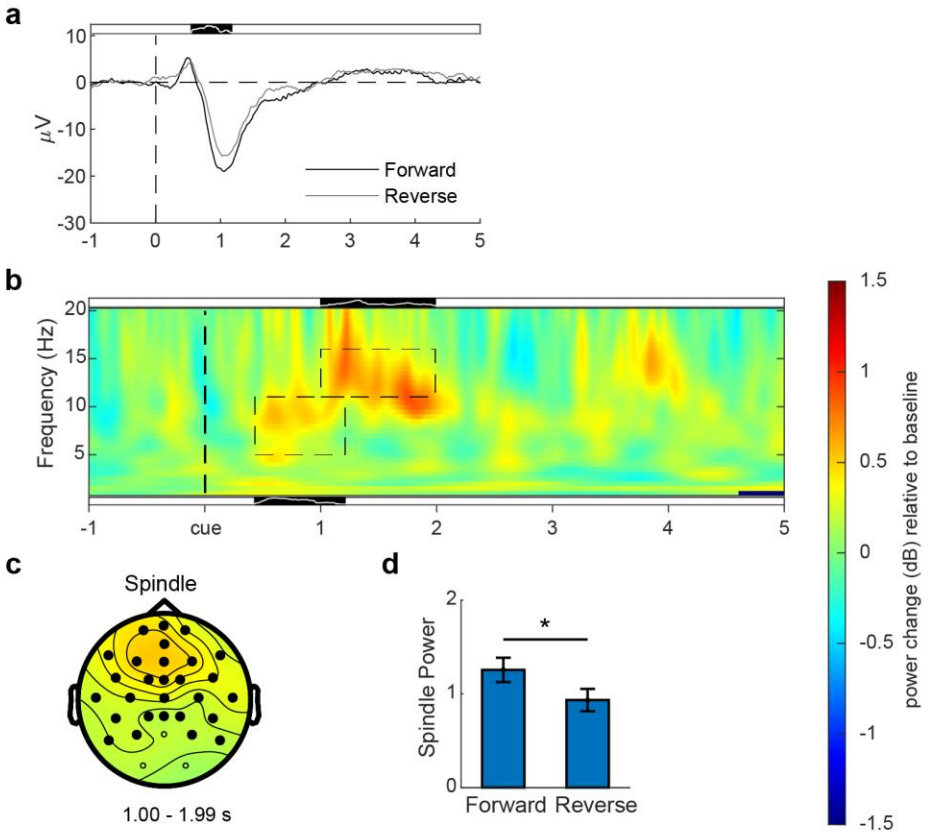
Supplementary Information

Supplementary Figures



Supplementary Figure S1. Regions of interest in the power and slow-wave analyses. Each cluster comprised 4 electrodes. Power analysis was conducted within all 6 clusters. Slow-wave detection was conducted on the average signal of the frontal and parietal clusters.



Supplementary Figure S2. Event-related responses of forward and reverse words. (**a**, **b**, **c**, **d**): Presentation of understandable words during non-rapid eye movement sleep (forward words) elicited a higher negative evoked potential 548–1174 ms after cue onset compared with reverse words (cluster p = .010; **a**), and a higher increase in spindle power (11–16 Hz; 1000–1990 ms; cluster p = .030; **b**) and theta to alpha power (5–11 Hz; 430–1210 ms; cluster p = .030; **b**). The black areas above the plots indicate significant time intervals, while the white line in the black areas display the number of significant areas (full height = 31 electrodes). (**c**): The increase in spindle power was most prominent over frontal brain regions (significant electrodes = filled black dots). (**d**): Mean power in the significant cluster, averaged over significant electrodes, duration and frequency band of interest, was higher for forward vs. reverse words (t_{99} = 2.54, p = .013). Values in (**d**) are displayed as mean ± SEM. * p < .05.

Supplementary Movie

Supplementary Movie S1. Event-related slow wave activity power of relaxing compared with control words. Available here: Supplementary Movie S1

Supplementary Tables

Supplementary Table S1. Sleep parameters in the night with control and relaxing words

Parameter	Control night	Relax night
SPT	456.98 ± 2.96	460.69 ± 2.37
SOL (min)	20.32 ± 2.62	17.24 ± 2.07
WASO (min)	12.04 ± 1.84	10.32 ± 1.43
N1 (min)	29.43 ± 2.13	28.53 ± 1.93
N2 (min)	190.89 ± 6.01	189.4 ± 5.32
SWS (min)	130.99 ± 7.39	136.21 ± 6.68
REM (min)	93.63 ± 2.62	96.23 ± 2.80
WASO (%)	2.67 ± 0.42	2.26 ± 0.32
N1 (%)	6.49 ± 0.48	6.21 ± 0.43
N2 (%)	41.81 ± 1.32	41.19 ± 1.20
SWS (%)	28.59 ± 1.58	29.49 ± 1.42
REM (%)	20.44 ± 0.52	20.84 ± 0.56
SWS lat	15.25 ± 1.10	14.38 ± 1.01
REM lat	81.74 ± 3.33	82.98 ± 3.49
Sleep efficiency	92.78 ± .79	93.90 ± 0.62

Note. Means in minutes ± SEM and % ± SEM relative to sleep period time. Sleep period time (SPT) including time spent awake after sleep onset (WASO), sleep onset latency (SOL, first N1 followed by a N2 epoch), sleep stage N1 and N2, slow-wave sleep (SWS), rapid eye movement (REM) sleep and sleep efficiency (time asleep / time in bed * 100). No significant differences between both nights ($p > .13$).

Supplementary Table S2. Task performance in the control and relax cueing night

Parameter	Control night	Relax night	*p*-values
PAL pre-sleep performance (%)	73.13 ± 2.40	74.44 ± 2.14	.30
PAL post-sleep performance (%)	71.94 ± 2.56	71.56 ± 2.44	.67
PAL improvement (pre-sleep = 100%)	98.10 ± 1.06	95.66 ± 1.33	.12
RWT	-1.38 ± 0.85	-0.26 ± 0.84	.35
RWT improvement (pre-sleep = 100%)	104.32 ± 7.18	104.87 ± 6.16	.95
SVF	-0.24 ± 1.27	-1.31 ± 1.23	.57
SVF improvement (pre-sleep = 100%)	105.08 ± 6.43	108.65 ± 9.43	.77
PVT MeanRT (ms)	337.29 ± 4.59	336.12 ± 4.06	.70
PVT MeanRRT	3.05 ± 0.04	3.05 ± 0.36	.86
PVT lapses	4.19 ± 0.96	4.56 ± 0.68	.69
PVT false starts	6.46 ± 2.29	10.25 ± 5.25	.52

Note. Means of parameters ± SEM of the word pair associate learning task (PAL), the Regensburger Wortflüssigkeitstest (RWT), semantic verbal fluency test (SVF) and a psychomotor vigilance test (PVT). MeanRRT was calculated by dividing the RT (ms) by 1000 and then transform it reciprocally (1/RT), mean reaction time (MeanRT), number of lapses (lapses), number of false starts (false starts). Right column displays *p*-values of paired Student's *t*-tests.

Supplementary Table S3. List of words played during non-rapid eye movement sleep (English translation in parentheses)

Relax words	Control words	Reverse words
abtauchen (to submerge)	anreichern (to enrich)	ausruhen (to relax)
angenehm (pleasant)	ausscheiden (to discard)	Blei (lead)
Atemzug (breath)	beansprucht (claimed)	Delphin (dolphin)
ausruhen (to relax)	Beispiel (example)	einfach (easy)
beruhigend (reassuring)	besteht (exists)	erzeugen (to produce)
dahintreiben (to drift)	Bildung (formation)	Magmen (magmas)
Delphin (dolphin)	Blei (lead)	Meer (sea)
einfach (easy)	Boden (soil)	Phase (phase)
einsinken (to subside)	eingeteilt (rationed)	
eintauchen (to plunge)	entstehen (to produce)	
entfernen (to depart)	erstrecken (to extend)	
entspannen (to ease)	erzeugen (to generate)	
entspannt (relaxed)	fest (solid)	
erholen (to recuperate)	Gänge (veins)	
Fisch (fish)	gebunden (bound)	
Fische (fishes)	Gesteine (rocks)	
geniessen (to enjoy)	Gold (gold)	
Korallen (coral)	Kalke (chalk)	
Korallenfelder (coral fields)	Kristallisation (crystallisation)	
langsam (slow)	Kupfer (copper)	
leicht (light)	Lagerstätten (deposits)	
loslassen (to release)	Lösungen (solutions)	
Meer (sea)	Magmen (magmas)	
müder (more tired)	Metalle (metals)	
mühelos (effortless)	Oberfläche (surface)	
Ruhe (quiet)	Öl (oil)	
Schlaf (sleep)	Phase (phase)	
schlafen (to sleep)	Prozess (process)	

Schlaftiefe (sleep depth)	Restschmelze (residual melt)
Schwimmen (to swim)	Rohstoffe (resources)
sicher (safe)	schichtförmig (layered)
sinken (to sink)	Schichtung (stratification)
spüren (to sense)	sieden (to seethe)
tauchen (to dive)	stark (strong)
tief (deep)	Stockwerk (storey)
tiefer (deeper)	Stoffe (materials)
wahrnehmen (to perceive)	Trennung (segregation)
Wasser (water)	verengen (to straiten)
weiter (further)	willkürlich (arbitrary)
wohltuend (soothing)	Zinn (tin)

Supplementary Table S4. Cue characteristics

Parameter	Relaxing words	Control words	Reverse relaxing words	Reverse control words
Mean duration (s)	1.24 ± 0.21 [0.89 – 1.67]	0.83 ± 0.15 [0.55 – 1.20]	1.11 ± 0.23 [0.97 – 1.45]	0.80 ± 0.08 [0.69 – 0.88]
Sound pressure level (dB)	51.00 ± 3.09 [44.80 – 57.40]	51.61 ± 2.51 [43.70 – 55.30]	52.43 ± 2.39 [50.30 – 55.60]	51.08 ± 1.83 [49.00 – 53.10]

Note. All values are means ± SD of all presented words with maximum and minimum value in parentheses. Sound pressure level was measured directly at the loudspeaker.

Supplementary Materials and Methods

Paired-associate Learning Task

The word-pair associate learning task (PAL) was conducted (Rasch et al., 2006) and was programmed as well as presented using E-Prime software (2.0 SP2, Psychology Software Tools, Pittsburgh, PA) before and after sleep. In the evening, three blocks were executed: a learning block, a recall block with feedback and a recall block without feedback. Participants learned 80 German semantically associated word pairs (e.g., orchestra – concert) and were asked to memorize as many pairs as possible. Two different lists of 80 word pairs were randomly assigned to the first or second experimental session. Both words of the word pair were presented together for 3000 ms in white font on a black screen. A subsequent black screen was displayed as a random interstimulus interval for 250-750 ms. During the following recall block, the first word was presented, and subjects were asked to type the second word without any time limit. After the input, the correct word pair was displayed for 1000 ms followed by another random interstimulus interval of 250-750 ms (black screen). Afterwards, subjects completed another recall block without feedback. The order of word pairs was randomized for both recall blocks, but the same for all participants. The next morning, another recall block without feedback was conducted with the same word pair order as in the last recall block before sleep. Memory performance was measured as the percentage of correctly recalled word pairs in the last recall block before sleep and in the morning. To assess relative overnight memory improvement, pre-sleep performance was set to 100%. Three out of the 160 learned words were also presented during sleep as relaxing (1) or control words (2).

Verbal Fluency Tasks

During a semantic verbal fluency test, subjects were asked to write down as many words as possible within a given category (fruits, hobbies, profession or animals) in two minutes. The four categories were randomized across the two experimental sessions and the pre- and post-sleep session. Multiple named words and words containing the same word stem were excluded. Retrieval performance of long-term memory storage was measured as the number of valid, listed words (Lezak, 1995). To assess relative overnight memory improvement, pre-sleep performance was set to 100%. Comparably, the Regensburger Wortflüssigkeitstest (Aschenbrenner et al., 2000) was executed to provide the initial letters (T, N, I, R) of the words to write instead of categories.

Psychomotor Vigilance Test

After waking up, subjects performed a psychomotor vigilance test (PVT) for 10 min to overcome sleep inertia and to assess alertness. Five red zeros were presented as a millisecond counter in the center of a black screen. Participants were asked to press the space bar as quickly as possible when the clock started to run. After the input, the reaction time was displayed in ms for 1 s. As previously suggested (Basner & Dinges, 2011), the reciprocal response time (mean 1 / RT) was used to assess alertness sensitive to sleep deficits.

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Study 2:

Stress Dynamically Reduces Sleep Depth: Temporal Proximity to the Stressor is Crucial

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Abstract

Psychosocial stress affects our sleep and is an essential factor in the development and maintenance of sleep disturbances. However, inducing an acute and completed psychosocial stressor before sleep has only minor effects on sleep and mainly affects early sleep periods. In contrast, research assessing the effect of an anticipated stressor after sleep suggests that physiological changes might occur in particular during later periods of sleep with mixed results on overall sleep parameters. In the current study, we examined the effect of an anticipated psychosocial stressor, the Trier Social Stress Task (TSST), on subjectively and objectively measured sleep as well as arousal, in 33 healthy female participants in comparison to a within-subject relaxation task. To investigate if the timing of the stressor differentially affects sleep parameters across the sleep period, we compared the results to an additional group ($N = 34$) performing the same tasks directly before sleep and analyzed overall and dynamic changes of sleep oscillations. Anticipating a stressor after sleep reduced overall SWA/beta power ratio, SWS, sleep spindles and slow-wave parameters, in particular during late sleep, which was not mediated by somatic arousal. In contrast, pre-sleep psychosocial stress deteriorated the same parameters during early sleep with a concomitant increase in somatic arousal. Our results show that pre-sleep cognitions directly affect sleep in temporal proximity to the stressor. While somatic arousal might mediate the effects of pre-sleep stress on early sleep, we suggest that the effects of anticipated stress on late sleep originates from a repeated reactivation of mental concepts associated with the stressful event during sleep.

Keywords: sleep, stress, cognition, arousal, slow-waves, spindles

Introduction

Stress is our response to threats and challenges in order to adapt to such situations. On a physiological level, the stress response is modulated by activation of the hypothalamic pituitary adrenal (HPA) axis and the autonomic nervous system comprising sympathetic (SNS) and parasympathetic nervous system (PNS). Short term responses to the increased metabolic demands of acute stress comprise an increased heart rate, blood pressure, breathing and gluconeogenesis as well as an inhibition of growth, reproduction, digestion and immune response systems (Black, 2002; Charmandari et al., 2005; Dickerson & Kemeny, 2004; Drake et al., 2017). On a cognitive level, acute stress leads to an increased cognitive arousal, alertness, vigilance, analgesia as well as a suppression of appetite (Charmandari et al., 2005; Dickerson & Kemeny, 2004). In addition, the acute stress response depends on the cognitive evaluation and subjective perception of the stressor (Lazarus & Folkman, 1984; McEwen, 1998; van Reeth et al., 2000). Most stressors induces stress responses at both the physiological and cognitive levels, particularly those that involve a psychosocial component (Kogler et al., 2015). A widely used and standardized stress paradigm to induce acute psychosocial stress is the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), which targets a combination of social-evaluative threat and uncontrollability (Dickerson & Kemeny, 2004), reliably activates the HPA-axis and induces cognitive arousal in real and virtual reality settings (Allen et al., 2017; Zimmer et al., 2019). Research suggests that stress and stress regulatory systems have a major impact on our sleep and the development of sleep disturbances (Drake et al., 2017; Lattova et al., 2011; Riemann et al., 2010; van Reeth et al., 2000). Sleep is important for our recovery, and impaired sleep can lead to several health problem such as obesity, cardiovascular diseases, cognitive impairments and neurodegenerative disease (Fan et al., 2020; Hale et al., 2020; Xie et al., 2013).

Experimental studies inducing psychosocial stress and cognitive tasks in a laboratory directly before sleep and collecting objective polysomnographic data (Ackermann et al., 2019; Wuyts, Valck, Vandekerckhove, Pattyn, Bulckaert, et al., 2012), reported a prolonged sleep onset latency and a decrease in low/high frequency power in the electroencephalogram (EEG) during non-rapid eye movement (NREM) sleep, which is a measure of objective sleep quality (e.g., Cordi et al., 2019; Hall et al., 2007; Hogan et al., 2020; Maes et al., 2014). These changes were limited to early periods of sleep and pre-sleep stress did not affect sleep parameters during later sleep periods. Other studies reported inconsistent results: While Vandekerckhove and colleagues

observed changes in sleep architecture (but not on sleep onset, amount of SWS or EEG power bands) after a negative experience before sleep (Vandekerckhove et al., 2011), Kim and coauthors reported no changes on sleep architecture at all after a pre-sleep TSST (Kim et al., 2019). Therefore, the effects of pre-sleep stress induction on sleep seem to be smaller than expected and mostly affecting early sleep. Interestingly during wakefulness, stress-induced changes in heart rate recovers between 10 – 30 minutes after the TSST induction, while cortisol recovers about 30 – 90 minutes after finishing the task (Janson & Rohleder, 2017; Kirschbaum et al., 1993; Yamanaka et al., 2019). Thus, changes in sleep after pre-sleep stress induction might be mainly related to the physiological component of stress, which covers the sleep onset and early sleep periods but vanishes throughout later periods of sleep.

These limited effects of acute stress on sleep stand in contrast to the well-documented notion that stress is a major factor causing sleep disturbances (Drake et al., 2017; Lattova et al., 2011; Riemann et al., 2010; van Reeth et al., 2000), possibly throughout the whole sleep period. In contrast to time-limited physiological responses after acute stress, anticipation of future stress preserves negative cognitive activity over a longer time period (Brosschot et al., 2006). Importantly, anticipation of future stress – also referred to as repetitive negative thinking (Watkins et al., 2005) or more generally cognitive arousal – is a main factor for the development and maintenance of sleep disturbances (Ballesio et al., 2020; Clancy et al., 2020; Kalmbach et al., 2020; Lemyre et al., 2020). Thus, Brosschot proposed that unconscious cognitive representations of anticipation of future stressful events are causing the detrimental long-term effects of stress and might also be responsible for the detrimental effect of stress on sleep (Brosschot, 2010; Brosschot et al., 2018).

Several studies have already examined the effects of anticipating stressful events on sleep: Anticipating an early awakening or a stressful workday negatively affects sleep architecture (Kecklund et al., 1997; Kecklund & Åkerstedt, 2004) and induces changes in stress-related hormone levels during later parts of sleep (Born et al., 1999). In addition, the mere instruction to be on-call disturbs sleep (Wuyts, Valck, Vandekerckhove, Pattyn, Exadaktylos, et al., 2012) and if subjects have to get up during the night, sleep disturbances can already be observed before the actual alarm rings (Torsvall & Åkerstedt, 1988). Anticipating a stressful speech after a nap delays sleep onset, decreases the amount of N2 sleep and increases the amount of wake (Gross & Borkovec, 1982). Similar trends were observed in a night study, where

subjects anticipated demanding cognitive tasks after sleep (Elder et al., 2018). Two additional studies investigated the effect of anticipating a stressful speech after sleep and did not find any effects on overall sleep parameters (Germain et al., 2003; Hall et al., 2004). However, they observed physiological changes during later periods of sleep, including the number of rapid eye-movements during REM sleep at the end of the night (Germain et al., 2003) and a constant increase of high frequency power in the electrocardiography (ECG) across successive NREM periods (Hall et al., 2004). Thus, studies examining the effect of anticipating a stressful event on sleep support the notion that changes occur during later sleep periods which are closer to the time-point when the event is expected.

In sum, the effects of stress on sleep are probably dynamic: While acute and completed stressful events before sleep (pre-sleep stress) might mainly impact early sleep periods (possibly mediated by the time-limited occurrence of physiological stress-responses), anticipation of stressful events after sleep (post-sleep stress) might mainly rely on maintained cognitive arousal and occurs during later sleep periods. To our knowledge, no study so far has directly compared the dynamic effects of direct pre- vs. anticipated post-sleep stress on sleep. Moreover, previous studies are lacking and in-depth analysis of sleep physiology by including analysis of EEG power and sleep oscillations such as slow-waves and sleep spindles. Our study aims to fill these gaps.

Due to inconsistent results of anticipating stress on sleep physiology, we first aimed to investigate and replicate the previously reported negative effect of anticipating stress on subjective and objectively measured sleep. In addition, we examined how the effect of stress on sleep differs when stress is anticipated vs. conducted directly prior to sleep. In two counterbalanced within-subject experimental nap sessions, 67 healthy young subjects performed the TSST and a relaxation task in a virtual reality environment. In addition, half of the subjects only received the task instructions directly before sleep and anticipated to perform the tasks after sleep (post-sleep), while the other half performed the tasks directly before sleep (pre-sleep). We preregistered our hypothesis that cognitive arousal is increased in the stress condition compared with the relaxation condition and decreases objective (sleep onset latency and SWA/beta power ratio) and subjective sleep quality in the post-sleep group. Furthermore, we explored effects of stress compared with relaxation on heart rate, sleep stages and sleep parameters including an in-depth analysis of slow-waves, slow and fast spindles and their progression across the nap. We

explored effects of the type of stress (post-sleep vs. pre-sleep) on all parameters. We were particularly interested in possible differences in dynamic changes of sleep parameters and assumed that the effect of stress on sleep occurs more strongly in temporal proximity to the stressor. Thus, we hypothesized that direct stress before sleep mainly affects early sleep whereas anticipating stress mainly affects later periods of sleep.

In line with our hypothesis, anticipation of a stressful task increased pre-sleep cognitive arousal, while subjective and objective physiological arousal remained unchanged. As preregistered, the anticipation of a stressful task decreased objective as well as subjective sleep quality. Likewise, performing the tasks before sleep induced cognitive arousal and decreased objective as well as subjective sleep quality, but additionally increased subjectively rated and objective somatic arousal. Moreover, objective sleep quality, slow-wave parameters and the number of spindles were decreased in both studies across the whole sleep period, but the progression of parameters across the nap differed between both groups. In line with our hypothesis, sleep in the post-sleep group was especially affected during late sleep, while sleep in the pre-sleep group was mainly affected during early sleep. This trajectory was mirrored by an increased heart rate during early sleep in the pre-sleep group.

Materials and Methods

Participants

The experiment examined the effect of a stress-inducing task compared with a relaxation task on sleep according to a within-subject design. Seventy-one healthy German- or French-speaking subjects participated in the experiment. Four subjects were excluded from all analysis due to no sleep in at least one of the naps (3 subjects) or a sleep period time lower than 3 SD below the mean (7 min; 1 subject). The final sample consisted of 67 young females (mean age = 21.84 ± 2.84 y [M±SD], age range 18–30 y). In an additional group factor, half of the subjects (N = 33) anticipated the tasks after sleep (post-sleep group; mean age = 22.30 ± 2.87 y [M±SD], age range 18–30 y), while another group of subjects (N = 34) conducted the tasks directly before sleep (pre-sleep group; mean age = 21.38 ± 2.79 y [M±SD], age range 18–30 y).

Subjects neither took any sleep influencing medication nor reported any neurological, psychiatric or sleep-related disorders and confirmed that no surgical procedures had been performed within the three months prior to the experiment. None of the subjects reported taking

regular naps, working shift work, or having been on an intercontinental flight six weeks prior to the experiment. All participants were instructed to wake up before 08.00 h and not to drink alcohol or caffeine on experimental days. Subjects were compensated CHF 110 for attending all three sessions. The study was approved by the internal review board of the University of Fribourg (No. 475). Participants signed an informed consent form after an experimenter explained the study procedure and possible consequences.

Design and Procedure

Subjects participated in three sessions including a 90-minute nap. After an adaptation nap, participants slept in the laboratory for two sessions while polysomnographic data (EEG, electromyography (EMG) and electrooculography (EOG)) were recorded. Participants arrived at the sleep laboratory between 10.30 am and 1.00 pm. Both experimental sessions took place on the same day of the week, one week apart, and participants completed questionnaires throughout the experiment. During the experimental sessions, either a stressful or a relaxing task was performed using a head-mounted display. The order of condition was counterbalanced across participants according to a within-subjects design. In an additional between-subject factor, half of the sample received the instruction for the tasks before sleep and performed the tasks after the nap (post-sleep group), while the other half of subjects conducted the tasks directly before sleep (pre-sleep group).

Stress and Relaxation Tasks in Virtual Reality

Tasks were conducted using an HTC VIVE PRO head-mounted display (https://www.vive.com) with two 3.5” AMOLED displays with a resolution of 1440 x 1600 per eye (2880 x 1600 combined), 90 Hz refresh rate, 110° field-of-view and attached stereo headsets (HTC Corporation, Taoyuan, Taiwan). Tracking of the headset was achieved with two SteamVR Base Stations 2.0 using the runtime software SteamVR (Valve Corporation). The headset was connected to a PC running Windows 10 Enterprise (64-bit), an Intel Core i7-8700k, 64 GB RAM, NVIDIA GeForce GTX 1080 Ti and 512 GB SSD.

In the stress condition, a virtual reality version of the Trier Social Stress Test (TSST) was performed (Kirschbaum et al., 1993). The TSST is an established test method to induce acute social stress in a laboratory setting (Allen et al., 2017) and induces a similar stress response, when conducted in virtual reality (Liszio et al., 2018; Zimmer et al., 2019). During this test, subjects had to give a 5-minute speech to convince a panel of three people why they would be

the best candidate for a job position. If participants stopped before the 5 minutes expired, an experimenter asked standard questions according to the TSST manual. Subsequently, in a second math task in front of the panel, participants were requested to count continuously backwards from 2023 in increments of 17, again for 5 min. If subjects made a mistake, they were asked by an experimenter to start again at 2023. In this study, the panel was presented with a pre-recorded virtual reality video showing three university professors sitting behind a table. The 15-minute video was played using the Skybox VR Player (https://skybox.xyz/en/). Subjects were standing throughout the task and instructions and questions during the task were provided by an experimenter located behind the subject.

In addition, participants were informed on-screen prior to the task that they would be recorded with a video camera and microphone for later behavioral and vocal analyses and that the task has been shown to successfully induce psychological and physiological stress. Moreover, they were informed that high task performance reflects good resilience and stress management and is associated with job satisfaction and career success, while low performance is associated with a higher risk for cardiovascular diseases, sleep disturbance, depression, and burnout. Additionally, they were told that they would receive results on their performance with comparative values for their age group and an additional payment of 10 CHF if they performed very well in both stress-inducing tasks. Lastly, it was pointed out that high performance is crucial for the bachelor and master theses and dissertations associated with the project.

In the relaxation condition, subjects were told to relax in a beautiful virtual reality environment, without further instructions. We used Nature treks VR (https://greenergames.net/), a relaxation game that allows the user to explore nature-based virtual reality environments such as tropical beaches, green meadows and underwater oceans. The game was launched via Steam (Valve Corporation). First, subjects selected 2 out of 9 virtual reality environments based on a representative image of an environment in the game's menu, where they assumed to be able to relax best. Next, participants were familiarized with the motion controls using the righthand controller. To avoid motion sickness, movement was only possible via a teleport function. All other functions of the game were disabled. Subjects were instructed to search for a relaxing place within both environments. After visiting both environments, they were asked to choose the environment perceived as more relaxing and to continue the task in this environment at the previously chosen relaxing place. At this location, the experimenter withdrew the controller and

informed participants that they would now remain at this place for about 10 minutes and relax. No further instructions were provided and subjects were allowed to design the relaxation exercise individually. Subjects sat during the task and questions during the task were delivered by an experimenter who was located behind the subject.

In addition, participants were informed on-screen prior to the task that no video or audio recording would be made and that the task has been shown to successfully induce psychological and physiological relaxation. Moreover, they were informed that relaxation tasks are helpful for good health and lasting well-being, and that frequent practice of relaxation tasks is associated with high resilience and stress management, job satisfaction and career success, and reduces the risk of cardiovascular disease, sleep disturbances, depression and burnout. Furthermore, they were told that no other tasks would follow after the relaxation task, there will be no comparison to other subjects and that the payment would not be affected by this task.

After reading through the on-screen task instructions, subjects were given 3 minutes to take notes, either for their speech to the panel or on how they planned to relax in the virtual reality environment. They were informed that the notes could not be accessed at a later time. The post-sleep group received the task instructions and completed taking notes on the tasks before sleep. Again, after sleep, they received the task instructions and conducted the tasks. After performing the stressful task, subjects in both groups were provided with their best performance in the arithmetic task and verbally debriefed that no further feedback on their performance would be given, as no further analyses (e.g., voice, behavior) would be performed, no video or voice recording would be made, and that all subjects would receive the additional payment of CHF 10. A written debriefing sheet including this information was signed by each subject at the end of the experiment.

Questionnaires

During the adaptation session, subjects completed a questionnaire on general personal information (sex, age, education status, handedness, native language), the Pittsburg Sleep Questionnaire Inventory (Buysse et al., 1989), the Morningness-Eveningness-Questionnaire (Griefahn et al., 2001), the Tellegen Absorption Scale (Tellegen & Atkinson, 1974), the Resilience Scale for Adults (Friborg et al., 2003), the rumination subscale of the Rumination-Reflection Questionnaire (Trapnell & Campbell, 1999) and the trait-anxiety subscale of the State-trait Anxiety Inventory (Spielberger, 1970). At the beginning of all three sessions, subjects

were asked about their sleep the previous night, anticipation of an important or stressful task, general stress level within the past week and consumption of alcohol, caffeine and drugs. After sleep, subjects filled out the Pre-sleep Arousal Scale (Nicassio et al., 1985) and the SF-A/R (Görtelmeyer, 2011). The Multidimensional Mood Questionnaire (MDBF, short form A; Steyer et al., 1997) and a single question about their stress level (10 – point Likert scale from 1 = not at all to 10 = very much) was performed at the beginning of the each session, directly before sleep as well as after sleep in all three sessions. After the virtual reality tasks, subjects filled out the Simulator Sickness Questionnaire (Kennedy et al., 1993) and the Igroup Presence Questionnaire (Schubert et al., 2001). In addition, the single stress question was asked at the beginning, after 5 minutes and at the end of the virtual reality tasks. One additional measurement of the MDBF was conducted after the virtual reality tasks for participants in the post-sleep group.

The Pre-sleep Arousal Scale (PSAS; Nicassio et al., 1985) was the first questionnaire completed after waking up to assess pre-sleep cognitive and somatic arousal. Subjects rated how intensely they experienced 16 pre-sleep symptoms during the pre-sleep period before the nap on a 5-point likert-scale from 1 (not at all) to 5 (extremely). Eight items referred to cognitive arousal (PSAS-C; e.g., worry about falling asleep; thinking or ruminating about events of the day) and another eight concerned somatic arousal (PSAS-S; e.g., heart racing, pounding, or beating irregularly; a cold feeling in your hands, feet or body in general). Subscale scores ranged from 8 to 40 with higher scores indicating increased cognitive or somatic arousal. Both subscales are internally consistent with a Cronbach's alpha of 0.88 for the PSAS-C and 0.79 for the PSAS-S in college students (Nicassio et al., 1985). For the PSAS-C, values > 16 (with a mean item-level response higher than 'slightly') have been suggested as high cognitive arousal and values ≤ 16 as low cognitive arousal (Kalmbach et al., 2020) and increased values for insomnia patients (Vochem et al., 2019). In addition, subjects were asked on a single item, if they were worried about the announced task or about the already conducted task before sleep.

Subjective sleep quality was assessed via the sleep quality subscale of the SF-A/R (Görtelmeyer, 2011) after the nap. The scale includes four indices indicating difficulty in initiating sleep (1 item), difficulty in maintaining sleep (2 items), early waking with inability to return to sleep (1 item), and general sleep characteristics (6 items). Scores between 1–5 indicate absent (1) or strongly distinct (5) characteristics of good sleep quality. Cronbach's alpha with respect to the subscale sleep quality is .89 in healthy subjects.

Polysomnographic Recording

Electroencephalographic data were recorded at F3, F4, C3, C4, P3, P4, O1, O2 and left and right mastoids using single (Ag/AgCl) electrodes with a BrainAmp amplifier (Brain Products, Gilching, Germany), a sampling rate of 500 Hz, Cz as a physical online reference and Fpz as a ground electrode. Two electrodes were placed laterally to the outer canthi of the left and right eye to collect electrooculographic (EOG) data. Two bipolar chin electrodes collected electromyogram (EMG) data, and two bipolar electrodes collected electrocardiogram data. Impedances were kept below 10 kΩ for EEG, EOG and EMG electrodes.

For sleep scoring, data were re-referenced against contralateral mastoids, and standard filter settings suggested by the AASM (Iber et al., 2007) were applied (e.g., EEG 0.3–35Hz) with an additional notch filter (50 Hz). Data were exported in EDF format and scored by a central scoring facility following the AASM guidelines with a validated scoring algorithm and visual quality control (Anderer et al., 2010). Results were manually checked by additional scorers, who were blind to the experimental condition. In addition to sleep scoring data, the scoring algorithm also provided microstructural arousal and stage shift parameters. Sleep scoring parameters were computed using the SleepTrip toolbox (https://www.sleeptrip.org/; RRID: SCR_017318).

Preprocessing and Artifact Rejection

EEG data preprocessing was conducted using BrainVision Analyzer software (2.2; Brain Products, Gilching, Germany). Data were filtered using a high- (0.1 Hz) and low-pass (40 Hz) filter with an additional notch filter at 50 Hz and re-referenced to averaged mastoids. Next, data were segmented in 30 s epochs of NREM sleep based on sleep scoring results. Afterwards, data were further segmented into equally sized segments of 2048 data points (4s, 102 points overlap). Next, an automatic artifact rejection was applied (Ackermann et al., 2015) based on the following three criteria: (1) the maximum difference in EMG activity < 150 µV, (2) maximum voltage step in all EEG channels < 50 µV/ms, (3) maximum difference in EEG activity < 500 µV in all EEG channels. The number of removed segments were manually checked. For analysis of oscillatory activity during sleep (power analysis, spindle detection and slow-wave detection), artifact rejected data were exported as continuous data and further analyzed using the SleepTrip toolbox (https://www.sleeptrip.org/; RRID: SCR_017318), which is based on FieldTrip functions (http://fieldtriptoolbox.org; RRID: SCR_004849; Oostenveld et al., 2011) and the SpiSOP tool (www.spisop.org; RRID: SCR_015673).

Power Analysis

To investigate differences in EEG power during sleep, we used the default settings of SleepTrip (10% segment overlap, 20% Hanning window). Mean power values (μV^2) of each channel were exported for SWA (0.5–4.5 Hz), theta activity (4.5–8 Hz), alpha activity (8–11 Hz), slow spindle activity (11–13 Hz), fast spindle activity (13–15 Hz) and beta activity (15 – 30 Hz) during NREM sleep. As preregistered, we computed the ratio between SWA and beta activity.

Outliers were identified based on SWA values in both studies (outlier criterion: 3 SD +/– mean) and replaced with values from the contralateral electrode. If both hemispheres exceeded the outlier criterion over one lobe, we replaced the values with data from the nearest electrode. One subject was excluded from the power analysis due to SWA values exceeding the outlier criterion in all electrodes in the stress condition and three electrodes in the relaxation condition. Additional exploratory analysis on 5 min segments of sleep was conducted on the sleep scoring data without an artifact rejection procedure.

Slow-wave Detection

Slow-wave detection was conducted with the default settings from SleepTrip, which are comparable to previously reported settings (Beck, Cordi, & Rasch, 2021). Two parameters were adjusted compared with the previously reported setting, which are a reduced amplitude threshold for artifact detection of 600 µV (previously 1000 µV) and a decreased factor of 1.00 (previously 1.25) for the means of the amplitudes and the negative half-wave peak potential. As a result, number of slow-waves, density per 30s epoch NREM sleep, mean amplitude, duration, down slope (value of the negative half-wave peak divided by the time from the first zero-crossing to the trough in µV/s) and up slope (absolute value of the negative half-wave peak divided by the time from the trough to the next zero-crossing in µV/s) were calculated for each participant and channel during NREM sleep.

Spindle Detection

Prior to the detection of sleep spindles, individual slow and fast spindle frequency peaks were visually determined based on the NREM power spectrum of each dataset. Slow spindle peaks were determined in frontal channels (F3, F4) and fast spindle peaks in parietal channels (P3, P4) due to expected power maxima over those regions (Mölle et al., 2011). Similar to a previous nap study (Beck, Cordi, & Rasch, 2021), average slow spindle peaks ranged between

9.5 and 13.3 Hz with an average frequency of 11.71 ± 0.81 Hz (*M* ± *SD*), and fast spindle peaks ranged between 12.5 and 15.5 Hz with an average frequency of 14.16 ± 0.45 Hz (*M* ± *SD*).

To detect sleep spindles, default settings from SleepTrip toolbox were used. They are based on algorithms used in (Mölle et al., 2002; Mölle et al., 2011) and have been explained in detail (Beck, Cordi, & Rasch, 2021). Two parameters were adjusted, which are an increased minimal amplitude threshold factor of 1.75 SD (previously 1.5 SD) and a reduced maximum duration of each spindle to 2 s (previously 3 s).

Electrocardiography

Electrocadiographic (ECG) data were cut into the whole sleep time and 15 min segments and exported in EDF+ format using the BrainVision Analyzer software (2.2; Brain Products, Gilching, Germany). Data was further analyzed using Kubios HRV Premium 3.2.0 (Kubios Oy, Kuopio, Finnland). The software includes an automatic artifact correction based on successive RR peak intervals. Data were analyzed in the time and frequency domain and the following variables were included in our analysis: mean heart rate (as an index for physiological arousal (Kogler et al., 2015)) and the activity of the parasympathetic (PNS-index, based on mean RR peak intervals) as well as sympathetic nervous system (SNS-index, based on mean heart rate) to assess physiological stress.

Statistical Analysis

Statistical analyses were performed using Rstudio version 1.1.456 (R Core Team, 2018). We initially report the results of our preregistered analyses of the post-sleep group, which received only task instructions before sleep and performed the tasks after sleep. We performed repeated-measures analysis of variance (ANOVA) containing the within-subject factor condition (stress vs. relaxation) to analyze cognitive (PSAS-C) and somatic pre-sleep arousal (PSAS-S), objective sleep quality (SOL, SWA/beta power ratio) and subjective sleep quality (subscale SQ, SOL). For the analysis of SWA/beta power ratio, we added the within subject factors hemisphere (left, right) and lobe (frontal, central, parietal). Post-hoc tests for significant main effects with more than two levels and interactions comprised paired Student's *t*-tests and Welch's *t*-test.

To examine whether anticipating a stress or relaxation task after sleep affects arousal and sleep differently than performing a stress or relaxation task before sleep, we added data from our second group to the analyses that means those subjects who performed the stress and relaxation task before sleep (pre-sleep group), and therefore included the between-subject factor group

(post-sleep vs. pre-sleep). First, we analyzed if the group factor affected the objective (ECG) and subjectively rated (PSAS-C, PSAS-S) arousal level. Next, we explored effects on the subjective evaluation of sleep (SF-A/R), objective sleep parameters (SWS, N2, N1, REM, WASO) and sleep oscillations (power bands, sleep spindles and slow-wave parameters). For objective sleep parameters and sleep oscillations, we additionally explored the progression over the nap in 5-min segments by adding the factor segment (0, 5, 10, … 80 min). Associations were explored using Pearson product-moment correlations. In case of statistically significant results, effect sizes are reported with partial eta squared (η_p) for main effects and interactions and Cohen's *d* for *t*-tests. If the assumption of sphericity was violated, Greenhouse-Geisser corrected *p*-values are reported. Data are presented as means ± standard error. The level of significance was set at $p < .05$ (two-tailed). For the pre-registered directional hypothesis, one-sided significance thresholds were used.

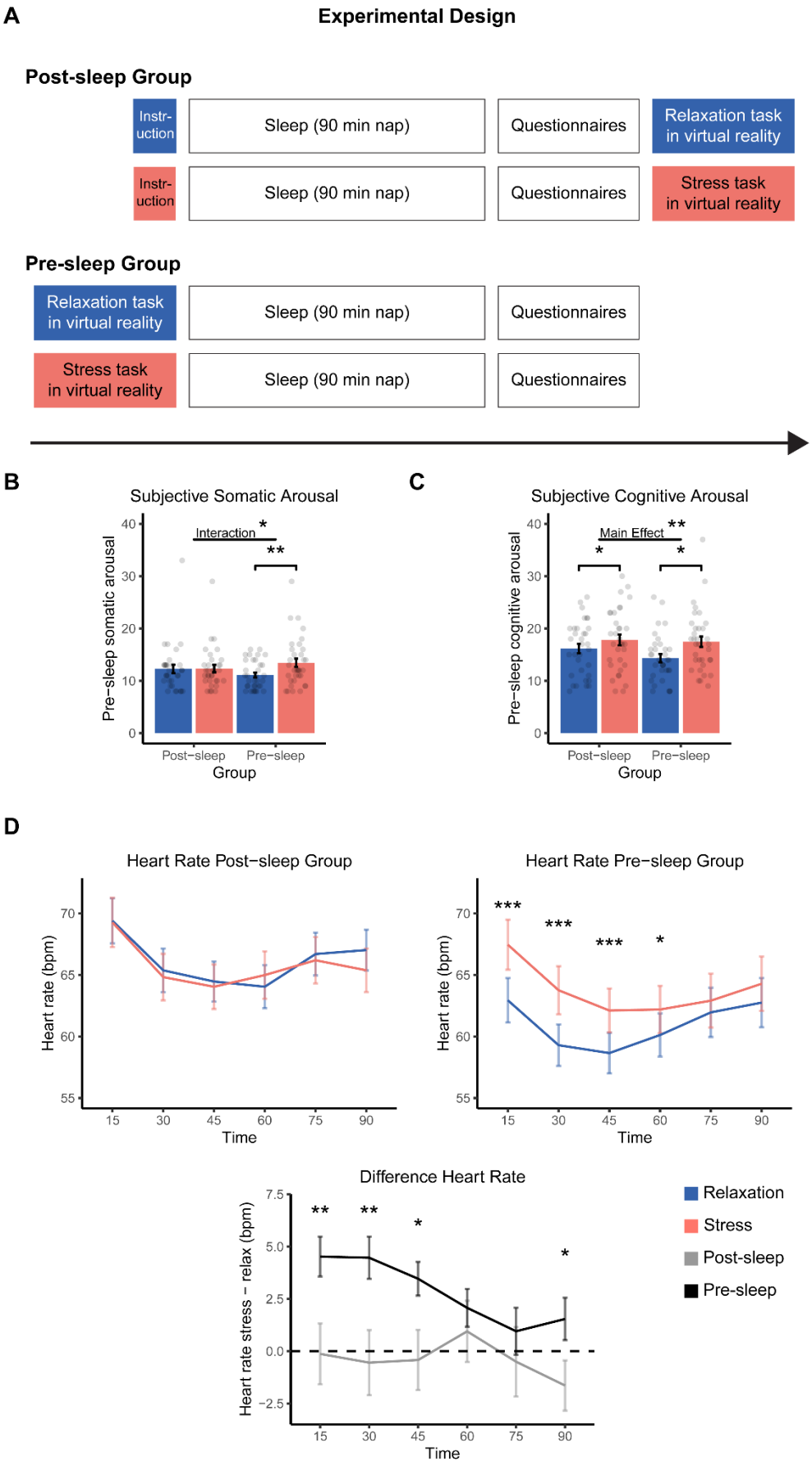

A
Experimental Design
Post-sleep Group
Instr-uction
Sleep (90 min nap)
Questionnaires
Relaxation task in virtual reality
Instr-uction
Sleep (90 min nap)
Questionnaires
Stress task in virtual reality
Pre-sleep Group
Relaxation task in virtual reality
Sleep (90 min nap)
Questionnaires
Stress task in virtual reality
Sleep (90 min nap)
Questionnaires
B
Subjective Somatic Arousal
Interaction
Pre−sleep somatic arousal
Post−sleep
Pre−sleep
Group
C
Subjective Cognitive Arousal
Main Effect
Pre−sleep cognitive arousal
Post−sleep
Pre−sleep
Group
D
Heart Rate Post−sleep Group
Heart rate (bpm)
Time
Heart Rate Pre−sleep Group
Heart rate (bpm)
Time
Difference Heart Rate
Heart rate stress − relax (bpm)
Time
Relaxation
Stress
Post-sleep
Pre-sleep

Figure 1. Experimental design and results of subjective and objective arousal. (**A**) Sixty-seven healthy participants either anticipated a stress or a relaxation task after sleep (post-sleep, $N = 33$) or conducted the tasks before sleep (pre-sleep group, $N = 34$). In the stress condition, a virtual reality version of the Trier Social Stress Test (TSST) was performed, while in the relaxation task, subjects were told to relax in a beautiful virtual reality environment without further instructions. (**B**) Subjective pre-sleep somatic arousal was comparable between the stress and the relaxation condition in the post-sleep group. In contrast, subjective somatic pre-sleep arousal was increased in the stress compared with the relaxation condition in the pre-sleep group. These differences between groups were supported by a significant interaction between condition and group. (**C**) Subjective cognitive pre-sleep arousal was increased in the stress compared with the relaxation condition in both groups. (**D**) In the post-sleep group, objective physiological arousal (heart rate, bpm) was comparable between the stress and the relaxation condition across the sleep period (**D**, left plot). In the pre-sleep group, objective physiological arousal was increased in the stress compared with the relaxation condition during the first hour of sleep (**D**, right plot). Changes in heart rate from the relaxation to the stress condition in the pre-sleep group mainly differed during early sleep from the post-sleep (**D**, bottom plot). For the preregistered directional hypotheses in the post-sleep group (left bars, **A** and **B**), one-sided significance thresholds were used. Values are displayed as mean ± SEM. *** $p < .001$, ** $p < .01$, * $p < .05$.

Results

Preregistered analysis: Effects of anticipated stress vs. anticipated relaxation

Pre-sleep Subjective Arousal. First, we tested the effects of the post-sleep group, which only received the instructions before sleep and performed the tasks after sleep, on subjective arousal. The anticipation of stress significantly increased cognitive arousal (17.82 ± 1.03 on the PSAS-C scale, range 8–30) compared with the relaxation condition (16.18 ± 0.91; range 8–26; $F(1,32) = 3.79$, $p = .030$, $\eta_p = .11$, see Figure 1 C). However, anticipation of stress did not increase subjective somatic arousal (stress: 12.33 ± 0.70; relaxation: 12.27 ± 0.80; $F(1,32) = 0.02$, $p = .45$, $\eta_p < .01$, see Figure 1 B). Therefore, anticipating stress selectively increased cognitive, but not somatic arousal, which was further supported by an interaction between the two arousal scales and the experimental condition reached significance ($F(1,32) = 4.19$, $p = .049$, $\eta_p = .12$).

Subjective Sleep Quality. For subjective sleep quality, our two preregistered hypothesis in the post-sleep group were not confirmed: Subjective sleep quality did not differ between the anticipated stress and relaxation condition ($F(1,32) = 0.00$, $p = .48$, $\eta_p < .01$, Figure 2B, post-sleep group). In addition, the difference in subjective sleep onset latency did not reach significance (18.84 ± 1.86 min vs. 16.45 ± 1.72, for stress vs. relaxation condition, respectively, $F(1,30) = 2.20$, $p = .074$, $\eta_p = .07$, see Figure 2A, post-sleep group). For subjective sleep onset latency, two subjects had to be excluded due to values larger than 3 SD from the mean.

Objective Sleep Quality. For objective sleep quality, we preregistered a decrease by anticipated stress in two variables: sleep onset latency (SOL) and the ratio of SWA and beta power during NREM sleep (SWA/beta power). As predicted, anticipated stress significantly increased SOL in the anticipated stress condition (16.76 ± 2.57 min) compared with the relaxation condition (12.94 ± 1.74 min; $F(1,32) = 4.26$, $p = .024$, $\eta_p = .12$; see Figure 2C, post-sleep group). Similarly, anticipation of stress after sleep significantly decreased the SWA/beta power ratio (329.39 ± 44.37) compared with the relaxation condition (417.90 ± 54.26; $F(1,31) = 2.90$, $p = .049$, $\eta_p = .09$; see Figure 2D, post-sleep group). One subject had to be excluded in this analysis due to values larger than 3 SD of the mean. Thus, both our pre-registered hypotheses were confirmed therefore showing that anticipation of stress significantly decreases objective sleep quality.

Comparisons Between Direct Pre-sleep vs. Anticipated Post-sleep Stress

In addition to our pre-registered analysis in the post-sleep group, we recruited a second experimental group which performed the stress and relaxation directly before the nap (pre-sleep group). We repeated our analyses on our main parameters with the time of intervention (post-sleep vs. pre-sleep) as additional group factor.

Pre-sleep Subjective Arousal. The analysis on cognitive arousal revealed a main effect of condition (stress vs. relaxation; $F(1,65) = 10.79$, $p = .002$, $\eta_p = .14$), but neither a significant interaction with the time of the intervention (post-sleep vs. pre-sleep) nor a main effect of this group factor (both $p > .30$). Thus, both the anticipation of post-sleep stress and real pre-sleep stress increase cognitive arousal to a similar extent compared with the relaxation condition (see Figure 1C). In contrast, we observed a significant interaction between condition and the time of intervention for somatic arousal ($F(1,65) = 6.44$, $p = .014$, $\eta_p = .09$; see Figure 1B): While somatic arousal was rated comparably between both conditions in the post-sleep group ($p = .90$),

subjects reported significantly higher somatic arousal in the pre-sleep group after stress compared with the relaxation condition ($t(33) = –3.09$, $p = .004$, $d = .53$).

Objective Arousal. The findings for subjective somatic arousal were supported by heart rate measured during the nap period. In the post-sleep group, which anticipated stress or relaxation task after the sleep period, the mean heart rate (beats per minute, bpm) during sleep was comparable between the stress (66.36 ± 1.73 bpm) and the relaxation conditions (65.77 ± 11.79 bpm; $p = .67$; see Figure 1D, left plot). In contrast, mean heart rate was increased in the stress (63.72 ± 1.94 bpm) compared with the relaxation condition in the pre-sleep group (60.97 ± 1.78 bpm; $t(33) = –3.50$, $p = .001$, $d = .60$; see Figure 1D, right plot). The interaction between condition and group (i.e., timing of the intervention) was significant ($F(1,65) = 4.39$, $p = .040$, $\eta_p = .06$). Interestingly, the differences between the stress and relaxation condition in the pre-sleep group were only present during the first half of the nap, whereas later time periods did not differ (interaction condition × time: $F(5,165) = 5.18$, $p = .002$, $\eta_p = .14$), suggesting an increased somatic arousal only during the first half of the nap. This was further supported by a significantly increased SNS index and decreased PNS index only during the first half of the nap in the stress compared with the relaxation condition in the pre-sleep group (interaction condition × time: SNS: $F(5,165) = 4.29$, $p = .004$, $\eta_p = .12$; PNS: $F(5,165) = 2.20$, $p = .105$, $\eta_p = .06$). In contrast, the SNS and PNS indices in the post-sleep group were comparable between the stress and relaxation condition at all timepoints.

Subjective Sleep Quality. Ratings of subjective sleep quality were not strongly affected by the stress vs. relaxation condition, irrespective of whether the intervention occurred before sleep or was only anticipated. We neither observed a significant main effect of condition nor an interaction with group (both $p > .15$, see Figure 2B). Exploratory post-hoc tests yielded a trend for an increased sleep quality in the pre-sleep group in the relaxation compared with the stress condition ($p = .071$). For subjective SOL, we observed a significant main effect of condition over both studies (($F(1,61) = 5.26$, $p = .025$, $\eta_p = .08$; Figure 2A). Two additional subjects had to be excluded due to values larger than 3 SD of the mean. The increase in subjective sleep onset latency in the stress compared to the relaxation condition occurred similarly in the post-sleep and the pre-sleep group, as we did not observe an interaction with the group factor ($p > .60$).

Objective Sleep Quality. Similar to subjective sleep onset latency ratings, stress increased objective SOL in both groups from 11.75 ± 1.17 minutes in the relaxation condition to

18.87 ± 1.87 in the stress condition (main effect of condition: $F(1,65) = 17.99$, $p < .001$, $\eta_p = .22$; see Figure 2C). However, the increase in objective SOL tended to be larger in the pre-sleep group compared with the post-sleep group (interaction condition × group: $F(1,65) = 3.82$, $p = .055$, $\eta_p = .06$). For objective sleep quality measured by the SWA/beta power ratio, we also observed a significant main effect of condition independent of the timing of the intervention. The SWA/beta power ratio was decreased in the stress condition (263.28 ± 24.52) compared with the relaxation condition (332.15 ± 33.22; $F(1,64) = 5.30$, $p = .025$, $\eta_p = .08$; see Figure 2D). The SWA/beta power ratio was equally decreased by anticipated and direct stress before the nap, as we observed no significant interaction between the condition and group factor (post-sleep vs. pre-sleep; $p = .53$). Exploratory post-hoc comparisons revealed a significant difference between the stress and relaxation condition only when the intervention was anticipated (post-sleep group), but not when it actually occurred before the nap (pre-sleep group; $p = .13$; see Figure 2D). Interestingly, beta power was comparable between the stress and the relaxation condition in both groups (main effect condition: $p > .80$; see supplementary Figure S1A).

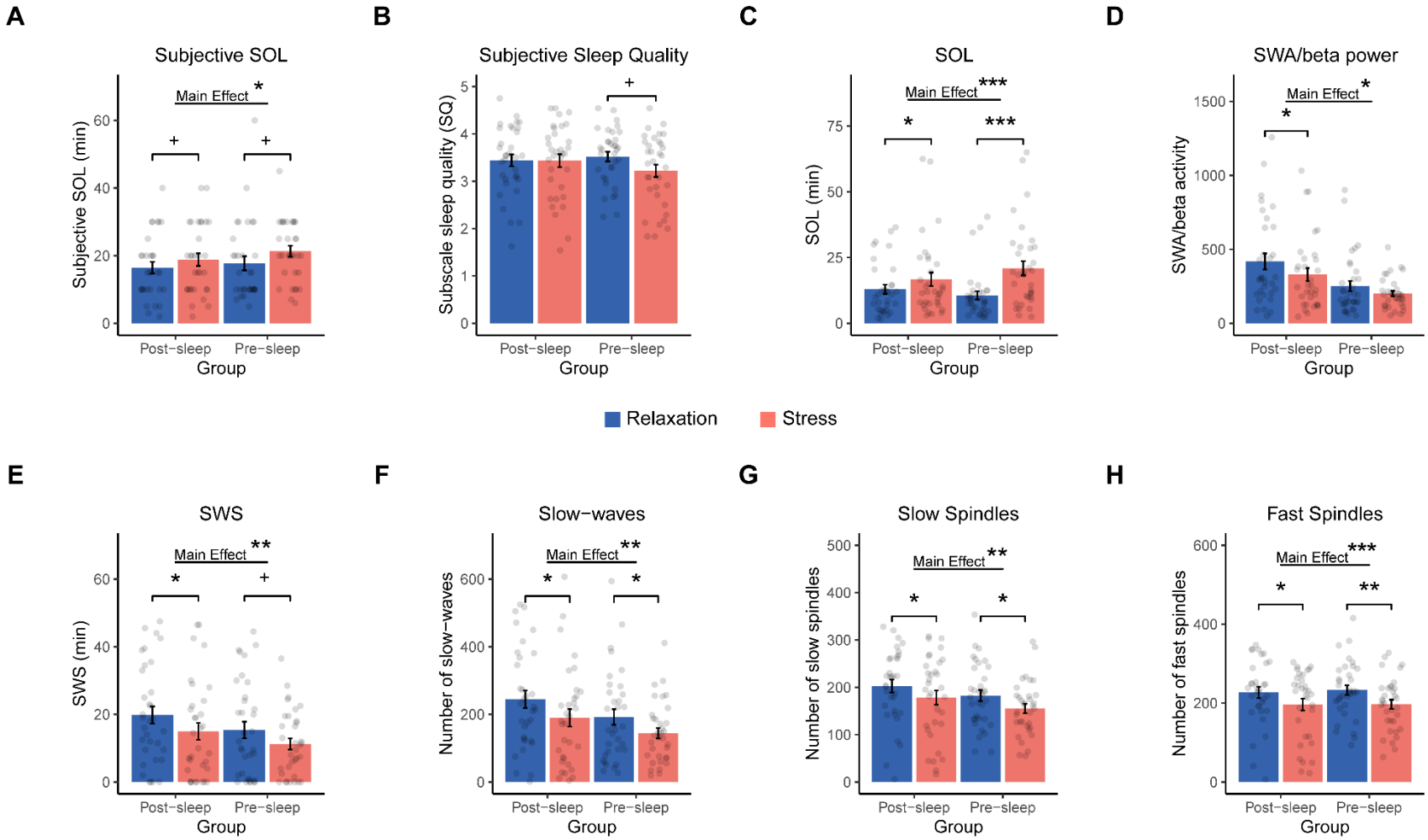


Figure 2. Effect of anticipated post-sleep stress vs. direct pre-sleep stress on sleep. Data are shown for the relaxation (blue bars) and the stress condition (red bars) separately for the post-sleep group anticipating the tasks after sleep and the pre-sleep group conducting the tasks before sleep. Displayed main effects refer to the factor condition (relaxation vs. stress). Significant main effects of condition suggested an increased subjective (**A**) and objective (**C**) sleep onset latency (SOL) in the stress condition, while subjective sleep

quality was comparable between conditions (**B**). In addition, the ratio between slow-wave activity and beta power (SWA/beta power, **D**), the amount of slow-wave sleep (SWS, **E**) and the number of slow-waves (**F**), slow spindles (**G**) and fast spindles (**H**) was similarly decreased in the stress condition of the post-sleep and the pre-sleep group. For the pre-registered directional hypotheses in the post-sleep group (left bars, **A–D**), one-sided significance thresholds were used. Values are displayed as mean ± SEM. *** $p < .001$, ** $p < .01$, * $p < .05$, $^{+}p < .10$.

Table 1. Sleep parameters in the stress and relaxation condition in the post-sleep and pre-sleep group

Parameter	Post-sleep relaxation	Post-sleep stress	Pre-sleep relaxation	Pre-sleep stress	*p*-value main effect condition	*p*-value interaction
TST	68.30 ± 3.16	63.67 ± 3.47	**70.82 ± 2.72**	**60.49 ± 3.30***	**.001***	.20
WASO	**3.72 ± 0.84**	**7.18 ± 1.89**$^{+}$	3.40 ± 0.66	3.88 ± 1.12	**.059**$^{+}$	.14
N1	11.26 ± 1.35	13.14 ± 1.64	11.34 ± 1.06	11.04 ± 1.02	.36	.21
N2	28.50 ± 2.06	26.50 ± 2.21	**34.62 ± 1.91**	**31.31 ± 2.04**$^{+}$	**.065**$^{+}$	.64
SWS	**19.80 ± 2.56**	**14.97 ± 2.52***	**15.40 ± 2.44**	**11.24 ± 1.65**$^{+}$	**.008***	.84
REM	8.74 ± 1.42	9.06 ± 1.38	9.47 ± 1.65	6.90 ± 1.43	.37	.25
Sleep efficiency	76.45 ± 3.54	71.11 ± 3.88	**79.11 ± 3.01**	**67.50 ± 3.69***	**<.001***	.20

Note. Means in minutes ± SEM. *p*-values are reported for the main effect of condition (stress vs. relaxation, within-subject) and the interaction between condition and the group factor (post-sleep vs. pre-sleep, between-subject). Total sleep time (TST), wake after sleep onset (WASO), sleep stage N1 and N2, slow-wave sleep (SWS), rapid eye movement (REM) sleep and sleep efficiency (time asleep / time in bed * 100). Effects are reported with * $p < .05$ and $^{+}p < .10$.

Sleep Architecture, Slow-waves and Sleep Spindles. Anticipated post-sleep stress and direct pre-sleep stress had also similar effects on sleep architecture. Participants spent less time in SWS in the stress condition (13.07 ± 1.50 min) compared with the relaxation condition (17.57 ± 1.78 min; main effect of condition: $F(1,65) = 7.54$, $p = .008$, $\eta_p = .10$; Figure 2E). This decrease occurred similarly in the post-sleep and the pre-sleep group (interaction condition × group: $p > .80$; see Table 1). A similar results pattern was observed for sleep efficiency and total sleep time. Trends for main effects of condition without an interaction with the group factor were also observed for wake after sleep onset (WASO) and sleep stage N2. In contrast, N1 and REM sleep remained unaffected by our manipulation (see Table 1).

To further explore whether certain characteristics of slow-waves might have responded differently to anticipation vs. real pre-sleep stress (in spite of the comparable effects in SWS and SWA/beta power ratio), we analyzed various parameters of single slow-waves during NREM sleep (count, density, amplitude, up- and down-slope, duration). Significant main effects of condition (stress vs. relax) independent of the timing of the intervention (pre- vs. post-sleep group) were observed for the number of slow-waves ($F(1,65) = 11.88$, $p = .001$, $\eta_p = .15$, see Figure 2F), the density of slow-waves ($F(1,65) = 4.76$, $p = .033$, $\eta_p = .07$), and the down-slope of slow-waves ($F(1,65) = 4.42$, $p = .039$, $\eta_p = .06$). The amplitude of slow-waves revealed a statistical trend for the factor condition ($F(1,65) = 3.78$, $p = .056$, $\eta_p = .05$), while the up-slope, mean frequency and duration of slow-waves were comparable between conditions. In addition to these main effects of condition, a significant interaction with group (pre- vs. post-sleep) and condition only occurred for slow-wave density in interaction with the factors lobe (frontal, central, parietal) and hemisphere (left vs. right; $F(2,130) = 4.48$, $p = .013$, $\eta_p = .06$). Post-hoc tests revealed that the reduction of slow-wave density in the stress condition was more pronounced in the post-sleep group ($t(32) = 1.96$, $p = .059$, $d = .34$) compared with the pre-sleep group ($p = .28$). Moreover, the main effect of condition within the post-sleep group anticipating the tasks after sleep was most pronounced and significant over the left frontal ($p = .042$) and right parietal cortex ($p = .047$), but also evident over the frontal right ($p = .067$), central left ($p = .10$), central right ($p = .053$), parietal left ($p = .08$) cortices. In addition, no significant differences appeared between the stress and relaxation condition in the pre-sleep group over any of the specific hemispheres and lobes (all $p > .19$).

Except for slow-wave density, the anticipation of stress and real pre-sleep stress appear to affect overall slow-wave parameters in a comparable manner. Moreover, we observed a similar results pattern for slow and fast spindles. Both slow and fast spindles were significantly decreased in the stress condition compared to the relaxation condition (both main effects of condition $p < .002$; see Figure 2G and 2H). We did neither observe an interaction between condition and the group factor (i.e., the timing of the intervention) for slow nor for fast spindles (both $p > 0.70$). In addition, a trend for a main effect of condition was also observed for frontal slow spindle density ($p = .082$), while the amplitude ($p = .70$) and frequency ($p = .22$) of frontal slow spindles was comparable between conditions. Parietal fast spindle density ($p = .42$), amplitude ($p = .23$), duration ($p = .18$) and frequency ($p = .13$) were comparable between conditions.

Dynamic Changes of SWA/beta Power Ratio, Slow-waves and Sleep Spindles.

Our previous analyses have almost uniformly shown that anticipating a stressful task after sleep and performing the stressful task before sleep have comparable effects on objective sleep parameters. However, direct stress before sleep increases subjective somatic arousal and dynamically affects heart rate mainly during the first half of sleep (Figure 1D), whereas anticipation of post-sleep stress does not change heart rate and subjective ratings of somatic arousal. Thus, we examined whether the effect of stress on sleep could show different dynamics of sleep parameters in the post-sleep stress group (only cognitive arousal) compared with the pre-sleep stress group (somatic and cognitive arousal).

We explored the progression of SWA/beta power ratio, SWS, SWA, beta power, slow-wave parameters and the number of slow spindles and fast spindles over the course of the nap, focusing on differences between the post-sleep and pre-sleep group. Over all these parameters, we observed a consistent pattern: Performing the stressful task before sleep resulted in a deterioration of sleep parameters in the first half of the nap, while anticipating the stressful task after sleep resulted in a deterioration of sleep parameters during the second half of the nap compared with the relaxation condition. This pattern was most pronounced for slow-wave parameters (Figure 4A–D) and spindles (Figure 3B and 3C) and supported by significant interactions between the factors condition (stress vs. relaxation), group (post-sleep vs. pre-sleep) and time (0, 5, 10, …, 80 min) for the number of slow-waves ($F(16,1040) = 2.78$, $p = .029$, $\eta_p = .04$), slow-wave density ($F(16,1040) = 2.83$, $p = .025$, $\eta_p = .04$), amplitude of slow-waves

($F(16,1040) = 4.12$, $p < .001$, $\eta_p = .06$), down-slope of slow-waves ($F(16,1040) = 3.69$, $p = .001$, $\eta_p = .05$), up-slope of slow-waves ($F(16,1040) = 3.03$, $p = .003$, $\eta_p = .04$), number of frontal slow spindles ($F(16,1040) = 3.82$, $p = .001$, $\eta_p = .06$) and number of parietal fast spindles ($F(16,1040) = 3.75$, $p = .001$, $\eta_p = .05$). The same interaction did not reach significance for SWA/beta power ratio ($p = .15$, see Figure 3A), SWA ($p = .061$) and SWS ($p = .073$), however the progression pattern remained the same: Anticipating stress after sleep reduced SWA/beta power ratio, SWA and SWS at the end of the nap (post-sleep group), while performing the tasks before sleep resulted in decreased SWA/beta power ratio, SWA and SWS in the first half of the nap (pre-sleep group). Interestingly, beta power was comparable between the stress and relaxation condition during late sleep in the post-sleep group (see supplementary Figure S1B) and even decreased during early sleep in the stress compared with the relaxation condition in the pre-sleep group (see supplementary Figure S1C).

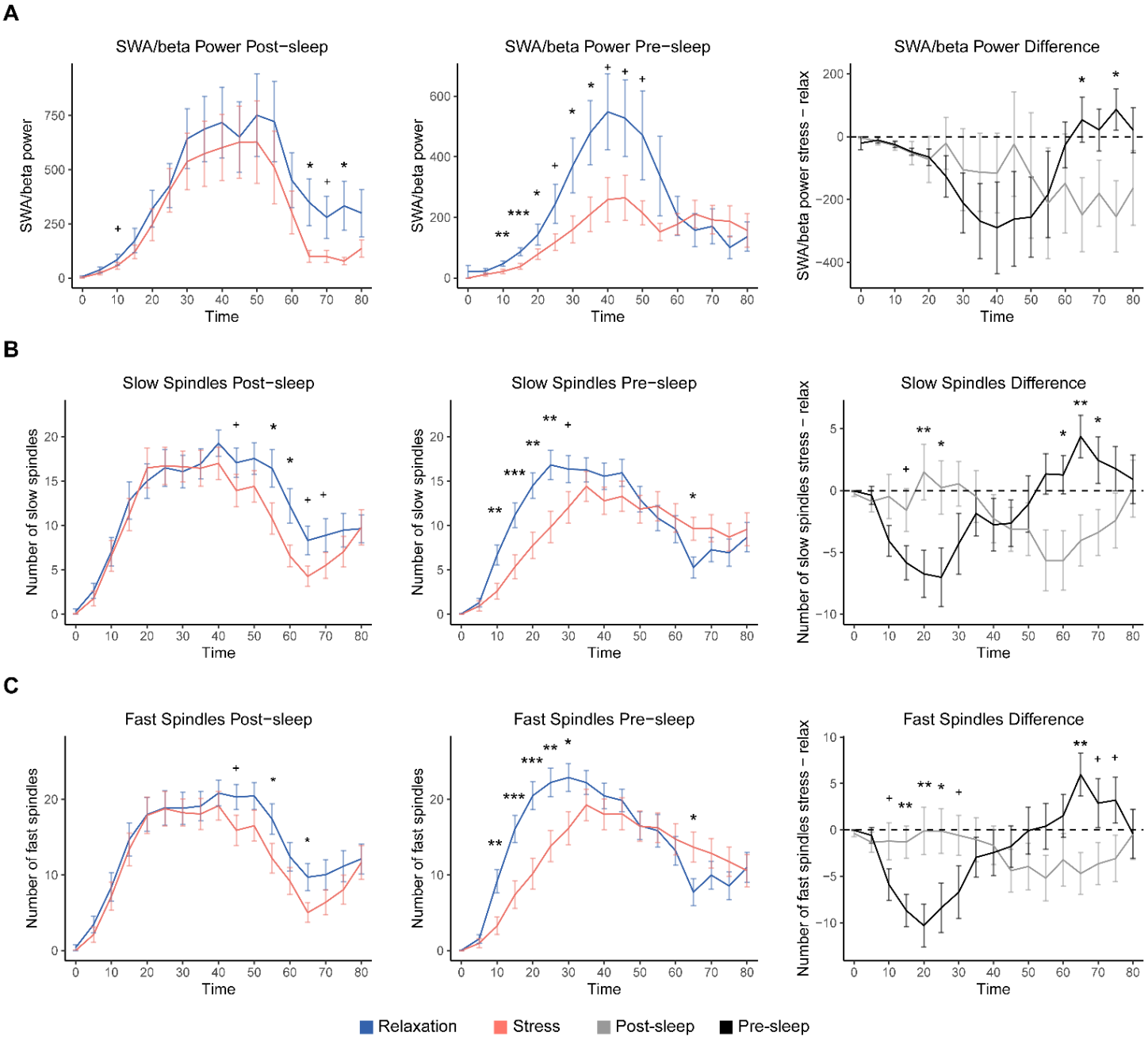
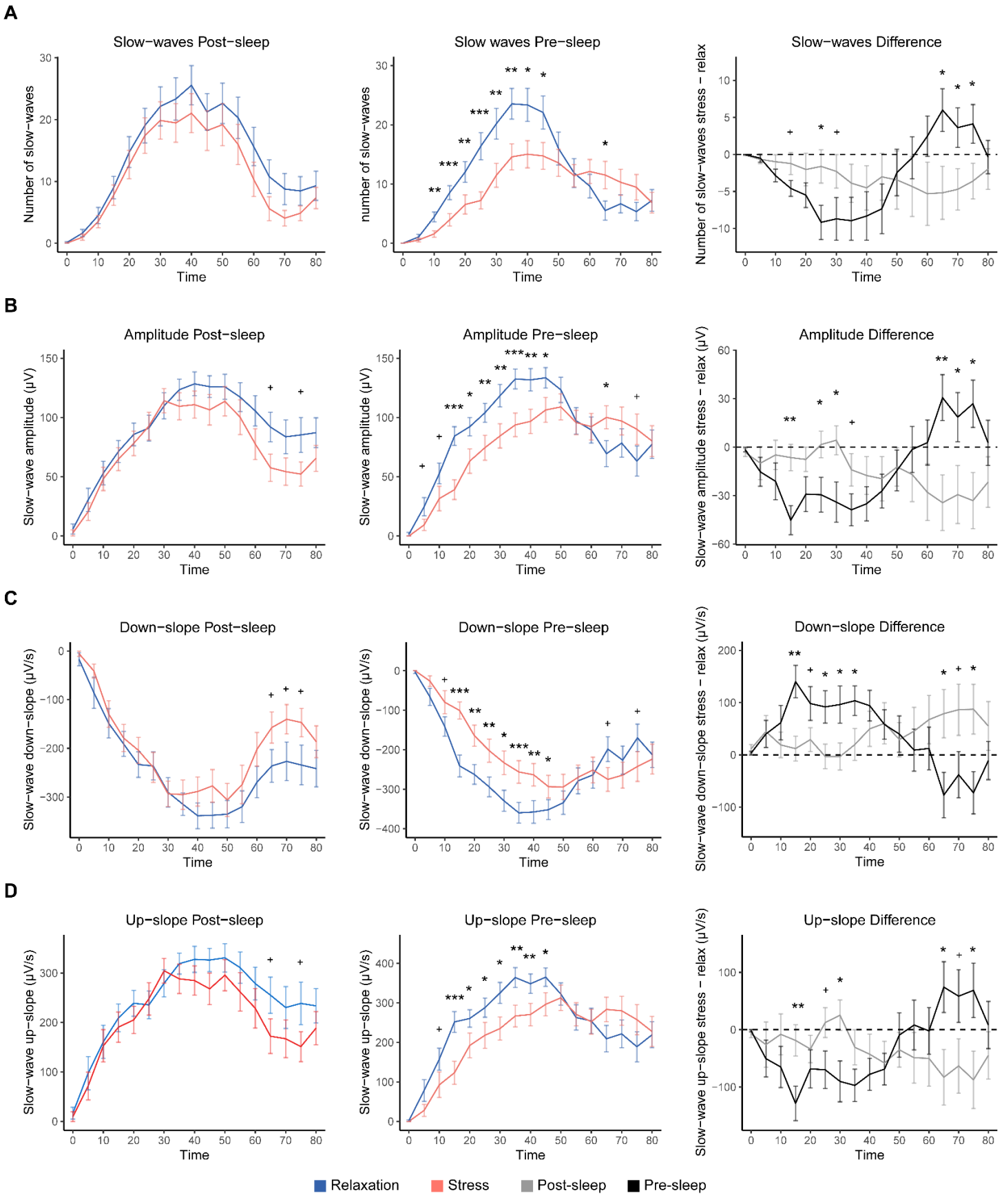


Figure 3. Dynamic changes of the ratio between slow-wave activity and beta power and of sleep spindles across the nap. Data are shown as mean ± SEM averaged over 5-minute time segments for the relaxation condition (blue line) and the stress condition (red line). The left column displays the data from the post-sleep group anticipating the tasks after sleep. The middle column displays the data from the pre-sleep group conducting the tasks before sleep. Differences between the stress and the relaxation condition are shown separately for the post-sleep (grey line)

and the pre-sleep group (black line) in the right column. Performing the stressful task before sleep resulted in a decrease in the ratio between slow-wave activity (SWA) and beta power, number of slow-spindles and number of fast spindles in the first half of the nap in the pre-sleep group (**A–C**, middle and right column), while anticipating the stressful task after sleep resulted in a decrease of these parameters during the second half of the nap (**A–C**, left and right column). Dynamic differences between groups were supported by significant interactions between the factors condition (stress vs. relaxation), group (post-sleep vs. pre-sleep) and time (0, 5, 10, …, 80 min) for the number of frontal slow spindles ($p = .001$) and number of parietal fast spindles ($p = .001$). *** $p < .001$, ** $p < .01$, * $p < .05$, $^{+}$ $p < .10$.


A
Slow−waves Post−sleep
Number of slow−waves
Time
Slow waves Pre−sleep
number of slow−waves
Time
Slow−waves Difference
Number of slow−waves stress − relax
Time
B
Amplitude Post−sleep
Slow−wave amplitude (µV)
Time
Amplitude Pre−sleep
Slow−wave amplitude (µV)
Time
Amplitude Difference
Slow−wave amplitude stress − relax (µV)
Time
C
Down−slope Post−sleep
Slow−wave down−slope (µV/s)
Time
Down−slope Pre−sleep
Slow−wave down−slope (µV/s)
Time
Down−slope Difference
Slow−wave down−slope stress − relax (µV/s)
Time
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Up−slope Post−sleep
Slow−wave up−slope (µV/s)
Time
Up−slope Pre−sleep
Slow−wave up−slope (µV/s)
Time
Up−slope Difference
Slow−wave up−slope stress − relax (µV/s)
Time
Relaxation
Stress
Post−sleep
Pre−sleep

Figure 4. Dynamic changes of slow-wave parameters across the nap. Data are shown as mean ± SEM averaged over 5-minute time segments for the relaxation condition (blue line) and the stress condition (red line). The left column displays the data from the post-sleep group anticipating the tasks after sleep. The middle column displays the data from the pre-sleep group conducting the tasks before sleep. Differences between the stress and the relaxation condition are shown separately for the post-sleep (grey line) and the pre-sleep group (black line) in the right column. Performing the stressful task before sleep resulted in a decreased number of slow-waves, amplitude, down-slope and up-slope in the first half of the nap in the pre-sleep group (**A–D**, middle and right column). Anticipating the stressful task after sleep (post-sleep group) resulted in a decrease of these parameters during the second half of the nap (**A–D**, left and right column). Dynamic differences between groups were supported by significant interactions between the factors condition (stress vs. relaxation), group (post-sleep vs. pre-sleep) and time (0, 5, 10, …, 80 min) for all four slow-wave parameters (all $p < .029$). *** $p < .001$, ** $p < .01$, * $p < .05$, $^{+}$ $p < .10$.

Discussion

The current study confirms previous findings that anticipation of psychosocial stress negatively affects subjective and objective sleep parameters. In addition, to our knowledge this study is the first study directly assessing systematic differences between the effect of anticipated vs. pre-sleep stress on both cognitive and physiological arousal as well as sleep. Anticipation of a psychosocial stressor increased cognitive arousal without a concomitant increase in subjective and objective somatic arousal. Moreover, the anticipation of stress reduced the SWA/beta power ratio, SWS, number of spindles and slow-wave parameters during late sleep. In contrast, pre-sleep psychosocial stress increased subjective and objective somatic arousal in addition to subjective cognitive arousal. This increase in somatic arousal mainly occurred during early sleep and in conjunction with a deterioration of sleep parameters.

Our study suggests that anticipating a psychosocial stressor after sleep overall deteriorates objective measures of sleep such as the SWA/beta power ratio, SWS, the number of slow-waves, slow- and fast spindles and sleep onset latency. These results are in line with previous research showing that anticipation of stress negatively affects SWS (Kecklund & Åkerstedt, 2004), decreases low/high EEG power (Wuyts, Valck, Vandekerckhove, Pattyn,

Exadaktylos, et al., 2012) and tends to decrease sleep efficiency and total sleep time and increase WASO (Elder et al., 2018). In addition, subjectively as well as objectively measured physiological arousal was comparable between the stress and the relaxation conditions in the post-sleep anticipation group, while cognitive arousal was increased. These results show that cognitive arousal without a concomitant physiological arousal is sufficient to disturb sleep and thereby suggests a direct effect of anticipated psychosocial stress on sleep physiology. This is in line with results showing an effect of anticipating a psychosocial stressor on sleep physiology, while physiological arousal measures could not account for these changes (Gross & Borkovec, 1982). In addition, the overall effect on sleep parameters in the post-sleep group were similar in comparison with the group conducting the same stressful task directly before sleep, which highlights the importance of future stressors for the effect of stress on sleep.

Such detrimental effects of the anticipation of a stressor on sleep are in line with findings in insomnia literature. The anticipation of a stressor is closely linked to the construct of worry, and more generally to cognitive arousal, which was increased in both groups of our study. Cognitive arousal is a decisive factor in the development and maintenance of sleep disturbances (Ballesio et al., 2020; Clancy et al., 2020; Kalmbach et al., 2020; Lemyre et al., 2020) and increased in insomnia patients compared with healthy controls (Spiegelhalder et al., 2012), especially while falling asleep (Hantsoo et al., 2013; Harvey, 2000; Jansson-Fröjmark & Norell-Clarke, 2012; Kalmbach et al., 2020). It has been shown to mediate the effect of stress on sleep (Tousignant et al., 2019) and is a key component in insomnia models (Espie, 2002; Harvey, 2002; Ong et al., 2012; Riemann et al., 2010). It is associated with subjective sleep quality and difficulties falling asleep (Pillai et al., 2014; Takano et al., 2012; Zoccola et al., 2009) and mediates the effect of sleep disturbances on future depressive symptoms (Batterham et al., 2012; Danielsson et al., 2013). In addition, cognitive arousal has been associated with objective sleep disturbances and physiological hyperarousal during the day and night and has been suggested to be a promising target for severe sleep disturbances (Kalmbach et al., 2020). In line with these results, reducing cognitive arousal with cognitive behavioral therapy for insomnia (CBT-I) has been linked to decreased post-treatment depression and anxiety symptoms (Ballesio et al., 2020). In addition, subjective data suggests that cognitive pre-sleep arousal predicts the effect of stress on sleep to a greater extent as compared to somatic arousal (Tousignant et al., 2019).

In contrast to our findings, several previous studies which experimentally induced anticipated stress before sleep, failed to show effects of anticipated stress on sleep depth (Elder et al., 2018; Germain et al., 2003; Gross & Borkovec, 1982; Hall et al., 2004). This might be explained by a failure to induce sufficient stress (Elder et al., 2018) or featuring an underpowered design to detect effects on overall sleep ($N = 15$, within subjects comparison (Born et al., 1999); $N = 40$, between subjects (Elder et al., 2018); $N = 63$, between subjects comparison (Germain et al., 2003); $N = 59$, between subjects comparison (Hall et al., 2004)). Moreover, a between subjects control group together with the lack of an adaptation session (Germain et al., 2003; Gross & Borkovec, 1982; Hall et al., 2004) could have resulted in a generally elevated stress level and changes in sleep physiology in both groups (e.g., a decreased amount of SWS, increased WASO and SOL) due to the first-night effect (Agnew et al., 1966; Le Bon et al., 2000; Lee et al., 2016). Thus, the negative effect of anticipatory stress in a laboratory setting on sleep might have been superimposed by this effect. In addition, none of the studies conducted an in-depth sleep analysis on slow-waves and sleep spindles and analyzed the progression of sleep parameters across sleep. Thereby, these studies could have missed dynamic changes during sleep, which might have been too small to affect overall sleep parameters.

Strikingly, we found differences in the course of various sleep parameters across the nap between the group anticipating the stressor after sleep and the group experiencing the stressor before sleep. Differences between groups were observed for SWA/beta power ratio, SWS, slow and fast spindles and various slow-wave parameters such as the number, amplitude, up- and down-slope of slow-waves. The pre-sleep group displayed a result pattern similar to previous studies, with pre-sleep stress mainly affecting early sleep (Ackermann et al., 2019; Vandekerckhove et al., 2011; Wuyts, Valck, Vandekerckhove, Pattyn, Bulckaert, et al., 2012). This was accompanied by an increase in subjective as well as objective physiological arousal in our study. Therefore, effects of pre-sleep stress on sleep could be caused by an increased physiological arousal level in response to the stressor, which would be incompatible with sleep. In this scenario, cognitive arousal, which was also increased in the pre-sleep group, could have further fueled increases in physiological arousal and thereby affect sleep. This would be in line with early insomnia models assuming that the effect of psychosocial stress and cognitive arousal is mediated by an increase in physiological arousal (Morin, 1993; Perlis et al., 1997; Spielman et al., 1987). Such an explanation would also fit with later insomnia models, which highlight an

interaction between both types of arousal in their effect on sleep (Espie, 2002; Espie et al., 2006; Harvey, 2002; Riemann et al., 2010). This approach could also explain, why the effect of pre-sleep stress fades after about 45–50 minutes, when the physiological stress response to the TSST also starts to decline (Janson & Rohleder, 2017; Kirschbaum et al., 1993; Yamanaka et al., 2019) and vanishes during late sleep. The decline of physiological arousal could have been enhanced by the extensive debriefing of the subjects after the stressful task to not expect any further stressful events within the study. This might also explain why a study applying an additional memory task in between the TSST and sleep did not find any effect of the stressful task on overall sleep parameters (Kim et al., 2019). The physiological stress response might have already declined or been too small to affect sleep at all.

In the post-sleep anticipation group, we only found minor effects on early sleep with an increased sleep onset latency. Strikingly, after about 30–50 minutes asleep, anticipating a stressor after the nap started to gradually deteriorate sleep with the largest differences in the second half of the nap that means closer to the stressor. These results are in line with previous research showing that anticipation of a stressor after sleep affects sleep physiology during late sleep (Born et al., 1999; Germain et al., 2003; Hall et al., 2004). However, these studies only reported changes of specific physiological measures such as high frequency ECG power, blood ACTH concentration and changes in the number of rapid eye-movements. In addition, they did not report any changes in sleep parameters and also lacked an in-depth analysis of the progression of sleep parameters across sleep. Previously mentioned methodological issues and the lack of in-depth sleep analysis might be responsible for missing effects of anticipated stress on sleep parameters in these studies. In contrast, we did not find an effect of anticipated stress on physiological arousal throughout sleep in our study, based on ECG measures. Therefore, our results suggest a direct effect of anticipatory stress on sleep physiology without a mediation by physiological arousal.

Given the changes in the progression of sleep parameters across the nap, the question arises how the anticipation of a stressor can affect sleep over an hour after having fallen asleep. In recent stress models, Brosschot and colleagues assume that a large part of the detrimental and prolonged effect of stressors on health and sleep is caused by unconscious perseverative cognition, for example unconsciously worrying about a future stressor (Brosschot et al., 2007; Brosschot et al., 2010, 2018). They assume that a mental representation of the stressful event is

created and continuously activated by unconscious cognitive processes and thereby induces a prolonged physiological response to an anticipated event. This notion could account for the physiological changes observed during sleep in previous studies (Born et al., 1999; Hall et al., 2004), but cannot explain our results as we did observe changes on sleep parameters but not on physiological arousal during late sleep. Thus, concerning early insomnia models, an increased physiological arousal cannot explain our results (Morin, 1993; Perlis et al., 1997; Spielman et al., 1987). However, an assumed general interaction between physiological and cognitive arousal does not contradict our findings, but the models fail to provide an underlying mechanism, how such an interaction could look like and affect sleep (Espie, 2002; Espie et al., 2006; Harvey, 2002). The neurocognitive and the hyperarousal model of insomnia provide a link between cognitive and physiological arousal by introducing cortical arousal as a physiological measure that is high frequency EEG activity (beta and gamma power, > 14 Hz) of cognitive functions (Perlis et al., 1997; Riemann et al., 2010). Such cortical arousal during NREM and possibly REM sleep is assumed to directly affect sleep via enhanced sensory processing, information processing and memory formation, leading for example to a facilitated disruption of sleep by ambient noise. Such a mechanism could explain how cognitive processes directly affect sleep and might have contributed to our findings on overall SWA/beta power ratio, sleep latency, WASO and TST. Though, this explanation is unlikely based on comparable amounts of beta power over the whole nap and during the second half of sleep in the post-sleep group (see supplementary Figure S1B), where changes of other sleep parameters were most pronounced. Moreover, this approach cannot explain dynamic changes in the progression of various sleep parameters across the nap and the differences in this dynamic between the pre- and the post-sleep group.

We recently proposed that mental concepts that are active during sleep are able to affect sleep physiology including sleep-depth regulatory systems and the subjective evaluation of sleep (Beck, Loretz, & Rasch, 2021). As an underlying mechanism, we assume that mental concepts related to sleep or wake are closely linked to somatosensory bodily functions. This assumption is supported by recent results showing that semantic processing of sleep-related words is facilitated when the subjects are in a body position congruent to sleep that is lying down, while processing of activity-related words is enhanced when subjects are standing upright (Hülsemann & Rasch, 2021). This notion is further supported by theories and empirical findings from grounded and

embodied cognition research, which assume that semantic meaning is stored in multimodal neuronal networks (Barsalou, 2008; Shapiro, 2014). In support of this notion, several studies showed that semantic processing of words leads to an activation of related somatosensory brain areas (Boulenger et al., 2012; Dreyer & Pulvermüller, 2018; Moseley et al., 2012). The second assumption of our theory is based on memory consolidation research (Oudiette & Paller, 2013; Rasch & Born, 2013) and assumes that the pre-sleep activation of mental concepts associated to sleep or wake increases the likelihood that such concepts are reactivated during subsequent sleep. This is also in line with previously mentioned stress models assuming that unconscious cognitive representations of a stressor are active during sleep (Brosschot, 2010; Brosschot et al., 2018). Lastly, we provided evidence for the core mechanism of the framework meaning that the activation of sleep- or wake-related semantic concepts during sleep is capable of affecting sleep itself. We showed that activation of a relaxation concept by presenting relaxation-related words during NREM sleep prolongs the time spend in SWS, promotes subjective sleep quality and increases power in the SWA band after relaxing word presentations (Beck, Loretz, & Rasch, 2021).

Within this framework, a generally prolonged effect of pre-sleep stress on sleep originates from a repeated reactivation of mental concepts associated with this stressor during sleep. Due to their close link to somatosensory brain functions including wake, stress and sleep regulatory systems, sleep depth is thought to be directly reduced. The model does not exclude that physiological measures such as heart rate, cortisol or ACTH are also increased, but it does not require physiological arousal as a mediator to affect sleep depth. In addition to this general effect of stress on sleep physiology, an explanation for the differences in dynamic changes between the pre-sleep and post-sleep group could be that the frequency of reactivations of mental concepts associated with the stressor increases with temporal proximity to the stressor and decreases with temporal distance to the stressor. Such a mechanism might explain the decreasing effect of stress on sleep in the pre-sleep group performing the stress-inducing task before sleep and the increasing effect of stress on late sleep in the post-sleep group anticipating the stressor to happen after sleep. This could also explain, why studies including a temporal delay between a stressor and sleep do not report an effect of stress on sleep physiology (Kim et al., 2019).

So far, our results are limited to a daytime nap setting and should be further investigated in future studies assessing sleep over a full night. Such studies should include an analysis of

dynamic changes of sleep parameters and oscillations as well as measures of cognitive and physiological arousal to further elucidate the effects of anticipated future vs. past stressors on sleep physiology. We would assume that over a whole night of sleep, cognitive arousal might contribute even more strongly to the detrimental effect of stress on sleep. Physiological arousal in response to a pre-sleep stressor would decline and affect sleep similarly as in our nap study, however reactivations of mental concepts and their associated bodily functions might affect night time sleep over a longer time period compared with a nap design. In addition to a nighttime design, a more direct measures of the HPA-axis activity such as ACTH or cortisol concentrations (Dickerson & Kemeny, 2004) could provide additional information about the association between cognitive and physiological arousal and their progression across sleep. However, choosing a measure of autonomic nervous system activity such as heart rate has the advantage to be less affected by habituation to the TSST (Allen et al., 2017). As the TSST is a well-established and frequently used task, subjects who have already conducted the TSST in previous studies would need to be excluded when cortisol or ACTH measures are administered. In our study, a virtual reality version of the TSST comprised a video of a panel, while one real and non-visible experimenter was located behind the subject. This setup differs from the standard TSST procedure and could have affected the stress response, also in comparison with previous virtual reality applications utilizing fully animated and interacting experimenters (Zimmer et al., 2019). Yet, such effects would have only affected the pre-sleep group, as the post-sleep anticipation group did not receive information that the task will be conducted in a virtual reality environment after sleep. Moreover, a limitation of the current study is the comparison of the stress condition to a relaxation instead of a neutral control condition. Therefore, the effect of the stress condition on sleep might have been overestimated in this study as sleep in the relaxation condition could be improved compared to sleep without a manipulation. In addition, this study is restricted to the effects of a psychosocial stressor on sleep. Future experiments could study different types of cognitive arousal, such as cognitive demanding tasks, which have shown to affect sleep without a concomitant emotional arousal (Wuyts, Valck, Vandekerckhove, Pattyn, Bulckaert, et al., 2012), or the effect of positive emotional arousal such as an anticipated birthday or concert one is looking forward to attend to.

In conclusion, our results show that our pre-sleep cognitions have a direct effect on sleep, which is not mediated by physiological arousal. We suggest that the mental representations with

links to somatosensory bodily functions are repeatedly activated during sleep and thereby directly affect sleep physiology during early, but also during later parts of the sleep period. In addition, our results suggest that the effect of cognitions on sleep is enhanced with temporal proximity to the stressor. This effect could also act on a larger scale, with sleep disturbances occurring weeks or months before an anticipated stressful event and more frequently when the stressful event approaches. This proposed mechanism might be especially relevant for early awakening insomnia, where the stressful event comprises an early awakening and its daytime consequences. Futures studies in healthy individuals as well as in insomnia patients should include a systematic assessment of cognitive and physiological arousal and an analysis on the progression of arousal and sleep parameters across the sleep period to further elucidate the relationship between stress, cognition and sleep. This would provide a basis for the development of non-pharmacological preventive measures and therapy options of stress-related sleep disturbances.

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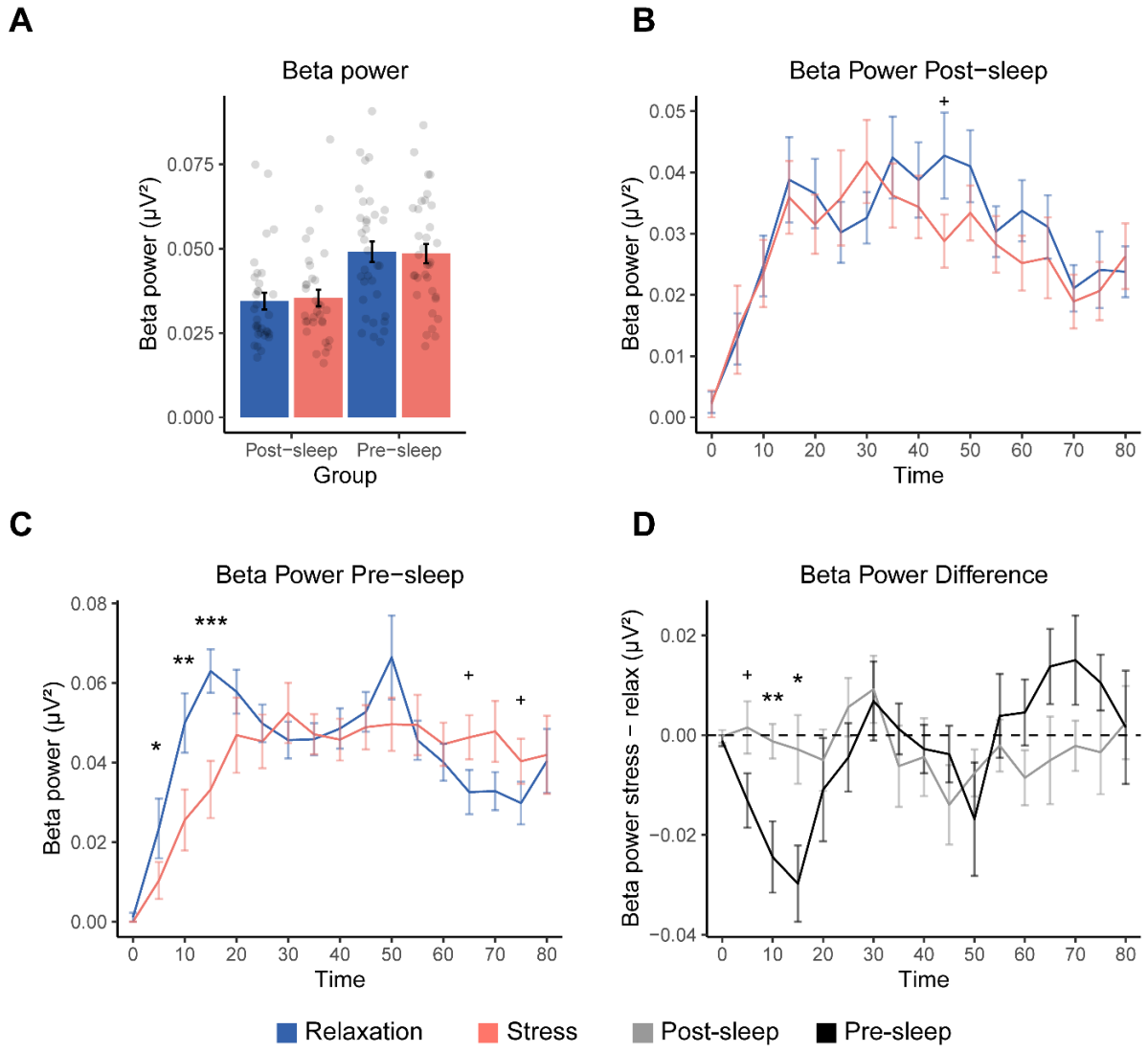
Supplementary Information

Supplementary Figures



Supplementary Figure S1. Effect of stress on beta power. Data are shown for the relaxation (blue) and the stress condition (red) separately for the post-sleep group anticipating the tasks after sleep and the pre-sleep group conducting the tasks before sleep. (**A**) Beta power (15 – 30 Hz) was comparable between both conditions over the whole nap (main effect condition: $p > .80$; interaction group × condition: $p > .30$). (**B**) Beta power was comparable at all time-point across the nap in the post-sleep group. (**C**) In the pre-sleep group, beta power was reduced during early sleep in the stress condition. (**D**) The effect of stress on sleep mainly differed during early sleep between the post-sleep (grey) and the pre-sleep group (black). Values are displayed as mean ± SEM. *** $p < .001$, ** $p < .01$, * $p < .05$.

Study 3:
Hypnotic Suggestions Increase Slow-wave Parameters but Decrease Slow-wave Spindle Coupling

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Abstract

Sleep, in particular slow-wave sleep, is beneficial for memory consolidation. In two recent studies, a hypnotic suggestion to sleep more deeply increased the amount of slow-wave sleep in both a nap and a night design. In spite of these increases in slow-wave sleep, no beneficial effect on declarative memory consolidation was found. As coupling of slow-waves and sleep spindles is assumed to be critical for declarative memory consolidation during sleep, we hypothesized that the missing memory benefit after increased SWS could be related to a decrease in slow-wave/spindle coupling. Data from 33 highly hypnotizable subjects were retrieved from a nap (n = 14) and a night (n = 19) study with a similar design and procedure. After an adaptation session, subjects slept in the sleep laboratory for two experimental sessions with polysomnography. Prior to sleep, a paired-associate learning task was conducted. Next, subjects either listened to a hypnotic suggestion to sleep more deeply or to a control text in a randomized order according to a within-subject design. After sleep, subjects performed the recall of the memory task. Here, we conducted a fine-grained analysis of the sleep data on slow-waves, spindles and their coupling. In line with our hypothesis, listening to a hypnosis tape decreased the percentage of spindles coupled to slow-waves. Slow-wave parameters were consistently increased, but sleep spindles remained unaffected by the hypnotic suggestion. Our results suggest that selectively enhancing slow-waves without affecting sleep spindles might not be sufficient to improve memory consolidation during sleep.

Keywords: memory consolidation, learning, SWS, co-occurrence, slow-oscillation, hypnosis

Introduction

Sleep is beneficial for the consolidation of memory (Rasch & Born, 2013). In particular deep sleep, also called slow-wave sleep (SWS) is characterized by cortical slow-waves (measured with scalp electroencephalogram, EEG) and assumed to play a functional role in memory consolidation during sleep. According to the synaptic down-selection theory, neural slow oscillations (< 1 Hz) and their excitatory up- and inhibitory down-states provide the basis for net synaptic downscaling of synapses, thereby increasing signal-to-noise ratio and improving memory recall the next day (Tononi & Cirelli, 2014). Thus, increasing SWS and slow oscillations should lead to a better memory recall the next day. According to the active systems consolidation theory, slow oscillations provide a synchronizing time frame for reactivation-related hippocampal sharp-wave ripples (transient network oscillations with 80–200 Hz) and sleep spindles. Sleep spindles are short bursts (0.5–3 s) of oscillatory activity (9–16 Hz) with a waxing and waning shape in the surface sleep EEG. In particular, the theory assumes that the interplay and precise timing of these sleep oscillations is crucial for the beneficial effect of sleep on memory consolidation (Fernandez & Lüthi, 2020; Peyrache & Seibt, 2020; Rasch & Born, 2013; Schreiner & Staudigl, 2020). Thus, increasing SWS and slow oscillations should only lead to a better memory consolidation during sleep when the precise timing between spindles, ripples and slow oscillations is also maintained.

One parameter used to describe the interplay between these oscillations on the cortical level is slow-wave/spindle coupling (SW/SP coupling). Importantly, several studies have shown that increased SW/SP coupling is related to better sleep-mediated memory consolidation, for example in ageing (Helfrich et al., 2018; Muehlroth et al., 2019). Pharmacologically increasing coupling between slow-waves and spindles improved verbal memory in humans (Niknazar et al., 2015). In addition, optogenetic induction of thalamic spindles phase locked to the neural slow oscillation up-state has been shown to enhance coupling of spindles, slow oscillations and ripples as well as improve consolidation of hippocampus dependent memory (Latchoumane et al., 2017). Furthermore, precision of SW/SP coupling has been linked to the strength of endogenous memory reactivations, which were associated with memory consolidation in an episodic memory task (Schreiner et al., 2021). Thus, SW/SP coupling might be crucial for benefits of sleep on memory consolidation.

In two of our recent studies, we reported a prolongation of SWS which did not translate into improvements in declarative memory consolidation during sleep (Cordi et al., 2014; Cordi et al., 2020). The increase in SWS was induced in healthy, medium-to-highly hypnotizable participants using a hypnotic suggestion to sleep more deeply before sleep. One study was conducted as a midday nap, the other as a night-time sleep study. While the increase in SWS was significant in both studies compared to a within-subject control condition, we did not find a beneficial effect of the hypnosis tape on the performance in a declarative paired-associate learning task. However, no fine-grained analysis on slow-waves, spindles and SW/SP coupling was conducted. Thus, we reanalyzed the data of the two studies to examine whether changes in slow-waves, sleep spindles, and in particular their coupling, could explain why memory consolidation was not enhanced after increasing the amount of SWS. We expect the hypnotic suggestion to not increase SW/SP coupling in spite of increasing cortical slow-waves.

In line with our hypothesis, we found that the amount of coupling between both frontal slow spindles and parietal fast spindles with slow-waves was reduced when subjects listened to a hypnosis tape to sleep more deeply prior to sleep. Generally, hypnotic suggestions increased the density of slow-waves and several other slow-wave parameters, whereas overall spindle density was comparable between the two sessions.

Materials and Methods

We used data from two previous studies with a similar design and procedure. Both studies followed a within-subject cross-over design to compare the effects of a deep sleep hypnosis tape vs. a control tape on sleep depth of high and low hypnotizable participants. The first study was conducted as a midday nap study in German-speaking females and will hereinafter be referred to as the "nap study" (Cordi et al., 2014). The second study assessed a full night of sleep including both sexes and will hereinafter be referred to as the "night study" (Cordi et al., 2020). For the purposes of this study, we only analyzed data from the high hypnotizable subjects.

Participants

In the nap study, 14 healthy, German-speaking young females (mean age, 23.36 ± 2.65 y [$M \pm SD$], age range 18-29 y) participated in the experiment. In the night study, 19 healthy, French-speaking young subjects participated in the experiments (9 males, $M = 22.32 \pm 3.06$ y, age range 19-31 y) and mean age was comparable between studies ($p = .14$). None of the

subjects were shift workers nor had they been on any intercontinental flights six weeks prior to the experiment. They neither took any sleep influencing medication nor reported any neurological, psychiatric or sleep-related disorders. All participants refrained from drinking alcohol and caffeine on experimental days. Subjects were payed 140 CHF in the nap and 150 CHF in the night study for participation in all sessions. The studies were approved by the Ethics Committees of the University of Zurich (nap study) and Lausanne (night study). Hypnotizability was assessed by a German version of the Harvard Group Scale of Hypnotic Susceptibility (HGSHS; Bongartz, 1985) in the nap study and by a French version translated by Laurent Rossier, a German- and French-speaking hypnotherapist, in the night study (Cordi et al., 2020). The HGSHS was conducted in a group session prior to the experiment with a cutoff score of ≥ 7 for highly hypnotizable subjects (nap: HGSHS = 7.71 ± 0.73; night: HGSHS = 7.36 ± 0.69). The percentage of high hypnotizable subjects within the initial screening was 35 % in the nap study and 33 % in the night study.

Design and Procedure

The design of the nap study equaled the design of the night study with the exception of sleep, which either occurred during a midday nap or during the night (Cordi et al., 2014; Cordi et al., 2020). Subjects participated in four sessions, three of which were sleep sessions. During a first group session, participants were informed that a hypnosis tape will be used to deepen their sleep and hypnotizability was assessed using the HGSHS (Bongartz, 1985; Cordi et al., 2020). After an adaptation nap or night, participants slept in the laboratory for two sessions, while polysomnographic data (electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG)) was recorded. Both experimental sessions took place on the same weekday, spaced one week apart. Prior to sleep, a declarative paired-associate learning task (PAL) was conducted. In a randomized order, participants listened to either a hypnotic suggestion tape to sleep more deeply or a control tape about natural mineral deposits in a within-subject design (see Figure 1A, for an overview of the procedure). They were asked to listen to the tape but were allowed to fall asleep at any time. The tape was started with the lights switched off and subjects were awoken 90 min (nap) or 8 h (night) later. After sleep, subjects performed a psychomotor vigilance task, filled out a subjective sleep quality questionnaire (Schlaffragebogen A, SF-A/R; Görtelmeyer, 2011) and conducted the recall of the PAL. After the PAL in the nap

study participants performed a procedural sequence finger tapping task whereas after the PAL in the night study subjects performed two declarative verbal fluency tasks.

Hypnosis and Control Tape

The hypnosis text was written by a hypnotherapist (A. Schlarb) treating sleep problems and sleep disorders with hypnosis (Cordi et al., 2014) The hypnosis text started with focusing the attention of the listener from the environment to internal processes, including suggestions to close the eyes and to relax. Next, it was slowly counted from 1-10 with each step indicating deeper relaxation and leading the listener into the hypnotic trance state (4 min). Subsequently, the listener was invited to imagine a picture of a sea and to follow a fish swimming progressively deeper and deeper into the sea, symbolizing the depth of sleep (9 min). This was accompanied by suggestions that swimming deeper and deeper is safe and risk free. When the fish arrived at the bottom of the sea, the listener was suggested to continue to sleep deeply. Afterwards, the tape stopped and left the listener in the hypnotic trance, which invited them to fall asleep. The control text was designed to match the hypnosis text with respect to length in minutes and volume and to be as neutral and objective as possible. The German tapes were spoken and recorded by B. Rasch (Cordi et al., 2014), the French versions were translated, spoken and recorded by Laurent Rossier (Cordi et al., 2020). The hypnosis texts were spoken with a soft and calming voice, while the control texts were spoken with an everyday intonation and speed. The tapes are available on our homepage: https://www.unifr.ch/psycho/en/research/biopsy/hypnosis.html

Paired-associate Learning Task

A German and a French version of the PAL were conducted similarly to previous studies (Rasch et al., 2006). In the evening, participants learned 80 semantically associated word pairs (e.g. clock – church) and were asked to memorize as many pairs as possible. During this learning phase, the word pairs were presented sequentially for 1000 ms in black font on a white screen. A blank screen of 200 ms separated the two words of a word pair. Each trial was preceded by an interstimulus interval of 500 ms and a fixation cross of 500 ms. After the learning phase, subjects retrieved the word pairs in a cued-recall task. The first word of the word pair was presented and they were asked to name the corresponding second word with unlimited response time; if they were unable to recall the matching word they were asked to click “next”. The first word was presented in black font on a white screen for 1000 ms followed by a question mark. The experimenter noted if the answer was correct without giving feedback to the participant. Another

blank screen of 500 ms preceded the next trial. Selection of the word list and the order of word pair presentation was randomized. In the morning, memory performance was tested a second time using the cued-recall task without a learning phase. Memory performance was measured as the percentage of correctly recalled word pairs before and after the sleep period. To assess relative overnight memory improvement, pre-sleep performance was set to 100%.

Polysomnographic Recording

EEG was recorded using a 128-channel Geodesic Sensor Net (nap, Electrical Geodesics, Eugene, OR) or a 32-channels Easycap Net (night, Easycap GmbH, Herrsching) with a sampling rate of 500 Hz in both studies. Offline EEG preprocessing was conducted using BrainVision Analyzer software (version 2.0 in the nap and 2.1 in the night study; Brain Products, Gilching, Germany). Data were referenced against contralateral mastoids in the nap study and against average mastoids in the night study. Standard filter settings suggested by the America Academy of Sleep Medicine (AASM; Iber et al., 2007) were applied (e.g. EEG 0.3 – 35Hz) with an additional notch filter (50 Hz) in both datasets. Sleep was visually scored offline by two independent sleep scorers in 30 second epochs, based on derivations F4, C4, O2, HEOG, VEOG and EMG according to the AASM standard criteria (Iber et al., 2007). In case of disagreement, a third expert was consulted. All scorers were blind to the experimental condition.

Detection of Spindles, Slow-waves and Their Coupling

Analysis of slow-waves, spindles and their coupling was performed on frontal (F3, F4) and parietal (P3, P4) electrodes using the open-source SpiSOP tool (www.spisop.org; RRID: SCR_015673) based on MATLAB 2013b (Mathworks, Natick, USA; RRID: SCR_001622). Standard settings of SpiSOP were applied based on previously published algorithms (Mölle et al., 2002) and are explained in the following.

Slow-wave Detection. First, the signal was first filtered in each channel during NREM sleep between 0.3 and 3.5 Hz. Second, all intervals with consecutive positive-to-negative zero crossings (down – up – down) were marked as putative slow-waves. They were only kept for further analyses if their durations matched with a frequency between 0.5–1.11 Hz, while down-zero-crossings marked the begin and end of a slow-wave. Possible matches were considered as artifacts and excluded, if their amplitude exceeded 1000 μV or both negative and positive half-wave amplitudes lay between –15 and +10 μV. Finally, a slow-wave was identified if the following two criteria were met: the negative half-wave peak potential was lower than 1.25 × the

mean negative half-wave peak of all allegedly detected slow-waves within the respective EEG channel (see Figure 1C, Threshold 1); the amplitude (trough to peak) was larger than 1.25 × the mean amplitude of all other allegedly detected slow-waves within this channel (see Figure 1C, Threshold 2). As a result, number of slow-waves, density per 30s epoch NREM sleep, mean amplitude, duration, down slope (value of the negative half-wave peak divided by the time from the first zero-crossing to the trough in µV/s) and up slope (absolute value of the negative half-wave peak divided by the time from the trough to the next zero-crossing in µV/s) were calculated for each participant and channel during NREM sleep.

Spindle Detection. First, individual slow and fast spindle frequency peaks were visually determined based on the NREM power spectrum of each dataset. Slow spindle peaks were determined in frontal channels (F3, F4) and fast spindle peaks in parietal channels (P3, P4) due to expected power maxima over those regions (Mölle et al., 2011). Slow spindle peaks ranged between 9.5 and 13.2 Hz with an average frequency of 11.99 ± 0.79 Hz in the nap and 11.13 ± 0.79 Hz in the night study. Fast spindle peaks ranged between 11.5 and 15.2 Hz with an average frequency of 13.99 ± 0.71 Hz in the nap and 13.46 ± 0.40 Hz in the night study.

Second, the EEG signal of each channel during NREM sleep was filtered with the frequency determined by an individual slow- and fast spindle power peak ± 1 Hz. Next, the root mean square (RMS) signal was computed using a sliding window with a size of 0.2 s and the resulting signal was smoothed in the same window with a moving average (see Figure 1D). A spindle was detected, when the smoothed RMS signal exceeded an individual amplitude threshold by 1.5 standard deviations (*SD*) of the filtered channel signal once for 0.5 to 3 s. The threshold crossings marked the beginning and end of each spindle event and determined their duration. Amplitude of sleep spindles was defined by the voltage difference between the largest trough and peak (peak to trough potential). Spindles with an amplitude above 200 µV were excluded. Analysis resulted in data of the number of detected spindles, spindle density (per 30s NREM sleep epoch), mean amplitude (trough to peak potential), average oscillatory frequency and duration for each participant and channel (frontal slow spindles, parietal fast spindles) during NREM sleep.

Coupling of slow-waves and spindles. After detecting slow-waves and spindles, additional analyses were conducted to identify the coupling between slow-waves and spindles (see Figure 1B). These coupling analyses were performed within the time window starting with

the trough of the slow-wave until 1.2 s after this trough for slow and fast spindles. We identified coupling events where at least one detected sleep spindle trough (maximum negative amplitude) was detected within the specified time window. As a result, the number of matches and the percentage of matches relative to the total amount of slow-waves were calculated for each participant and lobe (frontal slow spindles, parietal fast spindles) during NREM sleep.

Statistical Analysis

Statistical analysis was performed using Rstudio version 1.1.456 (RStudio Team, 2015). Normality was tested using Shapiro-Wilk's test. As slow-wave density ($W = 0.99$, $p < .001$) and spindle density ($W = 0.98$, $p < .001$) were both non normally distributed, Tukey's rule (Tukey, 1977) using the interquartile range (IQR, $[Q_1 – 1.5 \times IQR, Q_3 + 1.5 \times IQR]$) was applied to detect possible outliers in non-normally distributed data. Application of this outlier criterion on the slow-wave and spindle density data of frontal and parietal electrodes from both studies suggested a slow-wave density range between –0.10 and –3.83 and a spindle density range between 0.75 and 3.58. Based on these criteria, three datapoints were excluded in the spindle and coupling analysis and replaced with data from the contralateral hemisphere. The same corrections were applied to the analyses of all other spindle and coupling parameters.

We analyzed slow-wave density and spindle density as well as coupling between slow-waves and spindles. Analyses were conducted separately over the frontal and over the parietal lobes. To compare the results of the nap and the night study, we only analyzed data within the first hour of sleep in the night study. We calculated mixed analyses of variances containing the within subject factors condition (control vs. hypnosis) and hemisphere (left vs. right) as well as the between subject factor study (nap vs. night). Post-hoc tests comprised paired *t*-tests and Welch *t*-tests for unpaired data. In case of significant findings, partial eta-squared (η_p) and Cohens *d* are reported as effect sizes for analyses of variances and *t*-tests, respectively. For correlational analysis, we used Pearson product-moment correlations. Correlations were compared according to Lenhard and Lenhard (2014) based on single sided testing. The level of significance was set to $p < .05$.

Results

Slow-wave Sleep and Memory Consolidation

In a first analysis, we reanalyzed SWS and memory consolidation data together for both the nap and night study. After listening to the suggestion to sleep more deeply, participants spent 29.95 ± 2.35 % of their total sleep time in SWS, whereas in the control condition subjects only spent 22.73 ± 2.30 % of their total sleep time in SWS. Thus, the hypnotic suggestion increased the time spent in SWS to 131.76 % compared with listening to the control text (set to 100%; $F(1, 31) = 13.94$, $p < .001$, $\eta_p = .31$). This increase was more pronounced in the nap compared with the night study (interaction condition × study: $F(1, 31) = 6.77$, $p = .014$, $\eta_p = .18$). Adding age as a covariate yielded the same interaction between condition and study ($F(1, 30) = 10.18$, $p = .003$, $\eta_p = .25$). Moreover, an interaction between age and condition ($F(1, 30) = 5.88$, $p = .022$, $\eta_p = .16$) suggested that the effect of condition was stronger in younger participants. However, the correlation between age and the effect of hypnosis on SWS did not reach significance ($r(31) = –0.28$, $p = .11$).

In contrast to this substantial increase in SWS, we did not observe any effect on declarative memory consolidation during sleep. Retention performance in the paired-associate word learning task (with performance during encoding set to 100%) was comparable between the hypnosis condition (98.44 ± 2.07 %) and the control condition (99.42 ± 2.07 %; $F(1, 30) = 0.06$, $p = .81$). Furthermore, we observed no significant interaction between condition and study (nap vs. night; $F(1, 30) = 1.58$, $p = .22$)). Interestingly, the amount of SWS showed a trend for a negative correlation between SWS and memory retention performance in the hypnosis condition ($r(30) = –.33$, $p = .061$), while no such correlation was found in the control session ($r(30) = –.09$, $p = .61$). These correlations were significantly different from each other ($z = –3.87$, $p < .001$).

Effect of Hypnosis on Coupling Between Slow-waves and Spindles

As coupling of slow-waves and sleep spindles is assumed to play a functional role for memory consolidation during sleep, we tested whether the missing effect on sleep-mediated memory consolidation in the hypnosis condition might be explained by a reduction in SW/SP coupling. We calculated SW/SP coupling as the percentage of co-occurring slow-waves and sleep spindles (time period: 1.2 seconds after slow-wave trough) relative to the total amount of slow-waves. As predicted, we observed a significant reduction in SW/SP coupling when participants listened to a hypnotic suggestion to sleep more deeply. Over the frontal lobe, participants

exhibited a significantly lower amount of coupling of slow spindles and SWs when they listened to the hypnosis (14.40 ± 0.96 %) compared with a control text before sleep (17.78 ± 1.23 %; ($F(1, 31) = 13.12$, $p = .001$, $\eta_p = .30$; Figure 2A). Similarly, over the parietal cortex, coupling of fast spindles and slow-waves was reduced after listening to the hypnosis (12.67 ± 0.84 %) compared with a control text before sleep (15.09 ± 1.21 %; $F(1, 30) = 4.58$, $p = .041$, $\eta_p = .13$; Figure 2B).

To further examine the underlying mechanisms of the reduced SW/SP coupling after hypnosis, we analyzed the density per 30s epoch of slow-waves and sleep spindles separately during NREM sleep (stages N2 and N3 combined). In accordance with the increases in SWS induced by hypnotic suggestions, slow-wave density over the frontal lobe was significantly increased in the hypnosis condition (2.00 ± 0.11 slow-waves/30s) compared with the control condition (1.76 ± 0.12 slow-waves/30s; $F(1, 66) = 6.62$, $p = .015$, $\eta_p = .18$; Figure 2C). Similarly, over the parietal cortex, participants showed an increased parietal slow-wave density in the hypnosis (1.70 ± 0.10 slow-waves/30s) compared with the control condition (1.42 ± 0.12 slow-waves/30s; $F(1, 31) = 9.65$, $p = .004$, $\eta_p = .24$; Figure 2D). Generally, slow-wave density was higher in the night study compared with the nap study, over both frontal and parietal regions (both $p < .001$). In addition to slow-wave density, significant main effects of condition (control vs. hypnosis) were found for all other slow-wave parameters except the duration of frontal slow-waves (see Table 1). Listening to a hypnotic suggestion before sleep significantly increased the number, amplitude, down slope and up slope of frontal and parietal slow-waves as well as the duration of parietal slow-waves (all $p < .038$). These increases were less pronounced over the frontal lobe in the night study and more consistent across studies over the parietal lobe (see Table 1). The most robust effects across both studies were found for the amplitude of parietal slow-waves, which were significantly increased in the hypnosis compared with the control condition in the nap ($t(13) = –3.35$, $p = .005$, $d = 0.90$) and in the night study ($t(18) = –3.08$, $p = .006$, $d = 0.71$).

In contrast to slow-wave density, we did not observe any differences between the hypnosis and control condition for sleep spindles. Both frontal slow spindle density (hypnosis: 2.06 ± 0.09 spindles/30s; control: 2.06 ± 0.08 spindles/30s; Figure 2E) and parietal fast spindle density (hypnosis: 2.28 ± 0.06 spindles/30s; control: 2.26 ± 0.06 spindles/30s; Figure 2F), were comparable between the two experimental conditions (both $p > .55$). In addition, and contrary to

parietal slow-waves, listening to a hypnotic suggestion before sleep decreased the duration of parietal fast spindles (p = .033, see Table 1). Together with the lack of effect on other spindle parameters and the increases found for slow-wave parameters, these results might facilitate and explain a reduced coupling of slow-waves and spindles.

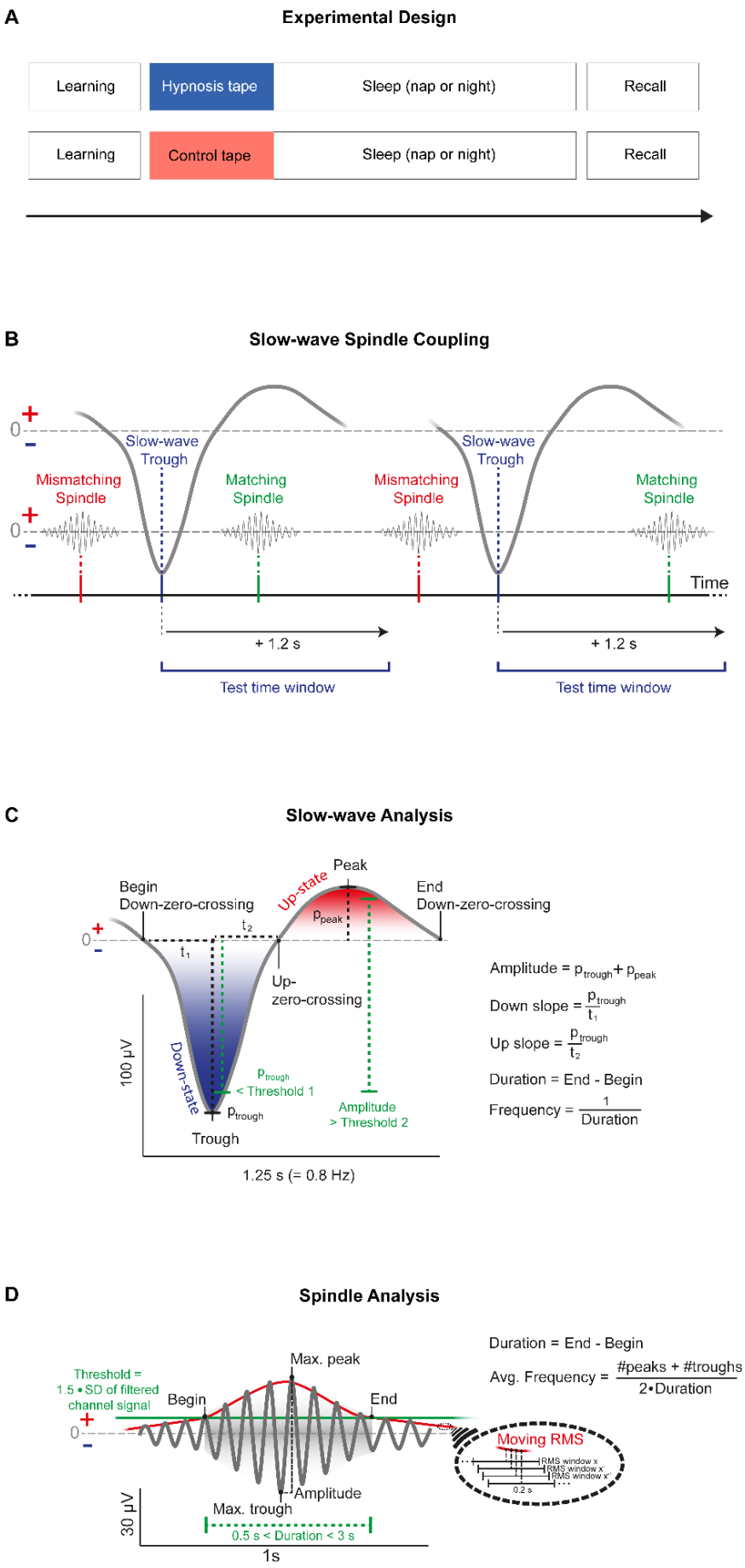
A
Experimental Design
Learning
Hypnosis tape
Sleep (nap or night)
Recall
Learning
Control tape
Sleep (nap or night)
Recall
B
Slow-wave Spindle Coupling
Slow-wave Trough
Mismatching Spindle
Matching Spindle
Slow-wave Trough
Mismatching Spindle
Matching Spindle
Time
+ 1.2 s
+ 1.2 s
Test time window
Test time window
C
Slow-wave Analysis
Begin Down-zero-crossing
Peak
Up-state
End Down-zero-crossing
Up-zero-crossing
Down-state
Trough
100 µV
1.25 s (= 0.8 Hz)
Amplitude = p_trough + p_peak
Down slope = p_trough / t_1
Up slope = p_trough / t_2
Duration = End - Begin
Frequency = 1 / Duration
D
Spindle Analysis
Threshold = 1.5 • SD of filtered channel signal
Begin
Max. peak
End
Amplitude
Max. trough
0.5 s < Duration < 3 s
30 µV
1s
Moving RMS
0.2 s
Duration = End - Begin
Avg. Frequency = (#peaks + #troughs) / 2•Duration

Figure 1. Experimental procedure and analysis of sleep-oscillations. (**A**) Thirty-three high hypnotizable subjects listened to a hypnosis (blue) or a control tape (red) while falling asleep according to a within-subject design. In both sessions participants either slept during a midday nap (90 min) or during the night (8h). Learning of a declarative paired associate learning task (PAL) was conducted before sleep and the recall of the same task after sleep. Analyses of slow-waves, sleep spindles and their coupling were conducted using the open-source SpiSOP tool (www.spisop.org; RRID: SCR_015673). (**B**) Coupling analyses were performed within the time window starting with the trough of the slow-wave until 1.2 s after this trough for slow and fast spindles. We identified coupling events where at least one detected sleep spindle trough (maximum negative amplitude) was detected within the specified time window. As a result, the number of matches and the percentage of matches relative to the total amount of slow-waves were calculated for each participant and lobe (frontal slow spindles, parietal fast spindles) during NREM sleep. (**C**) For detection of slow-waves, the signal was initially filtered between 0.3 and 3.5 Hz in each channel during NREM sleep. Second, all intervals with consecutive positive-to-negative zero crossings (down – up – down) were marked as putative slow-waves. They were only kept for further analyses, if their durations matched with a frequency between 0.5–1.11 Hz, while down-zero-crossings marked the begin and end of a slow-wave. Possible matches were considered as artifacts and excluded if their amplitude exceeded 1000 μV, or if both negative and positive half-wave amplitudes lay between –15 and +10 μV. Finally, a slow-wave was identified if the following two criteria were met: the negative half-wave peak potential (p_{trough}) was lower than 1.25 × the mean negative half-wave peak of all allegedly detected slow-waves within the respective EEG channel (Threshold 1); the amplitude (trough to peak) was larger than 1.25 × the mean amplitude of all other allegedly detected slow-waves within this channel (Threshold 2). As a result, number of slow-waves, density per 30s epoch NREM sleep, mean amplitude, duration, down slope (value of the negative half-wave peak divided by the time from the first zero-crossing to the trough in μV/s) and up slope (absolute value of the negative half-wave peak divided by the time from the trough to the next zero-crossing in μV/s) were calculated for each participant and channel during NREM sleep. (**D**) For the detection of sleep spindles, the EEG signal of each channel during NREM sleep was filtered with the frequency determined by an individual slow- and fast spindle power peak ± 1 Hz. Next, the root mean square (RMS) signal was computed using a sliding window with a size of 0.2 s and the resulting signal was smoothed

in the same window with a moving average. A spindle was detected when the smoothed RMS signal exceeded an individual amplitude threshold by 1.5 standard deviations (*SD*) of the filtered channel signal for 0.5 to 3 s at least once. The threshold crossings marked the beginning and end of each spindle event and determined their duration. Amplitude of sleep spindles was defined by the voltage difference between the largest trough and peak (peak to trough potential). Spindles with an amplitude above 200 μV were excluded. Analysis resulted in data of the number of detected spindles, spindle density (per 30s NREM sleep epoch), mean amplitude (trough to peak potential), average oscillatory frequency (Avg. Frequency using number of peaks (#peaks) and number of troughs (#troughs)) and duration for each participant and channel (frontal slow spindles, parietal fast spindles) during NREM sleep. (**B-D**) Figures were retrieved from www.spisop.org/documentation/ and adapted with permission from the copyright owner (Frederik D. Weber).

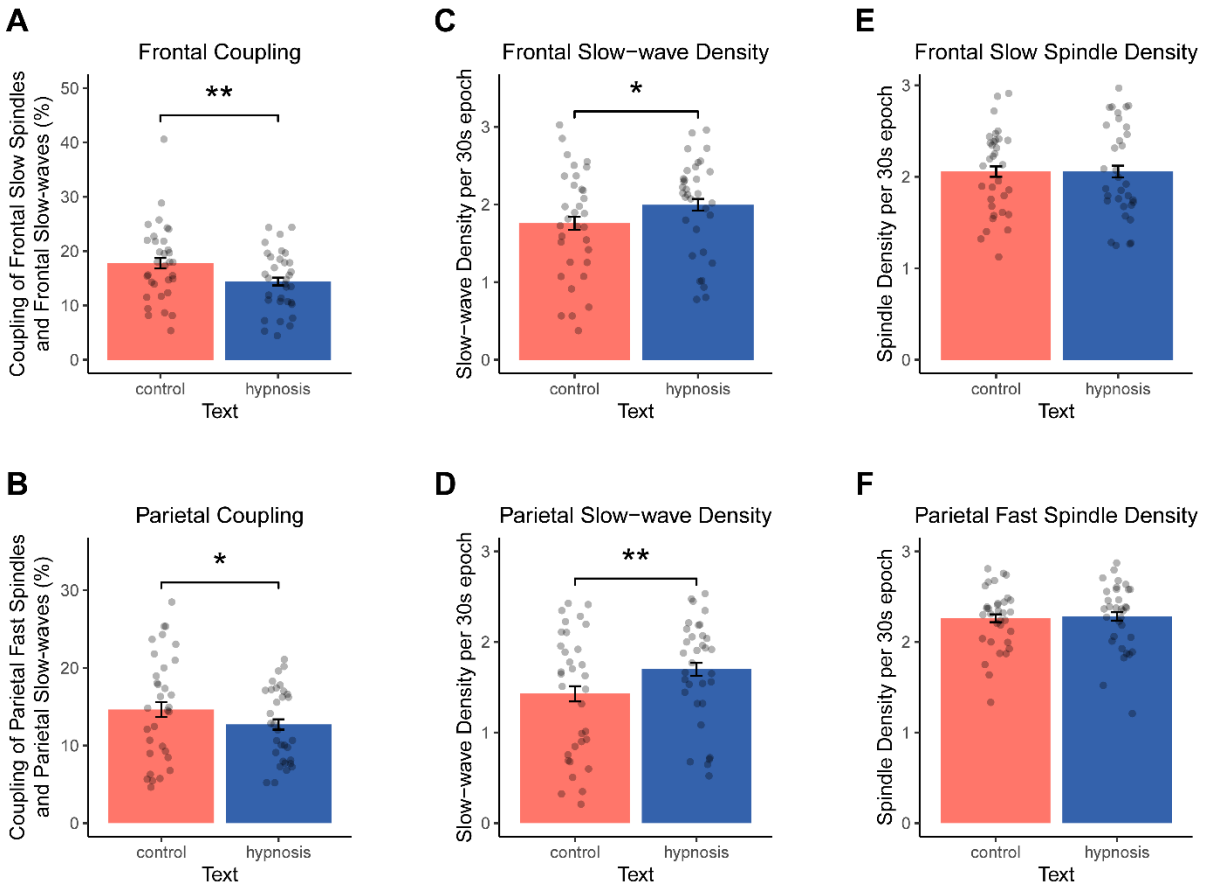

Figure 2. Results of coupling, slow-wave and spindle analysis. Data are shown separately for the control (red bars) and the hypnosis condition (blue bars). (**A**, **B**) Here provided are the percentages of matches between slow-waves and spindles relative to the total amount of slow-waves in NREM sleep. Listening to a hypnotic suggestion to sleep more deeply reduced (**A**) coupling of frontal slow-waves and slow spindles and (**B**) coupling of parietal slow-waves and fast spindles compared with a control tape. Listening to a hypnotic suggestion to sleep more deeply increased (**C**) frontal as well as (**D**) parietal slow-wave density per 30s epoch of NREM sleep compared with a control tape. Listening to a hypnotic suggestion to sleep more deeply did neither affect (**E**) frontal slow spindle nor (**F**) parietal fast-spindle density per 30s epoch of NREM sleep compared with a control tape. Values are displayed as mean ± SEM. ** $p < .01$, * $p < .05$.

Table 1. Coupling, slow-wave and spindle parameters in the hypnosis and control session for the nap and night study

Parameter	Nap study (n = 14)		Night study (n = 19)		p-Values	
	Control	Hypnosis	Control	Hypnosis	Main effect condition	Interaction condition × study
Frontal coupling						
number matches	24.00 ± 4.60	25.00 ± 3.81	35.47 ± 3.80	35.42 ± 4.17	.84	.82
coupling (%)	**19.74 ± 1.33**	**14.70 ± 1.13***	16.34 ± 1.86	14.18 ± 1.47	**.001***	.16
Parietal coupling						
number matches	14.08 ± 2.86	16.62 ± 2.81	27.29 ± 3.04	26.21 ± 2.43	.69	.32
coupling (%)	15.35 ± 2.20	13.36 ± 1.38	**14.91 ± 1.43**	**12.19 ± 1.08**$^{+}$	**.041***	.74
Frontal slow-waves						
number	130.54 ± 25.62	179.18 ± 28.33	226.84 ± 14.95	248.74 ± 11.05	**.032***	.40
density (1/30s)	**1.22 ± 0.11**	**1.55 ± 0.11**$^{+}$	2.15 ± 0.08	2.32 ± 0.07	**.015***	.42
amplitude (μV)	**151.05 ± 13.37**	**175.30 ± 11.58***	221.54 ± 12.18	226.62 ± 9.71	**.003***	**.041**
duration (s)	1.16 ± 0.01	1.16 ± 0.01	1.17 ± 0.01	1.17 ± 0.02	.68	.79
down slope (μV/s)	**–405.63 ± 42.18**	**–479.58 ± 34.07***	–629.27 ± 38.97	–632.64 ± 33.26	**.031***	**.048***
up slope (μV/s)	**433.29 ± 39.69**	**499.42 ± 39.08***	630.02 ± 28.92	630.14 ± 32.91	**.017***	**.017***
Parietal slow-waves						
number	101.42 ± 22.45	143.75 ± 23.62	**191.13 ± 15.16**	**217.63 ± 8.84**$^{+}$	**.017***	.47
density (1/30s)	**0.91 ± 0.14**	**1.24 ± 0.14**$^{+}$	**1.81 ± 0.12**	**2.03 ± 0.07***	**.004***	.58
amplitude (μV)	**116.17 ± 9.62**	**135.27 ± 8.36***	**154.83 ± 7.96**	**166.29 ± 7.70***	**< .001***	.25

duration (s)	**1.14 ± 0.01**	**1.17 ± 0.01**$^{+}$	1.23 ± 0.01	1.24 ± 0.02	**.038***	.33
down slope (µV/s)	**–297.29 ± 27.40**	**–351.02 ± 22.11***	**–405.94 ± 23.56**	**–427.09 ± 24.68**$^{+}$	**< .001***	.12
up slope (µV/s)	**306.29 ± 20.75**	**339.92 ± 23.72***	362.40 ± 18.86	377.25 ± 19.93	**.003***	.22
Frontal slow spindles						
number	190.46 ± 25.61	214.64 ± 22.97	215.39 ± 12.40	218.05 ± 13.44	.27	.37
density (1/30s)	2.04 ± 0.13	2.07 ± 0.14	2.07 ± 0.10	2.04 ± 0.12	.93	.60
amplitude (µV)	36.17 ± 2.07	36.10 ± 2.47	38.40 ± 2.18	38.57 ± 2.46	.95	.88
duration (s)	0.87 ± 0.02	0.84 ± 0.02	0.83 ± 0.01	0.81 ± 0.02	.13	.74
core frequency (Hz)	11.32 ± 0.35	11.13 ± 0.29	10.84 ± 0.19	10.84 ± 0.18	.58	.58
Parietal fast spindles						
number	209.07 ± 29.72	239.86 ± 20.49	243.23 ± 10.11	241.68 ± 9.20	.24	.20
density (1/30s)	2.16 ± 0.10	2.30 ± 0.10	2.34 ± 0.07	2.27 ± 0.09	.55	**.090**$^{+}$
amplitude (µV)	30.03 ± 1.45	29.08 ± 2.04	27.79 ± 1.53	27.45 ± 1.27	.35	.66
duration (s)	0.88 ± 0.02	0.84 ± 0.01	**0.84 ± 0.02**	**0.82 ± 0.02***	**.033***	.55
core frequency (Hz)	13.52 ± 0.27	13.72 ± 0.14	13.11 ± 0.10	13.07 ± 0.11	.54	.36

Note. Means ± SEM during NREM sleep (stages N2 and N3 combined). Coupling is reported as the absolute number of matches and as the percentage of matches relative to the total amount of slow-waves in %. For detected slow-waves, slow spindles and fast spindles, the absolute number (number), density per 30 s epoch of NREM sleep, mean amplitude and duration are given. Additionally, average up and down slope are given for slow-waves and core frequency for slow- and fast spindles. Data of the night study refers to the first hour of sleep. *p*-values are reported for the main effect of condition (control vs. hypnosis) and the interaction between condition and study (nap vs. night). Bold values indicate significant differences between the hypnosis and control session with + $p < .10$ and * $p < .05$.

Discussion

In the current study, we show that hypnotic suggestion before sleep promotes slow-waves, but leaves spindles unaffected and hence results in a decreased SW/SP coupling during both a nap and nighttime sleep. Previous research, which experimentally enhanced slow-waves, suggested a causal contribution of slow-waves to the consolidation of hippocampus-dependent declarative memory (Marshall et al., 2004; Marshall et al., 2006; Ngo et al., 2013). Here, we found that listening to a hypnotic suggestion to sleep more deeply enhances slow-waves by increasing the number, density, amplitude, up- and down-slopes in highly hypnotizable participants. Despite these improvements, we did not find any effect on declarative memory consolidation during sleep. The current findings offer an explanation for this lack of memory consolidation effect as slow – as well as fast spindles remained unaffected and coupling between slow-waves and spindles was decreased in the hypnosis condition.

Sleep spindles are assumed to represent the reinstatement of a memory trace with reactivation occurring during spindle events (Antony et al., 2018; Cairney et al., 2018; Jegou et al., 2019). Spindle activity is increased when memory cues associated with previously learned content are presented during sleep (Cairney et al., 2018). During this increase in spindle activity, memory content associated with the stimuli presented could be reliably decoded, which further strengthens the view of a reactivation of memory content during the occurrence of spindles. In addition, results from a simultaneous EEG and fMRI study support the notion that cortical reactivation occurs during spindles (Jegou et al., 2019). Therefore, an invariant amount of sleep spindles in the control and hypnosis condition might represent similar amounts of reactivation and consolidation during sleep, and thereby explain the comparable amounts of memory consolidation in the control and hypnosis condition.

After reinstatement of a memory trace represented by a spindle event, additional processing is assumed to occur during a spindle refractory period (3–6 s; Antony et al., 2018). This refractory period is thought to be crucial for protecting memory reprocessing from interference and spindle refractory periods are thought to optimize oscillatory interactions supporting systems consolidation. Increasing slow-waves within these refractory periods might be ineffective for promoting memory consolidation and possibly even disturb oscillatory interactions favoring memory consolidation.

Besides findings that slow-waves and spindles are relevant for memory consolidation, SW/SP coupling has repeatedly been reported to be crucial for the beneficial effect of sleep (Helfrich et al., 2018; Latchoumane et al., 2017; Schreiner et al., 2021). Animal studies using two-photon imaging have shown that the co-occurrence of a spindle within the up-state of a slow-wave might optimize conditions for synaptic plasticity in local cortical circuits by maximizing calcium activity in excitatory pyramidal cells (Niethard et al., 2018). Thus, one conclusion could be that enhancing slow-waves or changes in their characteristics due to hypnotic suggestions alone are not sufficient to benefit memory if spindles and their coupling are not enhanced in a similar way. This notion is consistent with the assumption that the interplay and precise timing between these sleep oscillations is crucial for the beneficial effect of sleep on memory consolidation (Fernandez & Lüthi, 2020; Peyrache & Seibt, 2020; Schreiner & Staudigl, 2020).

Our interpretation is in line with the active system consolidation hypothesis (Rasch & Born, 2013), which stresses the importance of the precise timing between different types of sleep oscillations in the consolidation of memory. In contrast, the missing effect on memory consolidation despite increases in slow-waves are difficult to explain via the synaptic down-selection theory (Tononi & Cirelli, 2014), where slow-waves are thought to directly contribute to synaptic depression in two possible scenarios: burst firing, which occurs during transitions between up and down states leading to enduring depression of excitatory postsynaptic potentials (Czarnecki et al., 2007); decoupling through synchronous burst firing during slow-waves by spike-timing-dependent plasticity mechanisms (Lubenov & Siapas, 2008). Within this framework, increasing slow-waves should increase the activity-dependent down-selection of synapses, decrease the net synaptic strength, restore cellular homeostasis and thereby favor memory consolidation during sleep.

Besides the interpretation that spindles and their coupling to slow-waves is essential for improvements in memory consolidation, another potential factor has been discussed in the literature. The pre-sleep performance level in the declarative memory task might have been not optimal (37.57–43.13 %) to profit from sleep dependent memory consolidation (Drosopoulos et al., 2007; Schoch et al., 2017; Wilhelm et al., 2012) and an additional recall trial with feedback before sleep or repeated learning until reaching 60% could have benefitted memory consolidation (Plihal & Born, 1997; Rasch et al., 2006; Wilhelm et al., 2011).

The present study shows that selectively enhancing slow-waves using a hypnotic suggestion without affecting sleep spindles is not sufficient to support memory consolidation during sleep. Our results are in line with the notion that the interplay and timing between slow-waves and sleep spindles is essential for the beneficial effect of sleep on memory consolidation. Future studies examining memory consolidation during sleep have to consider and target slow-waves in conjunction with spindles and especially their coupling during sleep.

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Disclosure Statement

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Discussion

After a brief summary of the results from the three included studies, the key findings are interpreted against the background of the models presented in the Introduction. Next, possible sleep regulatory networks are presented, followed by an excursion about dreams as a special form of cognitions during sleep. Finally, limitations of the present dissertation and future research directions are discussed.

Summary of Results

The present dissertation aimed to contribute to a deeper understanding of mechanisms on how cognitions affect sleep. Study 1 investigated the core mechanism of our recently proposed MemoSleep hypothesis assuming that semantic concepts, which are active during sleep, are able to affect sleep physiology (Rasch, 2016). The activation of a relaxation concept during sleep by repeatedly presenting words associated to relaxation (e.g., “quiet” or “easy”), yielded a prolonged time spent in SWS during the period of word presentation and an increased subjective sleep quality compared with a control condition listening to control words (e.g., “produce” or “materials”). In addition, SWA was increased directly after the cue compared with the same words played in reverse and compared with control words. These results suggest that the semantic meaning of words presented during sleep is, in principle, capable of affecting sleep depth regulatory systems. Thereby, the results provide empirical support for our notion that active semantic concepts during sleep are capable of affecting sleep physiology.

Study 2 aimed to replicate negative effects of anticipating stress on sleep physiology with similar strong effects on sleep compared with the confrontation of the same stressor before sleep. Therefore, one group of subjects anticipated a stressful task to happen after sleep, while a second group performed the same task before sleep. The effects of stress on sleep physiology were compared to a within-subjects relaxation condition. In addition to the overall expected negative effects on sleep, we expected stress to affect sleep most strongly in temporal proximity to the stressor. Our results confirmed both of our hypotheses, with similar strong effects in both groups on overall sleep parameters including SOL, SWS, SWA/beta power ratio, slow-wave parameters (number, amplitude, up- and down-slope), slow-spindles and fast spindles. Moreover, we observed dynamic changes of these sleep parameters in accordance with our hypothesis: Anticipating stress after sleep deteriorated sleep especially during late sleep, while being

confronted with the same stressor before sleep mainly deteriorated early sleep. Interestingly, the changes in sleep parameters were accompanied by physiological arousal (increased heart rate) only in the pre-sleep group and not within the group anticipating stress after sleep. These results provide evidence that negative cognitions such as the anticipation of a future stressful event are able to directly affect sleep physiology without a concomitant increase in physiological arousal. Thereby, they suggest that cognitions dynamically affect sleep throughout the whole sleep period.

Study 3 aimed to examine the effect of a pre-sleep hypnotic suggestion to sleep more deeply on sleep parameters that are linked to memory processes. The sleep depth promoting effect was confirmed for numerous slow-wave parameters (number, density, amplitude, up-slope, down-slope) over frontal and parietal cortices. Thus, Study 3 extended our previous findings of an increased amount of SWS in highly hypnotizable subjects. However, sleep spindle parameters were comparable between the hypnosis and the control condition and the coupling between slow-waves and spindles was reduced in the hypnosis condition. These results might explain the lack of improvement in memory consolidation, despite increases in overall SWS. Thus, our results suggest that positive pre-sleep cognitions are capable of enhancing slow-waves in highly hypnotizable subjects. However, selectively enhancing slow-waves using a positive pre-sleep cognition without affecting sleep spindles might not be sufficient to support memory consolidation during sleep.

Taken together, the studies included in this dissertation provide evidence that our thoughts and cognitions before (Study 2 & 3) and during sleep (Study 1 & 2) are able to affect sleep physiology. The next chapter will discuss, if and how the models presented in the introduction are able to explain these findings.

Integration into Recent Models

Insomnia Models

Regarding the question how cognitions are able to affect sleep, most insomnia models assume that some sort of hyperarousal in the form of physiological arousal (Morin, 1993; Ong et al., 2012; Perlis et al., 1997; Riemann et al., 2010; Spielman, Caruso, & Glovinsky, 1987) or an interaction between physiological and cognitive arousal (Espie, 2002; Espie et al., 2006; Harvey, 2002; Riemann et al., 2010) is incompatible with sleep, and thereby affects sleep. This notion is

supported by our results in the pre-sleep stress group of Study 2. In line with previous research (Ackermann et al., 2019; Wuyts et al., 2012), we found an increase in physiological and cognitive subjective pre-sleep arousal and a decreased sleep quality during early sleep, which decreased continuously and in synchrony with objectively measured physiological arousal. The trajectory of decrease in physiological arousal can be related to the typical decrease of the physiological stress response to the Trier Social Stress Test (TSST) during wake, with a recovery of the heart rate about 10–30 minutes and cortisol levels about 30–90 minutes after the TSST induction (Janson & Rohleder, 2017; Kirschbaum et al., 1993; Yamanaka et al., 2019). Within the hyperarousal framework, cognitive arousal might have further fueled stress-induced increases in physiological arousal or affected sleep in interaction with physiological arousal.

However, the insomnia models focus on negative cognitions and fail to conceptualize how positive cognitions, like the hypnotic suggestion to sleep more deeply (Study 3), are able to promote slow-waves. Within the hyperarousal framework, one could still argue that sleeping in an unfamiliar environment and a full polysomnographic setup in the control condition leads to an increased arousal in both conditions, and the hypnotic suggestion reduces such an increased arousal. Within Espie's psychobiological inhibition model (Espie, 2002), a pre-sleep hypnosis could in general facilitate to de-arouse before sleep and thereby improve the sleep onset process. However, such mechanisms are highly unlikely based on the results of an additional control group in an earlier nap study (Cordi et al., 2014). In this group, highly hypnotizable subjects received a hypnotic induction suggesting to sleep shallower, which utilized the metaphor of a boat resting on the surface of the sea. Sleep depth was comparable to a within-subjects control condition, which suggests that the semantic content of the hypnosis is likely to be the key element of inducing the sleep promoting effect. A comparison of the two different hypnotic suggestion conditions regarding physiological arousal was not reported, yet they are likely to be comparable due to the high similarities in the induction process. In addition, if the sleep promoting effect of the hypnotic suggestion to sleep more deeply originated from a reduced arousal level in comparison with the control condition, we would assume that the quality of SWS, with respect to sleep oscillations, to be comparable between both conditions as well as comparable to naturally occurring SWS. However, we found that the hypnotic suggestion to sleep more deeply specifically targets slow-waves, leaving spindles unaffected and reducing the coupling between spindles and slow-waves (Study 3). Strikingly, these changes in sleep

oscillations reflect the semantic content of the suggestion to increase the depth of sleep. It would be fascinating to study whether a suggestion to increase sleep spindles, or more generally memory consolidation processes, would also show a specific effect on spindles and coupling parameters.

Thus, it is likely that the sleep promoting effect of the hypnotic suggestion to sleep more deeply does not originate from a reduced arousal level in comparison with the control condition, but from a positive effect of cognitive processes related to the semantic content of the hypnosis in the pre-sleep period and during early sleep. Therefore, the results support a direct effect of pre-sleep cognitions on early sleep and thereby suggest that negative pre-sleep stress might also directly deteriorate early sleep, without the need of physiological arousal as a mediator. In fact, this is further supported by our results from the anticipation group of Study 2, which showed an increased SOL without a concomitant increase in subjective pre-sleep and objective physiological arousal. However, the effects on early sleep were more pronounced in the pre-sleep stress group, which showed an increased subjective and objective physiological arousal. As previous research supports the notion that a purely physiological arousal influences early sleep (Marrosu et al., 1990; Schüssler et al., 2016), physiological and cognitive pre-sleep arousal might both directly affect early sleep and are likely to interact with each other, which would be in line with several insomnia models (Espie, 2002; Espie et al., 2006; Harvey, 2002; Riemann et al., 2010).

Most of the insomnia models focus on the effect of cognitions on sleep while we are awake that is during the day, during the pre-sleep period and during awakenings (Espie, 2002; Espie et al., 2006; Harvey, 2002; Morin, 1993; Ong et al., 2012; Spielman, Caruso, & Glovinsky, 1987). Such approaches cannot explain an effect of cognitions during sleep on sleep physiology, which has been supported by the results of Study 1 and 2 of the present dissertation: The semantic content of words presented during sleep can promote the depth of sleep (Study 1), and anticipating a stressful event after sleep resulted in a reduced sleep depth during late sleep (Study 2). However, the neurocognitive model of insomnia and its successor (Perlis et al., 1997; Riemann et al., 2010) introduced cortical arousal as a link between physiological and cognitive arousal with the capability of directly affecting sleep physiology during sleep. On a physiological level, cortical arousal is measured via an increase of EEG beta and gamma power during NREM sleep. The association of cortical arousal with cognitive processes (i.e., enhanced sensory

processing, information processing and memory formation) could also explain the effects of stress on sleep during later periods without the need for a concomitant physiological arousal observed in the post-sleep group anticipating stress after the nap. For instance, anticipation of stress could have induced an increased cortical arousal (increased beta and gamma power), which enhanced sensory processing and thereby facilitated processing of ambient noise in the sleep environment leading to a disruption of sleep including decreases in sleep depth.

Such mechanisms are supported by evidence from an early study, showing that arousal thresholds to auditory cues presented during sleep were reduced 10 min after sleep onset and 5 min after the first REM epoch in insomnia patients (Mendelson et al., 1986). Moreover, a recent study assessed the notion of an increased excitability of sensory pathways during sleep in insomnia patients measuring the ERPs to continuous low intensity auditory stimulation every 1-3 seconds over 8 hours in two nights (Feige et al., 2021). The results suggested an increased mismatch negativity to tones in insomnia patients especially during phasic periods of REM sleep that is epochs including eye movements. Mismatch negativity is an index of automatic change-detection, which follows in response to a change in regular sensory stimulus presentation (Fitzgerald & Todd, 2020) and an increased mismatch negativity can be viewed as a marker of enhanced sensory processing during sleep. In addition, the authors argue that such enhanced sensory processing might further increase subcortical and cortical arousal (Feige et al., 2021). They propose that the formation of new memory traces of mental activity associated with enhanced sensory processing is facilitated during sleep and thereby causes the impression of being awake. Yet, these results were shown with rather small effect sizes and exclusively during phasic REM sleep, which contradicts other findings suggesting that auditory stimuli affect ERP components also during NREM sleep (Campbell & Muller-Gass, 2011) and that cortical arousal is especially increased during NREM sleep (Riemann et al., 2015). Nonetheless, these results support the notion that cognitive processes associated with cortical arousal are active during sleep and are able to affect sleep physiology throughout the sleep period.

However, such mechanisms cannot explain the dynamic changes we observed on various sleep parameters in healthy subjects in Study 2. To dynamically affect sleep in this framework, cortical arousal would also be required to dynamically change across sleep. In Study 2, we observed decreases in SWA/beta power ratio during late sleep in response to anticipated post-sleep stress, which could reflect increases in cortical arousal. Yet, these changes can be ascribed

to decreases in SWA as beta activity was comparable during late sleep in this group (see supplementary Figure S1, Study 2), while extensive changes in slow-wave parameters were observed during the same period. It is therefore unlikely that the dynamic changes of sleep parameters occurred due to dynamic changes of cortical arousal in Study 2. Additionally, our results from Study 1 demonstrated the limits of the presented insomnia models as they cannot explain how the presentation of relaxing words in comparison with control words during sleep is able to increase the depth of sleep on a cue-level and over a longer period of time.

"Memories-of-Sleep" Hypothesis

In contrast to previous insomnia models, the MemoSleep hypothesis can explain the findings from Study 1 by assuming that semantic concepts that are active during sleep can affect sleep regulatory systems. Semantic meaning is thought to be stored and organized in multimodal neuronal networks (Barsalou, 2008; Shapiro, 2014) and activation of one part of the network is thought to spread over the whole network including links to sensorimotor bodily functions. Thereby, the presentation of relaxing words during sleep is thought to activate a semantic relaxation concept, which in turn activates brain regions involved in relaxation including sleep induction and maintenance systems. Our results support the proposed mechanism by showing that the presentation of relaxing words leads to a distinct increase in SWA power 2–3.5s after the word presentation. This increase is likely to occur due to the semantic meaning of the words, because it appeared after the typical K-complex-like response to auditory stimulation during sleep (Pratt et al., 1999) and it has been controlled for basic auditory properties of the words by subtracting the response to the same words played in reverse. In addition, the syllable length of relaxation words was matched with the control words and a non-native German speaking sample rated the relaxing words as phonetically comparable with the control words. Together with the results of an increased amount of SWS during the period of relaxing word presentations, our findings support the notion that repeatedly activated semantic concepts are able to affect sleep depth regulatory systems. Thereby, our results suggest that cognitions during sleep can affect sleep physiology, which supports the MemoSleep hypothesis.

Such mechanisms could also explain the negative effects of pre-sleep and anticipated stress on sleep parameters across the whole sleep period (Study 2) and the positive effects of a pre-sleep hypnotic suggestion to sleep more deeply on slow-waves (Study 3). Thus, the effect of stress or a hypnotic suggestion on sleep would depend on repeated endogenous reactivations of

semantic concepts linked to the stressor or to the metaphor of the hypnotic suggestion. This idea of reactivations is similar to Brosschot's notion that unconscious cognitive representations of stressful events remain active during sleep and lead to a prolonged physiological stress response (Brosschot, 2010; Brosschot et al., 2018). However, they focus on physiological stress responses in the form of increases in heart rate or cortisol levels during sleep and not on sleep physiology such as a decrease in sleep depth. In addition, we hypothesized (Study 2) to find dynamic differences based on previous literature showing that pre-sleep stress and relaxation mainly affect early sleep (Ackermann et al., 2019; Cordi et al., 2020; Wuyts et al., 2012) whereas the anticipation of a stressful event after sleep leads to physiological changes during later periods of sleep (Born et al., 1999; Germain et al., 2003; Hall et al., 2004). However, neither the MemoSleep hypothesis nor the extended perseverative cognition hypothesis predicts why pre-sleep stress vs. anticipated post-sleep stress should differentially affect the progression of stress-related changes on sleep parameters.

Yet, within the framework of the MemoSleep hypothesis, dynamic changes in the effect of stress on sleep could originate from differences in reactivations of semantic sleep or wake concepts during sleep. Such differences could contain an altered frequency of activations or reactivations of semantic concepts during sleep. Theoretically, a higher frequency of activations might induce a stronger activation of a sleep or wake concept and induce a stronger effect on sleep. In addition, the strength of activations of associated sleep or wake concepts might also influence the effect on sleep. Given the scenario of subjects in Study 2 anticipating a stressful task, activation of memories such as the chance for an additional payment or the feeling of standing and talking might also contain links to the anticipated task after sleep and more generally to embodied wake memories. However, activation of memories related to the pressure to perform well or a mental imagery of the situation to talk in front of a jury are likely to activate the semantic concept of the stressful task and associations to multimodal neuronal wake memories more strongly. As these memories are assumed to contain the links to associated sensorimotor bodily functions including sleep and wake regulatory systems (see Figure 13a), the effect on sleep could be increased as well. Thus, temporal proximity to a stressful or relaxing event might increase the frequency of memory reactivation associated with the event. In addition, the association strength of the activated memories with the actual event might possibly also increase with temporal proximity to the event.

As activations of semantic representations and concepts linked to stressful or relaxing events are assumed to be unconscious (Brosschot, 2010; Brosschot et al., 2018; Rasch, 2016), temporal dynamic changes in activations are also likely to vary unconsciously. Such temporal effects could also act on a larger scale leading to sleep disturbances even weeks to months before the anticipated event occurs and more frequently when the stressful event approaches. During waking, dynamic changes in temporal proximity to an anticipated stressor have already been shown, for example during the short-term anticipation period of the TSST, where physiological arousal gradually increases before the onset of the stressor (Ditzen et al., 2007; Engert et al., 2013; Kirschbaum et al., 1993). Therefore, unconscious activations might change similarly during approximation of the actual stressful or relaxing event and decline after the event occurred. Such mechanisms could explain how sleep is affected dynamically over the sleep period by negative (Study 2) and positive cognitions (Study 3). For instance, semantic concepts linked to pre-sleep stress (Study 2) or a pre-sleep relaxing hypnotic suggestion (Study 3) might be reactivated most frequently and with a stronger association to embodied wake or sleep memories during early sleep rather than during late sleep. However, these assumptions are speculative and have to be tested in future studies.

Another notion that could account for the increased effect of anticipated post-sleep stress during late sleep might be that especially REM sleep is involved in emotional memory processing (Goldstein & Walker, 2014; van der Helm et al., 2011; Walker & van der Helm, 2009). As REM sleep typically occurs during late sleep and the TSST is a highly emotional psychosocial stress task, endogenous reactivations and processing of memories related to the anticipated emotional task might have been enhanced during late REM sleep-rich sleep. Thus, the activation of associated embodied wake memories containing the links to sensorimotor bodily functions could have been increased/enhanced during late sleep. We did not find any differences between the stress and the relaxation condition concerning overall or dynamic changes in REM sleep in the post-sleep anticipation group, however enhanced processing during REM sleep could have affected subsequent periods of NREM sleep. Within this assumption, the effects on early sleep lacking REM sleep would thereby be solely or for the most part explained by the increases in physiological arousal.

In addition, the previously mentioned mechanism of altered reactivation patterns of semantic concepts associated with the respective events throughout the whole night might

interact and interfere with memory consolidation processes during sleep. In Study 3, we observed an increase in slow-waves in a nap and in a night study, but no beneficial effect on memory consolidation. Our analyses suggested that the hypnosis to sleep more deeply specifically increased slow-waves without affecting sleep spindles and reducing the coupling between spindles and slow-waves. Within the framework of the MemoSleep hypothesis, the hypnotic suggestion may have affected sleep due to repeated reactivation of the semantic concepts linked to the hypnotic suggestion, especially during early NREM sleep close to the suggestion. This might interfere with memory consolidation processes as they also rely on memory reactivations during sleep (see Chapter 2, e.g., O'Neill et al., 2010; Oudiette & Paller, 2013b; Rasch & Born, 2013; Schreiner & Staudigl, 2020). Therefore, the sleeping brain might have been occupied especially during early NREM sleep with processing the reactivations of the hypnotic suggestion or the control text leaving less resources to reactivate and consolidate the memory task.

Theoretical Implications

Taken together, negative effects of stress on sleep and effects of pre-sleep stress on early sleep can be explained by both insomnia models and the MemoSleep hypothesis. However, insomnia models struggle to explain negative effects of stress during late sleep without concomitant increases in physiological and/or cortical arousal. In addition, they cannot explain sleep promoting effects of positive cognitions such as pre-sleep hypnotic suggestions and the presentation of relaxing words during sleep. In contrast, the MemoSleep hypothesis offers a conceptual framework to explain such effects by highlighting that reactivations of semantic concepts during sleep, which are linked to multimodal sleep and wake memories, are able to directly affect sleep and wake regulatory systems.

Results from studies 2 and 3 support the notion that pre-sleep activations of embodied sleep/wake memories affect subsequent sleep. However, the results from Study 1 suggest that a pre-sleep activation of embodied sleep/wake memories is not necessary to affect sleep throughout the night. Existing sleep/wake memories may be sufficient to promote or disturb sleep when activated during sleep. Thereby, the association strength of pre-sleep activations to existing embodied sleep/wake memories might be essential for its effect on sleep. In addition, the results from Study 2 suggest that characteristics of pre-sleep activations such as future relevance (completed vs. anticipated stressor) differentially affect subsequent sleep. Thus, the effect of pre-

sleep activations related to embodied sleep/wake memories is more complex than assumed and has to be studied in future experiments.

Based on the findings from the present dissertation, I propose to add the following considerations to the MemoSleep hypothesis: (1) Repeated activations of sleep/wake memories does not require pre-sleep activations of related concepts; (2) Pre-sleep activations of sleep/wake-related memories should be described as one possible method to affect activation patterns of sleep/wake memories during sleep; (3) The strength of activation of embodied sleep/wake memories is essential for their effect on sleep physiology. Parameters affecting the strength of activation of embodied sleep/wake memories could be the frequency of activations of related semantic concepts and the association strength of activated semantic concepts with sleep/wake memories. Within this context, characteristics of pre-sleep activations (e.g., future relevance of a stressor, affective valence) could differentially affect these parameters and thereby differentially affect sleep physiology. In addition, the results from Study 2 suggest that pre-sleep physiological arousal mainly affects early sleep, while cognitive arousal is able to affect sleep throughout the whole sleep period, which could also be integrated into the model.

As all these considerations rely upon the notion that the activation of embodied sleep and wake memories during sleep affects sleep via links to sleep and wake regulatory networks, the question arises, which brain networks might be involved in the regulation of sleep and wakefulness. The next chapter will outline possible underlying networks by summarizing evidence from animal and human research.

Sleep Regulatory Networks

The animal flip-flop switch model (Saper et al., 2005) assumes that during wakefulness, the sleep promoting VLPO, which is a small cluster of neurons in the anterior hypothalamus, is inhibited by monoaminergic nuclei (noradrenergic locus coeruleus, histaminergic tuberomammillary nucleus, serotonergic raphe nuclei). These nuclei are also part of the ARAS. In addition, orexin neurons are thought to further reinforce the monoaminergic response. During sleep, the VLPO inhibits the monoaminergic nuclei and orexin neurons by releasing inhibitory neurotransmitters including GABA and galanin, which relieves its own inhibition. The model assigns orexin a stabilizing role in the switch between wakefulness and sleep. This model primarily explains how the transition between sleep and wakefulness is regulated, but the

corresponding structures could potentially be involved in regulatory processes during sleep as well and have been integrated in the hyperarousal model of insomnia (Riemann et al., 2010).

During sleep, inhibitory systems and thalamo-cortical loops are involved in sleep induction and maintenance (Chen et al., 2018; Mak-McCully et al., 2017; Neske, 2015). Chen and colleagues highlighted the role of galaninergic and GABAergic neurons in the dorsomedial hypothalamus in the regulation of NREM and REM sleep in mice (Chen et al., 2018). Thereby, one distinct subpopulation of galaninergic neurons was active during REM sleep, while a different subpopulation was inhibited during REM sleep. The subset of galaninergic neurons which was inhibited during REM sleep projects to the preoptic area, which includes the VLPO, while the subset of neurons active during REM sleep projects to the raphe pallidus nuclei, which are part of the raphe nuclei. Thus, the model also provides a link to brain structures mentioned in the earlier flip-flop switch model (Saper et al., 2005). Strikingly, optogenetically activating the subset of the galaninergic neurons which project to the preoptic area promotes NREM and suppresses REM sleep, while activating the neurons projecting to the raphe pallidum promotes REM and suppresses NREM sleep (Chen et al., 2018). Thus, these results suggest a causal contribution of these two distinct galaninergic circuits in the dorsomedial hypothalamus in the regulation of NREM and REM sleep.

Based on electrophysiological data from bipolar depth recordings in epilepsy patients, Mak-McCully and colleagues propose a model of generation and temporal sequence of thalamo-cortical slow-waves and sleep spindles during NREM sleep (Mak-McCully et al., 2017): First, distributed down-states of cortical slow-waves converge and lead to a thalamic down-state. Second, the hyperpolarization of this thalamic down-states triggers thalamic spindles. Third, the thalamic spindle is focally projected to the cortex and occurs during the down-to-upstate transition of a slow-wave. Within this interplay between the thalamus and cortical networks, the thalamic reticular nucleus has been shown to locally regulate sleep depth and local sleep features like spindles and slow-oscillations (Vantomme et al., 2019). Interestingly, recent results showed that silencing neocortical pyramidal cells in mice led to an increased amount of wakefulness and a decreased amount of SWA in response to sleep deprivation and thereby suggest that even the neocortex itself is involved in sleep-wake homeostatic processes and sleep regulation (Krone et al., 2021). Thus, in addition to supporting the organization of memory replay during sleep (Diekelmann & Born, 2010; Mak-McCully et al., 2017), thalamo-cortical loops also play an

important role in the generation of slow-waves and sleep spindles and are thereby likely to be involved in the reactivation of embodied sleep memories and sleep regulatory networks proposed by the MemoSleep hypothesis.

In insomnia research, a recent review highlights the view of insomnia as a disorder of arousal and affective processes (Schiel et al., 2020) and an involvement of the default mode network (DMN), the salience network and limbic circuits in the pathophysiology of insomnia. The DMN comprises brain areas which are active during resting wakefulness, such as the medial prefrontal cortex, the precuneus and angular gyrus, and is also active when thinking about oneself or others, remembering the past and planning the future (Buckner et al., 2008). Moreover, DMN activity has been associated with rumination and with dysfunctional affective cognition in depression (Berman et al., 2011; Lois & Wessa, 2016). Thus, the DMN might be involved in unconscious negative cognitive processes such as perseverative cognition during sleep (Brosschot, 2010). In addition, recent evidence suggest that thalamic nuclei are central to the function of the DMN (Alves et al., 2019), which also provides a link to previously mentioned sleep regulatory networks. The salience network comprises insular cortices, the anterior cingulate cortex and the amygdala, and is thought to coordinate neuronal resources and to be engaged in the recognition of behaviorally relevant stimuli (Khazaie et al., 2017; Schiel et al., 2020). Thus, the salience network might be involved in cognitive processes associated with the monitoring of the sleeping environment before and during sleep (Blume et al., 2018; Legendre et al., 2019; Tamaki et al., 2016). Within limbic circuits, which are involved during encoding and retrieval of emotional memory (Nieuwenhuis & Takashima, 2011), an altered function and physiology of the amygdala, hippocampus and the anterior cingulate cortex has been highlighted in insomnia (Baglioni et al., 2014; Regen et al., 2016; Wassing, Lakbila-Kamal, et al., 2019; Wassing, Schalkwijk, et al., 2019). Thus, the limbic system could especially be involved in cognitive processes associated with emotional memories during late REM sleep-rich sleep (Goldstein & Walker, 2014; van der Helm et al., 2011; Walker & van der Helm, 2009). Regarding all three networks, it has been suggested that connectivity within the DMN and the salience network is impaired in insomnia patients and a dysregulation of limbic circuits might further perpetuate such impairments (Schiel et al., 2020). Therefore, these three networks are likely to be involved in cognitive and sleep regulatory processes during sleep, also in healthy subjects.

The next chapter will outline results from the related field of dream research, which supports the notion that cognitions during sleep are able to affect sleep. This provides an additional perspective and offers methodological approaches to further study the effect of cognitions during sleep on sleep.

Dreaming as Cognitions During Sleep

The general notion that our thoughts and cognitions during sleep are capable of affecting sleep physiology is strengthened by results from dream research. During dreams, individuals have multiple sensory experiences including visual, but also auditory, olfactory and gustatory experiences (Zadra et al., 1998). In addition, emotions are present to a stronger or lesser extent in almost all of our dreams, with an equally distributed amount of negative, positive and neutral emotions (Schredl & Doll, 1998). Thus, dreaming is a special form of cognitive processes during sleep. The fact that such cognitions can affect sleep during sleep itself is made evident by the occurrence of nightmares that means vivid dreams characterized by intense dysphoric emotion (fear, anger, sadness), which frequently lead to an abrupt awakening (Levin & Nielsen, 2007). However, less extreme forms of dreaming occur during all sleep stages (Cavallero et al., 1992; Cicogna et al., 1991), which supports the assumption that cognitive processes are active across the whole sleep period. Regarding the content of dreams, the continuity hypothesis of dreaming posits that our daytime thoughts and experiences have an increased likelihood to appear during dreams in subsequent sleep (Schredl & Hofmann, 2003). This is further supported by studies showing that dreams incorporate elements of temporally close and distant experiences (Malinowski & Horton, 2014; Vallat et al., 2017). Moreover, the type of subjectively reported emotions during sleep has been shown to be similar to the emotion types of important life events, which suggests that daytime emotions are processed or active during subsequent sleep (Nielsen et al., 1991). This notion would be in line with the MemoSleep hypothesis and the active system consolidation hypothesis, which both assume that memories and concepts that are learned or activated before sleep remain active or are reactivated during subsequent sleep (Rasch, 2016; Rasch & Born, 2013). Additional support for this notion is provided by results from an EEG study using multivariate pattern classification showing that brain activity patterns related to categories of learning material before sleep (faces vs. houses) are spontaneously detected during subsequent NREM and REM sleep, especially during the second sleep cycle (Schönauer et al.,

2017). In addition, it has been suggested that memory replay of emotional memories during REM sleep decouples the emotional component from the memory (Goldstein & Walker, 2014; van der Helm et al., 2011).

Thus, memory consolidation and dream research highly overlap. However, unlike mere memory reactivations during sleep, dreaming requires a higher level of consciousness experienced during sleep and enhanced memory processes to access (i.e., remember) dream experiences after sleep. Thereby, it has been discussed and questioned if such increased levels of consciousness and memory processes are actually functionally relevant, for instance for an emotion regulatory or fear extinction function dreaming (Nielsen & Levin, 2007). For the purposes of this dissertation, the question arises if the content of our dreams (i.e., cognitions during sleep) is able to affect sleep itself.

One study using imagery rehearsal therapy and collecting polysomnographic data suggests that altering the content of dreams is indeed able to affect sleep physiology (Germain & Nielsen, 2003). During imagery rehearsal therapy sessions, patients with frequent nightmares chose one of their nightmares and wrote its content down in first person present tense. Next, patients were supposed to write down a new version of the nightmare, which was neither unpleasant nor distressing. Lastly, the patients imaginatively rehearsed the new version of the dream at least once every day for 4-6 weeks. The study compared baseline sleep with a follow-up sleep session 8.5 weeks later and found a significant reduction in nightmare frequencies together with changes in sleep parameters in idiopathic nightmare patients like decreases in SOL, SWS and increases in WASO, N2 and REM sleep (Germain & Nielsen, 2003). On a subjective level, a meta-analysis suggested that imagery rehearsal therapy reduces the frequency of nightmare and increases the subjective sleep quality in patients with post-traumatic stress disorder (Casement & Swanson, 2012). This suggests that deliberately altering cognitions during the day is able to affect cognitions during sleep and is able to promote sleep. Yet, another study found no effect of an imagery rehearsal treatment on objective sleep parameters like SOL, WASO and sleep efficiency (Germain et al., 2012). Thus, to elucidate if the dream content is causally affecting sleep physiology, future experiments would be required to manipulate the dream content, for example inducing positive vs. negative dreams, and measure the effect on sleep with polysomnography.

The targeted memory reactivation approach has already been used to induce task-related dreams (Picard-Deland et al., 2021; Picard-Deland & Nielsen, 2021). In these studies, a virtual reality flying task was paired with a four-tone melody prior to sleep and presented again during subsequent SWS or REM sleep. Results from dream reports suggested that subjects dreamed more about the task 1-2 days after the experimental session when cues were presented during REM sleep and 5-6 days later when cues were presented during SWS (Picard-Deland & Nielsen, 2021). Additional analyses on sleep parameters yielded that stimulation during SWS and REM sleep increased the time spent in REM sleep and reduced N1 and WASO compared with the control condition without cueing (Picard-Deland et al., 2021). Interestingly, stimulation during early SWS prolonged REM latency, which suggests a strengthening of SWS maintenance due to engagement of the sleeping brain in associated content. However, this could also just result as a byproduct of auditory stimulation inducing slow-waves during sleep. Another study paired negative and neutral pictures with sounds and presented both categories either during subsequent SWS or REM sleep (Hutchison et al., 2021). They found that sound presentation during REM sleep reduces stimuli-related subjective arousal of negative pictures, which supports the notion that REM sleep is involved in emotional memory processing (Goldstein & Walker, 2014; van der Helm et al., 2011). Moreover, playing sounds associated to negative stimuli during REM sleep reduced the total sleep time in comparison with the SWS stimulation group. Assuming that processing of emotionally negative content is facilitated during REM sleep, such enhanced processing might have led to an increased activation of associated embodied wake memories and thereby reduced the total sleep time. However, no effects on other sleep parameters were reported (Hutchison et al., 2021). In addition, the results cannot be related to the occurrence and content of dreams because no dream reports were collected and the results have not been compared to a within subject control group without stimulation.

Based on the presented literature from dream research, several research questions arise within the framework of the MemoSleep hypothesis. A replication of Study 1 of this dissertation including an additional group presenting relaxing words during REM sleep could elucidate if the effect of activation of semantic concepts on sleep physiology generally works and is possibly enhanced for emotional content during REM sleep. Additional studies could investigate, if such effects might be limited to emotional stimuli in general or to negative vs. positive stimuli in particular. In this context, it would be interesting to assess sequential effects on sleep episodes

that means if activation of concepts during REM sleep affects subsequent episodes of NREM sleep and vice versa. Moreover, future research might want to investigate the role of dreams as a state of increased consciousness and memory processes on the effects of cognitions during sleep on sleep architecture by including dream reports and multivariate pattern classification to decode dream content. To assess the effect of dream content on sleep parameters, the content of dreams would have to be manipulated and presented during the same sleep stages. If semantic concepts that are repeatedly activated using a TMR approach (e.g., associated with relaxation or stress) include a strong visual (e.g., a bed), auditory (e.g., screaming) or more generally a sensory component, they might at some point be strong enough to be incorporated into dreams. It would be fascinating to study whether surpassing such a threshold measurably boosts the effects of activation of semantic concepts on sleep parameters.

Limitations and Future Directions

In addition to already mentioned future research perspectives throughout the discussion, research needs to investigate several open questions within and beyond the scope of the MemoSleep hypothesis. First, we argue that the effect of cognitions on sleep architecture originates from reactivations of semantic concepts and their links to sensorimotor bodily functions during sleep. The results from Study 1 support this mechanism, but evidence that the semantic content related to the words is actually activated during sleep is still lacking. Thus, future studies could apply a combination of multivariate pattern classification to detect EEG activity patterns associated with the stimuli presented during sleep and actually wake subjects after a period of stimulation and collect dream reports. If EEG activity patterns match the activation during wake and dream reports are associated with the semantic content of the activated concept, such results would support this core assumption of the MemoSleep hypothesis. In addition, our results suggest that cognitions during sleep can dynamically affect sleep physiology and we argued that such effects might originate from changes in reactivation patterns of semantic concepts, but it remains unclear, how such changes could look like. Using a similar design as Study 1 of this dissertation, studies could manipulate the frequency and association strength to a sleep or wake concept of word presentations and measure the effect on sleep physiology. Such studies may provide evidence on how changes in reactivations of cognitive concepts during sleep might differentially affect sleep physiology.

Second, it remains unclear how such proposed semantic sleep and wake concepts look like and how to specifically target them. Future studies should investigate if general semantic concepts of sleep and wake vary between healthy individuals and patients with sleep disturbances. Results from Study 1 suggested that a targeted memory reactivation design is not required and pre-existing concepts related to relaxation and sleep are sufficient to induce a sleep promoting effect. However, this might highly depend on the pre-existence of sleep promoting concepts. For instance, hyperaroused insomnia patients might exhibit a general overactivation of semantic concepts associated with wake and less activations and connections to semantic concepts associated with relaxation and sleep. Moreover, the concept of "sleep" might actually be negatively associated in such patients and even cause sleep disruptions when activated during sleep. Thereby, insomnia patients might profit from a TMR approach, which would require the establishment or strengthening of relaxation and sleep promoting concepts prior to sleep.

Third, future studies need to investigate the relationship between cognitive and physiological arousal in their effect on sleep. Previous research suggested a causal contribution of physiological arousal to sleep disturbances (Ehlers et al., 1986; Holsboer et al., 1988; Marrosu et al., 1990; Opp et al., 1989; Schüssler et al., 2016) via an interaction of the HPS and the HPA systems (Dresler et al., 2014; Ehlers & Kupfer, 1987; Steiger, 2007). In addition, results from the studies included in this dissertation support a direct effect of cognitive processes on sleep regulation without the need for physiological arousal. While several insomnia models assume an interaction between physiological and cognitive arousal in their effect on sleep (Espie, 2002; Espie et al., 2006; Harvey, 2002; Perlis et al., 1997; Rasch, 2016; Riemann et al., 2010), future studies including a systematic analysis of both physiological and cognitive arousal as well as temporal dynamics throughout the sleep period need to be elucidated, in particular with regard to their relationship in affecting sleep. Within this context, the role of cortical arousal and associated cognitive processes during sleep have to be further studied. Moreover, pre-sleep cognitive arousal has been shown to affect sleep even without a concomitant emotional component. Conducting a series of cognitive tasks for half an hour before sleep has been shown to prolong sleep onset and increase high frequency EEG power during early NREM sleep (Wuyts et al., 2012). As Study 2 of this dissertation included a highly emotionally arousing task (TSST), future studies could also investigate the role of emotional arousal and whether it is essential in inducing dynamic effects on sleep parameters.

Fourth, despite the increased amount of SWS during the period of relaxing word presentation in Study 1, we did not find an increased amount of SWA and slow-wave density in the same time period. However, the presentation of relaxing words during sleep reduced the typical right-frontal predominance of SWA and slow-wave density (Mascetti, 2016; Sekimoto et al., 2000; Tamaki et al., 2016). It has been argued that a reduced amount of SWA in the left brain hemisphere represents an active "night watch" or "monitoring" system of the brain, because such hemispheric differences occur when sleeping in an unfamiliar environment (Sekimoto et al., 2007; Tamaki et al., 2016; Tamaki & Sasaki, 2019). This notion is supported by findings showing that the left hemisphere, which sleeps less deeply, produces an enhanced ERP response to deviant stimuli during sleep (Tamaki et al., 2016). In insomnia patients, studies assessing hemispheric asymmetry did not yield coherent results with differences between sleep stages, nights and subtypes of insomnia (Kovrov et al., 2006; St-Jean et al., 2012; St-Jean et al., 2013) and even suggesting intrahemispheric asymmetry patterns (Provencher et al., 2020). We argued in Study 1 that the activation of a relaxation concept during sleep via the presentation of relaxation-related words might have had a "calming" effect on the monitoring system. However, this assumption is speculative and requires further proof of future research examining the relationship between asymmetry of SWA, the sleeping environment and the activation of semantic concepts during sleep. For instance, creating a more dangerous sleep environment should lead to a more pronounced asymmetry compared with a safe sleeping environment. In addition, this effect could be further enhanced using a TMR approach to activate a safe or dangerous environment during sleep. When research has provided a better understanding of what the asymmetry of SWA represents, how it is manipulated most effectively and how it is altered in insomnia patients, it could be a promising method for future basic and clinical research applications to promote sleep.

Lastly, the empirical results of this dissertation are limited to healthy subjects in young adulthood. Yet, our results provide important theoretical implications for underlying mechanisms of how cognitions might affect and interact with sleep. Nonetheless, possible applications and underlying mechanisms in samples of middle and late adulthood and samples with sleep disturbances have to be examined in future research. In addition, Study 1 only represents a proof of concept and there are several opportunities to improve the sleep promoting effect of relaxing word presentations during sleep in future experiments. As our results suggest that already existing relaxation- and sleep-related concepts are sufficient to affect sleep when activated

during sleep, words associated with such concepts could be individually chosen before an experiment. After identifying a general pool of relaxation- and sleep-related words (e.g., 100) in the population using a survey, subjects could choose a subset of words (e.g., 10) from that list which they rated as most relaxing or sleep promoting. Assuming that concept reactivation works best during NREM sleep, which still has to be examined, individually chosen words could be presented during the up-state of slow-waves, where semantic processing might be enhanced (Göldi et al., 2019; Navarrete et al., 2020; Züst et al., 2019). Moreover, the presentation time could be extended to the whole sleep period including early NREM sleep, which we spared due to assumed ongoing processing of a pre-sleep hypnotic suggestion in a subgroup of our sample. In addition to the activation of a preexisting relaxation or sleep concept using auditory presentation of words, studies could explore different TMR approaches by pairing for example a relaxation exercise, such as a progressive muscle relaxation or the virtual reality relaxation task used in Study 2, with a pleasant odor or music and present them again during subsequent sleep. Such studies could also be taken to the homes of the participants to eliminate effects of the sleep environment in the sleep laboratory. The creation of a new relaxation concept might be especially relevant in insomnia patients, as existing sleep concepts might be associated with anxiety and fear. Relaxation concepts could also comprise therapeutic interventions to reduce perseverative cognitions, such as attentional trainings to reduce unconscious cognitive-emotional processes, expressive writing, and mindfulness-based trainings (Brosschot et al., 2010). Such studies could yield additional knowledge about the potential usability and limitations of reactivating previously associated, and already existing, sleep/wake promoting concepts during sleep.

Conclusion

The present dissertation examined the question of how our thoughts and cognitions can influence sleep. The included studies provide evidence that positive and negative cognitions are able to improve or deteriorate sleep physiology in healthy sleepers. In addition, the findings suggest that cognitive processes are active during sleep and capable of affecting sleep physiology throughout the sleep period. Our results cannot be fully explained by the presented insomnia models. The MemoSleep hypothesis offers a new and promising theoretical framework of how cognitions might affect sleep throughout the whole sleep period, however several open questions about the exact mechanisms remain unanswered. Therefore, many exciting studies are still to be conducted to investigate the underlying mechanisms of how cognitions are capable of influencing sleep in order to provide a solid basis for theory-driven interventions to improve sleep.

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