



Sweet Dreams Are Made of These:

Investigating the Neural Mechanisms
of Dream Traits and States

Mariana Pereira

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Sweet Dreams Are Made of These:
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Dream Traits and States

Mariana Eugênia de Carvalho Pereira

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Sweet Dreams Are Made of These:

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Chapter 1

General Introduction

The Sleeping Brain

From our first to our last day, sleep is a constant that marks the passing of time. Sleep is a naturally recurrent state of rest characterized by reduced physical activity, decreased responsiveness to external stimuli, and distinct neurophysiological patterns. There is probably no single activity we spend more time doing, but despite that, it has remained a puzzle throughout the history of humankind. The invention of electroencephalography (EEG) made it possible to monitor the brain's electrical activity non-invasively, leading to ground-breaking findings in early sleep research such as the discovery of rapid eye movements (REM), cyclic nocturnal sleep behavior (Figure 1 A), and the identification of neurophysiological events within sleep stages such as sleep spindles and slow waves as a marker of non-REM (NREM) sleep (Figure 1 B), or ponto-geniculo-occipital (PGO) waves, traceable in animal models, during REM sleep (Dresler et al., 2014). The human sleep cycle consists of regular progress through a series of global brain states characterized by specific neurophysiological changes. A typical sleep episode starts with light NREM sleep, progressing to deeper stages (N1, N2, and N3 sleep), and finally to REM sleep. Still, individuals do not remain in REM sleep, but cycle between NREM and REM stages an average of four to six times during the night. NREM sleep constitutes about 75 percent of total time spent in sleep, whereas REM sleep constitutes the remaining 25 percent. In healthy adults, NREM sleep accounts for the majority of sleep time in the first half of the night, as REM sleep increases as the night progresses and accounts for much of the sleep time in the second half (Carskadon & Dement, 2005). Although animal research has advanced sleep characterization across species, several pivotal questions about human sleep remain unanswered. One of the most intriguing is why we spend a significant portion of our sleep dreaming and how these often vivid conscious experiences arise from distinct neurophysiological states.

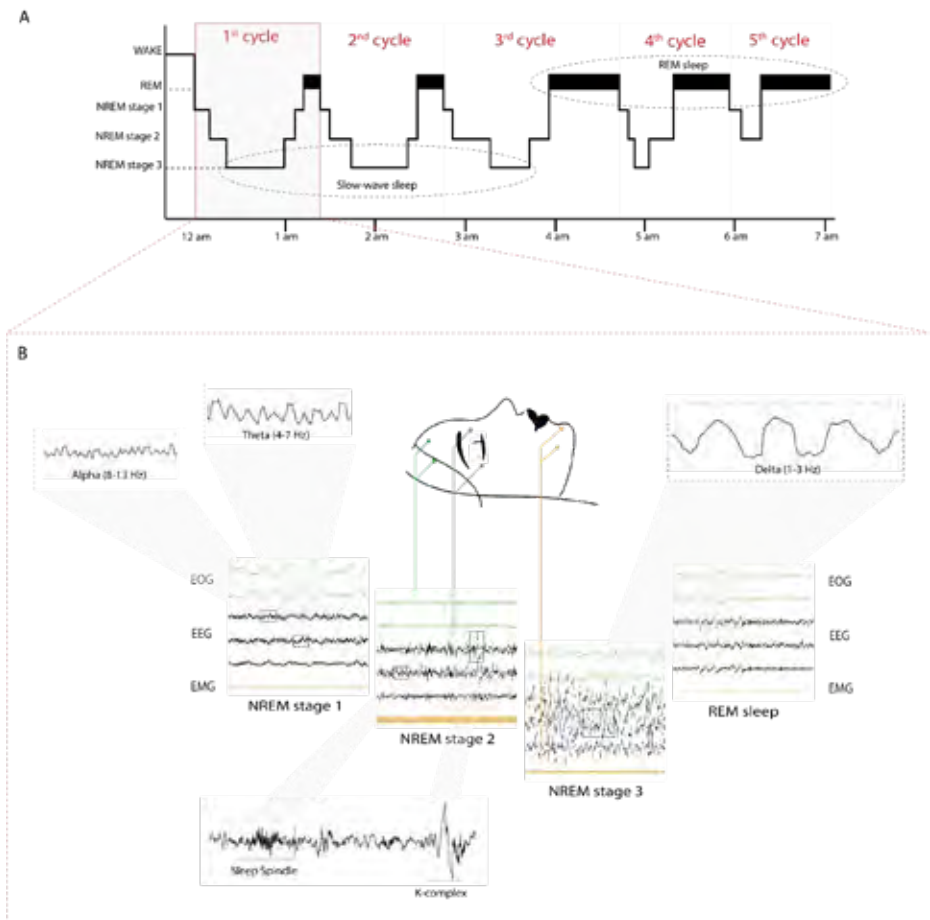


Figure 1: Hypnogram and Sleep Stage Characteristics. **A)** A full-night hypnogram showing approximately five sleep cycles, illustrating the progression through NREM stages 1, 2, and 3, followed by REM sleep. **B)** Close-up of the electrophysiological features characteristic of each sleep stage, including electrooculogram (EOG), electroencephalogram (EEG), and electromyogram (EMG) recordings, additionally, sleep stages' EEG spectral activity, highlighting key frequency bands, with examples of sleep spindles and K-complexes, hallmarks of NREM stage 2 sleep.

The Dreaming Brain

Dreams have influenced human society for as long as we can remember, from ancient cave paintings that may have depicted dream experiences (*The Cave of Forgotten Dreams*) to their future-telling importance in Ancient Egypt. But what is a plausible scientific interpretation of dreams? Sigmund Freud's theory of dreaming (Freud, 1983) was among the first to propose a psychological framework, suggesting that

dreams act as a window into the unconscious mind, primarily serving as a form of wish fulfillment for repressed desires. Although Freud's ideas laid the foundation for modern psychoanalysis and the study of dreams, they received considerable criticism, especially from behaviorists, causing dream research to stagnate for many years.

NREM and REM sleep dreaming

After Eugene Aserinsky and Nathaniel Kleitman discovered REM sleep in 1953 (Aserinsky & Kleitman, 1953), this paradoxical, wake-like cortical activation was initially believed to be the biomarker for the occurrence of dreaming, providing an efficient way to collect dream reports immediately after they occurred. In the following years, William Dement's work dove deeper into the exploration of "REM = dreaming," supported by electrophysiological findings, such as the cyclic variations during sleep and rapid eye movements (Dement & Kleitman, 1957; Dement & Wolpert, 1958). This led to a new research field, offering answers to decades-long standing questions about sleep and dreams. However, this surge of interest did not last long. As Foulkes (Foulkes, 1996) noted, the disinterest in dream research reemerged as early studies (Kamiya, 1961; Foulkes, 1962; Foulkes & Vogel, 1965; Monroe et al., 1965) revealed that dreaming also occurs outside of REM sleep. For instance, investigations into the onset of REM dreams showed that dreams could occur during NREM sleep, concluding that dreaming may be a continuous process throughout sleep. This conclusion was especially evident when the question asked upon waking shifted from "Did you dream?" to "What was going through your mind?" (Foulkes, 1962). The percentage of NREM sleep reports containing mentation increased significantly from about 0-8% in the 1950s to over 70% in the 1990s, reflecting the impact of more inclusive criteria for cognitive activity introduced in the 1960s (Nielsen, 2000). It is now clear that dreams are not exclusive to any specific sleep stage.

Later studies demonstrated that REM sleep dreams are generally more elaborate than those at sleep onset and are more "dreamlike" than typical NREM dreams. While external raters could not reliably distinguish between stage-specific dream reports (Vogel et al., 1972), REM dreams tend to be qualitatively richer than those from sleep onset or NREM periods. It has been suggested that differences in dream reports between stages may depend more on the length of the report than the stage itself. Longer REM reports often exhibit more continuity in characters and settings, whereas shorter reports from any stage display less continuity. However, despite controlling for length, some qualitative differences persist between REM and NREM dreams, such as character density and self-representation. Foulkes (Foulkes, 1982) proposed that dream production might share common mechanisms across sleep stages, with the complexity of dreams varying based on the intensity and continuity of mnemonic activation. While

memory retrieval processes contribute to these differences, Foulkes pointed to distinct underlying differences in dream production itself, not just memory recall after waking.

Following a similar rationale to the association between REM sleep and dreaming, two pivotal findings from lesion studies in animals and humans have challenged this hypothesis. First, research by Jouvet (Jouvet, 1959, 1961) demonstrated that the forebrain is not essential for REM sleep. When the cortex is disconnected from the brainstem, REM cycles are abolished in the forebrain but preserved in the isolated brainstem. This led to the view that the visual and motor phenomena of REM sleep, such as eye movements and PGO waves, are driven by brainstem neurons. Indeed, pontine brainstem lesions in cats have been shown to eliminate REM sleep, with similar observations reported in human cases. However, despite losing REM sleep, only one of 26 patients with pontine brainstem lesions ceased to dream (Feldman, 1971; Solms, 2011), leaving the relationship between REM sleep and dreaming ambiguous. Second, while the revised Activation-Input-output-gating-Modulation (AIM) model (Hobson et al., 2000) suggests that both REM and NREM components contribute to dreaming, the cessation of dreaming would require large lesions in the brainstem affecting both states. It is reasonable to conclude that such pontine lesions impair consciousness and are severe enough to have a significant effect on REM sleep, and thus, the evidence that dreaming persists regardless of REM sleep could not be confirmed (Solms, 2000, 2011). These pieces of evidence suggest that forebrain mechanisms, rather than brainstem structures, are crucial for dream generation, challenging the long-held assumption that REM sleep equals dreaming.

Beyond lesion studies, pharmacological research untangled this thread, showing that complex and bizarre dreams persist even when REM sleep is suppressed (Oudiette et al., 2012), supporting the “one-generator” model, which suggests that dreaming may depend more on overall brain activation levels than specific sleep stages. This perspective is reinforced by the persistence of vivid, bizarre dreams during NREM sleep and after REM suppression. Taken together, the results of both lesion and pharmacological studies suggest that, despite the distinctive characteristics of REM sleep dreams, dreaming is not synonymous with this sleep stage. Rather, it can be seen as a cognitive process intrinsic to the sleeping brain.

Clinical and electrophysiological neural correlates of dreaming

A contemporary view defines dreaming as a conscious experience during sleep that includes a spatially and temporally organized hallucinatory scene. This experience is marked by a first-person perspective, a sense of self-location within a defined space, and an awareness of temporal flow, giving the dreamer an experienced “now”

and a perception of duration (Windt, 2010). Thus, understanding the neural basis of dreaming is essential for unraveling how the brain generates subjective experiences during sleep and what these processes reveal about consciousness and brain function. Despite considerable developments, questions remain regarding the brain regions and mechanisms responsible for dream generation and the role of different sleep stages in shaping dream content. Clinical and electrophysiological studies have provided valuable insights into these processes, offering a framework to explore how structural and functional changes in the brain influence dreaming and its recall.

Early studies in clinical populations demonstrated that brainstem lesions can reduce or abolish REM sleep, but they are not the primary cause of dream loss. This led to a shift in focus toward other brain regions as potentially fundamental structures involved in dream generation. Subsequent clinical studies identified that damage to two major brain areas is directly linked to dream cessation. Firstly, posterior brain lesions, particularly those in or near the temporo-parieto-occipital (TPO) junction (Solms, 1997), are strongly associated with dream loss and visual imagery impairments (Kosslyn et al., 2001), which share neural substrates with dreaming. Secondly, lesions in regions such as the V4 or V5 visual cortices affect the representation of color or motion in dreams, whereas damage to primary sensorimotor areas does not disrupt dreaming (Solms, 2000).

In addition to posterior lesions, anterior brain lesions, particularly in the ventromedial prefrontal cortex (vmPFC) and surrounding white matter, have been linked to dream cessation (Solms, 2000, 2011). The involvement of dopaminergic pathways and limbic structures in this region suggests a role for emotional and cognitive processes in dream generation. Interestingly, lesions to the dorsolateral prefrontal cortex (dlPFC) do not appear to affect dreaming (Solms, 1997, 2000), despite their impact on self-monitoring and decision-making in waking life. Furthermore, bilateral damage to the basal ganglia can result in an "auto-activation deficit," where patients experience a lack of self-generated thoughts during wakefulness but report simple dreams during REM sleep (Leu-Semenescu et al., 2013). This suggests that basic dream imagery may originate from brainstem stimulation and are transmitted to the sensory cortex, while higher-order cortical areas are necessary for more complex dream content.

Studying altered dreaming and its associated brain areas also offers valuable insights. For example, patients with medial occipito-temporal lesions exhibited a selective loss of visual dream imagery while retaining non-visual dreams, such as those involving sensations or words (Solms, 1995). This mirrors their waking deficits in visual imagery and short-term memory, suggesting a close relationship between waking visual processing and the generation of visual dream content. In contrast,

patients with anterior limbic lesions experience an inability to distinguish dreams from reality, with many reporting an increased frequency of dreams and, in extreme cases, a blurring of boundaries between dreaming and wakefulness. These patients often exhibited broader neuropsychiatric disturbances, including hallucinations, delusions, and confabulatory amnesia, highlighting the critical role of anterior limbic structures in differentiating internal dream experiences from external reality (Solms, 1995). Meanwhile, patients with bilateral calcification of the basolateral amygdala reported a greater prevalence of pleasant dreams than controls (Blake et al., 2019). However, no significant results were found for levels of danger or fear. These findings suggest that the amygdala plays a role in the emotional experience of dreams, whereby patients with lesions in the area perceive dreams as less negative.

In summary, clinical lesion studies reveal that dreaming depends on a network of brain regions beyond the brainstem, with the posterior cortical areas, such as the TPO junction and visual association regions, supporting sensory and perceptual aspects of dreams. At the same time, the anterior system, including the vmPFC, contributes to emotional and cognitive processes. Additionally, findings on altered dreaming, such as increased dream frequency and difficulty distinguishing dreams from reality in patients with anterior limbic lesions, emphasize the role of these regions in regulating the boundary between dreaming and reality (Figure 2). Together, these insights highlight the intricate neural networks involved in creating rich, varied, and sometimes excessive dreaming experiences.

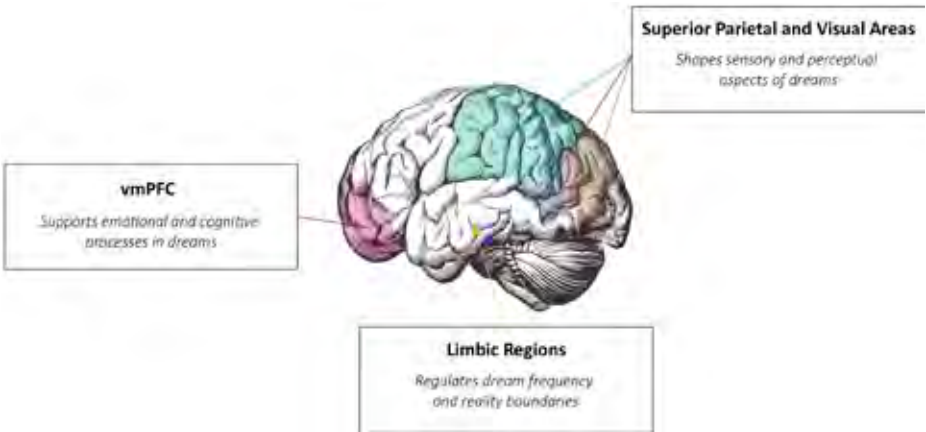


Figure 2: Brain regions involved in dream processes based on clinical studies. The ventromedial prefrontal cortex (vmPFC) contributes to emotional and cognitive aspects of dreams, while limbic regions regulate dream frequency and the boundary between dreams and reality. Superior parietal and visual association areas are critical for the sensory and perceptual features of dreams. These findings highlight the interplay between anterior and posterior networks in generating and modulating the dream experience.

Many studies have explored the electrophysiological correlates of dreaming during NREM and REM sleep stages and their relationship with dream recall as a proxy to investigate dream experiences. However, no consensus with early studies exists on the specific neural oscillatory features characterizing dreams (Table 2) (P. M. Ruby, 2020), which could be due to several methodological differences across studies: i) EEG recordings varied from a four-channel Grass-78 polygraph (Foulkes, 1962) to high-density EEG with 256 channels (Siclari et al., 2017); ii) participants ranged from mostly healthy young adults to unmedicated depressed patients (Rochlen et al., 1998); iii) studies differed in the design (between- and within-subjects), and in the number of participants, experimental nights, and awakenings; iv) the analyzed recording periods before awakenings also varied; v) a study included white dreams (Siclari et al., 2017) - the feeling of having had a dream experience without being able to remember the details of the experience - while others excluded or did not account for them, which is crucial for distinguishing dream recall from dream experience itself.

The incorporation of more awakenings throughout the night and high-density EEG recordings have improved the spatial and temporal resolution of neural correlates associated with dream experiences. These technical developments allow for a more precise mapping of electrical activity across the scalp, improving the accuracy of brain region localization while reducing errors in identifying the source of neural activity. Results show that dream experiences in REM and NREM sleep are associated with decreased low-frequency power (1–4 Hz) over parieto-occipital regions compared to non-experiences. Additionally, dream experiences are linked to increased high-frequency activity (25–50 Hz). Specifically, during NREM sleep, dream experiences show greater high-frequency activity over the parieto-occipital region, while during REM sleep, this increased activity is observed in frontal and temporal regions (Siclari et al., 2017).

Moreover, the study also identified the EEG patterns associated with dream experiences without recall of specific content (Siclari et al., 2017). During NREM sleep, these experiences are characterized by similar low-frequency power as dream experiences with recall, with no significant differences in the 1–4 Hz range. In contrast, during REM sleep, dream experiences without content recall showed no significant differences from non-experiences. These findings suggest that dreaming in both REM and NREM sleep may involve similar neural mechanisms and regions, supporting the "one-generator" model of dreaming. This model proposes that dream recall is linked to cortical activation across all sleep stages. Studies on the qualitative differences between REM and NREM dreams diminish when reports are controlled for length, and the presence of complex and bizarre dreams without REM sleep supports this idea (Foulkes, 1982; Oudiette et al., 2012).

Table 1: A review of studies investigating EEG spectral correlates during the pre-awakening phase and their association with the presence or absence of dream reports upon awakening (adapted from (P. M. Ruby, 2020)).

Study	N	δ (0.5-4Hz)	θ (4-7Hz)	α (8-12Hz)	β (>13Hz)
<i>REM sleep</i>					
Lehmann et al., 1981	6	↓	↓	↓	↓
Wollman and Antrobus, 1987	30	=	=	=	=
Rochlen et al., 1998	19	=	=	=	↑
Germain et al., 1999	41	=	=	↑	↑
Takeuchi et al., 2003	8	=	=	↓	=
Esposito et al., 2004	8	↓	=	↓	=
Marzano et al., 2011	30	=	↑	=	=
Chellappa et al., 2011	17	=	=	↑↓*	↓
Scarpelli et al., 2015	6	=	↑	=	=
Siclari et al., 2017	46	↓	=	=	=
<i>Non-REM sleep</i>					
Moffitt, 1982	8	↓	=	=	=
Williamson et al., 1986	6	=	=	=	=
Morel et al., 1991	40	=	=	=	=
Takeuchi et al., 2003	8	=	=	↑	=
Wittmann et al., 2004	6	=	=	=	=
Esposito et al., 2004	11	↓	=	↓	=
Marzano et al., 2011	35	=	=	↓	=
Chellappa et al., 2011	17	↓	=	=	↓
Scarpelli et al., 2017	14	↓	=	=	=
Siclari et al., 2017	46	↓	=	=	=

Note: ↑, the EEG spectral power is increased in this frequency band when subjects recalled a dream compared to when they did not recall one. ↓, the EEG spectral power is decreased in this frequency band when subjects recalled a dream compared to when they did not recall one. =, no significant EEG spectral power difference in this frequency band were observed, between the two conditions. *, higher occipital alpha, decreased frontal alpha. N = number of participants.

Further studies replicated these findings, finding that frontal theta oscillations during the last REM sleep segment were associated with successful dream recall (Scarpelli et al., 2019). In contrast, during NREM sleep, dream recall in older adults was linked to reduced delta power in the temporo-parietal regions (Scarpelli et al., 2020). Similarly,

in clinical populations of narcolepsy type-1 patients and sleepwalkers, dream recall was associated with lower delta power and higher beta power over centro-parietal areas (D'Atri et al., 2019; Cataldi et al., 2022). However, Wong et al. (2020), using blinded analyses, did not identify any EEG spectral markers of dreaming experiences, highlighting the challenges in the field. In addition to electrophysiological findings, neuroimaging studies have examined brain structural and functional measures and their potential association with dreams. These methodologies will be discussed in depth in the following chapters. To date, no definitive consensus neural marker of dream experiences has been established.

Influence of trait and state factors on dream recall and nightmare frequency

Dream research has long sought to understand the variability in how frequently individuals recall their dreams or experience nightmares. Dream recall frequency (DRF) refers to the number of dreams remembered over a specific period, and it can be distinguished from nightmare frequency as the latter narrows down to the occurrence of vivid, disturbing dreams often leading to awakenings. Decades of research have shown substantial individual differences in DRF, with estimates ranging from nearly zero to multiple dreams recalled per night. DRF tends to follow a typical profile: women report higher DRF than men, and recall frequency is highest in adolescence and early adulthood before declining in older age (Giambra, 1979; Nielsen, 2012; Schredl, 2008). Nightmare frequency exhibits a similar demographic pattern, with higher prevalence in women and a peak during adolescence and young adulthood (Levin & Nielsen, 2007). However, a recent large-scale study could not confirm these findings and has suggested that age and sex in DRF might be mediated by trait and state factors such as attitude towards dreams, more prevalent in female participants, and changes in sleep patterns, which may affect dream generation processes (Elce et al., 2025). This study also highlighted that previously reported demographic effects on DRF might be overstated if psychological traits are not considered. In their representative sample, Elce et al. (2025) found that trait factors such as positive attitude toward dreams, interest in dreams, and openness to experience were stronger predictors of DRF than demographic variables. Therefore, understanding the distinction between trait and state psychological factors is essential to investigate their impact on dream recall and nightmare frequency.

Trait factors are stable characteristics that remain relatively constant over time and across different life situations. In contrast, state factors refer to temporary conditions or emotional experiences that change over time. In the context of DRF, trait factors relate to consistent individual differences, such as individuals who

frequently remember their dreams across several nights. Conversely, state factors encompass transient influences, such as stress or fatigue, influencing an individual's ability to recall dreams on a particular day. When investigating the relationship between DRF and state or trait factors, three primary methods are commonly used, and they can be categorized into retrospective and prospective approaches: i) retrospective methods, such as questionnaires, rely on participants reporting whether they experienced a dream the previous night or estimating their DRF over a specified time frame. While these questionnaires provide a straightforward, minimally intrusive, and less expensive way to collect data, they are susceptible to recall bias, as participants must rely on their memory, and different rating scales across studies may result in inconsistent findings; ii) prospective methods, like dream diaries and sleep laboratory awakenings, in which the former requires participants to record their dreams each morning, which minimizes retrospective recall errors and enhances accuracy by capturing reports upon awakening. However, it may artificially inflate DRF and require long-term participant commitment. The latter represents another prospective method where participants are woken up from sleep to report their dreams. This method achieves high DRF rates (60%) and allows for collecting combined physiological data in a controlled environment. However, it is logistically complex, expensive and may disrupt normal sleep patterns due to the artificial setting and frequent awakenings (Schredl & Montasser, 1996; Nemeth, 2023). In summary, each method has a unique trade-off between accuracy, naturalistic representation, and feasibility, thus making method selection a critical aspect of designing effective studies that capture the complexity of dream recall.

The relationship between DRF and several trait and state factors has been extensively studied, revealing a complex interplay that shapes individual differences in dream recall. Numerous trait factors influence DRF, including sex, age, cognitive abilities, sleep physiology, and personality features. For instance, studies indicate that women report higher dream recall than men (Giambra, 1979; Schredl, 2008, 2010), and DRF exhibits a U-shape trajectory across the lifespan, peaking during young adulthood and around age 60 (Nielsen, 2012; Schredl, 2008). Sleep-related traits, such as habitual sleep duration and quality, have yielded inconclusive findings (Nemeth, 2023). Conversely, personality traits, such as boundary thinness, fantasy proneness, and absorption, are associated with more vivid and bizarre dreams, which may enhance recall (Hartmann et al., 1991; Cipolli et al., 1993). Additionally, attitude toward dreams significantly influences DRF, emphasizing the importance of motivational and attitudinal factors in the retrieval process (Schredl & Göritz, 2017; Elce et al., 2025). The findings of Elce et al. (2025) reinforce this point, showing that individuals with stronger positive attitudes and greater interest in dreams are

more likely to recall them. Their results emphasize the importance of motivational and attitudinal factors in shaping DRF, supporting the view that how people relate to dreaming significantly influences recall frequency.

In contrast, state factors are considered the primary basis of DRF, with significant intra-individual fluctuations influenced by the preceding sleep state, situational factors, and life events. Sleep duration (Schredl & Reinhard, 2008) and the sleep stage preceding awakening are key factors contributing to dream recall, possibly due to longer REM periods, with REM awakenings yielding a higher dream recall rate than NREM (Nemeth & Fazekas, 2018). However, as discussed in depth at the beginning of this chapter, sleep stage differences are better explained in terms of brain activity changes, particularly increased high-frequency oscillations in posterior parietal areas and pre-awakening frontal activity association with memory encoding. Emotional states, life events, and stressors also modulate dream features and recall, though the directionality of this influence remains uncertain, with inconsistent findings linking stress to DRF (Nemeth, 2023).

Emotional states, especially stress, are key players in nightmare frequency (Schredl, 2003). While trait factors, such as personality traits and individual differences in anxiety sensitivity, may influence basic nightmare tendencies, state factors, particularly acute stressors, and emotional states, have a more immediate and profound impact on the nightmare experience. For example, elevated stress levels may increase the frequency and intensity of nightmares, as stressful life events may disrupt sleep architecture and promote negative emotional content in dreams (Loveland Cook et al., 1990; Berquier & Ashton, 1992; Zadra & Donderi, 2000; Levin & Fireman, 2002; Zadra et al., 2006). The interplay between current stress and neurophysiological changes during sleep, such as changes in REM sleep dynamics and increased autonomic arousal, may increase the vividness and emotional intensity of nightmares. This suggests a complex relationship where situational factors, emotional regulation, and underlying neurobiological mechanisms converge to shape the frequency and quality of nightmares, highlighting the need for a better understanding of how trait and state variables influence nightmare frequency.

One theory that largely influenced this thesis proposes that dreaming reflects an intensified form of spontaneous, internally oriented cognition, closely related to mind-wandering, and is supported by the brain's default mode network (DMN) (Fox et al., 2013; William Domhoff, 2011; Domhoff & Fox, 2015). Within this framework, dream recall is thought to depend not only on transient sleep-related factors but also on stable neurocognitive traits. Neuroimaging studies have shown that individuals

with high DRF exhibit increased activity in DMN regions, particularly the medial prefrontal cortex (mPFC) and temporo-parietal junction, during both REM sleep and resting wakefulness (Eichenlaub et al., 2014). In addition, high dream recallers display heightened brain responsiveness to auditory stimuli during both sleep and wakefulness, as evidenced by larger EEG event-related potentials (Eichenlaub et al., 2014). This elevated neural reactivity is thought to increase the likelihood of intra-sleep awakenings, thereby facilitating the encoding and subsequent recall of dream content. Extending to functional Magnetic Resonance Imaging (MRI), Ruby (2022) demonstrates that high dream recallers also show increased bottom-up and top-down attentional processing during wakefulness, further supporting that dream recall frequency reflects stable differences in attentional engagement with salient stimuli. Structural imaging findings further support the role of stable neural traits, with high dream recallers showing increased white matter density in the mPFC, a region involved in self-referential processing, emotional evaluation, and episodic simulation, suggesting its involvement in dream production (Vallat et al., 2018). More recently, functional connectivity analyses revealed that individuals with high dream recall display enhanced connectivity within and between the DMN hubs and memory-related regions, such as the angular gyrus and hippocampus, immediately upon awakening. These connectivity patterns may support the short-term maintenance and retrieval of dream content during the sleep-wake transition (Vallat et al., 2020). Together, these findings imply that dream recall frequency is influenced by the interaction between trait and state factors and stable structural and functional brain characteristics. This integrative framework, linking spontaneous sleep-wake cognition, memory processing, and individual neurobiological differences, provides the conceptual and methodological foundation for the multimodal approach developed throughout this thesis.

Thesis Outline

This thesis investigated the relationship between retrospective trait dream recall and state-dependent factors in relation to structural and functional neuroimaging measures, aiming to advance the understanding of the neural correlates underlying dream experiences. In **Chapter 2**, I provide a comprehensive overview of the major findings in sleep research, focusing on two primary neuroimaging modalities: Positron Emission Tomography (PET) and MRI. This chapter covers both micro-level processes, such as sleep spindles and slow-wave sleep, as well as macro-level phenomena like dreaming and subjective sleep characteristics. I also discuss the specific challenges faced in sleep neuroimaging studies, including maintaining

sleep in the scanner environment, managing physiological artifacts, and accurately interpreting neuroimaging data across sleep stages. In **Chapter 3**, I delved deeper into the neural correlates of retrospective nightmare frequency, aiming to replicate previous findings in two large, independent cohorts. Additionally, I explore whether connectivity between the prefrontal cortex and amygdala, regions critical for emotional regulation, can predict nightmare frequency. These findings highlight the need to reconsider prior results and suggest new directions for future research. **Chapter 4** presents a multimodal fusion approach to examine dream recall frequency by integrating gray and white matter morphology with functional connectivity measures. This approach represents a novel contribution to dream research, as it moves beyond the traditional high versus low dream recall groups to consider a continuous spectrum of dream recall frequency across a large sample, providing more nuanced insights into the neural correlates of dream recall. In **Chapter 5**, I investigate the relationship between resting-state networks and dreaming using simultaneous EEG and functional MRI recordings collected during serial awakenings. Upon awakening, participants provided dream reports, and a global dreaming index was calculated based on both subjective metrics, such as emotionality, bizarreness, and visual vividness, and objective metrics, such as total word recall count. The thesis concludes with **Chapter 6**, where I discuss the findings within the broader context of sleep and dream research, discussing their implications and proposing directions for future studies.

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Chapter 2

Sleep Neuroimaging: review and future directions

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Abstract

Sleep research has evolved considerably since the first sleep electroencephalography (EEG) recordings in the 1930s and the discovery of well-distinguishable sleep stages in the 1950s. While electrophysiological recordings have been used to describe the sleeping brain in much detail, since the 1990s neuroimaging techniques are applied to uncover the brain organization and functional connectivity of human sleep with greater spatial resolution. The combination of EEG with different neuroimaging modalities such as Positron Emission Tomography (PET), structural MRI (sMRI) and functional Magnetic Resonance Imaging (fMRI) imposes several challenges for sleep studies. For instance, the need to combine polysomnographic recordings to assess sleep stages accurately, difficulties maintaining and consolidating sleep in an unfamiliar and restricted environment, scanner-induced distortions with physiological artifacts may contaminate polysomnography recordings, and the necessity to account for all physiological changes throughout the sleep cycles to ensure better data interpretability. Here, we review the field of sleep neuroimaging in healthy non-sleep-deprived populations, from early findings to more recent developments. Additionally, we discuss the challenges of applying concurrent EEG and imaging techniques to sleep, which consequently have impacted the sample size and generalizability of studies, and possible future directions for the field.

Keywords: sleep, neuroimaging, fMRI, PET, functional connectivity, rCBF

Introduction

From the first to our last day, sleep is a constant that marks the passing of time. There is probably no single activity we spend more time doing, but despite that it still remains a puzzle throughout the history of humankind. The invention of electroencephalography (EEG) made it possible to monitor the brain's electrical activity non-invasively, leading to ground-breaking findings in early sleep research such as the discovery of rapid eye movements (REM) and cyclic nocturnal sleep behavior. Later discoveries identified neurophysiological events within sleep stages such as sleep spindles and slow waves as a marker of non-REM (NREM) sleep, or ponto-geniculo-occipital waves, traceable in animal models, during REM sleep (for review see (Dresler et al., 2014)). The human sleep cycle consists of regular progress through a series of global brain states characterized by specific neurophysiological changes. NREM sleep is traditionally divided into three stages exhibiting distinct EEG patterns. Light NREM sleep, or stage N1, marks the transition from wakefulness to sleep, with low-amplitude theta waves (4-7 Hz), slow rolling eye movements, and lower muscle activity than wakefulness. Stage N2 features hallmark sleep spindles (brief bursts of 12-14 Hz activity) and K-complexes (large, isolated slow waves). Stage N3, or slow wave sleep (SWS), is characterized by high-amplitude, low-frequency delta waves (0.5-3 Hz), often associated with restorative processes. REM sleep, in contrast, is defined by low-amplitude mixed-frequency EEG activity featuring rapid eye movements and even lower muscle activity. Physiologically, eye movements, muscle tone, and autonomic activity further differentiate sleep stages, with muscle tone progressively decreasing through NREM stages and reaching near-complete atonia during REM sleep, alongside irregular heart rate and respiration. A typical sleep episode starts with light NREM sleep, progressing to deeper stages, and finally to REM sleep. Still, individuals do not remain in REM sleep but rather cycle between stages of NREM and REM throughout the night. NREM sleep constitutes about 75 percent of total time spent in sleep, whereas REM sleep constitutes the remaining 25 percent. In healthy adults, NREM sleep accounts for the majority of sleep time in the first half of the night as REM sleep increases as the night progresses and accounts for much of the sleep time in the second half of the night (Carskadon & Dement, 2005). Although animal research has advanced sleep characterization across species, several pivotal questions on why and how human beings sleep are still to be addressed. Brain imaging has played a role in understanding brain function and metabolism during sleep and associated sleep-specific features. Advances in neuroimaging may yield addressing remained unsolved questions, to name a few examples, the relationship between sleep and brain clearance, the causal relation with neurodegenerative diseases, and the possible functions of dreaming.

Neuroimaging can be defined as any technique capable of imaging the anatomy, function, or physiology of the brain. In this review, we will focus on Positron Emission Tomography (PET), and structural and functional Magnetic Resonance Imaging (sMRI and fMRI), but also briefly mention other neuroimaging techniques. The concept of tomographic imaging (Phelps et al., 1975; Ter-Pogossian et al., 1975) and the development of positron-emitting radiopharmaceuticals (Ido et al., 1978) led to the development of the positron emission tomography technology. PET imaging makes use of radioactive tracers to measure and visualize physiological information, such as glucose consumption, dopamine release, and blood flow (tissue perfusion) in the body. By detecting radioactive decay as an accumulated component in specific brain regions, H_2^{15}O PET imaging reveals the amount of blood flow across the whole brain, thus providing an indirect marker of neuronal activity. The increased ^{15}O oxygen labeled (H_2^{15}O) concentration in a brain area reflects locally increased (regional) cerebral blood flow (rCBF) resulting from higher energetic demands due to increased neural activity. Similarly, locally increased glucose-labeled (fluorodeoxyglucose or FDG-18) consumption reflects the energetic neuronal needs in the corresponding area, glucose and oxygen being the two primary sources of energy for brain activity (note that only a single image is acquired reflecting the time-averaged energy consumption).

Structural MRI takes advantage of the abundance of hydrogen atoms in biological organisms, particularly in water and fat. This method aligns the spins of hydrogen atoms using a large magnetic field, typically 1.5 or 3 T in human studies. After the spins orientations are perturbed using a radiofrequency pulse at the nuclear magnetic resonance (NMR) Larmor frequency, they precess around their axis (which generates the measurable signal) and dephase and realign with the magnetic field at different time rates determined by the local tissue properties. The decay rates are exploited to distinguish different brain tissues in structural MRI. Contrast in diffusion-weighted MRI (DWI) relies on the microscopic movement of water molecules, as the brain's various tissue types and geometries will affect the diffusive motion of water molecules in specific ways. A particular class of diffusion MRI is diffusion tensor imaging (DTI), which promises to characterize microstructural changes (Campbell & Pike, 2019). For instance, DTI is used to characterize the degree of anisotropy (fractional anisotropy), the orientation of directional diffusion (radial and axial diffusivity D_r/D_a), or magnitude characterization (mean diffusivity). For more in-depth details on DTI measures estimation, please see (Assaf & Basser, 2005; Alexander et al., 2007; Zhang et al., 2012; Stee & Peigneux, 2021) for reviews.

Functional MRI has become the most widely used technique for studying human cognitive processes since its development in the early 1990s (Kwong et al., 1992). BOLD fMRI measures changes in the total amount of deoxygenated hemoglobin in a voxel over time, and the quantity of deoxygenated hemoglobin depends not just on the extraction of oxygen by active neurons but also on blood flow and blood volume changes that together shape the BOLD hemodynamic response (Huettel et al., 2004). The BOLD signal primarily reflects the input and intracortical processing in a given region, rather than the output reflected in action potential firing. Compared to PET imaging, fMRI is non-invasive and can be repeatedly used in a broader range of individuals without the safety constraints of PET regarding radiation exposure. Finally, fMRI allows better spatial and temporal resolution (down to ~ 1 mm and a few seconds respectively, see Table 1) allowing the imaging of brain activity changes taking place over much shorter time spans closer to the dynamics of cognitive processes. Combined, these advantages explain fMRI's rapidly expanding application in cognitive neuroscience.

For sleep neuroimaging studies, the various features of each image acquisition technique not only determine the quality of the image itself but the success of the study, since it is necessary to have an adequate environment for the participants to consolidate and maintain sleep including its deeper stages (Table 1). For instance, the different tracers used in PET imaging have different kinetics, resulting in $H_2^{15}O$ shorter half-life allowing repeated measurements at the same night, whereas FDG-18's longer half-life allows only a single acquisition per night. However, the latter has the advantage that once the injection takes place during the night, imaging acquisition can be performed during awakening, thus enabling the subjects to sleep more comfortably in a bed. The complementary strengths of each method make simultaneous EEG and neuroimaging recordings crucial for sleep neuroimaging studies. EEG accurately identifies sleep stages and their characteristics using standard polysomnographic classification, while neuroimaging provides insight into brain activity and metabolism with superior spatial resolution. This combined approach allows novel interpretations of event-related activity or sleep stages time-locked to brain dynamics. However, integrating the two methods, especially in the case of fMRI, requires careful attention, as all EEG equipment must be non-magnetic to ensure safety and signal quality. A few example challenges for sleep research include the technical aspects impacting the final generalizability of results and data quality. For example, the MRI environment is extremely loud and uncomfortable for participants, often leading to inflated drop-out rates and, consequently, smaller sample sizes compared to other neuroimaging studies. While the use of noise-canceling headphones and custom-made earplugs are great mitigation strategies

(discussed further in the Discussion section), the smaller sample sizes limit the generalizability of findings, and larger studies are needed to confirm initial results while better representing the broader population. Additionally, technical factors such as MRI gradients switching and the cardio-ballistic artifacts affect EEG signal quality, further complicating data acquisition and interpretation.

Table 1. Comparison between neuroimaging methods for human sleep research.

Modality	Principle	Space Resolution	Acquisition time	Information	Cost	Environment & Requirements
SPECT	Radiation level from gamma-emitting injected blood-injected tracers	6-8 mm	Minutes	rCBF (perfusion)	Medium	Injection of radioactive tracer
PET	Gamma radiation level secondary to positron emission from blood-injected tracers	2-3 mm	Seconds-Minutes	rCBF (perfusion)	High	Injection of radioactive tracer
fNIRS	Blood oxygenation and blood volume dependent absorption of near-infrared light	Centimeter	Seconds	CBV, Blood oxygenation	Low	Required light avoidance
fMRI	Blood deoxyhemoglobin concentration dependent NMR relaxation	1-3 mm*	Seconds*	Blood Flow (vascular)	High	Required fixed head, in-scanner space limitation, acoustic noise. Disturbs EEG acquisition
sMRI	Density and NMR relaxation properties of water protons	0.5-1 mm	Seconds-Minutes	Tissue composition	High	Required fixed head, in-scanner space limitation, acoustic noise. Disturbs EEG acquisition
DWI/DTI	Water diffusion based on tissue structural properties	1-3 mm	Minutes	Tissue structure	High	Required fixed head, in-scanner space limitation, acoustic noise. Disturbs EEG acquisition

Note: CBV, cerebral blood volume; DWI/DTI, diffusion-weighted imaging/diffusion tensor imaging; EEG, electroencephalography; fMRI, functional Magnetic Resonance Imaging; fNIRS, functional Near-infrared Spectroscopy; PET, Positron Emission Tomography; rCBF, regional cerebral blood flow; sMRI, structural Magnetic Resonance Imaging; SPECT, Single-Photon Emission Computed Tomography. * These values are based on typical sleep neuroimaging studies, however modern fMRI can achieve higher spatiotemporal resolution.

The literature selection for this review was based on a systematic search of the online databases PubMed, Web of Science, and Google Scholar for English articles. The search terms included "sleep" and "neuroimaging" keywords present either in the title/abstract or abstract fields. The initial search returned a total of 1894 articles, and after removing duplicates and screening for non-sleep deprived studies in healthy adults, the remaining articles were selected by researchers based on their relevance to the following research questions: "How has sleep neuroimaging been conducted?", "What are the general neuroimaging discoveries to sleep research?", and finally "What are the advances in the field?". We decided to focus the review on two imaging modalities – PET and MRI – and two main aspects of sleep neuroimaging. First, we will summarize the results of sleep neuroimaging studies carried out in healthy non-sleep-deprived subjects. Secondly, we will examine the challenges associated with brain imaging in sleep research and discuss the potential future directions for the field. We will highlight the limitations and confounds that affect the interpretation of neuroimaging data, and explore emerging technologies and their potential applications in sleep research.

Neuroimaging of sleep macrostructure

Neuroimaging techniques allow new insights sleep macrostructure, allowing researchers to explore the neural activity and metabolic demands of the brain during different stages of sleep. This section covers two important sub-sections related to neuroimaging of sleep. The first one focuses on local changes in brain blood flow, which have been primarily measured using PET imaging. The results of these studies have shown that there are significant regional differences in brain activity and metabolic rate during the sleep-wake cycle, with decreases in activity observed during NREM sleep, and more heterogeneous activity observed during REM sleep. The second sub-section discusses resting-state networks and thalamocortical connectivity during sleep, which have been largely studied using fMRI. Researchers have observed changes in the integrity of the default mode network during different stages of sleep, as well as alterations in thalamocortical functional connectivity. These findings provide valuable insights into the mechanisms underlying sleep stages.

Local changes in brain blood flow

Regional changes in blood flow by increases or accumulation of tracer components is a pivotal indirect means to measure brain neural activity and metabolic consumption. As a consequence, the assessment of changes in regional brain blood flow has advanced our understanding of neural activity and metabolic demands throughout the sleep-wake cycle. Early PET studies assessed cerebral glucose metabolic rates

during sleep, measured by FDG-18, in comparison to wakefulness. These studies showed a continuous reduction in metabolic rate from wakefulness to NREM sleep, being greater in frontal than temporal areas, and even more evident in the basal ganglia and thalamus compared to most of the cortex, whereas activity was at similar levels or even higher during REM sleep than in wakefulness, but more heterogeneous (Buchsbaum et al., 1989; Maquet et al., 1990). Activity further decreased from NREM light stage N2 to deep NREM sleep stage N3 (Maquet et al., 1992), suggesting a continuous process in the transition from wakefulness to deep NREM sleep. Using $H_2^{15}O$ PET imaging, Maquet et al. (1996) more precisely delineated the structures in which rCBF is diminished during NREM sleep. Negative correlations within the mesencephalon and the dorsal pons during NREM or SWS were thought to reflect the decreasing neuronal firing of brainstem systems leading to the hyperpolarization of thalamic nuclei (M. M. Steriade & McCarley, 2013), eventually resulting in synchronized discharge patterns over large neuronal populations that generate the slow wave sleep hallmark's slow and high-amplitude oscillations measured by the EEG. These findings suggest that rCBF distribution is not homogeneous during slow wave sleep. With the exception of primary cortical areas, secondary and associative cortical areas (more specifically in prefrontal and parietal regions) presented larger decreases than others, indicating that cellular processes occurring during slow wave sleep might be modulated differently in these regions. Likewise, Braun et al. (1997) and Andersson et al. (1998) observed decrease in regional cerebral blood flow in the brainstem, thalamus, and frontoparietal cortex, concluding that these areas play a role in the mediation of arousal. An increasingly widespread deactivation of cortical regions during the descent from light to deep NREM sleep was also observed (Kajimura et al., 1999). On the subcortical level, activity of the midbrain reticular formation was maintained during light but not deep NREM sleep, thus representing a key distinguishing correlate of sleep depth. Further, in agreement with previous PET studies (Maquet et al., 1990, 1992), a significant decrease in rCBF, as a function of delta activity was observed in the thalamus, the cerebellum and the frontal cortex, specifically at the anterior cingulate and orbitofrontal cortex (Hofle et al., 1997).

Resting-state networks and thalamocortical connectivity

Functionally connected regions share information observed in correlated time series, forming connectivity patterns known as resting-state functional networks. These networks have been broadly categorized into cognitive control, sensory systems (visual, auditory, and sensorimotor), and the default mode network (DMN), which characterizes brain activity in the absence of goal-directed tasks, with much speculation about its integrity (stability) during sleep. The thalamocortical network plays a central role in sensory information processing, especially during states

of arousal (Castro-Alamancos, 2004). Thus, while thalamocortical connectivity is distinct from the arousal network, it is significantly influenced by it. Understanding the interplay between these networks is crucial for elucidating the mechanisms underlying brain function and dynamic changes within networks during sleep.

Despite the physiological and behavioral differences between sleep and wakefulness, the same resting-state networks still support the falling asleep process. For instance, the DMN is preserved as during wakefulness (Horovitz et al., 2008; Larson-Prior et al., 2009; Deco, Hagmann, et al., 2014), with observed increased activity changes in cortical areas at early N1 (Picchioni et al., 2008; Larson-Prior et al., 2011). Similarly, an increase in BOLD signal fluctuation levels at the visual cortex was observed (Horovitz et al., 2008) with no evidence of reduced functional connectivity in sensory and association networks (Larson-Prior et al., 2009). The dorsal attention network demonstrated a modest yet statistically significant increase in functional connectivity during light sleep (Larson-Prior et al., 2009). Despite the maintenance of these networks during light sleep, as sleep deepens, functional connectivity transitions from a globally integrated state to smaller independent modules, exhibiting decreased long-term temporal dependences (Boly et al., 2012; Spoormaker et al., 2012; Tagliazucchi et al., 2013). This is associated with the decreased conscious awareness and the brain's ability to integrate information. There is a gradual decrease in the connectivity of the frontoparietal regions, the posterior cingulate and retrosplenial cortices to the midposterior DMN node, and the contributions of the medial prefrontal cortex to the DMN (Sämann et al., 2011; Spoormaker et al., 2012). This occurs in a stepwise manner with increasing sleep depth, ultimately leading to the fragmentation of these connections, which sets the stage for subsequent sleep stages.

The transition to deep sleep is characterized by increased functional segregation (Madsen et al., 1991). This shift is consistent with changes in EEG delta power, suggesting a possible correlation between changes in brain network modularity and shifts in consciousness across sleep stages. Markers of reduced consciousness during deep sleep, such as preservation of posterior connectivity and decoupling of the medial prefrontal cortex, have been identified in studies (Horovitz et al., 2009; Koike et al., 2011; Sämann et al., 2011; Spoormaker et al., 2012). In addition, several studies have reported a decrease in DMN connectivity that correlates with the degree of consciousness impairment in minimally conscious, vegetative, and comatose patients (Vanhaudenhuyse et al., 2010). Other reports of DMN reductions are documented by (Boveroux et al., 2010; Blautzik et al., 2013). Reduced activity in frontal areas is consistent with previous PET studies reporting decreased metabolism in these regions during N3 sleep, suggesting the presence of local slow-wave activity (Stevner et al., 2019).

Brain connectivity during deep sleep reveals a nuanced landscape of consciousness modulation, as evidenced by the distinctive patterns of brain connectivity and activity identified during different sleep stages. The intriguing paradox of diminished consciousness coexisting with increased activity in specific cortical regions challenges our understanding of the complexities underlying the brain mechanisms during sleep.

There is a lack of consensus regarding REM sleep and resting-state networks connectivity. The connectivity of the DMN core regions appears to remain relatively stable across sleep stages, including REM sleep. Nevertheless, there is a notable reduction in the connectivity between the dorsomedial prefrontal cortex and the posterior cingulate cortex during REM sleep compared to NREM sleep. This reduction in frontoparietal connectivity is suggested to characterize REM sleep, with the ability to logically bind stored information significantly diminished due to dorsomedial prefrontal cortex dissociation, which may explain the prevalence of bizarreness in REM sleep dreams (Koike et al., 2011). Conversely, a reduction in DMN activity, occurring in synchrony with REMs, has been observed in the posterior cingulate and retrosplenial cortices (C. Hong et al., 2021), and fronto-parietal and sensory-motor networks have shown increases during REM sleep compared with decreased activity during SWS (Watanabe et al., 2014). Additionally, DMN hyperconnectivity during REM sleep was observed in a small sample of only two participants (Wu et al., 2012). In conclusion, the results of the studies reviewed indicate a complex connectivity pattern during REM sleep, with findings that are not entirely consistent with one another. A recent high-density EEG study has demonstrated that both the breakdown and reconnection processes occurring during REM sleep are network- and frequency-specific (Titone et al., 2024). This complexity, when considered alongside the challenges of acquiring REM sleep data inside the scanner, has resulted in undersampled studies. This highlights the necessity for increased efforts to investigate the neurocharacterization of REM sleep with reasonable sample sizes.

The thalamus serves as a gateway that regulates the flow of sensory inputs to the neocortex. It is highly connected to the cortex during wakefulness (Castro-Alamancos, 2004). However, the thalamus disconnects from higher functional brain networks in the process of falling asleep, excluding thalamic nodes and highlighting increased functional connectivity between cortical regions (Spoormaker et al., 2010). This phenomenon was further supported by findings emphasizing altered thalamocortical functional connectivity during light sleep and its association with specific thalamic subdivisions and cortical projections (Shmueli et al., 2007; Andrade et al., 2011; Picchioni et al., 2014; Hale et al., 2016). These findings were also evidenced in fast-fMRI (Setzer et al., 2022) and support the hypothesis that the thalamus plays

a critical role in sleep-wake regulation (Jiang et al., 2021). The transition to deep sleep has been shown to result in a nuanced rearrangement of thalamic connectivity, this connectivity shift showed preserved propagation within the brainstem-thalamic axis and region-specific effects in the cortex (Mitra et al., 2015). In summary, thalamic connectivity undergoes distinct patterns during different NREM sleep stages. The sleep onset shows a disconnection from higher brain networks, increased cortical connectivity, and specific thalamic and cortical associations. In contrast, the process of deep sleep involves a more intricate rearrangement of thalamic connectivity.

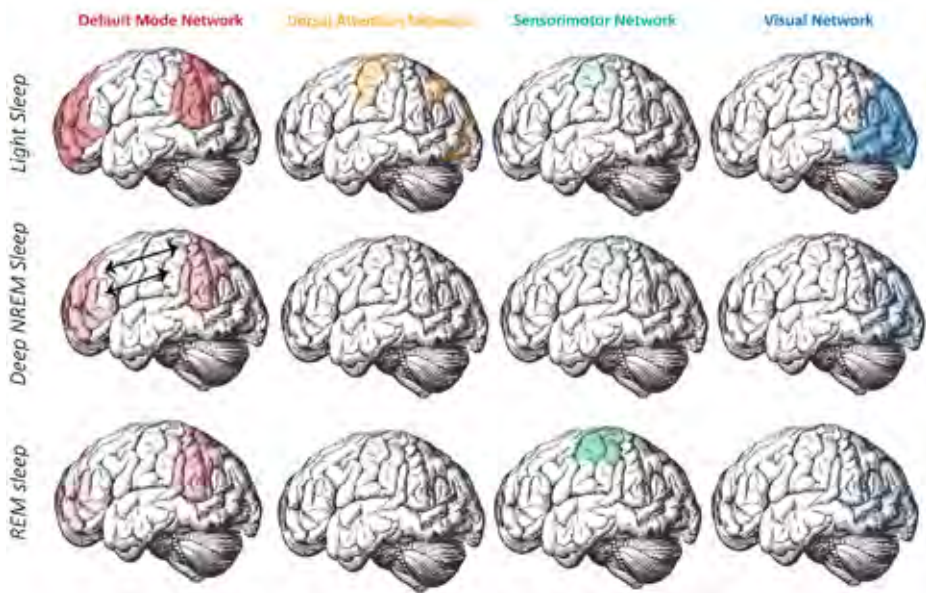


Figure 1: Functional connectivity patterns across different sleep stages. Light Sleep: The default mode network (DMN), which is characterized by brain activity without goal-directed tasks, is preserved similarly to wakefulness, with increased connectivity in the dorsal attention network and heightened BOLD signal fluctuations within the visual network. Deep NREM Sleep: DMN connectivity is significantly reduced, especially between the parietal cingulate cortex (PCC) and the medial prefrontal cortex, with the medial prefrontal cortex becoming decoupled from the rest of the DMN. REM Sleep: DMN activity is further reduced compared to deep NREM sleep, with decreased connectivity between the dorsomedial prefrontal cortex and the PCC. REMs-locked DMN activity is reduced, while activity in the sensorimotor network is increased.

In summary, the study of neural activity during different stages of sleep reveals a complex and dynamic interplay between brain networks and consciousness. Resting-state functional networks, such as the default mode network, are crucial in shaping connectivity patterns during wakefulness and sleep stages. The DMN shows preserved connectivity during light sleep but changes during deep sleep, accompanied

by a breakdown of long-range functional connectivity. Thalamic connectivity also undergoes distinct patterns, with light sleep onset showing disconnection from higher brain networks and increased cortical connectivity, while deep sleep involves subtle rearrangements. The DMN is attenuated during REM sleep, suggesting deactivation during this phase. However, connectivity involving the inferior temporal gyrus to core DMN regions is more robust during REM sleep than during deep NREM sleep, suggesting higher or wake-like brain activity during REM sleep (Figure 1). A caveat to REM sleep findings is that published studies have relied on small sample sizes due to the challenges of obtaining REM sleep in the scanner. More studies with larger sample sizes are needed to support or refute the current literature. As we unravel the complexities underlying brain mechanisms during sleep, these findings open new avenues for research and contribute to a broader perspective on the intricate relationship between brain networks, consciousness, and sleep stages.

Neuroimaging signatures of sleep microstructure

This section will provide an overview of the findings in the neuroimaging studies of sleep microstructure. The term "event-related" will be used to describe the correlation patterns in brain activity data during EEG-defined sleep stages. This type of study involves simultaneous EEG and another neuroimaging modality such as fMRI. We will examine the relationship between specific sleep features such as vertex waves, spindles, K-complexes, and slow waves with brain activity data. Each sleep stage has its own unique features, and brain oscillations are crucial in defining each stage and may serve particular functions in the brain. In this section, we will summarize the findings in two areas: NREM sleep features (vertex waves, spindles, slow waves, and K-complexes), REM sleep features (ponto-geniculo-occipital waves and rapid-eye-movements).

Vertex waves

Vertex sharp transients have gained less attention despite their frequent occurrence and relevance for sleep onset. The specific EEG features of vertex waves comprise a large negative discharge with a particular waveform, narrower and more focal than K-complexes. Vertex waves are thought to be a direct response to an external stimulus or a mechanism to sustain sleep after a stimulus. The first imaging study of the anatomical correlates of vertex sharp transients found regions of maximal local signal changes located at the paracentral cortex, medial occipital cortex, right and left superior temporal cortex, and right and left pre-central cortex (Stern et al., 2011). The findings indicate that vertex waves, which are associated with brief multimodal

sensory experiences and may modulate awareness of the external world during NREM sleep, are mainly localized at the primary sensorimotor cortices, a distribution that differs from that of sleep spindles. Therefore, it is suggested that vertex waves are not a gating of sensory function at a central location, such as the limbic system or the thalamus, but rather a distributed phenomenon in neocortex that may be correlated to hypnagogic experiences taking place at the beginning of NREM sleep.

Spindles

Sleep spindles are a hallmark pattern of NREM sleep stage 2 and can be defined as a train of distinct waxing and waning waves with a frequency between 11-16 Hz (most commonly 12-14 Hz) with a duration of at least 0.5 seconds (Berry et al., 2012). Sleep spindles were observed in the first sleep recordings by Loomis et al. (1935), mostly occurring in N2 stage of the night and uncorrelated with heartbeat, respiration or muscle activity. Over the last decades, interest in understanding the function of sleep oscillations has increased considerably. Although the function of spindles is still unclear, several studies indicated its important role in memory consolidation and the relationship between certain features of spindles with age and intelligence (De Gennaro & Ferrara, 2003; Ujma, 2021). The latter might be explained by the fact that spindles to some extent highlight the efficiency of brain connectivity mechanisms needed to ensure efficient processing and integration of information, as shown by the relation between sleep spindles and white matter diffusion (Piantoni et al., 2013).

Based on the division criterion that slow spindles ($<13\text{Hz}$) predominate over frontal EEG derivations and fast spindles ($>13\text{Hz}$) over centroparietal derivations, Schabus et al. (2007) investigated the brain regions related to the two distinct types of sleep spindles, while Andrade et al. (2011) analyzed the hippocampal-neocortex connectivity of sleep spindle occurrence. These results showed a same origin in thalamus for both spindles but different activation pattern in the cortex. Both spindle types showed a common activation pattern in hemodynamic encompassing the anterior cingulate cortex, left anterior insula, and superior temporal gyrus. But fast spindles expanded more broadly across the cortex, showing strong activations in the supplementary motor area, sensorimotor, and mid-cingulate cortex, whereas slow spindles correlated predominantly with activity in the right superior frontal gyrus (Caporro et al., 2012) also reported correlations with the posterior cingulate and right paracentral cortex, however, they only stated that these were central spindles, without specifying the frequency. These findings support the existence of two spindle types during human NREM sleep, and it has been suggested that fast spindles participate in the processing of sensorimotor and mnemonic information. Additionally, functional connectivity between the hippocampus and the neocortex

exhibited a stable interaction with fast spindles, most pronounced in the subiculum, lateral temporal, insula, cingulate, and medial prefrontal cortices (Andrade et al., 2011). However, no specific hippocampal activation was directly associated with slow or fast spindles. This suggests that spindle activity may increase functional connectivity between hippocampal and neocortical regions, but that it is not the only cause of connectivity. For more mechanisms and functions of spindles, see Fernandez's review paper (Fernandez & Lüthi, 2020).

Slow waves and K-complexes

NREM sleep is dominated by spindles and slow waves. The slow waves characterized by a frequency range of 0.5-2 Hz and peak-to-peak amplitude greater than 75 μ V, was first described in intracellular recordings obtained from anesthetized cats. Slow waves can be observed in most cortical areas, especially in the: primary sensory, association, and motor cortices. However, the prevalence of slow waves in the primary visual cortex is lower (M. Steriade & McCarley, 2005). Tüshaus et al. (2017) further confirmed the prefrontal cortex's role in slow wave generation. Frontal activation during slow-wave activity, although no association with the thalamus, was also reported using PET by Dang-Vu et al. (2005), in line with previous EEG studies (Finelli et al., 2001; Happe et al., 2002; Werth et al., 1997). Subsequent work has shown that the process of falling asleep can be characterized by large steep widespread slow waves, named type I slow waves, that are source-localized to the medial prefrontal cortex and sensory-motor areas and are thought to be generated in the brainstem. Once sleep deepens, type II slow waves are characteristically smaller and shallower and are not originated in any specific cortical area (Siclari et al., 2014; Bernardi et al., 2018). How does the amplitude of slow waves reflect in fMRI-assessed brain activity? Dang-Vu et al. (2008) studied medium (75-140 μ V) and high (>140 μ V) amplitude slow waves, and the results indicated an association between activity in mesial-temporal areas and slow-wave amplitude, with medium-amplitude waves preferentially activating frontal areas, and high-amplitude waves being related to brainstem and para-hippocampal activations. These findings suggested that different amplitudes are differently distributed across the scalp when compared with baseline activity. Specifically, higher neuronal synchronization results in larger amplitude of slow waves activating mesial-temporal areas and possibly facilitating memory consolidation during NREM sleep.

K-complexes are sparse occurrences of often large and isolated slow waves during N2 sleep and are characterized by a brief positive wave followed by a larger negative wave and then by a positive wave again (Loomis et al., 1935). They are generated by the widespread occurrence of outward dendritic currents in cortical areas from the

middle to upper layers of the cerebral cortex, usually accompanied by a decrease in EEG power, leading to reduced neural network activity (Cash et al., 2009). Caporro et al. (2012) investigated the functional MRI of K-complexes, finding the fMRI signal associated with K-complexes comprises regions involved with spindles and vertex sharp transients, being maximal at the right post-central gyrus, right pre-central gyrus, left pre-central gyrus, right thalamus, right insular cortex, and right superior temporal gyrus. These findings contrasted with previous results by Laufs et al. (2007) that identified widespread signal decreases involving the thalamus, frontal, central, temporal, and parts of the occipital cortices. However, both results are consistent with the cortical down-state theory of K-complexes (Cash et al., 2009). Jahnke et al. (2012) applied dynamic causal modeling (DCM) to fMRI data acquired during sleep to investigate the causal hierarchy associated with fMRI responses to K-complexes. This study revealed that K-complexes simultaneously inhibit arousals and allow passive processing of incoming sensory information.

Recently, Fultz et al. (2019) identified coupled electrophysiological, hemodynamic, and cerebrospinal fluid (CSF) dynamics during NREM sleep. By acquiring fMRI data at high temporal resolution, the fast acquisition can also detect fluid inflow arriving at the edges of the imaging volume, thus allowing the authors to measure CSF flow dynamics simultaneously with the BOLD signal. First, they reported that CSF signal shows large oscillations (~ 0.05 Hz) during NREM sleep, while CSF small-amplitude (~ 0.25 Hz) signal was observed during wakefulness. In addition, nearby non-CSF regions did not exhibit such an effect. Next, they observed increases in BOLD signal amplitude in cortical gray matter regions compared to wakefulness, consistent with previous studies showing low-frequency BOLD fluctuations during sleep. Additionally, the CSF signal was strongly temporally coupled to large fluctuations in the cortical gray-matter BOLD signal during sleep, showing a strong anticorrelation that may indicate an alternation of blood flow and CSF flow during NREM sleep. To understand the potential mechanism, the authors hypothesized that EEG slow-delta (0.2 to 4 Hz) oscillations might be coupled to blood volume oscillations, leading to changes in CSF flow. They found that neural oscillations preceded CSF oscillations with a peak in EEG slow-delta (0.2 to 4 Hz) oscillations occurring 6.4 s before the CSF peak. This work discovered that large waves of CSF flow appear during sleep, and identifies slow neural activity as a potential contributing mechanism to driving CSF flow.

Several researchers have found strong fMRI signal changes coinciding with K-complexes, including the above study (Caporro et al., 2012; Jahnke et al., 2012; Fultz et al., 2019; Özbay et al., 2019). These may reflect the temporary decrease in neuronal

activity during the cortical down state attributed to them (Cash et al., 2009). Fultz et al. (2019) found that these fMRI changes are associated with CSF pulsations and, therefore, that K-complexes may have relevance for brain waste clearance through the glymphatic system, which has been shown to be more active during sleep (Xie et al., 2013). However, it is important to consider that large slow waves during N1 and N2 sleep (called type I slow waves (Siclari et al., 2014; Bernardi et al., 2018)) are distinctly different than the type II slow waves that dominate N3. In fact, type I slow waves like K-complexes are often accompanied by autonomic arousal (Colrain, 2005) while the latter have little autonomic correlate. Importantly, autonomic variability, including changes in heart rate and respiration, have been recognized as strong contributors to BOLD fMRI global signal (GS) fluctuations (Birn et al., 2006; Shmueli et al., 2007; Chang et al., 2009). To investigate the possible contribution of sleep-specific autonomic contributions to CSF pulsations, recent work examined the lag between slow waves, GS reductions, and CSF pulsations (Özbay et al., 2019; Picchioni et al., 2022), and considered both electrocortical and autonomic contributors. In the neural pathway, vasoconstrictions lag reductions in electrocortical activity by the well-established 4-6 s delay dictated by the hemodynamic response. Autonomic pathway delays are longer and may reach 12-15 s, owing to the more sluggish effects of sympathetic and respiratory activity on vascular tone (Picchioni et al., 2022). Indeed, these researchers found the lag between SWA and BOLD to average 13.7 s for the about 30 hours of N2 data considered. Thus, autonomic activity is an important contributor to CSF pulsations during N2 sleep. Data from this and future studies should be further analyzed to quantify the relative contribution of autonomic effects.. This does not take away the possibility that during N3, where SWA is prevalent but not associated with autonomic arousals, neurovascular responses are the driving factor of CSF pulsations. However, since BOLD GS fluctuations (and accompanying CSF pulsations) are typically relatively small during N3 (see e.g. Fig. 2 in (Picchioni et al., 2022)), simply the density of slow waves does not appear to be the determining factor in the generation of CSF pulsations. However, precisely how large-scale CSF flow relates to clearance remains poorly understood. Intriguingly, a recent MRI study used a contrast agent injected into the CSF to directly measure brain waste clearance in humans, and showed that sleep induces faster clearance (Eide et al., 2021), highlighting the importance of understanding fluid transport during sleep. More research is needed to explore the relationship between slow-wave activity and brain clearance (reviewed in (Lewis, 2021)). As will be discussed below, these conclusions point to the importance of accounting for autonomic effects when interpreting EEG-fMRI correlations, especially with arousal variations (Özbay et al., 2019; Duyn et al., 2020; Soon et al., 2021).

Much of this discussion does not consider the functional role of K-complexes/type I slow waves and the associated neuroimaging activity in terms of waking cognitive

outcomes. As Naji et al. (2019) showed, there is a positive correlation between overnight improvement in a declarative memory task and the extent that phasic increases in heart rate are time-locked to 0.4 to 3.3 Hz waves during N2 and N3 sleep. This is aligned with prior work because, as reviewed by McGaugh et al. (2013), sympathetic nervous system activity occurring subsequent to memory encoding still improves recall. This or similar ideas must be considered when designing future neuroimaging studies of K-complexes/type I slow waves. wave sleep.

Ponto-geniculo-occipital waves and Rapid-eye-movements

Ponto-geniculo-occipital (PGO) waves are described as phasic bioelectrical potentials occurring either in isolation or in bursts during the transition from slow wave sleep to REM sleep or even during REM sleep itself. PGO waves that trigger the bursts of rapid eye movements observed in REM sleep are mostly recorded in the pons (Jouvet, 1959), the lateral geniculate bodies (Mikiten, 1961), the occipital cortex (Mouret et al., 1963), but can also be observed in other parts of the animal brain (Hobson, 1964). Among other functions, PGO waves during REM sleep are hypothesized to promote brain development and to facilitate brain plasticity (Gott et al., 2017). REMs during REM sleep are likely generated by similar PGO mechanisms in man as in animals. In humans, during REM sleep but not wakefulness, ocular movements density significantly correlated with rCBF in the mesencephalon and the thalamus, including the lateral geniculate body, the right parahippocampal gyrus, the striate cortex, the precuneus, the right anterior cingulate cortex, and the supplementary motor area (Peigneux et al., 2001). Similar findings were reported using fMRI by Wehrle et al. (2005), who found activity in secondary cortical areas, basal ganglia, the cingulate midline attentional system, and the midbrain. In the same line, Ioannides et al. (2009) took opportunity of the high temporal resolution of magnetoencephalographic (MEG) recordings to evidence that PGO activity bursts precede the onset of the rapid eye movement. Investigations of the visual cortices and their projections during REM sleep suggest a mechanism underlying REM sleep, where paralimbic projections of the visual cortices dissociate from the hierarchy of visual regions mediating perception of the external environment. Such a dissociation may explain some features of dreaming and the absence of reflective awareness (Braun et al., 1998).

PET studies correlated the occurrence of REMs with cerebral blood flow in the visual cortex, thalamus, dorsolateral prefrontal cortex, anterior cingulate cortex, putamen, pons, and amygdala (C. C. Hong et al., 1997; Peigneux et al., 2001). Using simultaneous fMRI and polysomnography recordings during REM sleep, Wehrle et al. (2005) found BOLD signal increases in the geniculate body and occipital cortex in close temporal relationship to REMs during human REM sleep. In subsequent studies, Miyauchi et

al. (2009) not only confirmed that significant activation accompanying REMs in the lateral geniculate nucleus and the bilateral primary visual cortex, but also revealed that activation of the pontine tegmentum, ventroposterior thalamus, and primary visual cortex started before REM onset, whereas activation of the putamen, anterior cingulate, parahippocampal gyrus and amygdala accompanied REMs using an event-related analysis time-locked to the occurrence of REMs. Moreover, as a control group, subjects made self-paced saccades in total darkness showing no activation in the visual cortex. The above brain regions whose activity correlates with REMs were also confirmed by Hong's (2009) research and those regions are similar to the brain structures involved in the generation of PGO waves, as previously reported in animal studies (Callaway et al., 1987), thus suggesting the presence of similar processes occurring during human REM sleep. Unexpectedly, Hong et al. (2009) showed REMs-related activation also occurred in non-visual sensory cortices, motor cortex, language areas and the ascending reticular activating system. One possible reason for their distributed REM-locked activation is that instead of gold-standard EOG they used video monitoring of eye movements which detected approximately four times as many REMs. In brief, these studies indicate a sharing mechanism beyond the expected visual scanning mechanisms between waking and dreaming. Regarding the studies conducted in REM sleep, it should be taken into account that whereas NREM sleep oscillations and phasic events (e.g., slow waves, spindles, K-complexes) have been extensively studied and delineated, more studies are still needed to address with the same level of details the heterogeneous nature of REM sleep with its phasic and tonic constituents (Simor et al., 2020).

Neuroimaging correlates of sleep phenomenology

Neuroimaging techniques have provided valuable insights into the neural correlates of sleep stages and subjective sleep experiences such as dreaming and sensory processing. This section will review the neuroimaging findings on background activity during sleep and its relationship with sleep phenomenology. Specifically, we will explore the concurrent brain activity during dreaming and sensory processing during sleep, linking brain structural measures to sleep-related behavior outcomes, and the coupling between sleep-features and brain structural measures. These subsections aim to provide a comprehensive overview of the neural underpinnings of sleep-related phenomena and the implications for sleep-related behavior outcomes.

Background activity concurrently with dreaming and sensory processing during sleep

The investigation into brain activity during sleep has greatly advanced through the application of neuroimaging techniques. These methodologies have not only provided insights into the neural correlates of sleep stages but have also offered valuable information on event-related activity and subjective sleep experiences such as dreaming, lucid dreaming, and sensory processing. This comprehensive understanding of background activity during sleep serves as a window into the underlying mechanisms of sleep and its various phenomena. In this section, we will review the neuroimaging findings on background activity during sleep and its relationship with sleep phenomenology. To investigate the neural mechanisms underlying the content of dream experiences during REM sleep, Dresler et al. (2011) exploited the rare phenomenon of lucid dreaming, in which individuals become aware of their dream state and exhibit wake-like cognitive abilities while in physiological REM sleep (Baird et al., 2019). Lucid dream experts were instructed to perform a sequence of left and right-hand movements, alternating with left-right-left-right eye movements, during lucid dreaming or while engaged in both an imagined and actual waking hand-clenching task. The fMRI recordings during lucid REM dreams revealed increased BOLD signals in the sensorimotor cortex contralateral to the side of movement. In particular, activation during dreaming showed more localized patterns than during wakefulness, consisting of small clusters indicating either weaker or focal activation exclusively in hand areas. These findings marked the first demonstration of specific dream content during lucid dreaming, reinforcing that activation of motor imagery closely aligns with patterns associated with motor execution. Subsequently, Dresler et al. (2012) directly compared the neural correlates of lucid dreaming versus non-lucid REM sleep using fMRI recordings from two stable lucid dreaming episodes. The study revealed increased activity in the right dorsolateral prefrontal cortex, consistent with previous EEG studies of lucid dreaming (Voss et al., 2009). The most pronounced activation occurred in the precuneus during lucid dreams as opposed to non-lucid REM dreams. Interestingly, despite the usual impairment of working memory in ordinary dreams, the authors observed activation in the parietal lobules and activation in the dorsolateral prefrontal cortex, suggesting potential working memory demands. In addition, increased activation in bilateral frontopolar areas was noted, suggesting a possible link to the processing of internal states.

Is functional connectivity at the anterior prefrontal cortex associated with lucid dreaming frequency? Frequent lucid dreamers, compared with a control group, showed increased resting-state functional connectivity between the left anterior prefrontal cortex and the bilateral angular gyrus, right inferior frontal gyrus and

bilateral middle temporal gyrus (Baird et al., 2018). These findings, combined with the reported case study of lucid dreaming (Dresler et al., 2012), suggest that lucid dreaming frequency is associated with increased BOLD connectivity between the anterior prefrontal cortex and temporoparietal areas. The anterior prefrontal cortex and inferior parietal lobule/angular gyrus also exhibit reduced rCBF during REM sleep compared to wakefulness (Braun et al., 1997, 1998; Maquet et al., 1996). In addition, Eichenlaub et al. (2014) found that high dream recallers show higher rCBF in temporoparietal junction and the medial prefrontal cortex during REM sleep and wakefulness compared to low dream recallers. These results suggest that the temporoparietal junction and the medial prefrontal cortex are involved in the dream recall process and support the hypothesis of an association between lucid dreaming frequency and increased BOLD connectivity between the anterior prefrontal cortex and temporoparietal areas.

Another interesting topic of research is how the brain process external stimuli during sleep. Although sleep is typically viewed as a state of behavioral unresponsiveness, it does not mean the brain is not receptive to external sensory inputs (Blume et al., 2018). In fact, a wide range of studies have shown that the primary sensory cortex can still be activated by external stimuli during sleep in adults (Portas et al., 2000; Wilf et al., 2016) and children (Wilke et al., 2003; Redcay et al., 2007). However, other studies have shown decreased activation of the sensory cortex when compared to wakefulness (Born et al., 2002; Czisch et al., 2002), with this decrease being linked to the presence of K-complexes, thought to be a sleep protection mechanism (Czisch et al., 2004). Event-related studies have also found that stimuli-related brain activation during NREM sleep is correlated with the presence of sleep spindles or the phase of K-complexes (Czisch et al., 2009; Dang-Vu et al., 2011; Schabus et al., 2012). Using an acoustic oddball paradigm, Czisch et al. (2009) reported a prominent negative BOLD response for (rare) tones, yet no wake-like activation of the auditory cortex. In their data, only rare tones, followed by an evoked K-complex, were associated with a wake-like activation of task-related areas in the temporal cortex. Additionally, the phase of the K-complex did not appear to alter brain responses in the thalamus and primary sensory cortex, it does modulate the responses at higher cortical levels as shown in the superior temporal gyrus (Schabus et al., 2012). Moreover, sound-related brain activations are constrained to the caudal part of the inferior colliculus when sounds are played during sleep spindles, whereas similar activations can occur in the auditory cortex when sounds are played in the absence of sleep spindles (Dang-Vu et al., 2011). These studies supported the 'Thalamic Gating Hypothesis', which proposes that the thalamus acts as a gatekeeper during sleep and is mediated by spindles and K-complexes that drive the activity of cortico-thalamic loops (McCormick &

Bal, 1994). These findings provide evidence that spindles and K-complexes serve as sleep protective mechanisms while partially supporting the role of the thalamus as a gatekeeper during sleep.

Sleep-features and brain structural coupling

Previous research has extensively investigated the correlation between brain activity and sleep characteristics. However, the relationship between brain structural measures and brain function during sleep remains under-investigated. Tagliazucchi et al. (2016) explored the influence of anatomical connectivity on changes in functional connectivity between wakefulness and deep sleep. Their findings revealed regional differences, with primary sensory, motor, auditory, and visual cortices showing increased structural-functional coupling during N2 and N3 sleep compared to wakefulness. In contrast, frontoparietal regions exhibited a disconnection between structure and function. Notably, coupling between structural and functional networks increased during deeper sleep NREM stages but not during light sleep (N1). These findings align with previous research indicating divergent cortical dynamics during NREM sleep and suggest a convergence of structural and functional connectivity near a critical point, facilitating efficient and controlled neural propagation (Deco, McIntosh, et al., 2014; Tagliazucchi et al., 2016).

Sleep spindles have been shown to have distinct features and can be characterized in terms of the frequency range, for instance slow (<13Hz) and fast (>13Hz) spindles (Schabus et al., 2007). Investigating the relationship between fast and slow spindles and structural measures can shed light on their precise functions. Saletin et al. (2013) combined EEG sleep recordings with high-resolution structural MRI to reveal that gray matter volume in interoceptive and exteroceptive cortical regions correlates with slow sleep spindles. Additionally, gray matter volume in the bilateral hippocampus was associated with fast sleep spindles, supporting their role in declarative memory processing. Individual differences in slow-wave oscillations, linked to gray matter volume in the basal forebrain and medial prefrontal cortex, further underscore the potential connection between sleep physiological phenomena and macroscopic brain structure. Another topic of interest is brain plasticity, i.e., the structural brain changes as a consequence of learning and post-training sleep, probing the links between MR structural measurement-related modifications and the underlying microstructural brain processes, and bidirectional influences between structural and functional brain changes (for a review, see (Stee & Peigneux, 2021)).

White matter tracts constitute the brain's neuronal structural foundation, and alterations in neural activation may alter sleep spindles and slow-wave oscillations.

Based on this association, Piantoni et al. (2013) observed that higher spindle power correlated with higher D_a (axial diffusivity) in the forceps minor, anterior corpus callosum, temporal lobe areas, and the thalamus. Individuals with a steeper rising slow-wave slope showed higher D_a in the temporal fascicle and frontal white-matter tracts. Consistent with these findings connecting white matter integrity as a predictor of quantitative and qualitative features of sleep spindles in young adults, Mander et al. (2017) showed that age-related degeneration of white-matter tracts is associated with reduced sleep spindles in older adults. Consequently, human brain white matter integrity influences sleep spindle decline in older adults, and thus sleep-dependent motor memory consolidation in later life more than age per se.

Neuroanatomical correlates of sleep-related behavior outcomes

The influence of brain structure on behavior is a central challenge in scientific research, with various statistical and mathematical models helping to identify significant relationships between brain structural metrics (e.g., cortical thickness, volume, microstructural estimates) and behavioral outcomes (e.g., questionnaires, task-specific scores). A study associating dream recall frequency with cerebral blood flow at the medial prefrontal cortex and temporoparietal junction linked increased white-matter density in the medial prefrontal cortex to high dream recallers, offering an anatomical counterpart to functional changes observed in previous studies. Vallat et al. (2018) compared gray and white matter measures between high and low dream recallers and did not find significant differences in gray matter density between high and low recallers. However, increased white-matter density in the medial prefrontal cortex was observed. This result introduces an anatomical counterpart to multiple findings reporting functional changes between high and low dream recallers. It also supports lesion studies that showed a cessation of dream reports after damage localized to the lateral ventricles' frontal horns (Solms, 1997). For frequent recallers of lucid dreams, Filevich et al. (2015) reported a higher grey matter volume in the frontopolar cortex compared with individuals with low lucid dreaming frequency. While Baird et al. (2018) were not able to replicate these structural findings, both studies reported functional differences related to the frontopolar cortex during wakefulness in high vs. low lucid dream recallers.

In sleep research, DTI has been employed, for instance, to investigate brain microstructural properties associations with sleep quality and duration. Khalsa et al. (2017) investigated changes in fractional anisotropy and mean diffusivity concerning these sleep variables. Sleep patterns were measured during 14 days using actigraphy and sleep diaries. The authors reported positive correlations between sleep duration and fractional anisotropy in the left orbitofrontal region and the

right superior corona radiata. In contrast, sleep duration negatively correlated with mean diffusivity in right orbitofrontal white matter and the right inferior fasciculus. Moreover, sleep quality was associated with fractional anisotropy measures in the left caudate. Takeuchi et al. (2018) extended these findings in a cohort of over more than a thousand healthy young adults, revealing negative correlations between sleep quality and mean diffusivity in the prefrontal cortex and right hippocampus, while positive correlations between sleep duration and mean diffusivity were found in the prefrontal cortex and dopaminergic systems. These results suggest that total sleep time and subjective sleep quality are associated with subtle brain microstructural changes.



Figure 2: The most common challenges conducting sleep neuroimaging studies. Since polysomnography must be recorded to perform appropriate sleep scoring and identify electrophysiological microprocesses of interest such as sleep spindles or slow waves, hardware constraints might emerge, such as the limitation of adequate equipment, for instance, MRI-compatible EEG caps and electrodes. Additionally, auxiliary electrodes and channels might be needed, which accounts for electrode placement, standardization, and signal quality challenges. Sleep scoring online or offline becomes problematic, as data cleaning and artifact removal must be performed, particularly a concern for MRI studies. The lack of open-source software does not facilitate individual-based artifact removal algorithms, greatly benefiting sleep studies. Except for fNIRS, any other scanner environment is restrictive, accounting for difficulties maintaining and consolidating sleep. Movement restrictions are a significant issue for MRI studies and can deteriorate the data due to movement artifacts. Acoustic noise in MRI could be reduced by developments and usability of silent MRI sequences combined with MRI-compatible noise-canceling devices, such as headphones. Data quality and interpretability are crucial to advancing science. However, neuroimaging suffers from autonomic physiological confounds, especially during sleep. Current approaches usually model and regress physiological signals, however, it may account for signal loss. Developments in animal models and theoretical advances will help understand the complex relationship between metabolism, blood flow, and neural activity.

Sleep Neuroimaging Challenges and Future Directions

Sleep neuroimaging comes with considerable challenges due to the unnatural environment that makes it difficult to consolidate and maintain sleep (Figure 2). The scanner setting requires movement restrictions, with the exception of NIRS, to avoid motion artifacts. The acoustic noise of MRI is not conducive to maintaining and consolidating sleep and may affect its brain activity patterns. A further complication of sleep neuroimaging is the need to include polysomnography recordings that includes recording brain activity (EEG), eye movements (EOG), and muscle activity (EMG). These needs lead to additional hardware constraints, like the availability of auxiliary electrodes and channels and the use of reference electrodes that may suffer from distortions and cardio ballistic artifacts (heart activity derived from electrodes placed near a pulsating vessel/artery) and are hard to correct. Furthermore, lengthy recordings cause discomfort to the subject, leading to difficulty maintaining sleep, EEG signal quality deterioration, and movement artifacts in the fMRI and EEG recordings, the latter through the induction of currents caused by the magnetic field. These limitations account for the high dropout rates in sleep studies compared to a standard task or resting-state imaging during wakefulness. Moreover, it also limits the research questions the field can address. For instance, the homeostatic changes over the course of sleep have yet to be investigated, which requires long recording times.

Currently, sleep neuroimaging studies must use simultaneous physiological EEG recordings to perform sleep scoring accurately. From this perspective, we see two major challenges that we will address in terms of software and hardware advances. The first is difficulties in removing irregular artifacts from the EEG data, which is particularly challenging for MRI studies. Artifact removal software is complex and mostly designed by private companies with closed-source code. Making such algorithms open-source or partially accessible to the public would enable improvements in the field (Levitt et al., 2022), potentially leading to advances such as an adapted individual-based artifact removal algorithm. Such a customized level would positively facilitate data pre-processing without compromising the EEG signal in special cases where artifact removal implies data loss. Another possible way to facilitate artifact removal is the use of newly developed hardware. For instance, Chowdhury et al. (2014) developed a new EEG cap that incorporates embedded electrodes in a reference layer with similar conductivity to tissue and is electrically isolated from the scalp. In this new setup, the standard electrode layer is placed under the reference layer, which is in direct contact with the scalp, allowing the acquisition of mixed signals containing artifacts and neurophysiological signals.

The reference layer electrodes are separated from the scalp, and only artifacts such as gradient artifacts, electrocardiogram, and motion artifacts can be acquired. Therefore, the EEG signal without artifacts can be separated by comparing signals obtained from the standard and reference electrodes. Another solution might be integrating a carbon-wired loop that has outperformed post-processing EEG/fMRI artifact corrections (van der Meer et al., 2016). This method makes use of carbon-wired loops as additional sensors that track both helium-pump and cardio ballistic artifacts. Another promising direction is to develop sleep staging algorithms based on electrocardiogram or respiratory signals, as electrocardiogram presents a higher signal-to-noise ratio than EEG signal, and wearable devices measuring respiratory signals are already available in the market (Sun et al., 2020). The development of MRI-based eye-tracking can assist in the detection of eye-movement positions during REM sleep, particularly interesting in lucid dreaming (Frey et al., 2021). Additionally, wearable and contactless devices could potentially help the field and decrease the experimental setup complexity.

To ensure optimal sleep stability in this unusual environment, the application of total or light sleep deprivation protocols is applied, thus ensuring increased sleep pressure leading to shorter sleep latency. However, sleep-deprived subjects may account for potential confounds in homeostatic sleep regulation and impaired coupling of the default mode network, among other physiological changes (Wang et al., 2020). In a recent study, Moehlman et al. (2019) confirmed a procedure to obtain all-night fMRI data in sleeping subjects without sleep deprivation. The key detail was to perform acquisitions in consecutive nights, hence the first night served as an adaptation night, eliminating the need for systematic sleep deprivation. Although the authors acknowledged that the subjects were slightly sleep-deprived after the first night (which may lead to sleep alterations on the second night), a washout period between the two nights might contribute overcoming changes in sleep architecture due to sleep deprivation, while preserving the stability of sleep in the scanner. Besides having a consecutive-nights experiment design, researchers should also consider using sleep hygiene protocols to enhance stable sleep under experimental conditions. For instance, maintaining a regular sleep routine, preferably overlapping with the experiment design, avoiding daytime naps, screen-light, and caffeinated beverages before bedtime can improve sleep quality and enhance the chances of falling asleep.

Movement restrictions during scanning are a critical restriction in sleep neuroimaging studies: both PET and MRI do not allow subjects to change positions, creating discomfort when measuring sleep, in particular during longer scanning periods. Additionally, PET imaging requires restricting one arm's movement as a

catheter must be placed during scanning. Ongoing developments in the field may lead to flexible MRI apparatus or even portable scanners (Corea et al., 2016; Cooley et al., 2021). Recent developments in wearable magnetoencephalography based on optically pumped magnetometers (Boto et al., 2018) have granted this electrophysiological imaging method a considerable advantage in comparison to neuroimaging modalities relying on rigid scanners such as MRI or PET. However, sleeping in different positions seems to cause alteration in brain activity patterns. In supine posture, the brain activities in the left precuneus and anterior cingulate cortex were greater than those in lateral positions (Xu et al., 2021). Once a flexible apparatus becomes a reality, more research is needed to investigate posture influence in brain activity and how upcoming research can correlated its findings with current literature.

The acoustic noise produced by MRI is not conducive to sleep and may affect brain activity during sleep. Silent sequences have been developed and applied, especially in acoustic stimulation tasks, for many years (Schmitter et al., 2008; Lövblad et al., 1999; Liebig et al., 2019). Since all-night sleep fMRI studies became feasible, silent sequences in combination with noise cancellation systems are welcome allies in noise reduction, thus diminishing subject discomfort and enhancing sleep maintenance mostly with the drawback of reduced spatial resolution. This is critical as studies have shown that REM sleep can be particularly suppressed by acoustic noise and drastic environmental changes, which accounted for fewer neuroimaging studies on REM than NREM sleep (Mulert & Lemieux, 2009). However, noise cancellation headphones can also cause EEG artifacts, and therefore should be used with care. Researchers should consider the limitations imposed by the scanner environment when planning their studies, especially the timeline required to acquire reasonable sample sizes and the methods to study the sleeping brain, for instance, seed-region, independent networks with component analysis, dynamic causal modeling, and graph theoretical analysis.

Among the most critical challenges for neuroimaging techniques are interpretability and signal quality. Since multiple neurophysiological and autonomic changes are correlated with neural activity, which fluctuates along the wake-sleep cycle, untangling these neural sources from their confounding consequences (e.g., changes in blood flow) is a complex challenge that cannot be overcome by recording and regressing physiological signals. Hence, one significant gap that needs to be addressed is how changes in autonomic physiology during sleep affect blood flow signals. Current approaches for minimizing effects contributing to the overall signal involve regressing out from the fMRI time-series signals that reflect the effects one wishes to remove, for instance, global signal, signals reflecting fluctuations in

heart rate or respiration, or reference signal from regions as the white matter of cerebrospinal fluid. However, depending on the study's goal, systemic effects may covary with neuronal effects, which might be partially excluded with the removal approach. This is crucial, especially for sleep studies, as cortical activity changes and systemic physiology may be derived from arousal state changes. Conversely, physiological changes may be triggered by neuronal activity. A good example is a study by Özbay et al. (2019) that analyzed the temporal relationship between amplitude variations of vascular tone derived from photoplethysmography signal and EEG K-complexes' occurrence. They observed that fMRI signal showed clear covariations with EEG K-complexes and vascular tone. More importantly, arousal changes lead to joint changes in cortical and autonomic activity (Özbay et al., 2019). These signal changes are related to shifts in autonomic and central nervous systems, emphasizing the importance of such contributions often neglected as noise when interpreting fMRI data. The autonomic system is also regulated by the central nervous system via the brainstem, which is a primary control center of sleep and arousal regulation and ties the common changes in electrocortical and autonomic activity that are so pronounced across the sleep-wake cycle (Duyn et al., 2020). These findings, also showed by Soon et al. (2021), emphasize the importance of modeling autonomic and neuromodulatory effects since these effects vary with the sleep stage, thus making comparisons of functional connectivity patterns across sleep states difficult. Importantly, the altered amplitude of BOLD signal fluctuations during sleep could modulate connectivity estimates even in the absence of any true change in correlation strength, due to the large change in signal amplitude. It seems unlikely that these challenges can be overcome without extensive animal studies and new theoretical insights on the relationship between metabolism, blood oxygenation, and neural activity. Future experiments should go beyond temporal averages and try to find the time-resolved signatures of different patterns of electrophysiological activity. Which local field potential (LFP) frequency bands contribute most to the signal acquired by different neuroimaging techniques? Can these methods pick up information beyond the characteristics of LFP oscillations, such as complexity? Is it possible to find a one-to-one relationship between electrophysiological activity parameters and the data provided by neuroimaging methods? Without advancing answers to these questions, the interpretability of neuroimaging data is very problematic. The assessment of signal quality depends on disentangling the contribution of neural activity from recording physiological and movement artifacts and therefore relates to the challenges concerning interpretability. Computational models could be helpful to encode theoretical knowledge on the mapping between neuroimaging and LFP data, allowing to transcend what is directly available from empirical data. Still, it is possible that we are reaching a limit about the amount of neural information that

can be decoded from standard neuroimaging data. Moving towards high-resolution modalities (e.g., layer BOLD fMRI) could be necessary to push the borders of our knowledge. However, these advances alone will not solve the autonomic confound. Besides, higher field strength, such as 7T, allows better resolution and sensitivity, but it compromises EEG signal quality. Hence, further development of EEG systems that can be used in higher field strength and suppress cardioballistic and gradient artifacts should be explored.

BOLD contrast results from various physiological variables, including blood flow and volume, local vascular architecture, cerebral oxygenation metabolic rate, and autonomic processes. Unlike BOLD signal, perfusion fMRI provides noninvasive and absolute quantification of cerebral blood flow analogously to PET scanning, utilizing standard MRI hardware and not requiring radioactive tracer administration (Detre et al., 2009). Perfusion techniques applied to fMRI are less sensitive to baseline shifts and do not rely on an imbalance between flow and oxygen consumption. Perfusion fMRI, such as arterial spin labeling (ASL), provides more of an absolute measure than BOLD, thus providing the opportunity to compare brain function without conventional task-correlated BOLD fMRI directly. For instance, a predictive model is needed to perform the analysis: hand clenching or eye signals during REM lucidity. ASL fMRI has been applied to sleep studies with promising results during sleep (Tüshaus et al., 2017). Although, some disadvantages must be considered in perfusion studies regarding brain coverage and signal-noise ratio. Perfusion fMRI has a low temporal and spatial resolution, and adding proper quantitation capability reduces its sensitivity and is cumbersome. Furthermore, as a hemodynamic signal, many of the same interpretation problems are still there, and more studies are needed to test its feasibility for sleep research.

In summary, advances in neuroimaging have significantly improved our understanding of brain activity during sleep beyond traditional polysomnography-based approaches. For instance, in Sections 2 and 3 of this review, we discussed in detail how early PET studies identified regional activations and deactivations across sleep stages, while newer techniques such as EEG/fMRI allow detailed characterization of transient sleep oscillations and neural processes within these stages. Functional neuroimaging research has revealed that the brain retains its capacity to respond to external auditory stimuli during sleep, indicating that certain aspects of information processing remain active. Additionally, spontaneous reactivation of brain regions associated with learning has been observed during sleep and studies triggering reactivation using contextual cues during sleep further support the idea that neuronal replay and reactivation play a causal role in

memory consolidation (for a review, see (Farthouat & Peigneux, 2015)). Sleep and wakefulness are now widely recognized to occur and be regulated locally. Multimodal imaging techniques, which allow for the simultaneous tracking of global and local brain states, may contribute to our understanding of these local phenomena (Song & Tagliazucchi, 2020). In particular, spontaneous oscillations in fMRI BOLD activity, observed across both cortical and subcortical regions, have been proposed as potential markers of local sleep. These oscillations, which are detectable at the level of individual neuronal populations, may reflect the intensity of local sleep and offer valuable insights into monitoring local neuronal states and identifying the brain regions that first transition into or out of sleep during wake–sleep transitions (Song et al., 2022). Clinically, recent studies show that low-frequency oscillations during sleep promote CSF dynamics, which aids in metabolic waste clearance (Fultz et al., 2019). This process is critical for clearing accumulated protein, such as amyloid beta and tau, associated with Alzheimer's disease, and sleep disturbances may reduce cerebrospinal fluid flow and clearance efficiency, potentially worsening memory impairment and disease progression. These findings point to potential biomarkers for diagnosing and managing conditions related to impaired sleep or clearance mechanisms, linking neural activity, CSF dynamics, and cognitive health. Additionally, data-driven methods such as Hidden Markov Models (HMM) combined with EEG/fMRI recordings offer a more in-depth understanding of brain states during sleep. Unlike arbitrary polysomnography-based sleep staging, which segments sleep into fixed 30-second epochs, HMM identifies temporally precise brain states and their transitions, revealing previously unobservable dynamics. Modular analyses of HMM states have identified distinct sub-states within NREM and REM sleep that correspond to PSG-defined stages while revealing new patterns, such as the duality between phasic and tonic REM (Stevner et al., 2019; Yang et al., 2024). These methods emphasize sleep's dynamic nature, highlighting the importance of using advanced multimodal imaging techniques to enhance our understanding of the relationship between sleep physiological mechanisms and their contributions to restorative and memory processes.

Conclusions

This review summarized neuroimaging approaches to sleep research in healthy and non-sleep-deprived populations. Different neuroimaging modalities, when combined with electrophysiological recordings, have helped to bridge animal and human research by measuring *in vivo* functional and metabolic information with good spatial and temporal resolution. The advance of novel techniques has

increasingly facilitated consecutive all-night imaging recordings, perhaps the final technical challenge of sleep neuroimaging. The field has grown considerably from early findings contrasting wakefulness vs. sleep measurements towards the analysis of fine-grained sleep-related events and the study of whole-brain functional coupling across the human wake-sleep cycle. The combination of neuroimaging methods and new experimental protocols is further extending our current knowledge of poorly understood phenomena such as lucid dreaming and local sleep. Neuroimaging has also improved the interpretation of sleep disorders, has demonstrated the importance of sleep for different cognitive functions, particularly memory consolidation and learning, and has raised concerns regarding the severe consequences of sleep deprivation. Despite the significant advances brought by neuroimaging to the field of sleep research, much room for future investigation remains, especially concerning the replication of initial findings and the study of REM sleep, which is especially difficult to capture in the environment of an MRI scanner. Although many studies yielded valuable discoveries, small samples can lead to significant variability and potentially limit the reliability of conclusions drawn about sleep neuroimaging across different demographics or clinical populations. Future studies should prioritize larger, multisite studies and collaborations to improve statistical power and ensure findings are more broadly applicable. Other interesting open questions in the field are investigating the impact of wake intrusions during sleep and how inter-individual and inter-regional differences play a role in local sleep, as well as examining the influence of circadian rhythms on this phenomenon. Finally, the functions and mechanisms underlying dreaming remains unknown, thus future research should focus on investigating brain changes during lucid and non-lucid REM sleep dreams and, in collaboration with thoughtfully-designed dream interviews, uncover the differences that exist between NREM and REM dreams.

Author Contributions

MP and MD conceptualized the review. MP developed the structure and wrote the first draft. MP, XC, AP, and YP conducted the literature search and selection. All authors reviewed and discussed the manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest disclose for this paper.

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Chapter 3

Neural correlates of nightmares revisited: findings from large-scale fMRI cohorts

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Abstract

Nightmares are associated with daytime distress and are common across psychiatric and neurological disorders, yet the neural mechanisms underlying their frequency remain poorly understood. This study investigated whether nightmare frequency is related to resting-state functional connectivity between the amygdala and prefrontal cortex, key regions involved in emotion regulation and fear extinction. Additionally, we aimed to replicate previous findings on the neural correlates of nightmares using two large independent cohorts. A total of 424 healthy participants underwent structural and functional MRI during wakeful rest and completed retrospective questionnaires of nightmare and dream recall frequency. Voxelwise general linear models assessed the relationship between amygdala–prefrontal connectivity and nightmare frequency. We also computed regional homogeneity (ReHo) maps and examined both group-level contrasts (high vs. low nightmare frequency) and continuous associations, controlling for age, sex, population, and dream recall frequency. Contrary to our hypothesis, nightmare frequency was not significantly associated with amygdala–prefrontal connectivity, and previous ReHo group differences could not be replicated. However, a significant association emerged between nightmare frequency and ReHo in the cerebellum when modeled continuously. These findings challenge existing knowledge of the neural correlates of nightmares production and frequency and highlight the importance of rigorous statistical controls and large sample sizes in neuroimaging research. The null results also suggest that individual differences, such as emotion regulation capacity, personality traits, or trauma history, may moderate the neural correlates of nightmare frequency. Overall, our study highlights the complexity of mapping the neurobiological basis of nightmares and emphasizes the need for refined models that account for both state and trait variability.

Keywords: nightmares, nightmare frequency, fMRI, functional connectivity, ReHo

Introduction

Nightmares are dreams characterized by strong negative emotions that can cause significant distress and affect daily functioning, with their frequency varying substantially within the population and the precise mechanisms underlying their formation remaining elusive. Nightmares have the potential to disrupt sleep by causing awakenings with vivid recollections of the unpleasant mentation (Nielsen & Levin, 2007; Zadra et al., 2006). Nightmares are common, however their frequency is substantially heterogeneous within the population (American Psychiatric Association, 2013): 85% of adult respondents reported having had a nightmare at least once a year, and about 2-6% reported suffering from weekly nightmares (Levin & Fireman, 2002; Zadra & Donderi, 2000). Some risk factors have been identified in people who experience nightmares frequently, including genetic predisposition (Hublin et al., 1999), state or trait anxiety (Schredl, 2003), increased stress (Picchioni et al., 2002; Schredl & Goeritz, 2019), psychopathologies such as schizophrenia (Levin, 1998), major depressive disorder and bipolar disorder (Akkaoui et al., 2020), and post-traumatic stress disorder (Campbell & Germain, 2016; Harvey et al., 2003; Ross et al., 1989). Despite the clinical relevance of diagnosing and treating nightmares, the exact mechanisms responsible for their formation remain unclear. Consequently, investigating the neurophysiological factors that contribute to nightmare frequency may significantly improve our comprehension of their underlying causes.

Theoretical models of nightmare production and emotion regulation highlight the functional interaction between the amygdala and prefrontal cortex, brain regions that play a central role in adaptive emotion processing across both sleep and wakefulness (Berboth & Morawetz, 2021; Nielsen & Levin, 2007). While theoretical debates persist regarding the extent of emotional regulation during sleep and its manifestation in dreams, accumulating evidence suggests that fear experiences in dreams can influence adaptive responses to threats in waking life (Sterpenich et al., 2020). However, the transition from adaptive dream mechanisms to impaired daily functioning, sleep disturbance, and vulnerability to psychological disorders remains unclear. The "Affect Network Dysfunction" model proposes that nightmares result from dysfunction within a brain network that oversees the adaptive function of fear extinction during dreaming (Nielsen & Levin, 2007). Neurobiologically, the basolateral amygdala is critical for fear encoding and extinction, whereas the medial prefrontal cortex mediates expression. In addition, the hippocampus and brainstem modulate contextual cues and suppress conditioned fear expression, respectively. This neural circuit involving the anterior hippocampus, amygdala, and prefrontal cortex is thus thought to influence the occurrence and severity of nightmares (Nielsen

& Levin, 2007). For emotion regulation, several prefrontal cortex regions consistently interact with the amygdala during emotional down-regulation via reappraisal (Berboth & Morawetz, 2021; Loos et al., 2020). In support of this, altered gray matter volume in the left inferior frontal gyrus is associated with depression in patients with idiopathic rapid eye movement sleep behavior disorder who have elevated negative emotional dreams (Bourgouin et al., 2019). Conversely, bilateral calcification of the basolateral amygdala correlates with more pleasant dreams, suggesting a role for the amygdala in shaping dream emotion, as patients with basolateral amygdala lesions perceive dreams as less negative (Blake et al., 2019).

Effective emotion regulation plays a key role in managing and responding to evolutionary relevant threats and stress experiences, thereby shaping emotional reactivity and overall well-being. The differential susceptibility framework (Carr & Nielsen, 2017) proposes sensory processing sensitivity as a trait relevant to the study of nightmares, with nightmare-prone individuals exhibiting heightened emotional reactivity to both positive and negative stimuli. Studies of nightmare frequency have shown an inverse relationship between nightmare severity scores and regional cerebral blood flow in the right medial frontal gyrus during negative image viewing (Marquis et al., 2019). This finding was partially replicated using functional near-infrared spectroscopy (fNIRS), suggesting a negative association between dysphoric dream distress and frontal activation during negative image viewing (Carr, 2020). In the context of threat perception and emotion regulation circuits, abnormal resting amygdala-prefrontal cortex connectivity has been associated with repeated childhood stress, contributing to heightened threat perception (Ochsner & Gross, 2005). Disturbances in this connectivity may serve as a prelude to heightened emotional reactivity during dream states, and the abnormal connectivity observed in individuals with psychological disorders suggests that resting-state patterns may provide valuable insight into nightmares and serve as a potential predictor of their occurrence.

Building on this perspective, recent theoretical work has highlighted a reciprocal feedback loop between impaired sleep and emotion dysregulation, especially regarding borderline personality disorder (BPD), which is characterized by chronic emotional instability (Van Trigt et al., 2025). Although our sample consists of psychologically healthy individuals, the frequency and distress of nightmares vary substantially within the general population, suggesting dimensional variability in emotional regulation capacity. According to van Trigt et al., REM sleep fragmentation, which is closely tied to nightmare-related insomnia, can impair the brain's ability to recalibrate limbic circuitry, resulting in sustained hyperarousal and heightened emotional reactivity. These emotional dysregulations can in turn perpetuate further

sleep fragmentation, reinforcing the cycle. Central to this mechanism is the integrity of amygdala-prefrontal cortex connectivity, which supports the downregulation of negative emotions during both wakefulness and sleep. Our investigation is thus motivated by the possibility that interindividual differences in the strength of prefrontal-limbic functional connectivity might modulate susceptibility to this feedback loop, making some individuals more vulnerable to recurrent nightmares even in the absence of clinical pathology. Understanding this relationship in healthy populations could help elucidate early neurophysiological markers of emotion regulation vulnerability and improve conceptual models of nightmare formation.

Few studies have investigated the neural correlates of nightmares from a whole-brain perspective. As a notable example, (Marquis et al., 2021) investigated the relationship between resting-state functional magnetic resonance imaging (fMRI) and nightmare frequency in a sample of 18 frequent nightmare recallers and 18 controls. They found altered regional homogeneity (ReHo, based on Kendall's concordance coefficient measures of BOLD time series for each and nearest voxels) in various brain regions, including frontal (medial prefrontal and inferior frontal), parietal, temporal, and occipital regions, as well as some subcortical regions such as the thalamus. Their findings partially support previous research by (Shen et al., 2016), who observed increased ReHo in the left anterior cingulate cortex and right inferior parietal lobule in 15 patients with nightmare disorder. However, when comparing nightmare disorder patients and matched controls, the latter study did not observe ReHo changes in the hippocampus and amygdala. These findings suggest that the severity and frequency of nightmares may be associated with altered neural activity in several brain regions, including those involved in emotion regulation. However, findings are inconsistent and limited by small sample sizes and heterogeneous populations.

To unravel the complex mechanisms underlying nightmare frequency, the present study had two primary goals. First, we aimed to elucidate the interaction between amygdala-prefrontal cortex connectivity and nightmare frequency in a large cohort of healthy volunteers. We hypothesized that robust functional connectivity between these regions may serve as a predictor of attenuated nightmare recurrence. We speculated that the strength of this connectivity promotes a more effective down-regulation process that not only contributes to effective emotional regulation during waking hours, but also positively influences nighttime processes. To strengthen the reliability of our results, we replicated our findings in another large independent cohort of subjects. Second, our research aimed to replicate and extend the existing literature on whole-brain correlates of nightmare frequency by employing ReHo analysis with a significantly larger sample size, while controlling for dream recall frequency. We

anticipated that the increased statistical power of a larger cohort would provide more robust insights into the neural correlates of nightmare formation. Consistent with our replication efforts, we anticipated a convergence of findings with previous work. To achieve this, we used voxel-wise correlations to assess amygdala-prefrontal connectivity and generate ReHo maps. We then examined the relationship between these measures and nightmare frequency in two independent analyses. Through these efforts, our study aimed to contribute significantly to understanding nightmares, elucidate the intricate neural mechanisms governing their recurrence, and potentially provide a pathway to more effective diagnostic and therapeutic interventions.

Materials and Methods

Study Population

The data were acquired in the context of a large multi-site cohort project as part of the EU COST Action CA18106 “The neural architecture of consciousness” (<https://neuralarchcon.org/>), and is composed of MRI and behavioral data collected from healthy participants at two data collection sites. For Dataset 1, the study was approved by the regional local ethics committee, *De Videnskabsetiske Komitéer for Region Midtjylland*, Denmark. For Dataset 2, the study was approved by the *Research Ethics Committee at the Institute of Psychology* and the *Komisja Bioetyczna* of the Jagiellonian University, Krakow, Poland. For both datasets, participants were recruited through a local participant database and local advertisements on various websites of the Jagiellonian University and Facebook. They were financially compensated for participation. The following inclusion criteria were used at both sites: brain damage or surgery, age between 18 and 50 years (40 for Dataset 2), normal or corrected-to-normal vision, and normal hearing. Exclusion criteria were standard MRI contraindications and the use of neuropharmacological or other medicine that may affect neural states, pregnancy, and skin diseases. *Dataset 1*: A total of 306 participants gave informed consent to participate in the study. From these 306 participants, fMRI data of 269 participants were available, and among those data, nine participants were excluded: five based on incomplete questionnaires and four based on incomplete fMRI data. Hence, data from a total of 260 participants (152 female, mean age of 24.78 ranging from 18-48 years) was used in this work. *Dataset 2*: A total of 302 participants gave informed consent to participate in the study. From these 302 participants, preprocessed and quality-checked fMRI data of 164 participants were available at the time of the analysis. Hence, data from a total of 164 participants (99 female, mean age of 23.31 ranging from 18-40 years) was used in this work. All participants completed an online questionnaire session from home with a total duration of

around 70 minutes, including a seven-point rating scale assessing their dream recall frequency, ranging from 0 (never) to 6 (every morning) (Schredl & Erlacher, 2004). Nightmares were assessed using the eight-point nightmare frequency scale, which asks participants to rate their nightmare frequency on a scale ranging from 0 (never) to 7 (several times per week). This scale has been used in prior studies examining nightmare prevalence and phenomenology (Carr et al., 2021, 2022). To ensure clarity, nightmares were defined as: “Nightmares are dreams with strong negative emotions that result in awakening from the dreams. The dream plot can be recalled very vividly upon awakening” (Schredl et al., 2014), distinguishing them from sleep terrors, which typically involve intense fear, autonomic discharge, and limited recall (Fisher et al., 1973). The questionnaires were administered in English for Dataset 1 and in Polish for Dataset 2. Participants were instructed to ensure it was completed in an undisturbed environment. The dream recall scale was recoded into units of mornings per week and the nightmare frequency scale into units per month (Stumbrys et al., 2015).

Data acquisition

As both sites were part of the same consortium, data collection was standardized for both datasets. Two resting-state fMRI runs (12 and 6 minutes) were recorded alongside quantitative multi-parameter mapping (MPM; (Weiskopf et al., 2013)) and diffusion-weighted imaging in one scanning session lasting approximately one hour. In this study, we restricted our analysis to resting-state fMRI and synthetically generated T1-weighted images (see “Structural data” section below for details). Dataset 1 was acquired at a Siemens Magnetom Prisma-fit 3T MR scanner. For each participant 1500 functional volumes were acquired using a echo planar T2*-weighted sequence sensitive to BOLD contrast with a multiband acceleration factor of 6 (TR/TE = 700/33 ms, flip angle = 53°, field of view = 200 × 200 mm, number of slices = 60, slice thickness = 2.5 mm [no gap], in-plane resolution = 2.5 × 2.5 mm). Dataset 2 was acquired at a Siemens Magnetom Skyra 3T MR scanner, with almost identical parameters, with the only differences being the number of functional volumes (1348) and the TR/TE (801/33 ms).

The MPM protocol was implemented based on the Siemens vendor sequence and was identical for both datasets. Three-dimensional (3D) data acquisition consisted of three multi-echo spoiled gradient echo scans (i.e., fast low angle shot [FLASH] sequences with magnetization transfer saturation (MT), T1, and effective proton density (PD) contrast weighting). Additional reference radio-frequency (RF) scans were acquired. The acquisition protocol had the following parameters: TR of PDw and T1w contrasts: 18 ms; TR of MTw contrast: 37 ms; minimum/maximum TE of PDw, T1w and MTw contrasts: 2.46/14.76 ms; flip angles for MTw, PDw and T1w contrasts: 6°, 4°, 25°,

respectively; six equidistant echoes; 1 mm isotropic reconstruction voxel size; Field of view $224 \times 256 \times 176$ mm; AP phase encoding direction; GRAPPA parallel imaging speedup factor of 2; T1w, PDw and MTw acquisition times: 3:50, 3:50, 7:52. The acquisition of low-resolution 3D spoiled gradient echo volumes was executed using both the RF head coil and the body coil. This dual acquisition facilitated the generation of a relative net RF receive field sensitivity (B_1^-) map for the head coil 120–122. The approach obtained rapid acquisition by maintaining a low isotropic spatial resolution of 4×3 mm³, a short echo time (TE) of approximately 2 ms, and a reduced flip angle of 6°, avoiding parallel imaging acceleration or partial Fourier. This procedure of capturing volume pairs with the head and body coils was systematically repeated before acquiring each of the MT, PD, and T1 contrasts.

Preprocessing

Data preprocessing was performed using the *fMRIprep* toolbox version 21.0.2 (Esteban et al., 2019). The toolbox pipeline utilizes a combination of several well-known software packages for fMRI data pre-processing and constitutes a robust tool that also generates quality reports.

Structural data

The synthetic T1w images were generated using the longitudinal relaxation rate (R1) and effective proton density (PD) high-resolution maps (acquired during the MPM sequence protocol). First, both maps were thresholded to achieve the required FreeSurfer units. The R1 map was divided by itself two times, thresholded at zero, and multiplied by one thousand. The PD map was thresholded by zero and multiplied by one hundred. All manipulations were performed using *FSL maths* commands. Subsequently, the *mri_synthesize FreeSurfer* command was applied to create a synthetic FLASH image based on the previously calculated T1 (thresholded R1 map) and proton density map. The optional flagged argument for optimal gray and white matter contrast weighting was used with the following parameters 20, 30, and 2.5. Finally, the synthetic T1w image was divided by four according to the scale *FreeSurfer* expected. The pre-processing of the structural data using the *fMRIprep* toolbox was performed in the following steps: firstly, the synthetic T1w images were corrected for intensity non-uniformity (INU) with *N4BiasFieldCorrection* (Tustison et al., 2010), distributed with *ANTs* 2.3.3 (Avants et al., 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the *antsBrainExtraction.sh* workflow (from *ANTs*), using *OASIS30ANTs* as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using *fast* (*FSL* 6.0.5.1:57b01774, RRID:SCR_002823, Zhang, Brady,

and Smith 2001). Brain surfaces were reconstructed using *recon-all* (FreeSurfer 6.0.1, RRID:SCR_001847 (Dale et al., 1999)), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of *Mindboggle* (RRID:SCR_002438 (Klein et al., 2017)). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with *antsRegistration* (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* ((Fonov et al., 2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym), *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* ((Evans et al., 2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6AsymO.)

Functional data

First, a reference volume and its skull-stripped version were generated by aligning and averaging 1 single-band reference (SBRef). Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using *mcflirt* (FSL 6.0.5.1:57b01774, (Jenkinson et al., 2002)). The estimated *fieldmap* was then aligned with rigid-registration to the target EPI (echo-planar imaging) reference run. The field coefficients were mapped on to the reference EPI using the transform. The BOLD reference was then co-registered to the T1w reference using *bbregister* (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with six degrees of freedom. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, (Power et al., 2014)) and Jenkinson (relative root mean square displacement between affines, (Jenkinson et al., 2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by (Power et al., 2014)). The three global signals were extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, (Behzadi et al., 2007)). Principal components were estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of (Behzadi et al., 2007) in

that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. Many internal operations of *fMRIPrep* use *Nilearn* 0.8.1 (Abraham et al., 2014), RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

For the streamlined application of additional noise components and data-cleaning strategies within a single framework, we utilized *rs-Denoise* (Dubois et al., 2018), see <https://github.com/adolphslab/rsDenoise>), an open-source Python-based pipeline. This pipeline involved several steps: (1) z-score normalization of the signal at each voxel; (2) removal of linear and quadratic trends with polynomial regressors; (3) utilization of *fMRIPrep*'s *aCompCor* parameters, to regress out five components derived from whole-brain mean signals; (4) utilization of translational and rotational realignment parameters and their temporal derivatives as explanatory variables in motion regression; (5) temporal filtering was performed with a discrete cosine transform (DCT) filter with a cutoff frequency of 0.008 Hz. Lastly, the pre-processed runs were smoothed using a 4-mm full-width at half maximum (FWHM) Gaussian kernel and merged on the temporal domain.

Data analysis

Amygdala-prefrontal cortex functional connectivity

First, binary masks of the two regions of interest were generated. For this purpose, a parcellation atlas that combined cortical (400 Parcels and 7 Networks) and subcortical

(Scale 1) parcellations was employed to delineate the amygdala and prefrontal cortex masks (Tian et al., 2020). Following this, since the data were already cleaned by regressing out the confounds of interest, the BOLD eigenvariate specific to the amygdala region was extracted as region average signal using the "fslmeans" command. Afterward, the extracted amygdala average signal was used as a regressor in a general linear model to correlate, per subject, the average amygdala activity with each prefrontal cortex voxel. Spatial maps for every subject were generated from the last step and merged into a 4D volume that was subsequently used as input to FSLrandomise (FSL version 6.0.3). Randomization, with ten thousand permutations, was used to associate the nightmare frequency scores to its participant functional connectivity map. The GLM included nightmare frequency as the main regressor of interest, as well as weekly dream frequency scores, sex and age as confound regressors.. After permutations, *FSL randomise* outputs a Threshold-Free Cluster Enhancement (TFCE) map corrected for multiple comparisons. TFCE aims to preserve the sensitivity advantages of cluster-based inference while avoiding arbitrary cluster-forming threshold. This approach yields an output image at the voxel level, where each voxel's value represents the accumulative cluster-like local spatial support at a range of cluster-forming thresholds (Salimi-Khorshidi et al., 2011; Smith & Nichols, 2009).

ReHo analysis

Single ReHo maps were generated by calculating Kendall's coefficient of concordance (KCC). This metric assesses the regional homogeneity of the blood oxygen level dependent time series within each voxel and its 26 adjacent voxels. The generation process used the *3dReHo* function in *AFNI* (versions 22.1.09 and 23.0.02 for Datasets 1 and 2, respectively) (Zang et al., 2004). Subsequently, the individual ReHo maps were normalized by dividing the KCC in each voxel by the mean KCC of the whole gray matter. Finally, the ReHo maps were smoothed using a 4-mm full-width at half maximum (FWHM) Gaussian kernel.

We adopted a dual approach to the statistical analysis. First, we examined differences between two groups: high nightmare frequency (at least one nightmare per week) and matched controls (less than one per year), as a direct replication of the previous literature, by pooling the two extreme groups from the combination of Dataset 1+2. Second, we examined parametric differences across the spectrum of nightmare frequency in a large dataset derived by combining Dataset 1+2 (see Table 1). For both the group-comparison replication analysis and continuous nightmare frequency scores, we used a more stringent threshold of $p < 0.001$ at the voxel level, contrary to the significance threshold from Marquis et al. and Shen et al. (Marquis et al., 2021;

Shen et al., 2016), set at $p < 0.01$ at the voxel level. It is important to note that choosing a critical statistical threshold (CDT) of 0.01 has been shown to yield excessive false positives (see (Eklund et al., 2016) for a detailed discussion). Cluster-level threshold values were estimated in *SPM*. Because parametric statistical methods for group analysis, such as *SPM*, can produce erroneously low FWE-corrected cluster p -values, thereby inflating statistical significance, we also used *FSL randomise* as a nonparametric method to evaluate our results (Eklund et al., 2016). Dream recall frequency, age, sex, and site were controlled for in the ReHo analyses. Statistical analyses were performed using *SPM12* (Statistical Parametric Mapping 12, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, United Kingdom) with *Matlab* (R2022a, The Mathworks, Natick, MA, United States).

Results

Demographics and questionnaires

Participants in Dataset 1 reported an average dream recall frequency of 2.18 times per week ($SD=2.05$) and experienced nightmares 1.34 times per month ($SD=3.31$), with a frequency ranging from once to several times per week. For Dataset 2, participants reported an average dream recall frequency of 2.10 times per week ($SD=2.16$) and nightmares at an average frequency of 1.02 times per month ($SD=2.83$). In partial agreement with a higher incidence of nightmares in females suggested in previous literature (Nielsen & Levin, 2007), for Dataset 1 the data indicated significant differences in nightmare frequency between females ($n=152$, $mean=1.61$, $SD=3.51$) and males ($n=108$, $mean=0.96$, $SD=2.97$), $W=5782$, $p < 0.001$ (two-tailed), but not in dataset 2 ($n=99$ females: $mean=1.28$, $SD=3.56$; vs. $n=65$ males: $mean=0.67$, $SD=0.99$), $W=2939$, $p=0.33$ (two-tailed). There was no evidence of age-related differences in dream recall frequency (Dataset 1: $\rho=-0.052$, $p=0.40$; Dataset 2: $\rho=-0.026$, $p=0.74$) or nightmare frequency (Dataset 1: $\rho=-0.059$, $p=0.347$; Dataset 2: $\rho=-0.037$, $p=0.638$). As expected, dream recall and nightmare frequency were significantly correlated in both Dataset 1 ($\rho=0.338$, $p < 0.001$) and Dataset 2 ($\rho=0.216$, $p < 0.005$) (Figure 1). When comparing the HNF group to the CTL group, a higher dream recall frequency was observed in the HNF group but there were no significant age or sex differences between the two groups ($p > 0.66$). To ensure that our results were not confounded by differences in dream recall frequency, sex, and age, factors previously associated with nightmare frequency (Gauchat et al., 2014; Sacher, 2013; Schredl, 2013; Schredl et al., 2014; Weber et al., 2022), we included them as covariates in our main analysis.

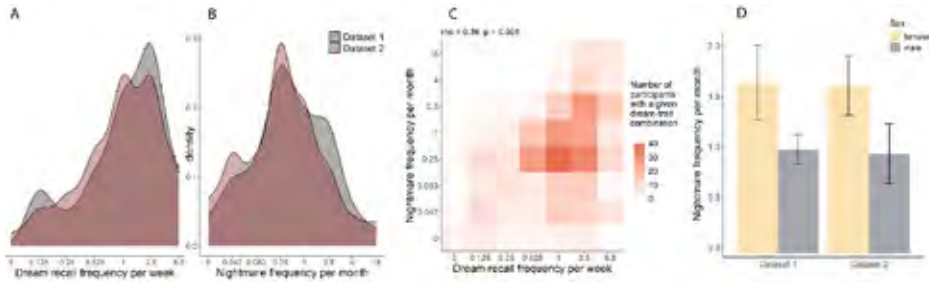


Figure 1: Overview of the behavioral data in the two Datasets. **A:** Density distributions of the dream recall frequency scores (recoded into units per week) for Dataset 1 and Dataset 2; **B:** Density distributions of the nightmare frequency scores (recoded into units per month) for Dataset 1 and Dataset 2; **C:** A heatmap for the combination of nightmare frequency and dream recall frequency scores across the two Datasets, and the correlation between the scores. Darker colors denote more frequent combinations; **D:** Average nightmare frequency scores for male and female participants, for both Dataset 1 and Dataset 2. The vertical bars denote standard errors.

Amygdala-prefrontal cortex functional connectivity relationship with nightmare frequency

In our investigation of functional connectivity between the amygdala and prefrontal cortex and its relationship to nightmare frequency, we first analyzed Dataset 1. This initial analysis revealed no significant voxels ($p_{FWEC} = 0.67$). To validate these findings, we replicated the analysis using an independent Dataset 2, which also showed no significant results ($p_{FWEC} = 0.65$). In other words, no functional connectivity between these regions were statistically significantly associated with nightmare frequency within the parameters of our study. Similar results were found when all analyses were repeated using raw nightmare frequency scores (Figure S1).

ReHo analysis

We performed a ReHo analysis to explore potential group differences between high and low nightmare frequency, as previously reported in the literature. The results showed no significant differences in ReHo scores between groups (Tables S1 and S2). However, when examining continuous nightmare frequency scores across the combined Dataset 1+2, we identified a significant cluster in the cerebellum (peak-voxel t -value=5.87, MNI $coor=24, -68, -60$, Figure 2a).

To robustly test these findings, we used a nonparametric permutation test in addition to a threshold-free cluster enhancement approach. This rigorous analysis revealed no significant clusters in the group comparison (Figure S2). However, in the analysis of the continuous nightmare frequency score, we identified a single significant cluster in the cerebellum (cluster size=150 voxels; $p_{FWEC} < 0.01$; MNI $coor=23.9, -67.5, -59.7$) This finding

is shown in Figure 2b. In addition, we repeated all analyses using raw nightmare frequency scores (i.e. the eight-point rating scale instead of the recoded monthly scale), which did not yield significant results (for group comparison, see Tables S3 and S4, Figure S3; for continuous nightmare frequency scores see: Tables S5, Figure S4).

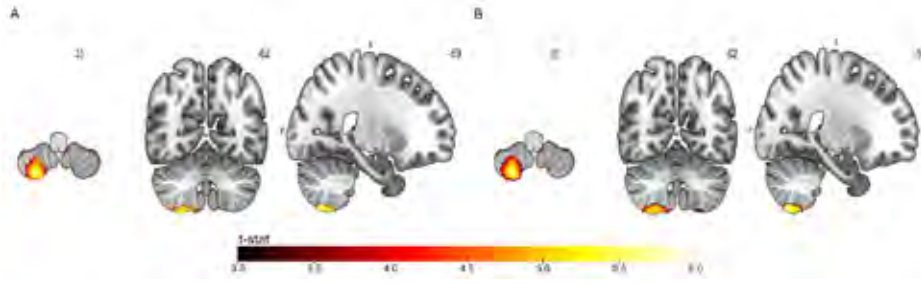


Figure 2: Regional homogeneity analysis results. **A:** Dataset 1+2 combined (N=424) SPM parametric analysis resulted in a significant cluster located in the cerebellum (peak-voxel t -value=5.87, MNI $coor$ =24,-68,-60); **B:** Dataset 1+2 combined (N=424) non-parametric FSL Randomise resulted in a similar significant cluster located in the cerebellum (peak-voxel t -value=5.96, MNI $coor$ =23.9,-67.5,-59.7).

Discussion

The present study had two main aims. First, to investigate the relationship between nightmare frequency and functional connectivity between two key regions, amygdala and prefrontal cortex, involved in emotional regulation and fear extinction processes, and second, to replicate the existing literature on the neural correlates of nightmares in two large study cohorts. Contrary to our initial hypothesis, our analysis did not reveal a significant relationship between nightmare frequency and functional resting connectivity between the prefrontal cortex and the amygdala. In addition, while we were able to partially replicate previous whole-brain ReHo findings on nightmare frequency, these findings did not withstand rigorous tests with appropriate statistical approaches. Despite our increased statistical power compared to previous studies, we could reliably identify only a single cluster located in the cerebellum and only when analyzing nightmare frequency scores continuously (as opposed to grouped scores as in previous studies).

Building on the sensory processing sensitivity framework for nightmares (Carr & Nielsen, 2017), we hypothesized that connectivity between the amygdala and prefrontal cortex might serve as a potential predictor of nightmare frequency. This hypothesis stemmed from previous studies linking such coupling to psychiatric conditions and disorders such as anxiety levels (Kim et al., 2011), anxiety disorders (Prater et al.,

2013), major depressive disorder (Tang et al., 2013), post-traumatic stress disorder (Sripada et al., 2012), dream emotionality (Blake et al., 2019), and threat perception (Ochsner & Gross, 2005). Our rationale was based on the expectation that heightened emotional reactivity will manifest in resting-state amygdala-prefrontal connectivity, especially given the known association between prefrontal cortex activation and nightmare severity/distress during negative emotional stimulation (Carr, 2020; Marquis et al., 2019; Sterpenich et al., 2020). Contrary to our predictions, our analysis of Dataset 1 and its independent replication in Dataset 2 did not yield statistically significant results. Although we did not expect nightmare formation to depend solely on amygdala-prefrontal cortex connectivity, we considered this to be the most prominent candidate for a trait correlate of nightmare frequency, considering the crucial role these regions play in relevant processes and existing models of nightmare formation. However, the lack of a significant relationship in our study despite a large sample size in two datasets may suggest that any potential association might be subtle if existent, potentially overshadowed by individual differences confounders such as personality traits including sensory processing sensitivity, or trauma history.

The absence of a detectable association between amygdala-prefrontal cortex connectivity and nightmare frequency in our sample may be consistent with recent theoretical accounts that frame nightmares within a broader cycle of emotional dysregulation and sleep disruption. Van Trigt et al. (2025) propose a reciprocal feedback model in which impaired REM sleep, such as through nightmares or fragmentation, prevents the recalibration of limbic circuits during sleep, resulting in elevated next-day emotional reactivity. This, in turn, promotes further sleep disruption, reinforcing the cycle. Although this model was developed in the context of BPD, a prototypical emotion dysregulation disorder, the underlying mechanism may extend dimensionally across the general population. Our study, which included only healthy young adults, may not have captured the threshold of dysfunction necessary for this cycle to become neurologically apparent. That is, functional alterations in the amygdala-prefrontal connectivity may only emerge when individuals cross a critical threshold of emotional dysregulation, chronic hyperarousal, or comorbid psychopathology, such as in BPD. In this context, our null findings may indicate a floor effect, where mild variations in trait emotionality or sleep disturbances are not enough to disrupt intrinsic connectivity at rest. In this light, our null findings may reflect a floor effect, whereby mild variations in trait emotionality or sleep disturbance are insufficient to disrupt intrinsic connectivity at rest. Alternatively, the amygdala-prefrontal interactions may fluctuate dynamically in response to emotional states or sleep history rather than manifesting as a stable trait detectable through resting-state measures in asymptomatic individuals.

In investigating ReHo in the neural correlates of nightmares, we attempted to replicate previous group comparison methodology while addressing concerns related to the reproducibility of fMRI studies. Shen et al. (Shen et al., 2016) found elevated ReHo in the left anterior cingulate cortex and right inferior parietal lobule in patients with nightmare disorder, while Marquis et al. (Marquis et al., 2021) found altered ReHo in several brain regions. In contrast to Shen et al., Marquis et al. did not find group differences in ReHo in the anterior cingulate cortex or inferior parietal lobule, and the studies had different sample populations. Shen et al. focused on patients with nightmare disorder and a strict group of healthy controls with minimal lifetime nightmares. In contrast, Marquis et al. included a mix of high nightmare frequency individuals and bad dream recallers with no awakenings after disturbing dreams. Population differences may have contributed to the contrasting results. Our study aimed to replicate the group comparison by focusing on high nightmare frequency individuals and realistic healthy controls. We calculated the group comparison analysis in two ways to control false positive rates: 1) using a similar approach and CDT ($p < 0.001$) but using *SPM* to estimate the cluster extension value, and 2) given the inflated statistical inference of parametric methods, we used a nonparametric permutation approach as implemented in *FSL Randomise*. No significant clusters survived these additional approaches. The fMRI community has faced a reproducibility problem in part because low CDT can produce misleadingly low cluster P-values, raising concerns about the accuracy of many published fMRI studies (Eklund et al., 2016). Nevertheless, previous work has used a $CDT = 0.01$, which is known to result in higher false-positive rates. We performed analyses analogous to those used for group comparisons to examine the neural correlates of nightmares across participants' continuous severity levels. Using a parametric (alpha-level voxel thresholding followed by Gaussian random field theory) and non-parametric (TFCE followed by permutation testing) cluster inference approaches, only the cerebellum cluster survived corrections. Previous studies have reported decreased ReHo values in the cerebellum in individuals with nightmare experiences, which is consistent with our findings (Marquis et al., 2021).

The cerebellum, traditionally associated with motor functions and considered less functionally significant than the cerebral cortex, in recent years has attracted increased attention also with respect to cognitive and emotional processing (Adamaszek et al., 2022; Baillieux et al., 2008; Sacchetti et al., 2009). For example, the cerebellum has been implicated in the formation, consolidation, and extinction of fear memories and other emotion modulations (Rudolph et al., 2023). Although poorly characterized in sleep and largely unexplored in nightmares, the cerebellum is linked to anxiety disorders (Moreno-Rius, 2018), major depression disorder

(Fitzgerald et al., 2008), and bipolar disorder (Hoppenbrouwers et al., 2008), which are all associated with nightmare distress and frequency. Anatomically, cerebellar connections to the limbic system suggest its potential role in the brain's emotional network (Çavdar et al., 2018; Hilber et al., 2019; Novello et al., 2024), and a recent study has demonstrated direct monosynaptic projections from the cerebellum to the amygdala (Zhang et al., 2024). Further cerebellar projections target the thalamus and the brainstem, which are implicated in REM sleep regulation (Sathyanesan et al., 2019), and also parts of the cerebellum have been shown to be activated during REM sleep (Braun, 1997; Canto et al., 2017; Sokoloff et al., 2015). Of note, anxiolytic benefits of physical activity have been correlated with increased activity of the cerebellar projections to the amygdala (Zhang et al., 2024), which is highly activated during REM sleep (Corsi-Cabrera et al., 2016; Maquet, 1997; Nofzinger et al., 1997). Considering that REM sleep dream narratives are characterized by a high level of experienced motor activity (Porte & Hobson, 1996), it is tempting to speculate that cerebellum-amygdala projections play a role in emotionally arousing dream content such as nightmares. To test this possibility, we added an analysis to probe the association between nightmare frequency and cerebellar-amygdala functional connectivity, using the results of the ReHo analysis to define a relevant cerebellar region of interest (See Supplementary Material for details on methods). No significant functional relationship between the amygdala and our specific cerebellar region was found, yet the above-mentioned results indicate that the cerebellum remains an important structure for future exploration, considering also the recent discovery of an amygdala-independent pathway for fear processing (Wang et al., 2024). Accordingly, the precise involvement of the cerebellum and interactions with other brain regions in the domains of emotion regulation processes and dream emotionality warrants further investigation.

Several limitations of our study have to be considered. First, the questionnaire assessing dreaming and nightmare frequency may have influenced the present results as they did not allow to check for levels of nightmare distress. Moreover, as our cohorts consisted of healthy young participants, generalizations to patients or the entire population are difficult. In addition, we carefully considered the methodological parameters for the ReHo analysis, guided by previous research (Maximo et al., 2013) and the literature we sought to replicate. Spatial smoothing was performed after ReHo computations to prevent inflation of correlation statistics by averaging signals over a larger area. Because ReHo measures local connectivity, the choice of neighborhood size for ReHo analysis is another important consideration, allowing researchers to specify the extent of the neighborhood to be tested for correlation with each voxel. This study chose a neighborhood size of 27 voxels to

replicate findings from previous literature (Marquis et al., 2021; Shen et al., 2016). In particular, choosing a neighborhood size of 27 voxels means that the analysis considers every voxel with an adjacent face, edge, or corner. This may explain why the significant cluster accounted for the edge of the cerebellum despite its proximity to the brain boundary. In spite of these shortcomings, it is clear that the large sample size and robust threshold correction methods are strong points to support the outcomes of our study.

The combination of dream research and neuroimaging comes with several challenges, as it is impossible to time-lock the exact time a dream experience occurred, and nightmares are rare in sleep laboratories and may imply major imaging motion artifacts. Future research should address these design limitations by combining dream diaries and retrospective questionnaires with all-night imaging recordings. A dream diary is an established method for evaluating dream content, however, it may overestimate dreaming and nightmare frequency as a continued dream diary enhances dream recollection (Stumbrys et al., 2013). In contrast, retrospective questionnaires have been shown to underestimate dreaming and nightmare frequency (Wood & Bootzin, 1990). Accordingly, a combination of the two approaches might give a more robust assessment of the occurrence of nightmares in the study population.

Conclusion

In summary, contrary to our initial expectations, we did not find a significant relationship between nightmare frequency and functional connectivity between the prefrontal cortex and the amygdala, key regions involved in emotional regulation and fear extinction processes. In contrast, probing the relationship between nightmare frequency and regional homogeneity in a whole-brain analysis, we did find a role of the cerebellum in nightmare frequency, supporting an increasingly discussed role of the cerebellum in emotional processing. Functional connectivity of this cerebellar region with the amygdala, however, was not associated with nightmare frequency.

While our study replicated the group comparison methodology used by Shen et al. and Marquis et al., the complexities surrounding the reproducibility of fMRI studies should be considered. Our efforts to control false-positive rates through various recalculations, including stringent cluster-defining thresholds and nonparametric permutation approaches, did not yield significant clusters except in the cerebellum, highlighting the intricacies involved in interpreting neuroimaging data in general

and our specific findings. The unexpected lack of robust significant results, especially given the larger sample size in the current study, prompts a reevaluation of existing models and emphasizes the need to account for individual differences, such as personality traits, trauma history, and cognitive processes. As we navigate the complexity of neural circuits and brain regions involved in nightmares, these findings contribute to the ongoing dialogue in the field, fostering a deeper understanding of the neurobiology behind nightmares and guiding future research efforts.

Data and Code Availability

Data cannot be shared publicly because it is part of an ongoing study and is thus considered unanonymized under Danish law even if pseudonymized. Researchers who wish to access the data may contact Dr. Kristian Sandberg (kristian.sandberg@cfin.au.dk) at The Center of Functionally Integrative Neuroscience and/or The Technology Transfer Office (TTO@au.dk) at Aarhus University, Denmark, and Dr. Michał Wierzbuch (michal.wierzbuch@uj.edu.pl) at the Institute of Psychology at Jagiellonian University, Poland, to make a data sharing contract. After permission has been given by the relevant data committee, data will be made available to the researchers. No custom code was used in this study. Publicly available software tools were used to perform analyses and are referenced throughout the manuscript.

Author Contributions

M.P.: Conceptualization, Investigation, Formal Analysis, Writing – Original Draft, Review & Editing, and Visualization; N.T.: Investigation, Writing – Review & Editing; R.R.: Writing - Review & Editing, and Visualization; K.S.: Writing – Review & Editing, Funding Acquisition; M.D.: Writing – Review & Editing, Supervision, Funding Acquisition; F.K.: Conceptualization, Writing – Review & Editing, Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary material

Functional connectivity relationship between amygdala-prefrontal cortex and nightmare frequency

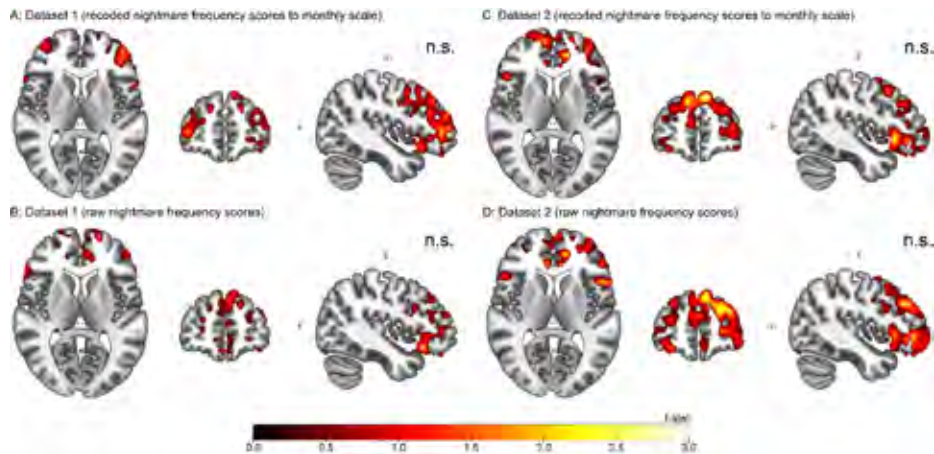


Figure S1: Amygdala-prefrontal cortex functional connectivity. Dataset 1 (N=260) resulted in non-significant clusters a) by using the recoded nightmare frequency scores to a monthly scale, according to Stumbrys et al., 2013 ($p_{FWEC} = 0.67$), and b) by using the raw nightmare frequency scores ($p_{FWEC} = 0.59$). Dataset 2 (N=164) also resulted in non-significant clusters c) by using the recoded nightmare frequency scores to a monthly scale ($p_{FWEC} = 0.48$), and d) by using the raw nightmare frequency scores ($p_{FWEC} = 0.36$). All t-maps are in MNI coord=-44,53,7). Please note that these results are not significant.

Regional homogeneity (ReHo) analysis

A: Group comparison replication analyses with recoded nightmare frequency scores on a monthly scale

Parametric results (SPM):

Table S1: High nightmare frequency > healthy controls: p-values adjusted for search volume.

cluster-level				peak-level		
p_{FWEc}	q_{FDRc}	K_{E}	T	x (mm)	y (mm)	z (mm)
0.999	0.859	8	4.39	66	-22	44
0.999	0.859	6	3.85	-38	-40	-50
0.995	0.859	13	3.68	-48	-44	42
0.999	0.859	7	3.67	38	-58	-62
1.000	0.859	5	3.62	-52	44	-14
1.000	0.859	4	3.58	50	-58	-52
1.000	0.859	4	3.55	10	-38	34
1.000	0.859	2	3.47	-26	-16	-36
1.000	0.859	4	3.44	54	-68	-18
1.000	0.859	1	3.34	10	-52	54
1.000	0.859	1	3.33	48	-50	-52
1.000	0.859	1	3.32	-42	-50	-58
1.000	0.859	1	3.32	34	-74	-58

Table S2: High nightmare frequency < healthy controls: p-values adjusted for search volume.

cluster-level				peak-level		
p_{FWEc}	q_{FDRc}	K_{E}	T	x (mm)	y (mm)	z (mm)
0.467	0.339	86	6.17	-58	-22	10
0.284	0.339	115	4.40	-60	-30	-18
0.830	0.586	45	4.30	4	-88	18
0.981	0.709	20	4.21	-14	-40	78
0.886	0.586	38	3.75	14	44	10
0.999	0.834	7	3.71	-4	44	16
1.000	0.859	2	3.70	-44	8	58

Table S2: Continued

cluster-level				peak-level		
p_{FWEC}	q_{FDRc}	K_E	T	x (mm)	y (mm)	z (mm)
0.971	0.709	23	3.63	-50	-44	-22
0.999	0.834	7	3.57	10	24	34
0.999	0.834	6	3.50	-18	-8	-18
1.000	0.834	5	3.49	-4	-60	0
1.000	0.859	1	3.34	-54	-16	54
1.000	0.859	1	3.32	4	56	12

Non-parametric results (*FSL randomise*):

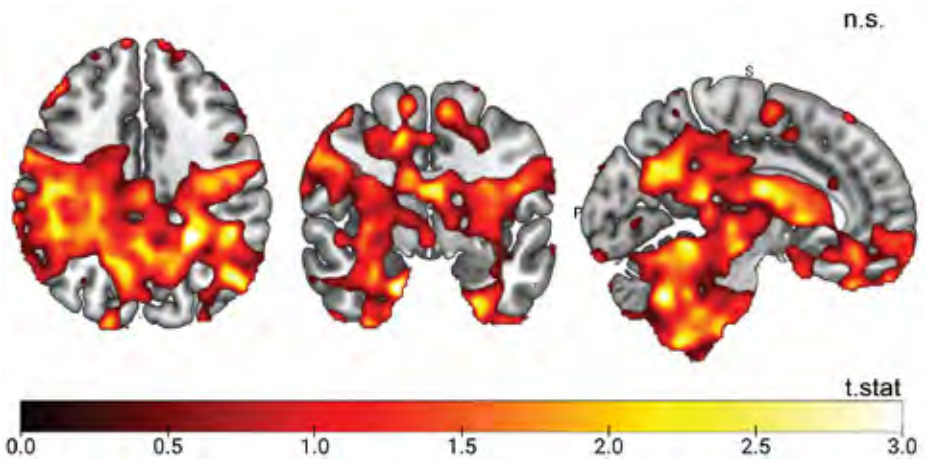


Figure S2: Group comparison replication analysis, high vs. low nightmare frequency score using the recorded nightmare frequency scores to a monthly scale ($p_{FWEC} = 0.294$) (Stumbrys et al., 2013). The t-map is in MNI coord=-6,-3.8,37). Please note that this result is not significant.

B: Group comparison replication analyses with raw nightmare frequency scores:**Parametric results (SPM):****Table S3:** High nightmare frequency > healthy controls: p-values adjusted for search volume.

cluster-level				peak-level		
p_{FWEc}	q_{FDRc}	K_{E}	T	x (mm)	y (mm)	z (mm)
1.000	0.860	4	3.87	66	-22	44
0.990	0.860	16	3.81	38	-58	-62
0.998	0.860	9	3.53	2	44	-18
1.000	0.860	3	3.46	52	-68	-18
1.000	0.860	2	3.43	46	14	-42
1.000	0.860	5	3.41	22	-40	-52
1.000	0.860	2	3.36	-40	-42	-50
1.000	0.860	1	3.32	48	46	-18

Table S4: High nightmare frequency < healthy controls: p-values adjusted for search volume.

cluster-level				peak-level		
p_{FWEc}	q_{FDRc}	K_{E}	T	x (mm)	y (mm)	z (mm)
0.346	0.195	104	7.13	-58	-22	10
0.166	0.167	146	4.31	-60	-30	-16
0.939	0.843	30	4.11	12	24	34
0.990	0.843	16	3.90	-18	-36	76
0.983	0.843	19	3.90	4	-90	18
1.000	0.860	3	3.49	-56	-18	52
1.000	0.860	5	3.49	-44	-52	-46
1.000	0.860	5	3.47	-50	-40	24
1.000	0.860	3	3.43	-30	-60	58
1.000	0.860	2	3.40	-46	-16	48
1.000	0.860	1	3.32	-48	-18	50

Non-parametric results (*FSL randomise*):

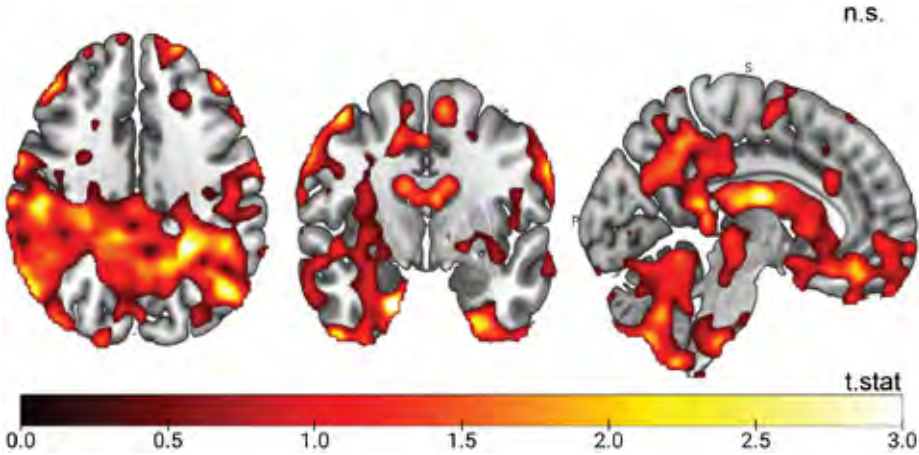


Figure S3: Group comparison replication analysis, high vs. low nightmare frequency score using the raw nightmare frequency scores ($p_{\text{FWEc}} = 0.844$). The t-map is in MNI coord=-6,-3.8,37). Please note that this result is not significant.

C: Parametric results of combined Datasets 1+2 (N=464) using raw nightmare frequency scores:

Parametric results (*SPM*):

Table S5: Statistics: p-values adjusted for search volume.

cluster-level			peak-level			
p_{FWEc}	q_{FDRc}	K_E	T	x (mm)	y (mm)	z (mm)
0.977	0.875	20	4.02	-50	46	12
0.948	0.875	28	3.53	-40	-14	24
0.997	0.875	9	3.31	-46	-6	6
1.000	0.875	2	3.27	62	-32	50
0.999	0.875	5	3.27	38	-22	-36
1.000	0.875	1	3.25	46	-52	58
0.999	0.875	4	3.25	-56	38	2
1.000	0.875	1	3.13	44	16	-34
0.999	0.875	5	3.13	-58	24	16
1.000	0.875	2	3.13	34	-62	-62
1.000	0.875	1	3.11	-40	40	2

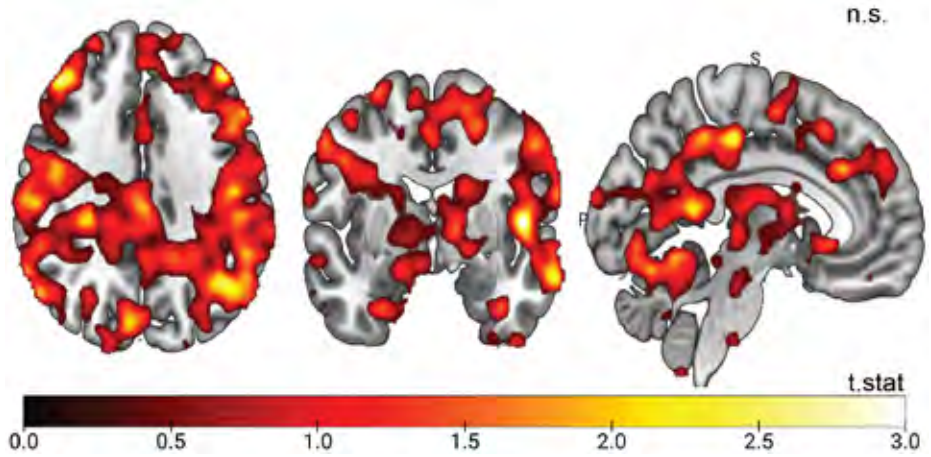
Non-parametric results (*FSL randomise*):

Figure S4: ReHo analysis combining Datasets 1+2 using the raw nightmare frequency scores ($p_{\text{FWEC}} = 0.676$). The t-map is in MNI coord= $-6, -3.8, 37$). Please note that this result is not significant.

Functional connectivity relationship between amygdala-cerebellum and nightmare frequency

A 5mm sphere was created around the significant cluster's peak voxel we identified in the non-parametric ReHo analysis. The BOLD eigenvariate specific to the amygdala region was extracted as region average signal used as a regressor in a general linear model to correlate, per subject, the average amygdala activity with each cerebellar voxel within the sphere. Spatial maps for every subject were generated from the last step and merged into a 4D volume that was subsequently used as input to *FSL randomise*. Randomization, with ten thousand permutations, was used to associate the nightmare frequency scores to its participant functional connectivity map. The GLM included nightmare frequency as the main regressor of interest, as well as weekly dream frequency scores, sex and age as confound regressors. We examined the cerebellar-amygdala functional connectivity independently in Dataset 1, which showed no significant voxels ($p_{\text{FWEC}} = 0.49$), as well as in the separate Dataset 2 ($p_{\text{FWEC}} = 0.65$), with a comparable outcome.



Chapter 4

The Neural Architecture of Dream Recall Frequency: Insights from Interindividual Variations in Brain Structure and Function

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Abstract

Dreaming represents a complex and universal aspect of human sleep, yet it remains an intriguing phenomenon, with the neural mechanisms underlying dream experiences and their frequency not fully understood. This study employs a multimodal neuroimaging approach, integrating quantitative multi-parameter mapping, diffusion tensor imaging, and resting-state functional MRI, to investigate the neural correlates of dream recall frequency (DRF) in a large cohort of 258 healthy individuals. By employing Linked Independent Component Analysis (LICA), we were able to discern distinctive patterns of brain structure and function that correlated with variations in DRF. Our findings elucidate a complex relationship between dream recall and brain microstructure integrity, particularly in white matter regions of the orbitofrontal cortex, parahippocampal gyrus, superior parietal lobule, and occipital cortex. Higher DRF was related to increased white matter microstructure integrity in these regions and decreased gray matter volume in occipital and temporal areas. In terms of functional measures, higher DRF was associated with reduced connectivity across a range of resting-state networks, including the default mode, visual, and dorsal attention networks. This was particularly evident in the right precuneus and posterior cingulate cortex. These results suggest that enhanced dream recall may be related to the organization of higher-order visual and cognitive processing areas, supporting a top-down model of dreaming. This study contributes to a more comprehensive understanding of the neural substrates underlying individual differences in dream recall, offering a foundation for future investigations into the neurobiology and causal relationships of dreaming.

Keywords: dream recall frequency, dream traits, dreaming, neuroimaging

Introduction

Humans spend approximately one-third of their lives asleep, with a considerable proportion of this time dedicated to dreaming (Simor et al., 2022). Although it is a common experience for many, dreaming encompasses a number of complex processes that remain largely unknown to scientists. Firstly, regardless of specific brain physiology and connectivity during different stages of sleep, content-specific regions in posterior cortical areas are activated, thereby resulting in a dream experience (Siclari et al., 2017; Cataldi et al., 2024). Nevertheless, the occurrence of a dream does not necessarily guarantee its recall upon awakening. For a dream to be remembered, it must undergo successful encoding, whereby the experience is transformed into a lasting memory trace, and then retrieved upon waking (Nemeth, 2023). Numerous hypotheses regarding the potential functions of dreams exist (Revonsuo, 2000). Yet, testing them empirically is challenging, particularly due to the lack of a physiological marker for dreaming and the reliance on subjective dream reports as the primary method for accessing oneiric experiences. Beyond exploring the neural correlates of dreaming while they are happening, investigating dream traits such as dream recall frequency (DRF) offers insight into the intricate processes that contribute to the phenomenon of dreams (Schredl & Montasser, 1996). Although retrospective dream recall has limitations, including the potential biases of self-report scales and the fragility of memory that can lead to false recollections (Beaulieu-Prévost & Zadra, 2015), it remains the most efficient and cost-effective method for studying trait dream recall. Furthermore, in contrast to the practice of clustering participants into predefined low- and high-dream recall groups, an analysis of the full distribution of recall frequency can elucidate the anatomical and functional variations in the brain that underlie normal inter-individual differences in DRF rather than just the extremes of the spectrum. Here, we employ a data-driven approach integrating multiple neuroimaging modalities in light of existing knowledge on dream generation and recall mechanisms.

Lesion studies and electrophysiological research have identified specific brain regions and neural oscillations associated with dream experiences, yet the precise roles these brain areas play in the generation, encoding, and retrieval of dreams remain unclear. The global cessation of dreaming has been associated with lesions in or near the temporal-occipital-parietal junction, posterior cortical regions, and ventromedial prefrontal areas, either unilaterally or bilaterally (Solms, 2000). Conversely, lesions in the prefrontal and anterior cingulate cortices have been linked to an increase in the frequency of dreams, as well as an increase in dream vividness and dream reality confusion (Solms, 2000; Vallat et al., 2018). From an electrophysiological

perspective, dream experiences during both non-rapid eye movement (NREM) and REM sleep exhibit common features. Local high-frequency (20–50 Hz) activity over the “posterior hot zone” correlates with dream content, while increased high-frequency activity over medial and lateral frontal areas is associated with memory formation and storage (Siclari et al., 2017). Among the various theories regarding the production and functions of dreams, certain aspects of this complex process may influence the extent to which a dream experience is successfully recalled. The occurrence and intensity of the dream, local brain activations, and post-awakening interferences may all be factors in determining whether a dream is recalled or not (for a detailed review of these factors, see (Nemeth, 2023)).

Considerable inter-individual variation in DRF is influenced by a range of behavior and cognitive factors that seem to be intricately linked to structural and functional brain differences. In the general healthy population, this variability has been associated with a number of individual factors, including age, gender, personality traits, sleep habits, visual imagery, and creativity (Schredl & Montasser, 1996). Furthermore, studies examining the relationship between DRF and neuroimaging have revealed a complex interplay of structural and functional brain differences contributing to individual variations. For instance, neuroanatomical measures of deep gray matter structures such as the amygdala and hippocampus are not associated with DRF *per se*. However, they relate to qualitative aspects of dreams, including length, emotional load, bizarreness, and vividness (De Gennaro et al., 2011). Individuals with high DRF demonstrate higher regional cerebral blood flow (rCBF) in the temporoparietal junction during REM sleep, NREM stage 3, and wakefulness, as well as in the medial prefrontal cortex during REM sleep and wakefulness. No significant differences were reported in the medial prefrontal cortex during NREM stages 2 and 3, and no behavioral or cognitive differences were identified between groups (Eichenlaub et al., 2014). A negative correlation was observed between DRF and cortical volume in the medial fusiform and parahippocampal gyrus in the right hemisphere but not in the left. White matter integrity in fibers connected to these regions, particularly in the fusiform gyrus and inferior longitudinal fasciculus, negatively correlates with DRF (Zhou et al., 2019). Another MRI study found no significant differences in grey matter density between high and low recallers. However, an increase in white matter density in the medial prefrontal cortex of high recallers was observed, suggesting a potential role in dream production (Vallat et al., 2018). In terms of functional measures, DRF is negatively correlated with connectivity in a number of networks, including the visual, thalamic, basal ganglia, and auditory networks. Of particular note are the lateral visual network during the night and the posterior cingulate cortex in the morning (Zou et al., 2018). These findings highlight the complex and multifaceted relationship

between DRF and a range of neuroimaging measures. They also suggest that both structural and functional brain differences contribute to individual differences in dream recall. However, the shared relationship across different neuroimaging modalities remains to be explored.

Linked independent component analysis (LICA) is a refined multimodal data fusion technique that simultaneously analyses multiple neuroimaging modalities, such as structural Magnetic Resonance Imaging (MRI), functional MRI, and diffusion tensor imaging (DTI), with the objective of identifying independent patterns of shared variance across these modalities (Groves et al., 2011; Llera et al., 2019). This method integrates input data at an early stage of the analysis pipeline rather than combining unimodal results post hoc, resulting in a more holistic understanding of brain-behavior relationships. LICA has been effectively utilized to elucidate the underlying neurobiology of several neurodevelopmental disorders, including autism spectrum disorder (Mei et al., 2023; Van Oort et al., 2023), obsessive-compulsive disorder (Xu et al., 2024), and attention deficit hyperactivity disorder (Itahashi et al., 2015), as well as demographic and behavioral characteristics (Llera et al., 2019; Kohn et al., 2021). The main advantage of LICA is its ability to enhance robustness to noise and its sensitivity to detect subtle effects in high-dimensional data that may be overlooked by univariate approaches. This is achieved by leveraging the complementary aspects of each imaging modality and efficiently modelling the shared variance. Moreover, LICA enables the investigation of inter-individual differences in brain measures and their relationships to behavioral and clinical phenotypes, which can offer insights into conventional diagnostic procedures. Additionally, it is emerging as a powerful tool for advancing our understanding of the complex interactions between brain structure, function, and behavior in both specific and transdiagnostic contexts.

This study leverages the power of this novel method to investigate the relationship between brain structural and functional characteristics with individual variations in DRF in a large dataset. We employed quantitative multi-parameter mapping and DTI to examine gray and white matter volume and morphology, respectively, and resting-state functional MRI to assess brain connectivity patterns associated with DRF. This comprehensive approach enabled the identification of potential anatomical and functional correlates of DRF, thereby providing a more nuanced understanding of the neural mechanisms underlying dream generation. By applying LICA to a large cohort of over 250 healthy individuals, we aimed to investigate the integrated structural and functional brain patterns that differentiate the full frequency spectrum of dream recall. This approach contributes to a broader understanding of how individual neurobiological variations influence DRF and the generation of dream experiences.

Methods

The data utilized in this study is part of a large, multi-site study under the EU COST Action CA18106 (The Neural Architecture of Consciousness). The dataset encompasses MRI and behavioral data collected from healthy participants. The local ethics committee, *De Videnskabetiske Komitéer for Region Midtjylland*, Denmark, approved the research protocol. The participants were recruited through the Center of Functionally Integrative Neuroscience (Aarhus University) participant database and local advertisement. Some data from the overall project has been published in other articles with different aims, and parts of the methods descriptions have been adapted from these articles as well as manuscripts in preparation. Specifically, dream recall data has previously been used in an article focusing purely on behavioral analyses (Tzioridou et al., 2022), and as a control variable in a manuscript investigating nightmare frequency in the context of emotional regulation (Pereira et al., 2024).

Participants

A total of 306 participants consented to participate in the study and were compensated financially for their time and contributions. Of the total number of participants, 269 had MRI data available, of which eleven participants were excluded: five due to incomplete questionnaires, three due to incomplete functional MRI data, and three due to poor structural MRI quality and excessive movement artifacts. Hence, the final sample consisted of 258 participants (152 female, with a mean age of 24.89 ranging from 18 to 48 years).

Behavioral materials and procedure

All participants completed an online questionnaire session from home with a total duration of around 70 minutes, including a seven-point rating scale assessing their DRF (Schredl & Erlacher, 2004), and general health. Typically within a few weeks of the scans, in an optional session, they completed the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Lichtenberger & Kaufman, 2012). The participants were instructed to ensure the questionnaires were completed in an undisturbed environment. The DRF scale was recoded into units of mornings per week (Stumbrys et al., 2015). Although the evidence for a direct association between DRF and IQ is inconclusive, there is a body of literature indicating a link between IQ and REM sleep density (Busby & Pivik, 1983). Therefore, we sought to adjust for this potential confounding variable in our analysis. Because thirty-one participants did not complete the WAIS-IV questionnaire, missing data were handled using mean imputation, an approach that is appropriate for datasets where missing values are considered to be missing completely at random (Rubin, 2004). While

mean imputation is a simple method, it can reduce variability in the data and avoid decreasing the sample size.

MRI data acquisition

The imaging procedures were performed using a Siemens Magnetom Prisma-fit 3T MRI scanner. Two resting-state fMRI runs (12 and 6 minutes) were recorded alongside quantitative multi-parameter mapping (MPM; (Weiskopf et al., 2013)) and diffusion-weighted imaging in an approximately one-hour scanning session. For each participant, 1500 functional volumes were acquired using an echo planar T_2^* -weighted sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast with a multiband acceleration factor of 6 (TR = 700 ms; TE = 33 ms; flip-angle = 53° , field of view = 200×200 mm, number of slices = 60; slice thickness = 2.5 mm [no gap]; in-plane resolution = 2.5×2.5 mm).

The MPM protocol was implemented based on the Siemens vendor sequence. Three-dimensional (3D) data acquisition consisted of three multi-echo spoiled gradient echo scans (i.e., fast low angle shot [FLASH] sequences with magnetization transfer saturation (MT), T_1 , and effective proton density (PD) contrast weighting). Additional reference radio-frequency (RF) scans were acquired. The acquisition protocol had the following parameters: TR = 18 ms (PDw/ T_1 w) and 37 ms (MTw); TE = 2.46/4.92/7.38/9.84/12.30/14.76 ms (PDw/ T_1 w/MTw); flip-angle = 6° (MTw), 4° (PDw), and 25° (T_1 w); voxel size = 1 mm³; field of view = $224 \times 256 \times 176$ mm; phase encoding direction = AP; GRAPPA = 2; acquisition times = 3:50 (T_1 w/PDw) and 7:52 (MTw).

Diffusion-weighted imaging (dMRI) data were acquired using a High-angular resolution diffusion imaging (HARDI) protocol conducted within the same session, lasting approximately 10 minutes. The HARDI sequence encompassed multiple diffusion directions: 75 at $b = 2500$ s/mm², 60 at $b = 1500$ s/mm², 21 at $b = 1200$ s/mm², 30 at $b = 1000$ s/mm², 15 at $b = 700$ s/mm², and 10 at $b = 5$ s/mm². These varying b-shells were acquired in a single series with the following parameters: flip angle = 90° ; TR = 2850ms; TE = 7 ms; voxel size = 2 mm³; matrix size of 100×100 , and 84 slices; phase-encoding direction = AP with an additional acquisition in the opposite phase-encoding direction (PA) at $b = 0, 700, 1000, 1200, 1500, 2500$ s/mm² for EPI distortion correction.

Structural MRI data pre-processing and gray-matter volume estimation

Synthetic T_1 w images were generated using the longitudinal relaxation rate (R_1) and effective proton density (PD) high-resolution maps (acquired during the MPM sequence protocol). First, both maps were thresholded to achieve the required

FreeSurfer units. The R1 map was transformed into a T1 map by inverting its values, then thresholded at zero, and multiplied by one thousand to convert to milliseconds. The PD map was thresholded by zero and multiplied by one hundred. All manipulations were performed using *FSL maths* commands. Subsequently, the *mri_synthesize FreeSurfer* command was applied to create a synthetic FLASH image based on the previously calculated T1 (thresholded 1/R1 map) and proton density map. The optional flagged argument for optimal gray and white matter contrast weighting was used with the following parameters: 20, 30, and 2.5. Finally, the synthetic T1w image was divided by four according to the scale *FreeSurfer* expected. The pre-processing of the structural data using the *fMRIPrep* toolbox was performed in the following steps: firstly, the synthetic T1w images were corrected for intensity non-uniformity (INU) with *N4BiasFieldCorrection* (Tustison et al., 2010), distributed with *ANTs* 2.3.3 ((Avants et al., 2008), RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the *antsBrainExtraction.sh* workflow (from *ANTs*), using OASIS3oANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using *fast* (*FSL* 6.0.5.1:57b01774, RRID:SCR_002823, (Zhang et al., 2001)). Brain surfaces were reconstructed using *recon-all* (*FreeSurfer* 6.0.1, RRID:SCR_001847, (Dale et al., 1999)), and the brain mask estimated previously was refined with a custom variation of the method to reconcile *ANTs*-derived and *FreeSurfer*-derived segmentations of the cortical gray-matter of *Mindboggle* (RRID:SCR_002438, (Klein et al., 2017)). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym, where MNI stands for Montreal Neurological Institute) was performed through nonlinear registration with *antsRegistration* (*ANTs* 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* ((Fonov et al., 2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym), *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* ((Evans et al., 2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym).

Voxel-Based Morphometry (VBM) data was derived from the synthetic T1w structural images via the standard SPM12 pipeline (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). This approach extracts spatially unbiased estimates of voxelwise GM volume. T1w images were automatically segmented into GM, WM, and cerebrospinal fluid and affine registered to the MNI template. A high-dimensional, nonlinear diffeomorphic registration algorithm (DARTEL) was used to generate a study-specific template from GM and WM tissue segments of all participants

and then to normalize all segmented GM maps to MNI space with 2-mm isotropic resolution. All GM images were smoothed with a 4-mm full width at half maximum isotropic Gaussian kernel. Total brain volume was calculated by summing together the non-zero voxels in the modulated and warped GM and WM images of the VBM output (Malone et al., 2015).

Functional MRI data pre-processing and connectome construction

First, a reference volume and its skull-stripped version were generated by aligning and averaging one single-band reference (SBRef). Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using *mcflirt* (FSL 6.0.5.1:57b01774, (Jenkinson et al., 2002)). The estimated *fieldmap* was then aligned with rigid-registration to the target EPI (echo-planar imaging) reference run. The field coefficients were mapped on to the reference EPI using the transform. The BOLD reference was then co-registered to the T1w reference using *bbregister* (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with six degrees of freedom. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed following Power (absolute sum of relative motions (Power et al., 2014)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., (2014)). The three global signals were extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor* (Behzadi et al., 2007)). Principal components were estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. (2007) in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted from a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each *CompCor* decomposition, the k components with the largest singular values are retained, such that the retained components'

time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. Many internal operations of *fMRIPrep* use *Nilearn* 0.8.1 ((Abraham et al., 2014), RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

For the streamlined application of additional denoising components and data-cleaning strategies within a single framework, we utilized *rs-Denoise* (Kliemann et al., 2022) (please see <https://github.com/adolphslab/rsDenoise>), an open-source Python-based pipeline. This pipeline involved several steps: (1) z-score normalization of the signal at each voxel; (2) removal of linear and quadratic trends with polynomial regressors; (3) utilization of *fMRIPrep*'s *aCompCor* parameters, to regress out five components derived from whole-brain mean signals; (4) utilization of translational and rotational realignment parameters and their temporal derivatives as explanatory variables in motion regression; (5) temporal filtering was performed with a discrete cosine transform (DCT) filter with a cutoff frequency of 0.008 Hz. Lastly, the pre-processed runs were smoothed using a 4-mm full-width at half maximum (FWHM) Gaussian kernel and concatenated along the time domain. Individual fMRI recordings were then parceled into 416 cortical and subcortical brain regions using the Melbourne Subcortex Atlas (Tian et al., 2020) (Schaefer2018, 400 Parcels and 7 Networks and Tian Subcortex scale 1), and functional connectivity (FC) matrices were generated for each participant.

Diffusion MRI data pre-processing and white-matter microstructure estimation

The preprocessing of dMRI data was executed using custom *MATLAB* scripts tailored in-house. These scripts proficiently filtered noise and eradicated prevalent artifacts such as Gibbs ringing, susceptibility distortion, motion, and eddy current-induced distortions. To provide further detail, data are denoised through the process of decomposition, which assumes that the variation occurring in the b-directions is similar in the neighborhood of the voxel. The method was adapted from Veraart et al. (2016). Gibbs ringing is corrected using the function 'unring', which is based on the approach

described by Kellner (Kellner et al., 2015). FSL's function 'eddy' (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/EDDY>) is an integrated approach correcting for off-resonance effects and subject movement in dMRI, and the methodology entails the following steps: first, FSL's 'topup' is employed to estimate the susceptibility field and generate unwarped $b=0$ images. Subsequently, the unwarped $b=0$ images are brain-masked using FSL 'bet'. Finally, a combined eddy current correction, unwarping, and motion correction are performed using FSL 'eddy'. Individual voxelwise fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (L1) maps were computed using *dtifit* within the FSL software package (Smith et al., 2004). These four DTI features were selected based on their ability to capture different aspects of white matter microstructure. For example, FA is a scalar value indicating the degree of anisotropy in water diffusion within a voxel, thus distinguishing directional orientation from isotropy; MD, another scalar value, reflects the average magnitude of water diffusion within a voxel and provides insight into the overall diffusion rate and structural properties of the tissue. Unlike MD, which provides information independent of direction, the first eigenvalue (L1) indicates the magnitude of diffusion along the primary direction, correlating with myelin structure or myelination. FA image processing involved a tract-based spatial statistics pipeline with registration to the *FMRIB58_FA* standard space. This was followed by the skeletonization of the mean group white matter and the projection of individual data onto the skeleton. The resulting mean skeleton image was thresholded at FA 0.2, with other DTI metrics (MD, L1) projected onto the FA skeleton using the *tbss_non_FA* option. Prior to integration into the subsequent data fusion model, all DTI data were standardized to 1 mm isotropic resolution.

Modalities fusion analysis

We employed LICA (Groves et al., 2011; Llera et al., 2019) to integrate inter-participant variability shared across five features: gray matter volume (VBM), white matter microstructure (FA, MD, L1), and functional connectivity (FC). LICA is a Bayesian multimodal extension of the ICA model that allows for simultaneous factorizations across multiple data modalities, connecting them at the participant level through a shared mixing matrix that represents each participant's contribution (one scalar value per participant) to each independent component. This technique provides, for each independent component (IC), a vector indicating the contribution (weight) of each modality and a spatial map per modality showing the extent of spatial variation (Beckmann et al., 2005). Considering our sample size and the recommendation that the model order be less than 25% of the sample size (Groves et al., 2012), we report results from a 63-dimensional factorization. Given our primary interest in multimodal components, and the fact none of the unimodal components correlated with DRF (Supplementary Table 1), we excluded any components where a single modality contributed more than

50% of the total variance (Kohn et al., 2021; Van Oort et al., 2023). Additionally, seven components were driven by a single participant, therefore, these components were not included in the correlation analysis (Supplementary Figure 2). To demonstrate the robustness of the factorization choice, different model order (60 and 65-dimensional factorizations) decompositions were also performed (Supplementary Figure 3, 4 and 5). For visualization purposes, the spatial maps were thresholded at $|Z| > 3.0$.

Statistical Analyses

Following the methodology of Llera et al., (2019), we conducted a permutation test to determine the significant Spearman partial correlations between the subject loadings on the independent components, derived from LICA, and our measure of DRF, controlling for age, sex, IQ, and total brain volume. Multiple comparisons were addressed using FDR correction ($p < 0.05$), according to Benjamini and Hochberg (1995). The analyses were performed in R, and a fixed random seed was used to ensure the reproducibility of our results.

Results

Study population and general results

Participants reported an average DRF of 2.17 times per week ($SD=2.05$) and an average WAIS-IV score of 112.05 ($SD=9.86$) (Figure 1A). There was no evidence of age ($\rho=-0.035$, $p=0.57$), sex ($\rho=0.116$, $p=0.062$), or IQ-related ($\rho=0.060$, $p=0.367$) differences in DRF. Nevertheless, in order to align with the methodology employed in previous studies, sex, age, and IQ were controlled for in the analyses.

LICA decomposition and statistical results

LICA was used to decompose the multi-modal MRI data into 63 ICs (Figure 1B and Supplementary Figure 1). Of the 63 components, 46 were identified as multimodal, reflecting shared variance across different modalities. The statistical analysis revealed a single significant correlation between independent component 51 (IC51) and DRF ($\rho=-0.20$, $p_{FDR}=0.03$), while controlling for total brain volume. To further confirm the stability of our results, we controlled for age, sex, and IQ in an additional partial correlation analysis ($\rho=-0.19$, $p_{FDR}=0.04$). From the robustness analysis, we observed that IC51 is reproducible across different model orders (see, Supplementary Material for more details). The relative contributions from different modalities to IC51 were as follows: 18.40% for radial diffusivity (L1), 25.02% for mean diffusivity (MD), 11.72% for fractional anisotropy (FA), 7.24% for gray matter volume (VBM), and 37.62% for functional connectivity (FC) (Figure 1C).

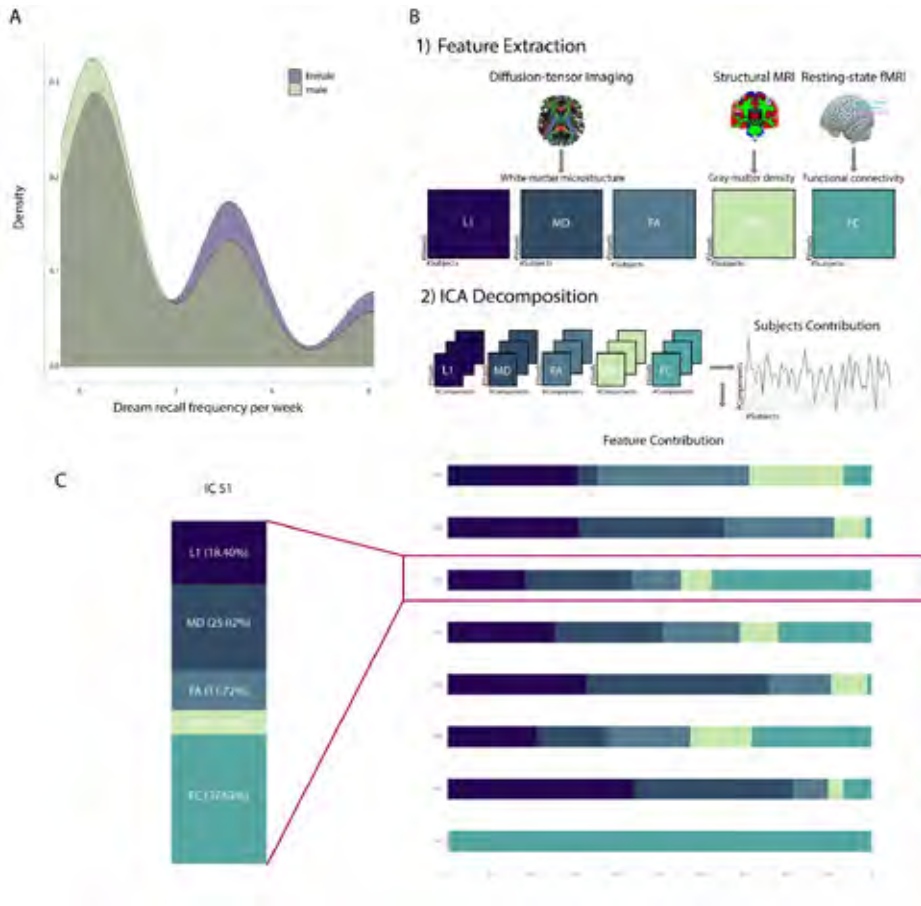


Figure 1: Demographic and LICA pipeline overview. **A:** Density distribution of the dream recall frequency scores (recoded into units per week) of females and males; **B:** (1) Diffusion-tensor, functional, and structural MRI data are used to extract relevant features, that is, radial diffusivity (L1), mean diffusivity (MD), fractional anisotropy (FA), gray matter volume as measured by Voxel-Based Morphometry (VBM), and functional connectivity (FC). (2) The aforementioned features are then utilized as input to the LICA algorithm, generating 63 independent components (IC), with the percentage of the distinct modalities contributions. Subsequently, the subject loadings of each independent component are combined with the behavioral data. (**C**) Among all independent components, multi-modal IC51 demonstrated a significant association with dream recall frequency.

Figure 2 presents the summarized images of each modality's spatial map of IC51. DRF was associated with greater white microstructure integrity (reduced MD/L1 values) located in the frontal orbital cortex, parahippocampal gyrus, superior parietal lobule, and occipital cortex, particularly in the higher-order visual areas (V3 and V4). Furthermore, DRF was associated with lower gray matter volume in the occipital cortex (specifically in the V1 and V2 areas).

Moreover, our results demonstrated enhanced functional connectivity within the occipital regions of the visual network, parietal regions of the default mode network, and sensorimotor networks (Figure 3A), and increased connectivity within the nucleus accumbens and left thalamus related to DRF. The observed relationships and the involvement of distinct brain regions underscore the complexity of the neural mechanisms underlying dream recall and emphasize the roles of microstructural and functional connectivity changes in this process.

Additionally, the analysis demonstrated a reduction in functional connectivity, particularly between the parietal and temporal regions of the default mode, visual, sensorimotor, and dorsal attention networks, as well as within the dorsal attention network (Figure 3B). In contrast, DRF was associated with regions exhibiting increased FA and GM values, indicative of superior white matter microstructural integrity and gray matter volume. These regions included the middle frontal gyrus and several small clusters in the occipital and temporal cortex.

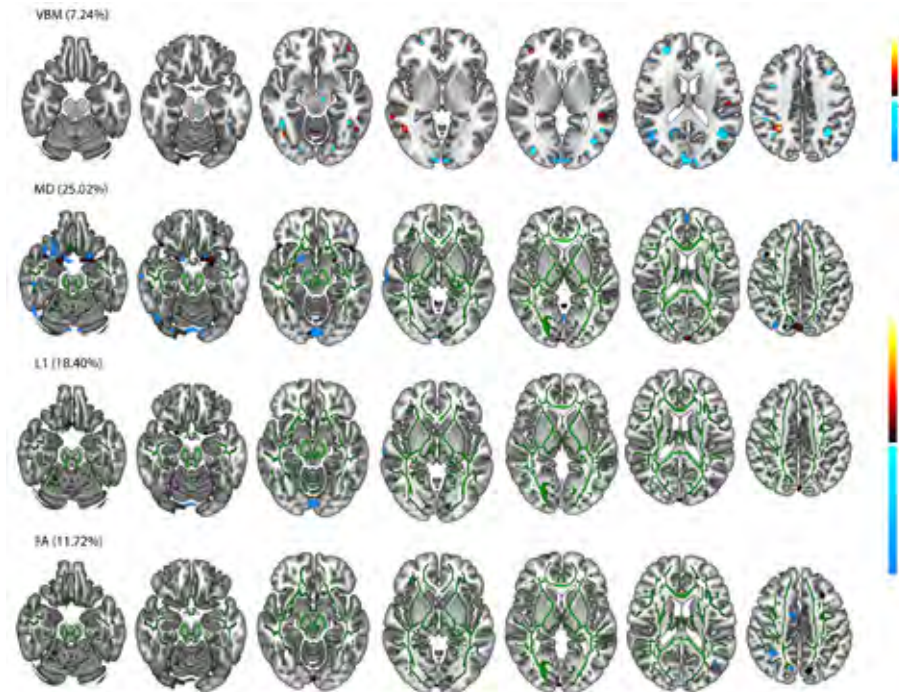


Figure 2: Brain Regions Associated with Dream Recall Frequency. Summary of the multimodal component (IC51) reveals the regions associated with dream recall frequency. The voxel-based morphometry (VBM) spatial map was thresholded at $3 < |z| < 8$. The clusters of diffusion tensor imaging features were filled and thresholded at $3 < |z| < 8$, then smoothed using a 0.3-mm Gaussian kernel in FSL for visualization purposes. Mean diffusivity (MD), radial diffusivity (L1), and fractional anisotropy (FA). The green map is the standard *FMRIB58_FA-skeleton* template provided in FSL.

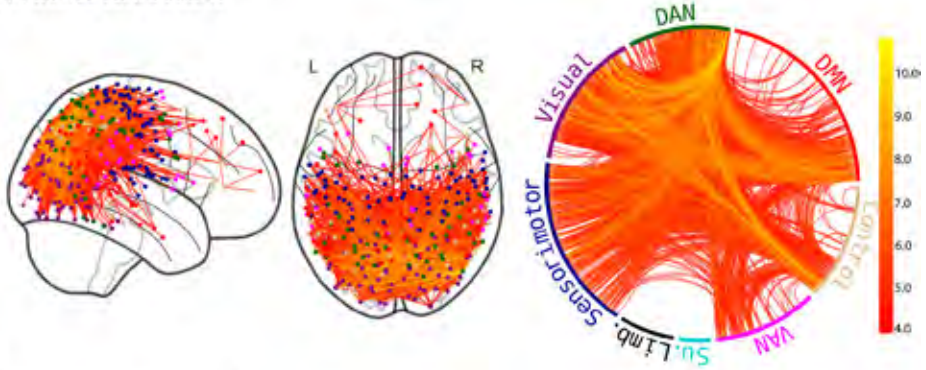
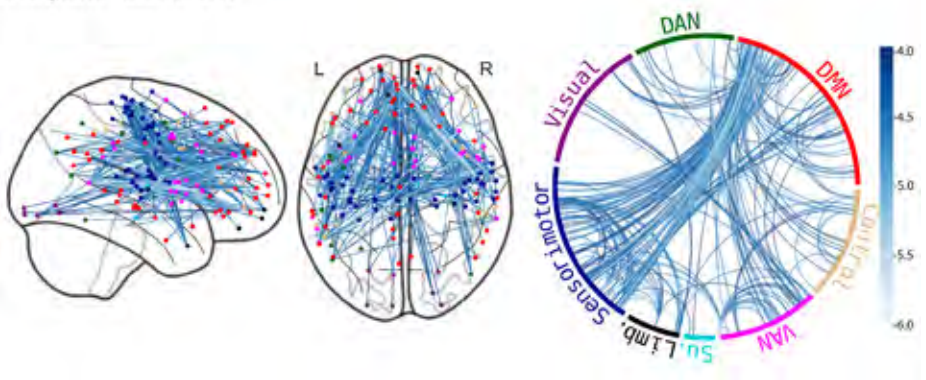
A: Positive connections**B: Negative connections**

Figure 3: Inverse Relationship Between Functional Connectivity and Dream Recall Frequency. Functional connectivity is inversely associated with dream recall frequency. The connections were initially thresholded at $|z| > 3$ and subsequently clustered according to their affiliation with the respective resting-state network. The positive (**Figure 3A**) and negative (**Figure 3B**) edges were thresholded at the 99th percentile for visualization purposes. DMN: Default mode network, Control: Control network, VAN: Ventral attention network, Su.: Subcortical network, Limb: Limbic network, Sensorimotor: Sensorimotor network, Visual: Visual network, and DAN: Dorsal attention network.

Discussion

The present study employs a comprehensive, multimodal neuroimaging approach to investigate the neural correlates of DRF, with a particular focus on both brain structure and function. Our findings indicate an inverse relationship between DRF and brain microstructure integrity, volume, and functional connectivity. It is crucial to highlight that among the selected DTI modalities, high and low FA values indicate greater and poorer white matter microstructure, respectively. Conversely, for the MD and L1 modalities, high values indicate poorer microstructure integrity, whereas low

values indicate greater white matter microstructure integrity. Our findings will be further interpreted in terms of their association between higher and lower DRF and the observed neuroimaging findings. For instance, we observed greater white matter microstructure integrity in several regions, including the frontal orbital cortex, parahippocampal gyrus, superior parietal lobule, and occipital cortex, particularly in the higher-order visual areas (V3 and V4) association with higher DRF. Furthermore, higher DRF was associated with lower gray matter volume in the occipital cortex (specifically in the V1 and V2 areas). Conversely, lower DRF was associated with reduced white-matter microstructure in the frontal orbital cortex, middle frontal gyrus, parahippocampal gyrus, and specific regions of the parietal cortex. These findings can be interpreted from a dual perspective: brain regions potentially contributing to dream generation and those related to DRF.

Gray and white-matter morphology relationship with dream recall frequency

Dream experiences have been linked to localized increases in electroencephalogram (EEG) high-frequency (20–50 Hz) and reduced low-frequency (1–4 Hz) delta activity within posterior-occipital cortical regions during both REM and NREM sleep (Siclari et al., 2017). Similar patterns have been observed in dreams following NREM parasomnia episodes, where conscious experiences were associated with reduced delta and increased beta activity in the posterior cortical regions, including the primary visual cortices, occipital-temporal areas, medial temporal regions, and parts of the precuneus and posterior cingulate cortex (Cataldi et al., 2024). These findings suggest that dream generation is driven by distinct oscillatory patterns characterized by decreased low-frequency and increased high-frequency oscillations across specific brain areas, regardless of the sleep stage. Our findings align with these observations, as we observed enhanced white matter microstructure integrity in parietal-occipital regions, which are associated with higher DRF. This microstructure reflects well-organized and densely packed fibers that may facilitate optimal neural coordination and, thus, oscillatory activity. These results highlight the importance of particular brain areas and their microstructure integrity in facilitating the neural activity that underpins dream experiences and their frequency.

Our findings revealed a link between reduced gray matter volume in early visual areas (V1 and V2) and enhanced white matter microstructure integrity in higher-order visual areas (V3 and V4) and higher dream recall. In addition to processing fundamental visual characteristics such as color and pattern, V4 plays a role in visual learning, stimulus selection, and the translation of learned pattern relationships across the visual field. Furthermore, this area is modulated by attention, stimulus

relevance, and perceptual context. V3 and V4 serve as critical connectors between early visual areas and higher-order cortical regions, integrating visual information across specialized channels and filtering it for higher-order brain regions (Farah, 1989). Empirical evidence supports the top-down model of dreaming, which proposes that cognitive processes, rather than sensory-motor inputs, primarily drive dream content (Foulkes & Domhoff, 2014). Studies have demonstrated that dreaming is associated with activity in higher-order brain regions, including the prefrontal cortex and association areas, which are crucial for imagination and narrative construction (Nir & Tononi, 2010). Increased high-frequency activity was observed in the frontal regions during NREM sleep when contrasting dream experiences with and without content recall (Siclari et al., 2017). This perspective is further reinforced by the observed greater microstructure integrity of the frontal orbital cortex, a region that integrates complex sensory information and is essential for processing reward values, learning associations, and emotional responses (Rolls, 2004). Our findings align with this perspective and support the idea that dreaming engages high-level cognitive processes, including those mediated by the frontal orbital cortex and higher-order visual areas. These results contribute to a more comprehensive model of dreaming, highlighting the importance of higher-order brain regions and cognitive systems in the formation and recall of dreams.

The findings presented here can be extended to other brain regions, such as the parahippocampal gyrus, which plays a crucial role in connecting the default-mode network with the medial temporal lobe memory system and mediating functional connectivity between the hippocampus and posterior cingulate cortex (Ward et al., 2014). Furthermore, the parahippocampal gyrus plays a pivotal role in the relay of information between the hippocampal formation and other regions of the cerebral cortex, particularly the association cortices in monkeys (Van Hoesen, 1982), the direct electrical stimulation of the parahippocampal place area evoked topographic visual hallucinations, thereby demonstrating that the stimulation of higher-order visual areas can induce complex hallucinations in humans (Mégevand et al., 2014). Taken together, our findings indicate that individuals with greater white matter microstructure integrity in the parahippocampal gyrus recall their dreams more frequently, in line with these regions' roles in processing contextual associations and memory processing. Given the methodological differences between our study and that of Zhou and colleagues (Zhou et al., 2019), a direct comparison is not possible. While Zhou et al. reported an inverse relationship between fiber integrity in the parahippocampal and fusiform gyri and DRF using a probabilistic tractography approach in an examination of 43 participants, we did not observe this same association in our data-driven analysis of white-matter integrity based on

distinct DTI modalities. Their method specifically traced fibers connecting the two regions and focused on tracts that were consistently present across participants. In contrast, our approach did not explicitly assess fiber connectivity between regions. Furthermore, we did not identify any significant clusters in the fusiform gyrus, which makes direct comparisons with this previous finding challenging. Nevertheless, further research is required to more accurately define the spatial relationship between the parahippocampal area, dreaming, and trait dream recall.

Although we observed an association between higher DRF and greater white matter integrity in the frontal cortex, we did not find a link between increased medial prefrontal cortex white matter integrity linked to high DRF, as reported by Vallat and colleagues (2018). This discrepancy may be attributed to methodological differences between the studies. Our study employed DTI to assess white matter integrity, whereas Vallat et al. utilized voxel-based morphometry to quantify white matter density. Moreover, Vallat et al. focused on specific regions, including the medial prefrontal cortex, temporoparietal junction, hippocampus, and amygdala, comparing individuals with low and high DRF. In contrast, our approach was a whole-brain analysis that did not restrict the investigation to between-group comparisons. Instead, we examined regions associated with trait dream recall across a continuous spectrum. Additionally, although high DRF has been associated with increased rCBF in the temporoparietal junction (Eichenlaub et al., 2014), our observation of decreased white microstructural integrity in the inferior temporo-occipital gyrus, which has been associated with reduced rCBF (Chen et al., 2013), suggests a possible divergence from these results. These differences underscore the importance of methodological considerations and highlight the need for further research to reconcile these findings and fully understand the neural correlates of DRF.

Functional connectivity relationship with dream recall frequency

Higher dream recall was associated with a widespread decrease in functional connectivity observed across various resting-state networks. This decrease was particularly evident between frontal, parietal and temporal regions of the default mode and visual networks, as well as between the sensorimotor and dorsal attention networks and within the dorsal attention network itself. A notable reduction in connectivity within the default mode network was observed, particularly in the right precuneus, prefrontal cortex, and posterior cingulate cortex. These findings are consistent with those of Zou and colleagues (2018), who reported a negative correlation between DRF and connectivity within the lateral visual network, the thalamus, and the posterior default mode network, thus indicating that decreased brain functional connectivity is linked to higher DRF. Similarly, we found that

decreased functional connectivity in the thalamus, amygdala, globus pallidus, left hippocampus, and specific subregions of the visual, sensorimotor and dorsal attention networks was associated with frequent dream recall. In terms of functional connectivity relationship with high-frequency (20–50 Hz) neural oscillations, a study using laminar fMRI found a negative correlation between beta power and interregional layer connectivity, indicating that increased beta power reflects reduced laminar-specific connectivity in the visual cortex. In contrast, gamma band activity did not show a relationship with laminar connectivity, suggesting that while gamma activity is associated with the strength of the BOLD signal in middle and superficial layers, it does not correlate with changes in laminar fMRI connectivity within and between brain regions (Scheeringa et al., 2023). Clinically, pathological high-frequency oscillations (>80 Hz) have been linked to decreased cortical functional connectivity during seizure initiation and propagation (Ibrahim et al., 2013). Together, these findings offer valuable insights for interpreting our results, as they suggest that dream experiences accompanied by content recall are characterized by heightened high-frequency power in medial and lateral frontoparietal areas, potentially reflecting distinct neural dynamics underlying the recall of dream content (Siclari et al., 2017).

In contrast, lower DRF was associated with increased functional connectivity in the occipital areas of the visual network, parietal regions of the default mode and sensorimotor networks, as well as in the nucleus accumbens and left thalamus. Although our results are based on data collected during wakefulness, the increased functional connectivity within these regions may reflect underlying neural activity that supports low-frequency oscillations during sleep. Prior research has demonstrated a close relationship between low-frequency electrophysiological signals, such as delta oscillations, and resting-state fMRI signals. Specifically, the BOLD hemodynamic response has been shown to correlate with power coherence in the low-frequency delta band across various states of consciousness, including wakefulness, REM sleep, and NREM sleep, in both human and animal studies (Lu et al., 2007; He et al., 2008; Wilson III et al., 2016). The increased connectivity in posterior parietal, occipital, and thalamic regions observed in our study may indicate a stable neural configuration that is optimal for delta oscillation synchronicity and propagation. This hypothesis aligns with the neural dynamics observed during sleep, particularly when dream content recall is low, where increased delta oscillations are associated with diminished cortical activation and reduced conscious awareness and, consequently, dream experiences (Siclari et al., 2017). Although drowsiness and sleep-like activity can be observed during resting-state fMRI (Tagliazucchi & Laufs, 2014), the total recording time in our study was 18 minutes, shorter than typical

resting-state or task-based recordings. While it is possible that some participants experienced brief periods of drowsiness, it is unlikely that most would have reached deeper sleep stages, where delta activity dominates. Instead, the association between resting-state functional signals and delta oscillations across various states of consciousness provides a plausible mechanistic explanation for our findings that increased functional connectivity observed in the parietal, occipital, and thalamic regions during wakefulness may serve as a precursor to the neural dynamics that occur during sleep, where local increases in delta power have been correlated with the absence of dream reports (Siclari et al., 2017). Further research is required to elucidate the relationship between functional connectivity and neural oscillations across different states of consciousness in humans.

Limitations and conclusions

In the present study, we employed LICA to explore the neural correlates of trait dream recall. While LICA is an effective method for integrating data from different modalities, providing a comprehensive and biologically informative view of complex phenomena, several limitations should be noted. First, the efficacy of the method may be affected by variability in the number of features and distributions across modalities. Moreover, it is important to interpret the results of correlational studies cautiously, as there is currently no causal evidence to suggest that specific brain structure and functional features are directly involved in dream experiences. Our investigation of trait dream recall frequency may potentially overlook state components that may have influenced factors such as sleep stages, dream diaries, and daily events. These factors may have functional correlates rather than anatomical correlates. Future research may address these limitations by exploring additional measures related to state dream recall and sleep. The combination of simultaneous EEG/fMRI recordings over consecutive days, assessing both trait, retrospective and prospective dream recall, with serial awakening paradigms, has the potential to provide ongoing insights into the relationship between brain activity, dream production and dream recall. Furthermore, the incorporation of dream diaries would facilitate a more comprehensive capture of state-related aspects of DRE, given the potential for these to vary over time and influence the associations with anatomical and functional brain measures. Ultimately, validating our findings with neurostimulation techniques and extending the analysis to encompass both structural and functional brain aspects will be vital for a more comprehensive understanding of the neural correlates of dream memory recall. Further research is required to confirm these findings, with more diverse samples.

Data and Code Availability

Data cannot be shared publicly because it is part of an ongoing study and is thus considered unanonymized under Danish law even if pseudonymized. Researchers who wish to access the data may contact Dr. Kristian Sandberg (kristian.sandberg@cfin.au.dk) at The Center of Functionally Integrative Neuroscience and/or The Technology Transfer Office (TTO@au.dk) at Aarhus University, Denmark. After permission has been given by the relevant data committee, data will be made available to the researchers. No custom code was used in this study. Publicly available software tools were used to perform analyses and are referenced throughout the manuscript.

Author Contributions

M.P.: Conceptualization, Investigation, Performed Analysis, Writing – Original Draft, Review & Editing, and Visualization; P.G.: Data Pre-Processing, Assistance with Analysis, Writing – Review & Editing; T.M.: Assistance with Analysis, Writing – Review & Editing; R.R.: Data Pre-Processing, Writing – Review & Editing; I.K.M.: Data Pre-Processing, Writing – Review & Editing; A.L.: Assistance with Analysis, Writing – Review & Editing; R.S.: Writing – Review & Editing; C.B.: Writing – Review & Editing; F.K., M.D., L.S.: Supervision, Conceptualization, Assistance with Analysis, Writing – Review & Editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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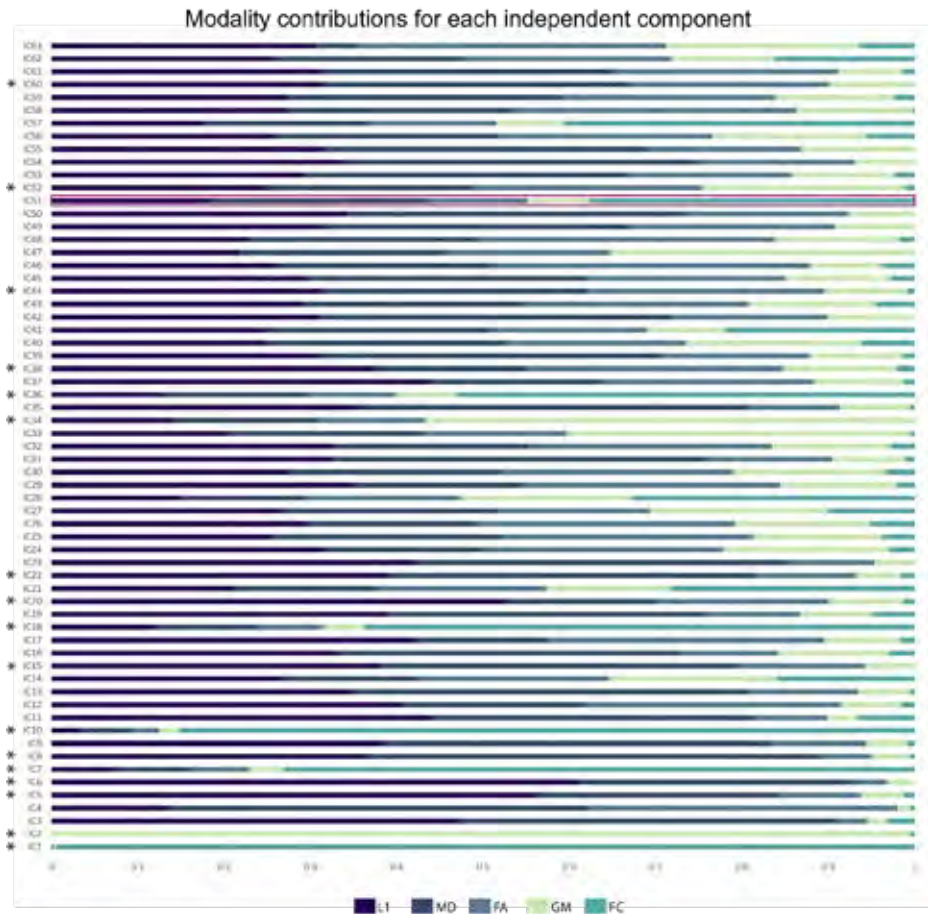
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Supplementary material

This supplementary material is intended to present the reader with further information about the analyses presented in the primary manuscript.

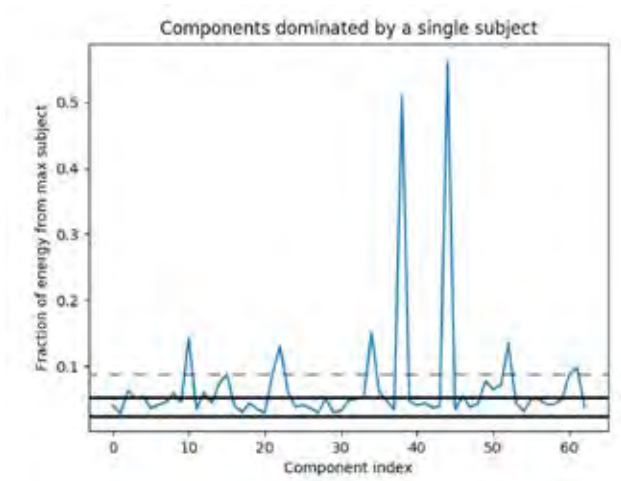
Linked-Independent Component Analysis of Model Order 63



Supplementary Figure 1: Modality contributions for the 63-dimensional factorization. This study examines the modality contributions of the 63-dimensional factorization. The independent component highlighted in red significantly correlated with dream recall frequency. From the 63 independent components, those marked with an asterisk were excluded from the statistical analysis. This was because one single modality contributed to more than 50% of the total contributions, as was the case with components 1, 2, 5, 6, 7, 8, 10, 18, 20, 34, and 36. Furthermore, components 10, 15, 22, 34, 38, 44, 52, and 60 were not included in the final statistical analysis. This was due to the fact that they were driven by a single subject. Radial diffusivity (L1), mean diffusivity (MD), fractional anisotropy (FA), gray matter volume (Voxel-Based Morphometry - VBM), and functional connectivity (FC).

Supplementary Table 1: Excluded unimodal independent components and their corresponding p-values uncorrected and corrected, respectively.

Excluded Unimodal Independent Components (ICs)			
IC	rho	p-value	p-value (corrected)
IC1	-0.0495	0.425	0.934642373
IC2	-0.09946	0.1177	0.934642373
IC5	0.050721	0.4312	0.934642373
IC6	-0.02418	0.6971	0.934642373
IC7	-0.03533	0.5811	0.934642373
IC8	0.091886	0.1408	0.934642373
IC10	-0.04008	0.5271	0.934642373
IC18	-0.05805	0.3484	0.934642373
IC20	0.048375	0.4464	0.934642373
IC34	0.043837	0.4974	0.934642373
IC36	0.038101	0.5464	0.934642373

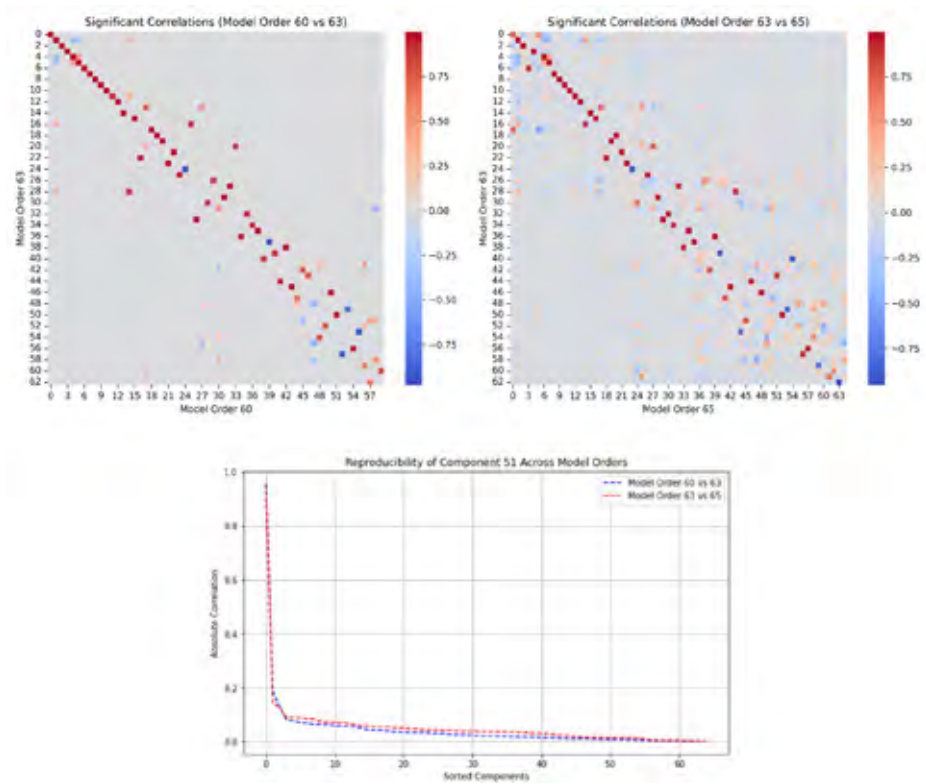


Supplementary Figure 2: The independent components dominated by a single subject, information output from LICA. Based on the fraction of energy, and represented by the dashed line, the following components were excluded from the statistical analysis: components 10, 15, 22, 34, 38, 44, 52, and 60.

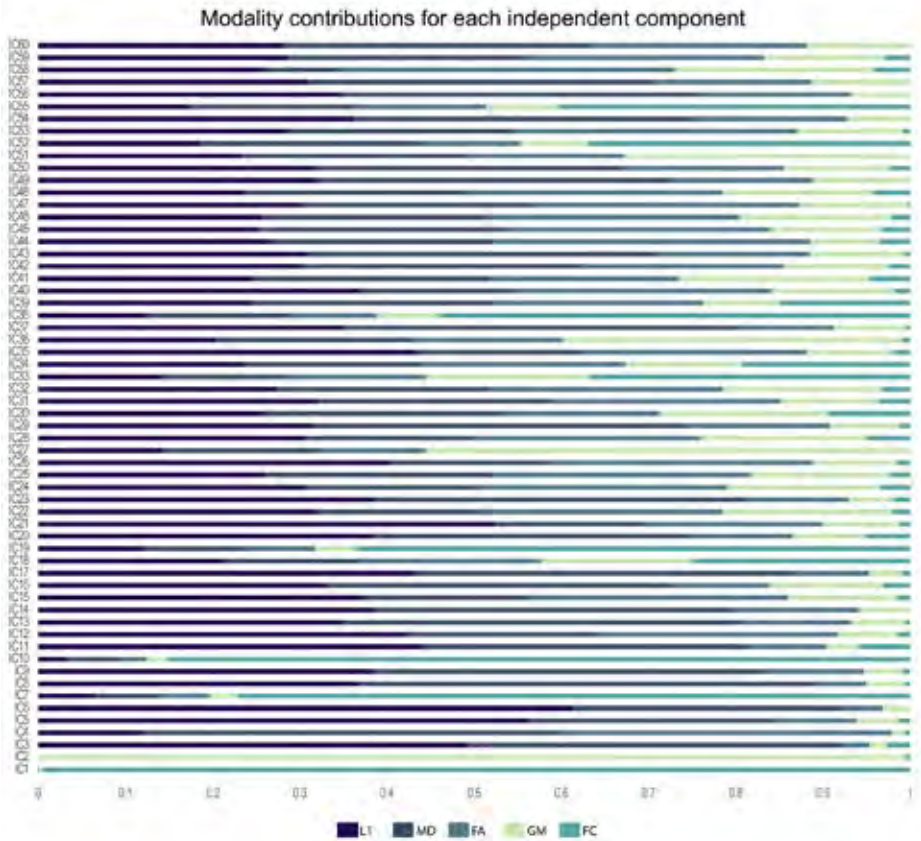
Robustness of the model order

To evaluate the stability of the results obtained when different model orders are selected. Correlation analyses were conducted between the subject-mode components of the presented 63-dimensional factorization and those of the 60- and 65-dimensional

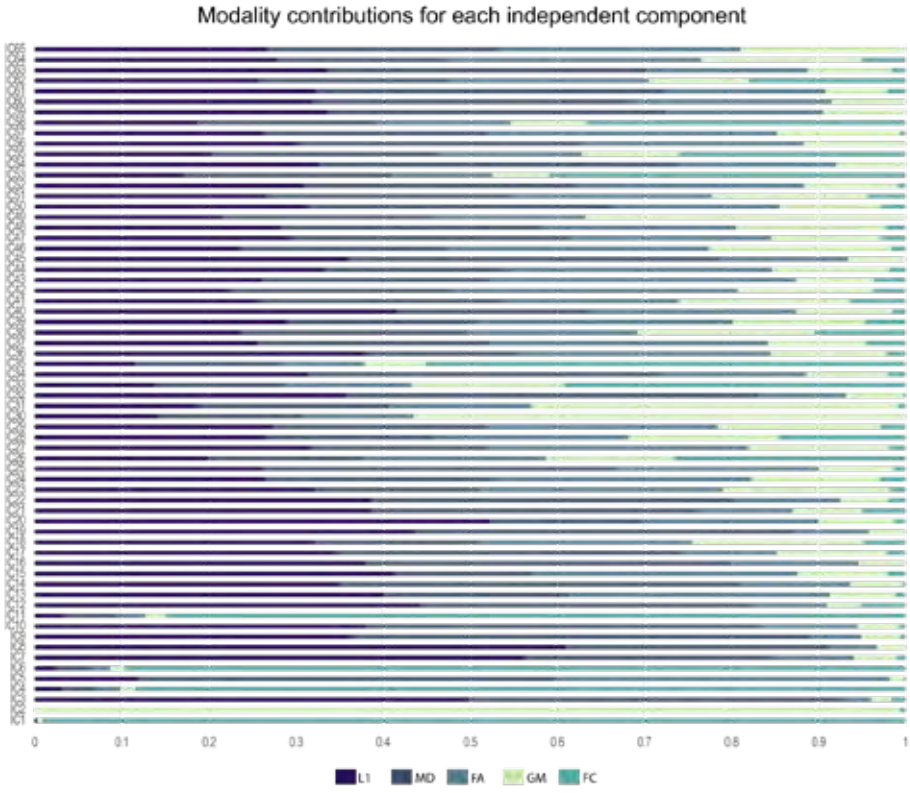
factorizations. The top row of Figure 1 depicts the correlation matrices between the 63-dimensional factorization (y-axis) and the factorizations with 60 and 65 components (left and right panels, respectively). Only those correlations that were statistically significant after the false discovery rate (FDR) correction are displayed; that is, those with p-values smaller than $0.05/(63 \times 60)$ and $0.05/(63 \times 65)$. Moreover, the bottom row of Figure 1 illustrates the reproducibility of independent component 51. The figure depicts the sorted absolute correlations for IC51 across the model orders (60 vs. 63 and 63 vs. 65), thereby demonstrating its stability across dimensionality choices. As illustrated in the plot, IC51 exhibits consistent high correlation values across different model orders, thereby underscoring its robustness and emphasizing its significance in our analysis.



Supplementary Figure 3: Correlation Stability of Independent Component 51 Across Model Orders: Significant correlations are demonstrated between the reported 63-dimensional factorization and the 60-dimensional (left panel) and 65-dimensional (right panel) factorizations. The bottom row presents sorted absolute correlations for independent component 51 for each of the 63-dimensional factorizations with the corresponding components from the other model orders, thereby highlighting its stability and robustness across model orders.



Supplementary Figure 4: Modality contributions for the 60-dimensional factorization.



Supplementary Figure 5: Modality contributions for the 65-dimensional factorization.



Chapter 5

Default-mode network involvement in non-REM sleep dreaming

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Abstract

Understanding the neural basis of dreaming has remained a puzzle in consciousness research, due to the lack of distinct neurophysiological markers. This study investigates the neural correlates of dreaming during light non-REM (NREM) sleep using simultaneous EEG/fMRI recordings and a novel Global Dream Index (GDI) that integrates subjective ratings of dream content, such as emotion, motivation and narrative coherence, with objective metrics such as total word count and long-term dream recall. Using a serial awakening paradigm, we examined the relationship between resting-state network connectivity and the GDI to elucidate the role of the default mode network (DMN) and other association networks in conscious experience during sleep. Our results show that functional connectivity within the DMN, frontoparietal and ventral attention networks is positively correlated with richer dream experiences. Specifically, positive connectivity between left temporal cortex and right dorsal medial prefrontal cortex (dmPFC), left parietal regions and right ventral prefrontal cortex, and connections between right parietal, dmPFC and precuneus regions within the DMN were associated with heightened GDI scores. Similar patterns emerged within the frontoparietal and ventral attention networks, linking parietal, temporal and insular regions to more elaborate dream reports. By integrating subjective and objective measures, our results highlight the critical role of resting-state networks in shaping conscious experience during sleep, suggesting a common neural substrate for dreaming and waking cognition. This study advances our understanding of dream experiences and sets the stage for future work on the neurobiology of dreaming across sleep stages.

Keywords: dreaming, functional connectivity, NREM dreams, DMN, frontoparietal

Introduction

Understanding the neural basis of dreaming is critical for advancing our knowledge of human consciousness. Sleep provides a unique and universally accessible window into consciousness, unlike anesthesia or other altered states, because it allows the study of spontaneous mental experiences under different physiological conditions. Investigating how and why we dream can provide unique insights into the neural mechanisms that support conscious experience, memory processing, and emotional regulation. Historically, rapid eye movement (REM) sleep (Aserinsky & Kleitman, 1953), has been associated with dreaming due to its neurophysiological features, including desynchronized cortical activity, rapid eye movements, and increased brain metabolism. Its resemblance to wakefulness, combined with the fact that early studies reported a higher frequency of dream reports from REM sleep compared to non-REM (NREM) sleep, led to the mistaken belief that dreaming was exclusive to this electrophysiologically active stage (Dement & Kleitman, 1957). However, subsequent research has demonstrated that dreaming can occur across all sleep stages (Foulkes, 1962; Siclari et al., 2013), challenging the traditional REM-centric view and highlighting the need for a broader investigation into the neural correlates of mental experiences across the sleep cycle.

Advances in functional neuroimaging have enabled the identification of seven general brain networks, which can be broadly categorized into sensory, visual and sensorimotor, and association networks, including the dorsal and ventral attention, limbic, frontoparietal, and default-mode networks (DMN) (Schaefer et al., 2018; Thomas Yeo et al., 2011). During waking states, the four association networks are in constant communication, however, after sleep onset, these interactions progressively diminish (Chang et al., 2013; Dixon et al., 2018). Notably, the DMN, which plays a crucial role in internally generated thought processes, including mind-wandering and self-referential cognition during wakefulness (Mason et al., 2007; Christoff et al., 2009), remains active into NREM sleep stage 2 (Horovitz et al., 2008; Larson-Prior et al., 2009; Sämann et al., 2011; Tagliazucchi et al., 2013), even as other networks deactivate, suggesting its involvement in maintaining internal mentation during sleep. Dreaming occurs across both REM and NREM sleep stages (Solms, 2000; Oudiette et al., 2012), and functional neuroimaging studies, including findings on dream recall frequency, support the idea that distinct brain regions contribute to the neurocognitive processes underlying dreaming (De Gennaro et al., 2011; Fox et al., 2013; Eichenlaub et al., 2014).

Empirical evidence supports the Internal Mentation Hypothesis, which proposes that the DMN facilitates self-reflective thinking, task-unrelated thoughts, mind-

wandering, autobiographical recall, and future planning (Binder et al., 1999; Gusnard et al., 2001; Buckner et al., 2008), which is consistent with the idea that DMN activity, particularly in passive states, reflects spontaneous internal thoughts rather than externally directed cognitive processes (Andrews-Hanna, 2012). A study investigating the specific nature of DMN-supported thinking identified two primary subsystems: the dorsal medial prefrontal cortex (dmPFC) subsystem and the medial temporal lobe (MTL) subsystem (Andrews-Hanna et al., 2010). The dmPFC subsystem, which includes regions such as the temporoparietal junction (TPJ), lateral temporal cortex, and temporal pole, is critical for reflecting on and evaluating personal and social mental states. This subsystem particularly engages in tasks involving social cognition, reasoning, moral dilemmas, and non-social cognitive functions, suggesting its broad involvement in introspective processes. On the other hand, the MTL subsystem, including regions such as the retrosplenial cortex, posterior cingulate cortex (PCC), posterior inferior parietal lobule, and medial prefrontal cortex, is central to memory retrieval and is engaged during tasks involving autobiographical memory, contextual associations, and self-related future scenarios and decisions. Notably, the anterior medial prefrontal cortex and PCC are functional hubs that share properties across both subsystems. Supporting this view, studies linking DMN activity to mind-wandering and self-referential thought processes during wakefulness (Mason et al., 2007; Christoff et al., 2009) and findings from lesion studies of dreaming further reinforce the role of the DMN. Specifically, lesions in the ventral medial prefrontal cortex or TPJ have been shown to result in the total cessation of dreaming. Together, these various lines of evidence point to the hypothesis that the neural substrate for dreaming may involve specific DMN subsystems (Fox et al., 2013) in coordination with other brain networks to underlie both the generation and recall of dream experiences, irrespective of sleep stage.

Dreaming, a key manifestation of mental experiences ranges from simple perceptual phenomena to elaborate, story-like narratives. Despite its importance in consciousness studies, investigating dreams comes with unique challenges, primarily due to their retrospective and subjective nature, marked by the absence of a clear neurophysiological marker for dreaming. While prior research has suggested that the DMN plays a crucial role in internally generated thought processes, the precise neural dynamics underlying dream generation remain unresolved. Specifically, it is unclear how different subsystems of the DMN interact with other large-scale networks during sleep to support the varied phenomenology of dreams. Additionally, while EEG studies have provided valuable insights into the electrophysiological correlates of dreaming, they lack the spatial resolution necessary to pinpoint the involvement of specific brain regions and network interactions. The combination of fMRI and

EEG presents a unique opportunity to overcome these limitations by combining high spatial and temporal resolution, allowing for a more comprehensive investigation of the neural basis of dreaming. However, EEG/fMRI sleep studies come with significant methodological challenges, including signal artifacts, participant discomfort, and the difficulty of maintaining sleep in the scanner (Pereira et al., 2025). Given these limitations, studies that combine EEG/fMRI with a serial awakening paradigm are essential, as they allow for the direct assessment of neural activity preceding dream reports, providing a novel and more precise approach to studying the neural mechanisms underlying dreaming.

This paper aims to explore light (N1 and N2) NREM sleep dreams, which we will refer to as NREM mentation, by using simultaneous EEG/fMRI recordings. Using a serial-awakening paradigm, we examined how resting-state networks relate to combined subjective and objective measures of dreaming. Given the inherent challenges of sleep imaging leading to a moderate sample size, analyzing individual measures separately would limit the scope of our findings and might increase false positives. Therefore, we developed a composite measure of dreaming, the Global Dream Index (GDI), which integrates subjective measures such as the amount of dreaming, emotion, storylikeness, and motivation, as rated by participants for each mentation report, alongside the objective measure of total recall count, which reflects the word count of each report, as well as memory on the next day and six months after the experimental nap. By combining these measures, the GDI provides a holistic index of dream richness, offering deeper insights into the interplay between subjective and objective aspects of dreaming. We hypothesized that DMN connectivity, particularly in regions related to introspection and self-referential thoughts, will positively correlate with richer dream reports. This study presents a novel approach to understanding the neural correlates of NREM mentation, contributing to a more comprehensive understanding of the relationship between brain connectivity and conscious experience.

Materials and Methods

Study Population

Ten healthy participants (six female, four male) aged 19 to 22 were recruited from Ruhr-Universität Bochum. Seven participants were students from the Department of Psychology who received academic credit, while three from other departments received financial compensation (€150 for four nights of participation). All participants provided informed consent, and the local ethics committee of the Ruhr-Universität Bochum

approved the study. Participant eligibility was determined through an online screening questionnaire, which gathered general health and demographic information. The selection criteria were as follows: i) Sleep Quality: participants were required to have a Pittsburgh Sleep Quality Index (PSQI) score of less than 5, indicating optimal sleep quality, and a habitual bedtime before midnight; ii) MRI Compatibility: all participants were confirmed to be MRI-compatible with no contraindications for scanning; iii) Handedness: handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 2013), and only right-handed individuals were included; iv) Body Mass Index (BMI): participants were required to have a BMI within the normal range (18.5-24.9); v) Dream Recall Frequency: dream recall was assessed via three questions regarding the frequency of dream recall, nightmares, and lucid dreaming. Only individuals who reported recalling dreams at least once a week were included. Exclusion criteria included any chronic medical condition or psychiatric diagnosis that could affect sleep, such as asthma or epilepsy (Benca et al., 1992; Guilleminault, 2005; Nofzinger, 2005). Additionally, participants were excluded if they were taking any regular medications (except oral contraceptives) or had a history of psychoactive drug use or smoking (both social and chronic), as these factors have been shown to alter natural sleep patterns (Domino & Yamamoto, 1965; Pagel, 2005).

Selected participants were provided comprehensive instructions delineating the study procedure. Subjects were instructed to maintain a regular sleep schedule and refrain from consuming alcohol or psychotropic substances for the three nights preceding each measurement. Furthermore, participants were obliged to complete a brief sleep diary for the aforementioned nights, in which they were required to document their sleep duration, the latency of their sleep onset, the duration of their wakefulness, and the quantity of alcohol consumed. Furthermore, the diary incorporated a rating scale for subjective dream content, which was also employed during the EEG/fMRI measurement. On the night preceding the measurement, participants were instructed to sleep for a duration that was two hours less than their usual amount. This mild sleep deprivation was implemented to facilitate sleep onset in the unfamiliar laboratory environment, a methodological approach that minimizes difficulties falling asleep without significantly affecting sleep architecture (Deuker et al., 2013). On the measurement day, participants were advised to abstain from caffeine, as it has been demonstrated to impact sleep quality (Hindmarch et al., 2000).

Data acquisition

Data acquisition sessions were conducted using a 3 Tesla Phillips Achieva MRI (Philips, Amsterdam, Netherlands) scanner at the Bergmannsheil Hospital in Bochum, Germany. For each volume, 50 slices (thickness = 2.5 mm without gap, FOV = 96 mm x 96 mm,

voxel size: 2.5 mm isotropic) encompassing the entire brain, oriented parallel to the inferior edge of the occipital and temporal lobes, were acquired with an EPI sequence. The slices had a repetition time (TR) of 3000 ms, an echo time (TE) of 30 ms, and a flip angle of 83. For each participant, structural images were acquired with a T1-weighted 3D sequence (TR/inversion time (TI)/TE/flip angle = 1570 ms/8.4 ms/3.42 ms/ 8, FOV = 256 × 256 × 220 mm³, matrix size = 256 × 256 × 220 voxels, voxel size = 0.929 mm × 0.929 mm × 1mm).

Simultaneous with the fMRI scanning, a 14-channel MR-compatible system (Brain Products GmbH, Gilching, Germany) was utilized, along with ten cortical (EEG) electrodes. Among these, two electrodes were positioned to record electrooculography (EOG), three electrodes on the chin monitored electromyography (EMG), and a single electrocardiogram (ECG) electrode was placed on the back to track participants' sleep patterns. Preprocessing was carried out using Brain Analyzer software (Brain Products GmbH, Gilching, Germany). Gradient artifacts were removed offline through a sliding average method using 21 intervals. The EEG data, originally sampled at 5000 Hz, was subsequently down-sampled to 500 Hz and low-pass filtered with a finite impulse response filter at a cutoff frequency of 70 Hz. To effectively remove ballistocardiogram and ocular artifacts, a template subtraction approach (Allen et al., 1998) was applied to handle artifacts. The preprocessed EEG data were then scored by three experts each, according to standardized American Academy of Sleep Medicine (AASM) polysomnographic criteria for sleep scoring (Iber, 2007).

The sessions began at 8:30 p.m. every week. Upon arrival at the medical facility, the EEG apparatus was prepared and ready for use within approximately 45 minutes. The environment was designed to promote relaxation, with the lighting adjusted to a low level to encourage the participants to become drowsy. Data collection started at approximately 9:15 p.m., following the participant's positioning within the scanner. The investigator monitored the participant's sleep status in real-time via EEG. Once it indicated that the participant was asleep for a stable period, the investigator proceeded to awaken them by calling their name. The mean number of awakenings per session was 10, ranging from four to 14 verbal reports per session, including reports when no dream was remembered. Communication following participant awakening was standardized and recorded. Upon being awoken in the MRI scanner, participants were asked to, "Please report everything that was going through your mind immediately before I called your name" (Foulkes, 1962). Following the verbal report, participants were asked to rate their mentation according to the following questions (in depth explanation in the following section): "How deep was your sleep?", "How much did you dream?", "How emotional was your dream overall?",

“How connected or storylike was the dream?”, “Were you trying to do anything in your dream, or did you feel motivated to do anything?”, and “How visual was the dream?”. If the initial report was brief or lacked detail, participants were asked the follow-up question: “Can you remember anything else?” or “Please provide a more detailed description”. After 90 minutes in the scanner, participants were woken for the last time and removed from the scanner. Participants were allowed to wash their hair and supplied with shampoo and a hairdryer if necessary.

Subjective and Objective Measures

The participants were requested to evaluate their dreams using a series of scales assessing various aspects of their sleep and dreaming experiences. The first scale was designed to assess sleep depth, with participants rating their sleep experience on a scale from 0 (indicating wakefulness) to 3 (indicating deep sleep). The second scale evaluated the amount of dreaming, with ratings ranging from 0 (indicating no dreaming) to 4 (indicating a significant amount of dreaming). The third scale was designed to assess the emotional intensity of the dreams, with ratings ranging from 0 (indicating no emotional intensity) to 3 (indicating a high level of emotional intensity). Should a participant assign an emotional intensity rating above 0, they must specify whether the dream was perceived as pleasant, unpleasant, or a combination of both. The fourth scale evaluated the coherence or narrative structure of the dream, which we will refer to as storylikeness, with scores ranging from 0 (indicating a lack of coherence) to 4 (indicating a high degree of coherence). The fifth scale evaluated the degree of motivation or goal-directed behavior exhibited by the participant within the dream, with responses ranging from 0 (indicating a lack of motivation) to 3 (demonstrating a high level of motivation). Lastly, the sixth scale evaluated the visual clarity of the dream, with ratings ranging from 0 (no visual imagery) to 4 (high detail and clarity, akin to waking life). Questions related to sleep depth and the amount of dreaming are regularly used in dream research to assess subjective sleep and dreaming quality (Roth et al., 1972; Kramer & Roth, 1979). The remaining questions were validated through a factor analysis of 159 dream reports, predicting three subscales: dream intensity, pleasantness, and visuality (Wainstein, 2013). These subscales accounted for 52.32% of the variance in the sample and correlated with previous objective analyses of dream dimensions (Hauri et al., 1967).

In addition to the subjective ratings, objective measures of the dream reports were conducted by two independent raters. The first measure, Total Recall Count, involved counting the meaningful words in each dream report to quantify the length and richness of the dream mentation, serving as an indicator of the amount of dreaming (Antrobus, 1983; Oudiette et al., 2012). The second measure, relation to everyday

experience, assessed the bizarreness of the dream by rating how realistically the dream content could occur in everyday life. This scale ranged from 1 (high relation to everyday experiences) to 5 (no relation to everyday experiences) (Foulkes & Pope, 1973).

Next Day Measures

Subsequent to the scanning session, participants were contacted by telephone at least 12 and no more than 20 hours later to ascertain whether they could recall any mental activities from the prior session. These telephone conversations were conducted in a standardized manner to ensure consistency across participants. Subsequently, the post-scan questionnaire, which included the transcribed dream reports from the previous night, was transmitted to each participant via email. The participants were then instructed to complete the questionnaire, which required them to assess a number of aspects related to their dream recall and significance.

First, participants were asked to rate the extent to which they recalled the dream after reading the transcription, using a scale from 0 (indicating no recall at all) to 4 (indicating complete recall). Secondly, participants were asked to evaluate the significance or meaningfulness of the dream on a scale from 0 (indicating no significance) to 5 (indicating extreme significance). Furthermore, participants were asked whether the dream was related to a current concern in their life, with a binary response option of "yes" or "no." If the response was affirmative, participants were instructed to rate the strength of this concern on a scale from 1 (very little concern) to 5 (extremely concerned). Finally, participants were requested to identify and mark any portions of the dream reports that they believed were related to real-life experiences from the previous week.

Long-Term Memory Recall

Six months after the final scanning session, participants were contacted by phone and asked to assess their memory of each mentation report after it was verbally recited to them. They rated their familiarity on a scale from 0 (no recollection) to 4 (a clear, vivid memory of the dream). Out of ten participants, only eight agreed to participate in this follow-up assessment.

Global Dream Index Calculation

To integrate the various subjective and objective dream measures into a single representative variable, we applied principal component analysis (PCA) to the behavioral dataset. Before performing PCA, all variables (amount of dreaming, motivation, emotion, storylikeness, visual, meaningful, concern, memory next day, memory six months, total recall count, and bizarreness) were subjected to a centering

and scaling process. The first principal component (PC1), which accounted for the greatest proportion of variance across the dream measures (34.9%), was extracted and utilized as the GDI. This index represents a composite score for each subject, encapsulating the shared variance among the original variables.

Preprocessing

Data preprocessing was performed using the *fMRIprep* toolbox version 21.0.2 (Esteban et al., 2019). The toolbox pipeline utilizes a combination of several well-known software packages for fMRI data pre-processing and constitutes a robust tool that also generates quality reports.

Structural Data

The pre-processing of the structural data using the *fMRIprep* toolbox was performed in the following steps: firstly, the T1w images were corrected for intensity non-uniformity (INU) with *N4BiasFieldCorrection* (Tustison et al., 2010), distributed with *ANTs* 2.3.3 (Avants et al., 2008), RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the *antsBrainExtraction.sh* workflow (from *ANTs*), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using *fast* (*FSL* 6.0.5.1:57b01774, RRID:SCR_002823, (Zhang et al., 2001)). Brain surfaces were reconstructed using *recon-all* (*FreeSurfer* 6.0.1, RRID:SCR_001847, (Dale et al., 1999)), and the brain mask estimated previously was refined with a custom variation of the method to reconcile *ANTs*-derived and *FreeSurfer*-derived segmentations of the cortical gray-matter of *Mindboggle* (RRID:SCR_002438, (Klein et al., 2017)). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with *antsRegistration* (*ANTs* 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* ((Fonov et al., 2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym), *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* ((Evans et al., 2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym.).

Functional Data

First, a reference volume and its skull-stripped version were generated by aligning and averaging 1 single-band reference (SBRef). Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using

mcflirt (FSL 6.0.5.1:57b01774, (Jenkinson et al., 2002)). The estimated *fieldmap* was then aligned with rigid-registration to the target EPI (echo-planar imaging) reference run. The field coefficients were mapped on to the reference EPI using the transform. The BOLD reference was then co-registered to the T1w reference using *bbregister* (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with six degrees of freedom. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed following Power (absolute sum of relative motions, (Power et al., 2014)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., (2014)). The three global signals were extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, (Behzadi et al., 2007)). Principal components were estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al., (2007) in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each *CompCor* decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. Many internal operations of *fMRIPrep* use *Nilearn* 0.8.1 ((Abraham et al., 2014), RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

For the streamlined application of additional data-cleaning strategies within a single framework, we utilized rs-Denoise (Dubois et al., 2018; Kliemann et al., 2022), see <https://github.com/adolphslab/rsDenoise>), an open-source Python-based pipeline. This pipeline involved several steps: (1) z-score normalization of the signal at each voxel; (2) removal of linear and quadratic trends with polynomial regressors; (3) utilization of *fMRIPrep's aCompCor* parameters, to regress out five components derived from CSF and white-matter signals; (4) utilization of translational and rotational realignment parameters and their temporal derivatives as explanatory variables in motion regression; (5) temporal filtering was performed with a discrete cosine transform (DCT) filter with a cutoff frequency of 0.008 Hz. Lastly, the pre-processed runs were smoothed using a 4-mm full-width at half maximum (FWHM) Gaussian kernel and trimmed to the last minute before each session ended (meaning the last minute before participants were awakened).

Connectivity-Correlation Analysis

In this analysis, we computed partial correlations between functional connectivity edges within the resting state networks and GDI, controlling for subject variability. First, trimmed individual time-series data were extracted from the preprocessed fMRI data using a predefined mask (Schaefer2018, 400 Parcels and 7 Networks and Tian Subcortex scale 1) (Tian et al., 2020) and transformed into functional connectivity matrices using Pearson correlation. From these, we isolated the lower triangular edges of each network. To account for individual differences, we performed Spearman partial correlation analyses on each edge using the *Pingouin Python* package, with subject IDs as a covariate to control for repeated measures. The resulting correlation coefficients and p-values were then corrected for multiple comparisons using the false discovery rate (FDR) method (Benjamini & Hochberg, 1995). Significant edges were identified, and results were visualized by plotting both the partial correlations and the connectivity matrices of significant correlations ($p < 0.05$). This approach allowed us to identify specific functional connections within resting-state networks significantly associated with GDI, independent of individual subject effects.

Results

Study Population and General Results

The average sleep quality index among participants was 3.4 ($SD = 0.7$), the average BMI index was 21.67 ($SD = 2.24$), and the average frequency of dream recall was 3.9 times per week ($SD = 1.94$). All participants slept a minimum of four times in the scanner,

two participants had five sessions. A total of 372 simultaneous EEG/fMRI recordings followed by a dream report were collected. Thirty recordings were excluded from the present analysis because the final epoch scoring indicated wakefulness. After conducting quality checks and identifying significant imaging artifacts, additional seventeen recordings were excluded. One further recording was removed due to the absence of the accompanying EEG recording. This resulted in 324 usable EEG/fMRI recordings across participants. Figure 1 illustrates the total amount of dreaming, a subjective measure rated by each participant for each collected dream report.

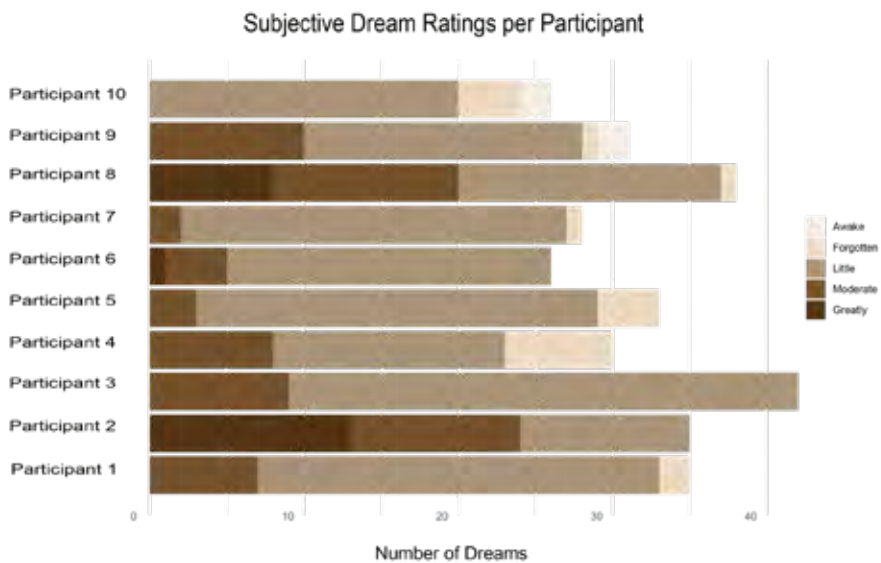


Figure 1: Subjective Dream Ratings per Participant. The amount of dreaming participants rated each awakening on a scale of 0–4: 0 – awake, 1 – forgotten/none, 2 – little, 3 – moderately, 4 – greatly.

A total of three participants indicated that they had experienced "greatly" dreams, with two of these participants, namely participants 2 and 8, providing the majority of these reports. Neither of these participants reported any instances of forgotten or no dreams. In contrast, participants 4 and 10 were notable for their frequent reports of forgotten or no dreams. The most prevalent category was "little" dreaming, constituting 212 out of 324 reports (65.43%). Similarly, participants exhibited variability in their categorization of thought-like dreams, with some labeling them as "little" and others as "forgotten." The dreams described as forgotten exhibited considerable variation. Some participants recalled vague details but felt they had forgotten most of the content, while others reported complete amnesia or the absence of dreaming. The bar graphs displayed in Figure 2 demonstrate the standardized

subjective emotion, visual perception, connectedness, and motivation ratings for each participant. It should be noted that these measures were only standardized to more clearly illustrate the extent to which participants fall above or below the group mean. Table 1 summarizes the relationship between subjective and objective dream ratings with the amount of dreaming.

Table 1: Dream Measure Means in Relation to Amount of Dreaming.

Amount	depth	moti	emo	story	vis	mean	con	mem	mem6	word	biz
<i>Forgotten</i>	1.60	0.14	0.57	0.71	1.00	1.60	2.00	0.20	0.28	3.95	0.82
<i>Little</i>	1.46	1.21	1.33	1.47	2.31	1.32	2.16	0.33	1.06	15.67	2.05
<i>Moderate</i>	1.87	1.54	1.40	1.80	2.62	1.62	2.13	0.34	1.60	25.25	2.24
<i>Greatly</i>	1.90	2.04	2.09	2.04	3.72	1.36	2.00	0.40	2.27	45.15	2.93

Moti=motivation in the dream, emo=emotions, story=storylikeness/ narrative cohesion, vis=visual perception, mean = whether the dream is meaningful, con = related to concerns in real life and the severity of the concerns, mem= cued next day memory, mem6 = cued memory at six months, word = total recall count, biz = bizarreness.

The correlation matrix (Figure 3) indicates that the GDI is strongly correlated with each of its component measures, thereby demonstrating its effectiveness in combining both subjective and objective scales into a representative index of global dreaming. Although future research may demonstrate that either subjective or objective measures are more closely correlated with neural activity, the current composite index is utilized under the statistical assumption that combining multiple measures of the same construct reduces measurement error, thereby enhancing both reliability and validity.

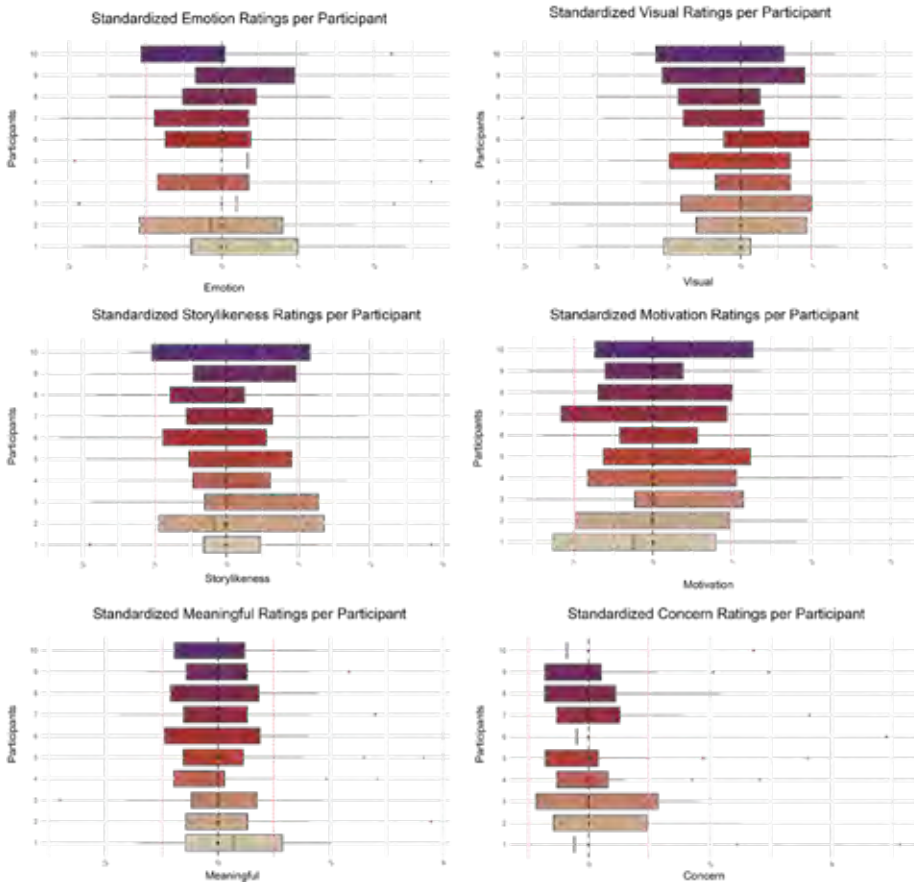


Figure 2: Standardized Subjective Dream Ratings per Participant. This figure presents dream ratings based on six subjective scales. Emotional intensity was rated from 0 (no intensity) to 3 (high intensity), with an additional categorization of dreams as pleasant, unpleasant, or mixed for ratings above 0. Visual clarity ranged from 0 (no visual imagery) to 4 (high clarity, resembling waking life). Storylikeness or narrative structure ranged from 0 (no coherence) to 4 (high coherence). Goal-directed behavior (scale 5) measured the degree of motivation within the dream, from 0 (no motivation) to 3 (high motivation). Next day measures assessed how meaningful the dream report was ranging from 0 (not at all) to 5 (extremely), and how concerning the dream report was, if the answer was yes, the concern severity ranged from 1 (very little) to 5 (extremely).

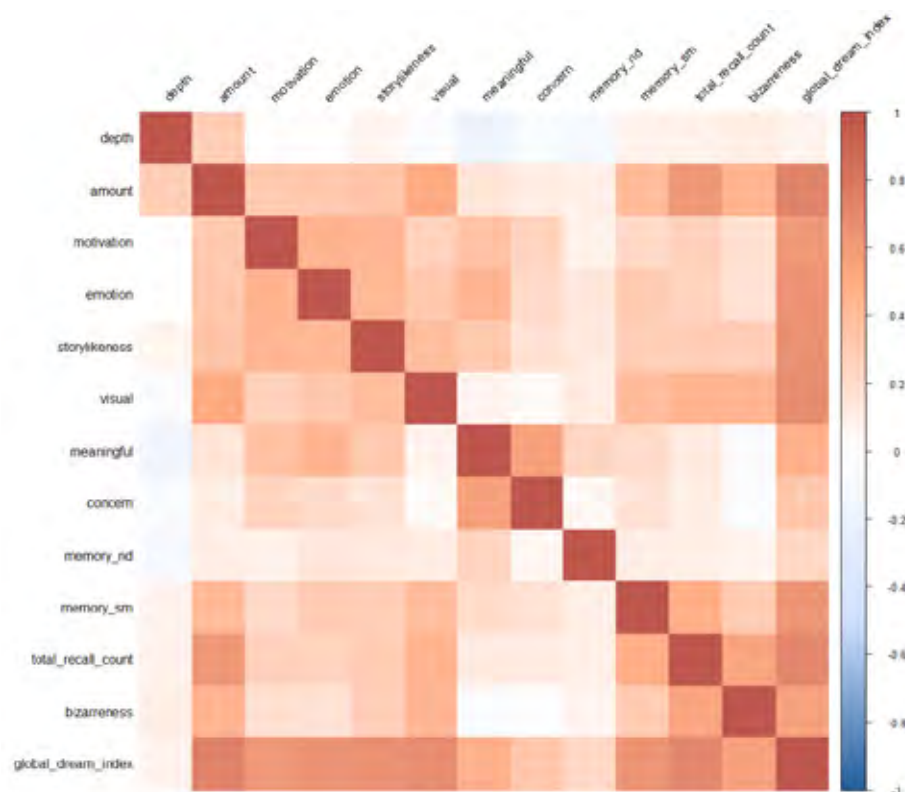


Figure 3: Correlation Matrix Between the Global Dream Index (GDI) and Its Component Measures. The correlation matrix demonstrates that GDI is strongly correlated with each of its component measures, effectively combining subjective and objective scales into a comprehensive index of global dreaming.

Functional Connectivity Association with Global Dream Index

We identified several functional connectivity edges across all seven resting-state networks and subcortical regions that survived multiple comparison corrections and were associated with GDI. Although these edges displayed positive functional connectivity values, the majority of correlations between the functional connectivity edges and GDI were negative. However, specific associations were positive, suggesting that stronger connections in these edges correlate with richer dream experiences. These positive correlations were exclusively found within the association networks: DMN, frontoparietal, and ventral-attention networks (Figure 4). Specifically, within the DMN, positive associations emerged between the left temporal cortex and the right dmPFC, left parietal regions and the right ventral prefrontal cortex, the right parietal cortex and both the right dmPFC and right ventral prefrontal cortex, as well as between the right dmPFC and the precuneus/posterior cingulate cortex. In the frontoparietal Network, positive associations were found between the right parietal

cortex and both the right precuneus and right temporal cortex. Lastly, in the Ventral Attention Network, a positive association was observed between the left temporo-occipital cortex and the frontal operculum/insular cortex.

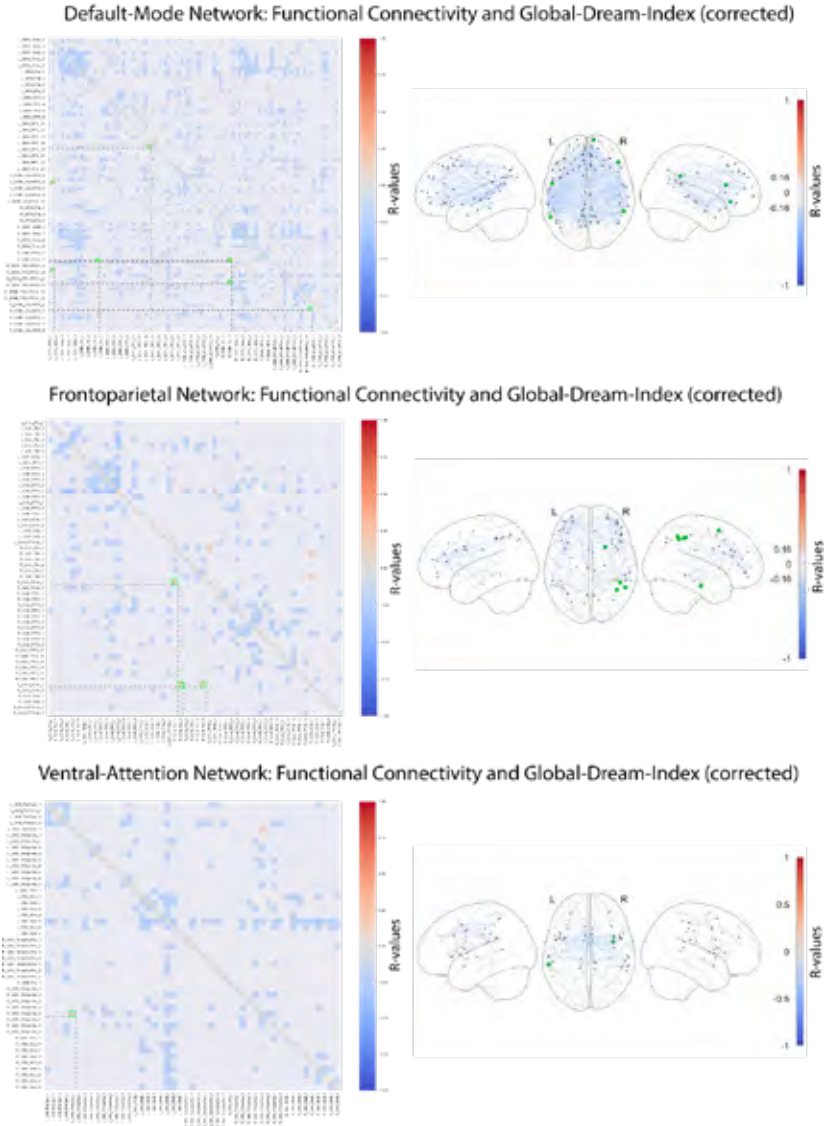


Figure 4: Correlation Matrix Between Resting-State Networks and Global Dream Index (GDI). In the top panel, the left side displays the correlation values between the connectivity edges of the Default-Mode Network (DMN) and GDI. In contrast, the right side shows a glass-brain illustration of these edges with their respective coordinates. The middle and bottom panels present the same information for the frontoparietal and ventral-attention Networks, respectively. Positive correlations are highlighted in green on the connectivity matrix and the glass-brain plots.

Discussion

This study explored how functional connectivity within resting-state networks supports NREM mentation, integrating subjective and objective dream measures through a combination of simultaneous EEG/fMRI and a serial awakening paradigm. Our findings reveal that resting-state networks, particularly the default-mode, frontoparietal, and ventral attention networks, contribute to dream experiences during light NREM sleep as measured by the newly developed GDI. Specifically, we found positive associations between functional connectivity within the DMN, frontoparietal, and ventral attention networks and richer dream experiences. These results support the hypothesis that the DMN, which facilitates self-reflection, mind-wandering, and memory retrieval (Binder et al., 1999; Buckner et al., 2008; Andrews-Hanna et al., 2010), may underlie internal mentation during light NREM sleep. This reinforces the value of GDI as a comprehensive metric that integrates both subjective and objective dimensions to capture inter- and intra-subject variability in dream experiences.

Extensive research has highlighted the role of the dmPFC in self-referential processing and its connectivity with the PCC across both wakefulness and sleep. Our findings align with studies that documented dmPFC-PCC connectivity during light and deep NREM sleep (Koike et al., 2011), suggesting that this connectivity supports integrative processes essential for constructing complex dreams. During wakefulness, the dmPFC shows heightened activity when individuals focus on their current self as opposed to their past or future selves (D'Argembeau et al., 2008, 2010). It also shows greater activation during self-focused thoughts and internally directed cognition, as opposed to externally focused tasks (Raij & Riekkki, 2017). In sleep, the dmPFC may facilitate the incorporation of self-reflective and social elements, enhancing dream complexity and narrative depth. This aligns with evidence showing that recent memories, especially from the preceding day, frequently appear in dreams during both light NREM and REM sleep (Picard-Deland et al., 2023), consistent with the dmPFC's role in processing the present self and integrating recent memories into dream contexts. While early PET studies found partial reactivation of the dmPFC during REM sleep but no significant connectivity with the PCC (Koike et al., 2011), a magnetoencephalography study report increased gamma-band activity in the dmPFC during both REM and late NREM sleep, suggesting that this region may play a broader role across sleep stages and may support dream experiences (Ioannides et al., 2009). Further research is needed to clarify dmPFC-PCC connectivity, particularly in deep NREM and REM sleep, and its relationship to dream content.

Our study also found associations between functional connectivity within the frontoparietal and ventral attention networks and richer dream experiences. The

frontoparietal network, which supports goal-directed behavior, cognitive control, and attention (Marek & Dosenbach, 2018), showed enhanced connectivity and relationship between the right parietal cortex, precuneus, and temporal cortex during NREM mentation, suggesting that these coordinated cognitive functions may support the formation of complex dream content during light NREM sleep. Previous research has shown that temporal coupling between the frontoparietal network and the DMN enables executive regions in the frontoparietal network to guide, evaluate, and select among streams of spontaneous thoughts and memories generated by the DMN (Andrews-Hanna et al., 2014; Fox & Christoff, 2014). This co-activation has been linked to processes such as autobiographical memory recall, mentalizing, and future-oriented thinking (Spiers & Maguire, 2006; Spreng et al., 2009; Christoff, 2012; Gerlach et al., 2014), which may similarly support dream coherence and narratives structure. Light NREM sleep, which is characterized by vivid visual imagery and brief but elaborate dreams (Nielsen, 1992; Hori et al., 1994; Hayashi et al., 1999), may engage frontoparietal regions, particularly the parietal-temporal connections, in sensory and mnemonic integrations rather than full executive control.

Within the ventral attention network, the frontal operculum plays a key role in regulating cognitive control by modulating activity in category-selective occipito-temporal regions (Higo et al., 2011), contributing to perceptual and attentional shifts relevant to dreaming. The frontal operculum's top-down modulation on posterior brain regions helps determining which representations are enhanced or suppressed based on behavioral relevance (Higo et al., 2011), consistent with our findings of functional connectivity between the frontal operculum and temporo-occipital areas associated with enhanced NREM mentation. Given the pivotal role of posterior cortical activity in shaping dream experiences (Siclari et al., 2017), such a regulatory influence could contribute directly to the richness of dream imagery. Notably, patients with lesions near or in the temporo-parieto-occipital junction report diminished or absent visual dream imagery (Solms, 1997), emphasizing the importance of connectivity between the frontal operculum and temporo-occipital regions in contributing to the vividness and complexity of dream narratives.

Our findings emphasize the essential role of the ventral prefrontal cortex and occipitotemporal connectivity in dream generation and content, supporting the notion that dreaming is driven by specific cerebral activations rather than being exclusive to REM sleep. Clinical lesion studies reveal that damage to the ventral prefrontal cortex, particularly the ventromedial white matter, leads to complete cessation of dreaming, highlighting this region's importance in generating the episodic qualities of dream cognition (Jus et al., 1973; Solms, 1997). This is consistent

with the ventral prefrontal cortex's involvement in value-based decision-making, future-oriented thought, and mind-wandering, all essential components of the imaginative and self-reflective nature of dreams (Bertossi et al., 2016; Bertossi & Ciaramelli, 2016; Schneider & Koenigs, 2017). Additionally, our findings implicate temporo-occipito-parietal regions, where connectivity appears essential for visual and spatial dream imagery, with lesions in these areas leading to dream imagery deficits similar to those observed in waking perception (Solms, 2000). We found no positive associations between the GDI score and limbic, subcortical, visual, and somatomotor networks, nor did we find any significant associations between resting-state network connectivity. Thus, our results support a framework in which specific activations within the ventral prefrontal cortex and temporo-occipital regions are crucial for translating sleep-related brain activity into the vivid, narrative experiences characteristic of dreams.

While our study focused on the relationship between large-scale resting-state network connectivity during NREM mentation and the richness of dream experiences based on the GDI score, it did not extend analyses into the immediate post-awakening period. Interesting findings by Vallat et al. (2020) demonstrate that brain functional connectivity upon awakening can significantly predict interindividual differences in dream recall frequency. Specifically, high dream recallers exhibited enhanced connectivity within the DMN and between the DMN and memory-related areas, for instance, the precuneus, medial prefrontal cortex, and angular gyrus, five minutes after awakening from sleep. These patterns suggest that successful dream recall may not only depend on neural activity during sleep but also on post-awakening reactivation and maintenance of memory-related connectivity. In contrast, our study showed that similar DMN nodes are already engaged during sleep and are associated with the richness of dream content. The convergence of these findings supports a broader model in which both intra-sleep and transitional neural dynamics contribute to the encoding and retrieval of dream experiences.

This study provides valuable insights into how functional connectivity within resting-state networks, particularly the default mode and frontoparietal networks, may support dream generation during light NREM sleep. However, several limitations should be considered. A primary limitation lies in the unnatural setting of the MRI scanner, which, while consistent across participants, could have impacted their natural sleep patterns and dream experiences. Additionally, the study did not specifically aim to investigate the behavioral effects of dream recall or memory consolidation, suggesting that future research designed to directly assess how sleep influences dream memory could yield more precise findings. Another

limitation involves the participant selection: this study exclusively examined high dream recallers, limiting generalizability, as dream recall frequency likely differs between high and low dream recallers (Schredl & Montasser, 1996). Expanding this research with a larger and more diverse sample across a full night of sleep, along with assessments of personality factors, could shed further light on the complex relationships between various sleep stages, their shared neural mechanisms for dream generation and recall, and associated memory processes. Tailored tasks, such as those directly targeting memory consolidation, may also help clarify these interactions more effectively. Finally, while the GDI was developed to address the challenge of analyzing individual measures with a moderate sample size, it introduces a new construct that, though valuable for this study, is difficult to compare with prior research that did not employ this composite measure.

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Data availability

Data will be available upon request.

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Chapter 6

General Discussion

In this thesis, I have presented a series of studies investigating the trait and state neural correlates of dreaming using several MRI modalities. My first goal was to review the progress made in sleep neuroimaging, focusing on influential studies and understanding the technical and methodological challenges that have emerged over time (**Chapter 2**). A significant limitation I identified in previous research is the small sample sizes that have understandably constrained many sleep neuroimaging studies. To address this limitation, a large cohort study was conducted to investigate whether dysfunction in emotional regulation processes, particularly involving the prefrontal cortex and amygdala, could be a predictor for nightmare frequency (**Chapter 3**). Interestingly, the results supported the null hypothesis, even when replicated in an independent large sample. This led me to critically replicate two whole-brain studies in the literature, which also yielded null findings. These results raised concerns about the need for greater statistical rigor in sleep neuroimaging studies. Another gap I identified in the field was the need for more research integrating multiple neuroimaging modalities. I applied a modality-fusion approach to address this, combining gray matter, white matter, and functional connectivity features to examine their relationship to dream recall frequency. This method provided a comprehensive, data-driven understanding of the structural and functional neural correlates of retrospective trait dream recall (**Chapter 4**). Next, I investigated the functional connectivity correlates of dreaming using simultaneous EEG/fMRI recordings combined with a serial awakening paradigm during sleep (**Chapter 5**). Many previous studies lacked quantified measures for each dream report, limiting their ability to systematically analyze the neural basis of dreaming. By implementing this combined methodology, I aimed to gain new insights into the neural dynamics of resting-state networks associated with dream experiences during light sleep. Here, I discuss key challenges in sleep neuroimaging, including methodological limitations and potential future directions, based on our experience collecting overnight sleep neuroimaging data. Finally, I interpret my findings in the broader context of dream research, highlighting how these studies advance our understanding of the neural mechanisms underlying dreaming.

Lessons learned: Methodological and technical challenges in sleep neuroimaging studies

Sleep neuroimaging studies present unique challenges compared to typical neuroimaging studies. The most significant is the difficulty of obtaining long, high-quality sleep recordings in an MRI scanner, which is an inherently uncomfortable and unnatural environment. This issue significantly contributes to the small sample sizes common in the field and is also why REM sleep remains understudied in neuroimaging research. Despite advances, the technical limitations of movement

restrictions and discomfort continue to pose significant barriers to collecting whole-night sleep data. Additionally, scanner noise has been demonstrated to suppress REM sleep, complicating efforts to study this stage. Nevertheless, the investigation of dreams through the use of neuroimaging during REM sleep is crucial for several reasons. Integrating neuroimaging data with dream content analysis has the potential to enhance our understanding of the possible functions of dreams, particularly in providing better spatial information concerning brain activation and organization during REM sleep. These studies may also offer insights into the role of dreams in emotional regulation. Furthermore, neuroimaging during REM sleep facilitates the differentiation between REM, NREM, and waking states, underscoring the parallels between mental experiences and brain physiology. This approach contributes to our growing understanding of the neurobiological underpinnings of the dream experience.

In **Chapter 2**, I discussed several strategies to increase recording durations from short naps to whole-night sleep studies. One promising approach is the use of adaptation nights, in which participants are familiarized with the scanner environment before the actual study. This method has been shown to improve sleep quality on subsequent nights without needing sleep deprivation protocols, which are effective but introduce their own confounds. A recent study also concluded that non-consecutive adaptation nights effectively control the first-night effect, justifying their current practice in sleep research (Wick et al., 2024). In addition, careful selection of participants based on sleep chronotype that aligns with recording times, combined with pre-study sleep hygiene protocols (e.g., maintaining a regular sleep schedule in the so-called "baseline week"), can further enhance sleep consolidation and stability. In our in-house study, these strategies have proven successful in prolonging recordings and achieving REM sleep, as we focused on the second part of the night instead of whole-night recordings. Despite high sleep pressure, one of the most significant obstacles is the discomfort participants experience in the scanner, particularly when asked to remain in a supine position. The discomfort and movement restrictions intended to prevent artifacts and the unavoidable loud scanner noise make it extremely difficult to obtain stable, long-duration sleep recordings. In total, 74 participants completed the intake session, but 32 were excluded based on our criteria, leaving 42 participants who were invited to the overnight imaging experimental sessions. Of these, 37 participants completed the two consecutive experimental nights, resulting in 79 overnight EEG/fMRI recordings and over 1,738 hours of data collection. Using our online sleep scoring method, 16 out of the 42 participants reached REM sleep during the experimental sessions, yielding a 38% success rate. We hope this number will

increase with offline scoring conducted by expert sleep scorers. This study could not be included in this thesis due to the time frame.

Although noise-canceling headphones have been marketed as a solution to reduce scanner noise, we have found that they do not always effectively cancel out the noise, depending on the specific imaging protocol. In addition, the added discomfort of wearing the EEG cap and noise-canceling headphones exacerbates participants' discomfort during long recording sessions and does not always fit the size of the MRI head coil. One strategy that showed some promise was to have participants listen to the scanner noise at home during the baseline week to habituate them to the scanner sound. However, more substantial technological advances in sleep neuroimaging, such as increased portability and reduced movement restrictions discussed in Chapter 2, have yet to emerge, leaving us dependent on the strategies mentioned above.

Going forward, the field will need to adopt innovative solutions to overcome these persistent challenges. One promising avenue is multi-site data collection. By combining resources across research centers and using standardized protocols, we can gather larger datasets that would otherwise be unfeasible for individual labs, allowing for larger samples and generalizable findings (called Multilab studies). Additionally, using preregistration reports and openly sharing data with the scientific community could increase collaboration, reduce redundancy, and accelerate progress in understanding sleep from neuroimaging lenses. In summary, sleep neuroimaging has many challenges, but it is not impossible to overcome them as technology advances. Continued improvement of research protocols and collaborative efforts across multiple sites will likely be vital to overcoming current limitations. With these strategies, the field can move towards a future in which full-night sleep recordings, including REM sleep, become feasible on a larger scale, ultimately advancing our understanding of the neural mechanisms of sleep and consciousness.

Reproducibility crisis

Over the past decade, reproducibility has received significant attention from the scientific community, driven by concerns about false positives and unreliable findings (Eklund et al., 2016; Gorgolewski & Poldrack, 2016). This effort to ensure reproducibility has led to the development of open science practices, including standardized tools, well-documented methods, transparent reporting, and public data-sharing repositories. Ensuring reproducibility is essential for validating scientific findings and advancing knowledge that can guide future research and benefit society. The credibility of published studies is critical for advancing science

and efficiently using public research funding. Irreproducible results waste resources and mislead subsequent studies, thereby stagnating progress.

In this context, reproducibility can be categorized into three types: 1) analytical reproducibility, which involves obtaining the same results using the original data and methods; 2) replicability, or the ability to replicate results with new data using the same methods, and 3) robustness, which refers to reproducing similar results using different methods on the same data (Botvinik-Nezer & Wager, 2023). Each type is critical in ensuring that findings can be reliably integrated into broader scientific knowledge and practical applications. In **Chapter 3**, I aimed to replicate previous findings that applied regional homogeneity (ReHo) analysis to investigate the neural correlates of nightmare frequency (Shen et al., 2016; Marquis et al., 2021) while addressing concerns about fMRI studies reproducibility. Using the same methods on a new dataset with an equivalent sample size, I employed two approaches to control for false positives: a traditional cluster-defining threshold with a parametric approach and a nonparametric permutation method. However, neither approach yielded significant results. False-positive rates are a well-documented challenge in neuroimaging studies, mainly when liberal cluster-defining thresholds are used, leading to spurious findings that do not replicate when tested in new datasets. Previous evaluations have demonstrated that parametric methods used in fMRI analysis can inflate false-positive rates due to violations of assumptions regarding spatial smoothness and independence (Eklund et al., 2016). Nonparametric permutation methods, while more robust, may still suffer from limited sensitivity when sample sizes are small or when the underlying effects are weak. These methodological limitations have prompted changes in the field toward stricter correction strategies, such as false discovery rate (FDR) correction, family-wise error (FWE) control, and open science practices emphasizing transparency and reproducibility. My unsuccessful replication analyses highlight the challenges faced in this field and emphasize the need to address false-positive rates through rigorous statistical methods. As neuroimaging continues to evolve, research on sleep and dreams must also adapt by incorporating these practices, particularly as we strive to increase sample sizes and enhance data recording durations. This chapter not only emphasizes the issues with reproducibility but also calls for a reassessment of the theoretical models that link specific brain regions associated with frequent nightmares, hoping that future studies will contribute to more reliable and robust scientific knowledge.

Neural Mechanisms of Dream Traits and States

This thesis offers original insights into the neural correlates and mechanisms underlying dreaming by examining both stable neural traits, such as individual differences in dream recall and nightmare frequency, and dynamic brain states associated with conscious mentation during sleep. The findings contribute to understanding how specific brain regions and resting-state networks facilitate dream experiences and recall frequency, thereby shedding light on the structural and functional neural mechanisms involved.

The phenomenon of nightmares, influenced by many psychological and neurophysiological factors, remains poorly understood mechanistically. While previous studies have accounted for nightmare distress (Marquis et al., 2021; Carr et al., 2022) or focused on populations with nightmare disorder (Shen et al., 2016), our null findings in **Chapter 3** suggest that future studies should carefully reconsider the variables and populations that are targeted in order to better understand the underlying causes of nightmare frequency and formation. The primary contribution of this chapter lies in its emphasis on the complexity of identifying the neural correlates of nightmare frequency as a proxy for nightmare formation across different populations. My work demonstrated the challenges in identifying consistent neural markers of nightmare frequency, even when robust statistics and large sample size were employed. Variability in study populations, such as healthy individuals versus those with nightmare disorder, and different measures (nightmare frequency or nightmare distress) emphasize the need for methodological standardization and larger, more representative sample sizes. From an alternative perspective, my findings suggest that nightmare frequency may not be strongly tied to specific, isolated functional differences. Instead, it may emerge from a dynamic interplay of factors, including neuronal mechanisms, personality traits, and emotional regulation abilities. This insight paves the way for future studies to adopt more integrative and systematic approaches. For example, multi-site studies combining retrospective and prospective trait-level assessments crucial to achieving reliable measurements that are less susceptible to memory bias, with task-based fMRI paradigms, such as emotional picture viewing tasks, could provide valuable insights. Furthermore, state-dependent factors, such as stress, anxiety, emotional reactivity, and trauma history, should be considered as potential confounding variables in future research to account for their potential influence on nightmare frequency. A key focus would be on functional connectivity, particularly between the amygdala and prefrontal cortex, still examining how regulatory processes differ under positive, neutral, and negative conditions. For example, the study could investigate whether functional connectivity in response to salient negative stimuli modulates nightmare frequency. Using the

prefrontal cortex as a seed, I would also explore if and how distinct connectivity patterns across conditions relate to nightmare frequency. As a secondary, exploratory analysis, I would investigate whether the observed cluster in the cerebellum displays different activation patterns across conditions and whether it contributes to frequent nightmares. By controlling state and trait factors, it will be possible to more accurately assess their role in the frequency and formation of nightmares and explore whether any residual variance might reveal core mechanisms underlying nightmare frequency. Ultimately, these refined methodological approaches may help clarifying the neuropsychological mechanisms driving nightmare experiences and facilitate more targeted interventions for affected individuals.

In **Chapter 4**, I showed that trait dream recall frequency was associated with distinct structural and functional brain features. A positive correlation was observed between higher dream recall frequency and increased white matter microstructure integrity in regions associated with memory integration and sensory processing, including the parahippocampal gyrus, superior parietal lobule, and occipital cortex. Conversely, a reduction in gray matter volume was observed in primary visual areas. These findings complement and extend the clinical-anatomical literature, as lesions in the visual association cortex have been demonstrated to impair specific dream imagery, such as color and facial imagery. In contrast, lesions in the primary visual cortex do not impact visual dreaming (Solms, 1997). For example, individuals who are cortically blind can still experience visual dream imagery, whereas those with lesions in V4 cannot generate faces or colors in their dreams. Similarly, lesions in primary sensory or motor cortices do not disrupt corresponding imagery in dreams, as evidenced by studies of regular somatosensory and aphasic patients (Solms, 1997, 2000). Moreover, regional cerebral blood flow (rCBF) activity in primary visual areas was reduced during REM sleep (Braun et al., 1998), which may corroborate our findings of decreased gray matter volume in these regions, as this reduction in rCBF may indicate diminished activity during dreams. Taken together, these findings suggest that regions actively involved in dream imagery, memory consolidation, and integration are microstructurally better organized in individuals with higher dream recall frequency, thereby enhancing trait dream content recall.

The results presented in **Chapter 5** also support clinical and anatomical observations indicating the importance of the ventral prefrontal, parietal, and occipitotemporal regions in dreaming. The study revealed a correlation between dream states, defined as conscious mentation during sleep, and functional connectivity patterns within resting-state networks during light NREM sleep. Functional connectivity within the default mode, frontoparietal, and ventral attention networks was essential for

facilitating the vividness and complexity of dreams, suggesting that dreaming results from specific functional processes that dynamically engage higher-order networks during sleep. Clinical studies have demonstrated that lesions in the ventromedial prefrontal cortex are associated with the complete cessation of dreaming (Solms, 1997), which was thought to be due to its connections with limbic structures. However, our results did not reveal significant associations between the limbic or subcortical regions and the global dream index or between resting-state networks and the global dream index, highlighting the importance of occipitotemporal-parietal and dorsal and ventral prefrontal-parietal interactions in generating complex dream imagery, further distinguishing the functional neural bases of dream traits and states. Furthermore, rCBF activity in the dorsolateral prefrontal cortex is significantly diminished during REM sleep (Braun et al., 1998), supporting that the executive functions associated with this region are suppressed during the dreaming state. It should be noted, however, that the results presented in Chapter 5 relate to functional connectivity rather than direct activity. Although connectivity patterns are indirectly related to activity, they represent different aspects of neural function since connectivity reflects how regions coordinate rather than their intrinsic activity levels.

Interpretation of Results and Their Contribution to Dream Research

Reflecting on my PhD journey, three seminal books have significantly influenced the direction of my work: *The Neuropsychology of Dreams* by Mark Solms, *Neurocognitive Theory of Dreaming* by William Domhoff, and *When Brains Dream* by Antonio Zadra and Robert Stickgold. Each of these works provided a unique perspective on understanding the neural correlates of dreaming. Solms' clinical-anatomical approach demonstrated that lesions affecting dreaming often paralleled deficits in waking cognition, challenging the traditional distinction between sleep and wakefulness. Domhoff emphasized the continuity of mental experiences across these states, urging a broader framework for dream research. Finally, Zadra and Stickgold's exploration of why we dream inspired my investigation into the mechanisms underlying dream traits and experiences. My studies sought to integrate two perspectives - dream traits (wakefulness) and dream experiences (sleep) - to bridge knowledge from neuroimaging with evidence from clinical and EEG studies of dreams, ultimately contributing to the broader understanding of the brain mechanisms involved in dreaming.

The default mode network (DMN), a large-scale brain network encompassing the medial prefrontal cortex, posterior cingulate cortex, precuneus, and parahippocampal gyrus, plays a central role in internally directed cognitive processes such as self-referential thought, memory retrieval, task-unrelated cognition, and

the mental simulation of imagined scenarios. As I reviewed in Chapter 2, the DMN remains active during light NREM sleep, decouples during deep NREM sleep, and reactivates during REM sleep. This activity pattern supports the hypothesis that dreaming represents an intensified and immersive form of spontaneous thought primarily driven by the DMN. This hypothesis also aligns with evidence showing that the same regions support both waking mind-wandering and dreaming, suggesting a continuum of internally directed cognition across states of consciousness (Domhoff & Fox, 2015).

My findings, presented in Chapters 4 and 5, support and extend this hypothesis by highlighting the critical role of the DMN and associated networks in both dream traits and dream states. Higher dream recall frequency was associated with enhanced brain microstructure in key DMN regions such as the parahippocampal gyrus and higher-order visual areas. These structural features likely facilitate the cognitive processes underlying vivid and complex dream content and recall. Functional connectivity analyses further revealed that interactions between the DMN, frontoparietal, and ventral attention networks during light NREM sleep are essential for generating organized and immersive dream narratives. These align with clinical evidence that lesions in ventral prefrontal and occipitotemporal regions disrupt dreaming, while lesions in primary sensory and motor cortices do not. My findings highlight the dynamic interplay between these regions, as dreaming involves both a decoupling from external sensory processing and a heightened engagement of higher-order networks.

One area where further research is needed is in directly comparing ongoing task-unrelated thoughts during wakefulness with dreaming. While dreaming significantly overlaps with waking mind-wandering in its reliance on spontaneous DMN activity, dreams' immersive, narrative-rich nature reflects a heightened recruitment of higher-order visual and cognitive systems. Although my work associates dream traits with brain activity during resting wakefulness, likely reflecting mind-wandering, there remains a gap in understanding how different task-unrelated thoughts map onto dreaming. Not all mind-wandering is equivalent to daydreaming, and although traditional research often uses these terms interchangeably, key differences exist (Dorsch, 2015). Daydreaming is more imagistic and purposeful, whereas mind-wandering can include diverse cognitive phenomena. Recent studies have started addressing these distinctions by comparing immersive and non-immersive mental imagery across waking and sleeping states (Kirberg et al., 2024) and addressing to what extent daydreaming involves an experience of dreaming while awake (Sanchez Alcaraz, 2024). Such approaches are imperative to differentiate and assess various

conscious experiences, serving as a valuable tool to facilitate the investigation of such differences and similarities at the mechanistic level.

My work substantiates and refines the DMN hypothesis of dreaming by combining multimodal neuroimaging and simultaneous EEG-fMRI with serial awakening paradigm to reveal the structural and functional correlates of dream recall and generation. This research highlights how structural traits, such as enhanced white matter microstructure in the parahippocampal gyrus and higher-order visual areas, overlap with and support functional processes like the dynamic interactions within the DMN, frontoparietal network, and ventral attention network. Together, these findings bridge the relationship between the neural substrates predisposing individuals to high dream recall and the functional mechanisms that generate the vivid, immersive, and narrative-driven dreaming experiences.

Future Directions and Research Outlook

The findings presented in this thesis contribute to the growing body of evidence regarding the neural mechanisms underlying sleep and dreaming. Future research could benefit from a multi-level characterization of dreams that integrates neuroimaging and neurophysiological data to explore the micro, meso, and macro aspects of dreaming. Replicating current findings in populations suffering from different types of parasomnia on a micro-scale will strengthen our understanding of the field, as has been done in sleepwalkers (Cataldi et al., 2024). Combining a minimal serial awakening paradigm with intracranial electrodes, particularly those placed in the frontal, parietal, and occipital regions, will provide finer evidence of neuronal firing through electrical potentials. To minimize patient burden, the study can focus on patients already undergoing intracranial EEG monitoring for clinical purposes, such as pre-surgical epilepsy evaluation. Additionally, limiting the number of serial awakenings by targeting key sleep stages (light/deep NREM and REM) based on real-time monitoring will reduce sleep disruption and fatigue. This integration could open new avenues for correlating brain activity with recalled dream content. On a meso scale, simultaneous EEG-fMRI recordings could be instrumental in identifying neuronal markers of dreaming, explicitly differentiating between dreams with and without content and forgotten and dreamless sleep. By combining these two neuroimaging techniques, we obtain better spatial information to identify a core "minimum dreaming network" integrating neurophysiological data with specific dream characteristics. On a macro scale, an emerging area of interest involves exploring mental experiences across the sleep-wake continuum. Evidence of local sleep and wake states has challenged the traditional binary distinction between sleep and wakefulness. Comparative studies of mind-wandering, daydreaming,

and dreaming may reveal shared cognitive and functional mechanisms underlying these internally generated experiences across various states of consciousness. Such investigations could clarify these mental states' roles in waking cognition and sleep function, particularly whether altered dreaming parallels altered mind-wandering or daydreaming. For instance, understanding the parallels between dreaming and mind-wandering could provide a novel framework for exploring the adaptive or maladaptive roles of these processes in clinical populations, such as individuals with PTSD and chronic ruminators.

From a clinical perspective, investigating dream alterations in specific populations could offer diagnostic and therapeutic benefits. For example, examining changes in dream content, such as increased vividness or violent themes in individuals with REM sleep behavior disorder (RBD), could yield insights into the neurological underpinnings of these alterations. Understanding if such changes correlate with dysfunctions in limbic, prefrontal, parietal, or occipital regions may help establish altered dreaming as a biomarker for neurological conditions like Parkinson's disease, where RBD is recognized as a prodromal marker. Since Parkinson's disease patients may also experience daytime hallucinations, it is essential to determine whether these are linked to sleep-related changes. These findings would enhance our theoretical understanding of dreaming and assist as an early detection and monitoring strategy for neurodegenerative disorders.

Overall, integrating neuroimaging techniques on various levels of characterization will strengthen our understanding of sleep-wake phenomenology and the potential translational of sleep and dreaming research to the clinical population. By bridging diverse methodologies, encouraging cross-disciplinary multi-site collaborations, and emphasizing robust and replicable findings, the field is well-positioned to make significant advances in understanding the interplay between brain activity and consciousness.

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Appendices

English Summary

Dutch Summary

Research Data Management

About the Author

Curriculum Vitae

Acknowledgements

Donders Graduate School

English Summary

Dreams have fascinated humankind for centuries, yet their neurobiological underpinnings remain elusive. This thesis investigates the neural mechanisms underlying dream traits and states by integrating multiple neuroimaging approaches, including structural and functional MRI, diffusion imaging, and simultaneous EEG/fMRI recordings. By addressing key methodological challenges in sleep neuroimaging and incorporating large-scale datasets, this work provides novel insights into the trait and state-dependent neural correlates of dreaming.

The first part of this thesis, Chapter 2, reviews the progress and challenges in sleep neuroimaging, highlighting the limitations of small sample sizes, lack of multimodal integration, and the difficulty of recording REM sleep in MRI environment. Chapter 3 critically reassesses the neural correlates of nightmare frequency, revealing null findings even in large cohorts and raising concerns about statistical rigor and reproducibility in the field. The study underscores the need for robust methodological frameworks and larger, well-controlled samples to establish reliable associations between emotional regulation processes (particularly prefrontal-amygdala interactions) and nightmare frequency.

To overcome the limitations of previous research, Chapter 4 employs a modality-fusion approach, combining gray and white matter microstructure with functional connectivity measures to examine their relationship with dream recall frequency. The findings reveal that individuals with higher dream recall exhibit enhanced white matter integrity in regions involved in memory integration and sensory processing, such as the parahippocampal gyrus, superior parietal lobule, and occipital cortex, while also showing reduced gray matter volume in primary visual areas. These results align with lesion studies demonstrating that visual association areas, rather than primary sensory cortices, are critical for dream imagery.

Chapter 5 shifts focus to state-dependent neural mechanisms of dreaming by utilizing simultaneous EEG/fMRI and a serial awakening paradigm. Functional connectivity analyses reveal that dreaming engages dynamic interactions between the default mode network (DMN), frontoparietal, and ventral attention networks during light NREM sleep. These findings refine existing models of dream generation, demonstrating that higher-order cognitive networks, rather than subcortical structures alone—play a central role in dream experiences. Importantly, while previous studies suggested limbic involvement in dreaming, this thesis finds no direct association between

limbic connectivity and dream experiences, emphasizing the role of occipitotemporal-parietal and prefrontal interactions in generating complex dream narratives.

This thesis contributes to dream neuroscience by integrating multimodal neuroimaging, large-scale replication studies, and rigorous statistical methods to reassess key theoretical models. The findings challenge traditional views of REM sleep as the primary substrate for dreaming and instead support a continuum model of internally generated cognition, where dreaming, mind-wandering, and spontaneous thought share overlapping neural mechanisms. Future research directions include multi-site collaborations, intracranial EEG studies, and comparative investigations of mind-wandering, daydreaming, and dreaming, which will further elucidate the relationship between conscious experience and brain activity.

By bridging insights from clinical lesion studies, functional neuroimaging, and electrophysiological research, this thesis advances our understanding of the neural basis of dream traits and states, paving the way for novel applications in sleep disorders, cognitive neuroscience, and consciousness research.

Dutch Summary

Dromen fascineren de mensheid al eeuwen, maar hun neurobiologische onderbouwing blijft onduidelijk. Dit proefschrift onderzoekt de neurale mechanismen die ten grondslag liggen aan droomkenmerken en -toestanden door meerdere neuroimaging benaderingen te integreren, waaronder structurele en functionele MRI, diffusiebeeldvorming en gelijktijdige EEG/fMRI opnames. Door belangrijke methodologische uitdagingen in slaapneurobeeldvorming aan te pakken en grootschalige datasets te integreren, biedt dit werk nieuwe inzichten in de kenmerken en toestandsafhankelijke neurale correlaten van dromen.

Het eerste deel van dit proefschrift, Hoofdstuk 2, geeft een overzicht van de vooruitgang en uitdagingen in slaapneuro-imaging, waarbij de beperkingen van kleine steekproefgroottes, het gebrek aan multimodale integratie en de moeilijkheid van het registreren van REM-slaap in MRI-omgevingen naar voren komen. In hoofdstuk 3 worden de neurale correlaten van de frequentie van nachtmerries kritisch opnieuw beoordeeld, waarbij zelfs in grote cohorten nulbevindingen naar voren kwamen en zorgen werden geuit over de statistische nauwkeurigheid en reproduceerbaarheid in het veld. De studie onderstreept de noodzaak van robuuste methodologische kaders en grotere, goed gecontroleerde steekproeven om betrouwbare associaties tussen emotionele regulatieprocessen (in het bijzonder prefrontale-amygdala interacties) en nachtmerrie frequentie vast te stellen.

Om de beperkingen van eerder onderzoek te ondervangen, gebruikt Hoofdstuk 4 een modaliteit-fusie benadering, waarbij grijze en witte stof microstructuur gecombineerd worden met functionele connectiviteitsmetingen om hun relatie met droomherinneringsfrequentie te onderzoeken. De bevindingen laten zien dat individuen met een hogere droomherinneringsfrequentie een verhoogde witte stof integriteit vertonen in gebieden die betrokken zijn bij geheugenintegratie en sensorische verwerking, zoals de parahippocampale gyrus, superieure pariëtale lobule en occipitale cortex, terwijl ze ook een verminderd grijze stof volume vertonen in primaire visuele gebieden. Deze resultaten komen overeen met laesiestudies die aantonen dat visuele associatiegebieden, in plaats van primaire sensorische cortex, cruciaal zijn voor droombeelden.

Hoofdstuk 5 verschuift de focus naar toestandsafhankelijke neurale mechanismen van dromen door gebruik te maken van gelijktijdige EEG/fMRI en een paradigma voor serieel ontwaken. Functionele connectiviteitsanalyses onthullen dat dromen dynamische interacties tussen het default mode netwerk (DMN), frontopariëtale

en ventrale aandachtsnetwerken inschakelt tijdens de lichte NREM-slaap. Deze bevindingen verfijnen bestaande modellen van droomgeneratie en tonen aan dat cognitieve netwerken van hogere orde - en niet alleen subcorticale structuren - een centrale rol spelen in droomervaringen. Belangrijk is dat, terwijl eerdere studies limbische betrokkenheid bij dromen suggereerden, deze dissertatie geen directe associatie vindt tussen limbische connectiviteit en droomervaringen, wat de rol van occipitotemporale-pariëtale en prefrontale interacties in het genereren van complexe droomverhalen benadrukt.

Deze dissertatie draagt bij aan de droomneurowetenschap door het integreren van multimodale neuroimaging, grootschalige replicatiestudies en rigoureuze statistische methoden om belangrijke theoretische modellen opnieuw te beoordelen. De bevindingen betwisten traditionele opvattingen van de REM-slaap als het primaire substraat voor dromen en ondersteunen in plaats daarvan een continuüm model van intern gegenereerde cognitie, waarbij dromen, dwalen door de geest en spontane gedachten overlappende neurale mechanismen delen. Toekomstige onderzoeksrichtingen omvatten samenwerkingsverbanden op meerdere locaties, intracraniële EEG-studies en vergelijkende onderzoeken naar dwalen in de geest, dagdromen en dromen, die de relatie tussen bewuste ervaring en hersenactiviteit verder zullen ophelderen.

Door inzichten uit klinische laesiestudies, functionele neuroimaging en elektro-fysiologisch onderzoek te combineren, bevordert dit proefschrift ons begrip van de neurale basis van droomkenmerken en -toestanden, waardoor de weg wordt vrijgemaakt voor nieuwe toepassingen in slaapstoornissen, cognitieve neurowetenschappen en bewustzijnsonderzoek.

Research Data Management

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethical Approval

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. All data collections of the three datasets in this thesis were approved by the local ethics committees.

Data Storage and Availability

The research data in chapters 3 and 4 are based on existing data that cannot be shared publicly because it is part of an ongoing study and is thus considered unanonymized under Danish law even if pseudonymized. However, researchers who wish to access the data may contact Dr. Kristian Sandberg (kristian.sandberg@cfin.au.dk) at The Center of Functionally Integrative Neuroscience and/or The Technology Transfer Office (TTO@au.dk) at Aarhus University, Denmark, and Prof. Dr. Michał Wierzbuch (michal.wierzbuch@uj.edu.pl) at the Institute of Psychology at Jagiellonian University, Poland, to make a data sharing contract.

The research data in chapter 5 have not been deposited in a public repository but is available upon request. Researchers may contact Prof. Dr. Nikolai Axmacher (nikolai.axmacher@ruhr-uni-bochum.de) at the Department of Neuropsychology, Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr-University Bochum, Bochum, Germany.

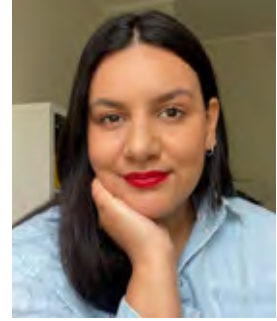
Interoperable and reusable

Each research chapter of this thesis provides a description of the experimental setup (including the used software and specific version), and access to the raw data needs to be requested. No custom code was used in this study. Publicly available software tools were used to perform analyses and are referenced throughout the manuscript.

About the Author

Mariana was born on July 19, 1990, in Barbacena, Brazil. Initially considering a career in medicine, she quickly realized that her aversion to blood made technology a better fit.

She earned a Bachelor's degree in Telecommunications Engineering from the Federal University of São João del-Rei (Brazil), where she first explored neuroimaging through EEG signal analysis.



Her interest in brain research deepened during an exchange program at the University of Alabama at Birmingham (United States), where she was introduced to MRI. This experience sparked her fascination with the neurological basis of neurodegenerative diseases, REM sleep, and vivid dreams.

Mariana went on to complete a Master's in Electrical and Computer Engineering at the University of Campinas (Brazil), applying deep learning algorithms to structural MRI data to classify different stages of Alzheimer's disease. Her growing passion for understanding the brain's activity during sleep led her to pursue a Ph.D. in Cognitive Neuroscience under the supervision of Dr. Martin Dresler at the Donders Institute (the Netherlands). Her research employs multimodal neuroimaging techniques to investigate the neural mechanisms underlying dreams, dream traits, and REM sleep.

Beyond science, Mariana enjoys traveling, fine arts, and cooking - using her travels as an opportunity to immerse herself in different cultures through food, art, and history. She is also a knitter, a huge tennis fan, and a lover of independent cinema.

Curriculum Vitae

Publications

- 2025 (In prep) **Pereira, M.**, Wainstein, D., Galdi, P., Krause, F., Axmacher, N., Dresler, M. Default-mode network involvement in non-REM sleep dreaming
- 2025 (Submitted) **Pereira, M.**, Terpstra, N., Rutiku, R., Sandberg, K., Dresler, M., Krause, F. Neural correlates of nightmares revisited: findings from large-scale fMRI cohorts. In bioRxiv: doi.org/10.1101/2024.07.02.601684
- 2025 (Submitted) **Pereira, M.**, Galdi, P., Mei, T., Rutiku, R., Mikkelsen, I.K., Llera, A., Scheeringa, R., Krause, F., Dresler, M., Sandberg, K. The Neural Architecture of Dream Recall Frequency: Insights from Interindividual Variations in Brain Structure and Function; In bioRxiv: doi.org/10.1101/2025.05.20.655114
- 2025 **Pereira, M.**, Chen, X., Paltarzhyskaya, A., Pacheco, Y., Muller, N., Bovy, L., Lei, X., Chen, W., Song, C., Lewis, L., Dang-Vu, T.T., Czisch, M., Picchioni, D., Duyn, J., Peigneux, P., Tagliazucchi, E., Dresler, M. Sleep Neuroimaging: review and future directions; *Journal of Sleep Research*
- 2024 Al-Shama, R., Uleman, J., **Pereira, M.**, Claassen, J., Dresler, M. Cerebral blood flow in sleep: a systematic review and meta-analysis; *Sleep Medicine Reviews*
- 2024 Rosenblum, Y., **Pereira, M.**, Stange, O., Weber, F.D., Bovy, L., Tziouridou, S., Lancini, E., Neville, D.A., Klein, N., Wolff, T., Stritzke, M., Kersten, I., Uhr, M., Classen, J., Steiger, A., Verbeek, M., Dresler, M. Divergent Associations of Slow-Wave Sleep versus Rapid Eye Movement Sleep with Plasma Amyloid-Beta; *Annals of Neurology*
- 2023 Kobayashi, I., **Pereira, M.**, Jenkins, K., Johnson III, F.L., Pace-Schott, E.F. Assessing the role of sleep in the regulation of emotion in PTSD; *Translational Methods for PTSD Research*

Conference Oral and Poster presentations

- International Association for the Study of Dreams – IASD, Kerkraide (2024): “Neuroarchitectural mapping of dream traits”
- SLAAP, Papendal (2023): “Neuroarchitectural mapping of dream traits: a promising perspective on deciphering excessive dreams and nightmares”
- World Sleep, Rio de Janeiro (2023): “Neuroimaging of dreaming: towards the neural correlates of trait dream recall”
- Dutch Neuroscience Meeting - DNM, Tiel (2023): “Neuroarchitecture mapping of dream traits”
- Sleep Europe, Athens (2022): “Neuroimaging of dreaming”
- Association For The Scientific Study Of Consciousness - ASSC25, Amsterdam (2022): “Nightmare frequency is associated with connectivity between the amygdala and prefrontal cortex”
- Association For The Scientific Study Of Consciousness - ASSC25, Amsterdam (2022): “A relationship between lucid dreaming and metacognitive capacity” – Poster presentation

Academic Courses

- DI Toolkit: Advanced course in fMRI data analysis (1EC)
- DI Toolkit: Advanced data analysis and source modeling of EEG and MEG data (1EC)
- DGS: GS Introduction Day (1/4 EC)
- DGS: Graduate School Day 1 (1/4 EC)
- DGS: Graduate School Day 2 (1/4 EC)
- DGS: Scientific Integrity Course (1/4 EC)
- DGS: Statistics for Absolute Beginners with JASP (2 EC)
- DGS: Peercoaching Peer (1/2 EC)
- RU: Poster Pitching (1 EC)
- RU: Presentation Skills (1,5 EC)
- RU: Scientific Writing for PhD Candidates (2 EC)
- RU: Academic English Conversation and Pronunciation (1,5 EC)
- RU: Writing a Review Article (1 EC)
- RadboudUMC: eBROOK course (1 EC)
- ESRS Sleep Science School (12 EC)
- Neurohackademy school

Extra-curricular training and certification

- Certified MRI user, Prisma and PrismaFit 3T scanner, Donders Centre for Cognitive Neuroimaging
- BROOK certification, by NFU eBROOK including CSB exam

International lab visits

- Lab of Prof. Dr. Karmele Lopez-de-Ipina, University of the Basque Country, San Sebastian, Spain (2023)
- Lab of Prof. Dr. Adrian Opre, Psychology Department, Universitatea "Babeş-Bolyai", Cluj-Napoca, Romania (2023)
- Lab of Prof. Dr. Michał Wierzchoń, Institute of Psychology, Jagiellonian University, Krakow, Poland (2022)
- Lab of Dr. Kristian Sandberg, Center of Functionally Integrative Neuroscience, Aarhus University, Aarhus, Denmark (2022)
- Lab of Dr. Claude Bajada, Faculty of Medicine and Surgery, L-Universita ta' Malta, Msida, Malta (2021)

Mentoring Experience

- Student supervision of bachelor internships: Noelle Terpstra, Biomedical Sciences, Nijmegen.
- Student Supervision of master internships: Erieta Bountouva, Cognitive Neuroscience, Nijmegen.

Lecturer and workshop teacher

- Summer School, Neuroscience of dreaming, Nijmegen, Netherlands: "Neuroimaging Roadmaps of Dreaming" (2024)
- BMS26 Neuroscience of Sleep, Master course for Biomedical sciences, Nijmegen, Netherlands: "Introduction to Sleep Neuroimaging" (2021)
- BMS26 Neuroscience of Sleep, Master course for Biomedical sciences, Nijmegen, Netherlands: "REM Sleep Behaviour Disorder and Narcolepsy" (2020-2021)
- BMS25 Medical Neuroscience: Functional imaging, Master Course, Nijmegen, Netherlands: "EEG Clinical Applications" (2020)

Societies and committees

- Member of the Radboud University Halkes Women+ Faculty Network (2021-2024)
- Member of the Nederlandse Vereniging voor Slaap-Waak Onderzoek (NWSO) Young Scientists Committee (2022-2024)

Grants and Awards

- | | |
|------|---|
| 2024 | Radboud Internationalization, for participating in World Sleep Conference (€400) |
| 2023 | Young Talent Fund, De Nederlandse vereniging voor Slaap – Waak Onderzoek (€800) |
| | COST Short-Term Scientific Mission, at University of the Basque Country (€1500) |
| | COST Short-Term Scientific Mission, at Universitatea "Babeş-Bolyai" (€1500) |
| 2022 | Radboud Internationalization, for participating in the Sleep Europe conference (€400) |
| | COST Short-Term Scientific Mission, summer school at Jagiellonian University (€1500) |
| | Dissemination Conference COST grant, for attending ASSC25 conference (€2000) |
| | COST Short-Term Scientific Mission, research stay at Aarhus University (€2500) |
| | Radboud Internationalization, for participating in ESRS Sleep Science School (€700) |
| 2021 | Science School, selected for the ESRS Sleep Science School |
| | COST Short-Term Scientific Mission, research stay at the University of Malta (€2500) |
| 2020 | Summer School, selected for the Neurohackademy school (online due to the pandemic) |

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First, I want to thank myself for being brave enough to complete this thesis and obtain a PhD title. If I look back at my younger self, I had always dreamed of this and always knew, deep down in my heart, that I was a scientist. I am proud to have fulfilled this dream. It was not always an easy-breezy ride of being a social butterfly enjoying conferences. There was a pandemic and countless curfews, which, as you know by now, have impacted the way we live our lives for good, and my initial PhD plan and mental health were no exception. I cannot count how many times I doubted myself, cried, broke down, and wanted to give up. I know I am not the only one to go through this during a PhD journey, but I wanted to make it real, and perhaps let you know that if this is your dream, you can do it too. I want to briefly thank everyone who supported me along the way.

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such as teachers in high school, or as lecturers in higher education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

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