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Variability in biological correlates of nightmares and implications for the development of new treatment options

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Clara Anna Luise Sayk

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1. BerichterstatterIn: Prof. Dr. Ines Wilhelm-Groch

2. BerichterstatterIn: Prof. Dr. Tanja Lange

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List of abbreviations

AASM	American Academy of Sleep Medicine
ANOVA	Analysis of Variance
APA	American Psychiatric Association
AVS	audiovisual stimulation
BAI	Beck's Anxiety Inventory
BDI	Beck's Depression Inventory
BPD	borderline personality disorder
CAP	cyclic alternating patterns
CGI	Clinician Global Impression scale
CTL group	control group
CTQ	Childhood Trauma Questionnaire
DBT	dialectical behavior therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiography
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
ERQ	Emotion Regulation Questionnaire
FFT	Fast Fourier Transform
FIRST	Ford Insomnia Response to Stress Test
HF	high frequency
HGSHS-5:G	Harvard Group Scale of Hypnotic Susceptibility 5-Item Short-Version
HRV	heart rate variability
ICA	independent component analysis
IES-R	Impact of Event Scale–revised
IRT	imagery rehearsal therapy
LF	low frequency
MeanRRI	Mean R-R interval
NBQ	Nightmare Behavior Questionnaire
NM group	nightmare group
NREM	non- rapid-eye-movement (sleep)

PANAS	Positive and Negative Affect Schedule
PGI	Patient Global Impression scale
pNN50	percentage of consecutive normal-to-normal intervals that differ by more than 50 milliseconds
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PTSD	posttraumatic stress disorder
REM	rapid-eye-movement (sleep)
RMSSD	Root Mean Square of Successive Differences
SCL-90-S	Symptom Checklist
SCR	skin conductance response
SDNN	Standard deviation of N-N interval
SF-A/R	Schlaffragebogen A
SPSS	Statistical Package for the Social Sciences
SWS	slow wave sleep
TAS	Tellegen Absorption Scale
TAU	treatment-as-usual
tDCS	transcranial direct current stimulation
TMR	targeted memory reactivation
VDAS	Van Dream Anxiety Questionnaire

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Abstract

Nightmares are very common in both the general population and individuals with psychiatric disorders. They can cause distress, sleep disturbance and impairment in daily functioning. Several biological correlates of nightmares have been investigated in the last decades, such as brain activity during sleep, changes in heart rate, electrodermal activity or cortisol levels. All of these measures indicate some form of hyperarousal which, together with impaired fear extinction, is indeed one of the central components of the integrative etiology model for nightmares. However, it is still unclear, how exactly hyperarousal and nightmares interact, i.e., whether hyperarousal actually is a causal mechanism or rather a byproduct of other processes. Likewise, it is still unknown whether it can be influenced through interventions for nightmares, such as imagery rehearsal therapy or - directly during sleep - with some form of stimulation or targeted memory reactivation (TMR). The aim of the three studies that constitute my thesis was to examine biological correlates of nightmares, especially cortical hyperarousal in individuals with frequent nightmares from different samples and the effects of imagery rehearsal therapy (IRT) and TMR on physiological correlates and nightmare symptoms using polysomnography and high-density EEG-measurements.

The first two studies focused on physiological correlates of nightmares and the effects of IRT. Study 1 addressed how physiological correlates differ between individuals with frequent nightmares and healthy controls and how an 8-week IRT group intervention influences nightmare symptoms and physiological correlates. Participants with frequent nightmares showed increased beta and gamma activity compared to healthy controls and their gamma activity during REM was reduced after the intervention.

In study 2, a similar paradigm was used to investigate the effects of imagery rehearsal therapy as an add-on to inpatient treatment for individuals with borderline personality disorder. While this study did not show any changes in physiological correlates, the intervention group experienced a significantly more pronounced reduction in anxiety, intrusions and hyperarousal.

Study 3 investigated the effects of experimentally manipulating these biological correlates. More specifically, whether reactivating a relaxation exercise with TMR in participants with frequent nightmares reduced hyperarousal and nightmare symptoms. While the reactivation did lead to a reduction in spindle count and density, another form of cortical hyperarousal, there was no influence on nightmare symptoms.

Taken together, I could demonstrate that i) increased (cortical) arousal plays an important role as biological correlate and shows sensitivity to treatment in various samples with frequent nightmares (participants with frequent nightmares but no severe co-morbidities as well as individuals with borderline personality disorder and frequent nightmares), ii) IRT is successful in reducing gamma activity and psychological arousal alongside nightmare symptoms and iii) the reactivation of relaxation associated contents influences spindle activity which is even associated with changes in subjective sleep disturbance, indicating that this is a promising novel technique to target hyperarousal. Future research should therefore focus on further attempts to experimentally manipulate cortical hyperarousal by stimulation methods or by reactivating IRT and should also include other factors of the integrative model of nightmare etiology, especially fear extinction.

Zusammenfassung

Alpträume sind sowohl in der Allgemeinbevölkerung als auch bei Menschen mit psychiatrischen Störungen sehr häufig. Sie können Ängste, Schlafstörungen und Beeinträchtigungen im Alltag verursachen. In den letzten Jahrzehnten wurden mehrere biologische Korrelate von Alpträumen untersucht, z. B. hochfrequente Gehirnaktivität während des Schlafs, Veränderungen der Herzfrequenz, der elektrodermalen Aktivität oder des Cortisolspiegels. Alle diese Maße deuten auf eine Form von Hyperarousal hin, das zusammen mit einer gestörten Furchtlöschung eine der zentralen Komponenten des integrativen Ätiologiemodells für Alpträume darstellt. Es ist jedoch noch unklar, wie genau Hyperarousal und Alpträume zusammenwirken, d.h. ob Hyperarousal tatsächlich ein kausaler Mechanismus oder eher ein Nebenprodukt anderer zugrundeliegender Prozesse ist. Ebenso ist noch nicht bekannt, ob es durch Interventionen bei Alpträumen, wie z. B. *Imagery Rehearsal Therapy* (IRT) oder direkt während des Schlafs, durch Stimulation oder *Targeted Memory Reactivation* (TMR) beeinflusst werden kann. Ziel der drei dieser Dissertation zugrundeliegenden Studien war es, die biologischen Korrelate von Alpträumen, insbesondere das kortikale Hyperarousal bei Personen mit häufigen Alpträumen aus verschiedenen Stichproben, sowie die Auswirkungen der IRT und der gezielten Gedächtnisreaktivierung auf die physiologischen Korrelate und die Alptraumsymptome mit Hilfe von Polysomnographie und hochauflösenden EEG-Messungen zu untersuchen.

Die ersten beiden Studien konzentrierten sich auf die Auswirkungen von IRT und die physiologischen Korrelate von Alpträumen. Studie 1 untersuchte, wie sich physiologische Korrelate zwischen Personen mit häufigen Alpträumen und gesunden Kontrollpersonen unterscheiden und wie eine 8-wöchige IRT-Gruppenintervention Alptraumsymptome und physiologische Korrelate beeinflusst. Teilnehmer mit häufigen Alpträumen zeigten im Vergleich zu gesunden Kontrollpersonen eine erhöhte Beta- und Gamma-Aktivität, und ihre Gamma-Aktivität während der REM-Phase war nach der Intervention reduziert.

In Studie 2 wurde ein ähnliches Paradigma verwendet, um die Auswirkungen der IRT als Zusatz zur stationären Behandlung bei Personen mit Borderline-Persönlichkeitsstörung zu untersuchen. In dieser Studie konnten zwar keine Veränderungen der physiologischen Korrelate festgestellt werden, aber in der Interventionsgruppe kam es zu einer deutlich ausgeprägteren Verringerung von Ängsten, Intrusionen und Hyperarousal.

Studie 3 untersuchte die Auswirkungen einer experimentellen Manipulation dieser biologischen Korrelate. Es wurde eine Entspannungsübung, von der bekannt ist, dass sie die Beta-Aktivität beeinflusst, mit TMR bei Teilnehmenden mit häufigen Alpträumen reaktiviert und deren Auswirkungen auf Hyperarousal und Alptraumsymptome untersucht. Die Reaktivierung führte zwar zu einer Verringerung der Spindelanzahl und -dichte, einer anderen Form des kortikalen Hyperarousals, hatte aber keinen Einfluss auf die Alptraumsymptome.

Insgesamt konnte ich zeigen, dass i) erhöhte (kortikale) Erregung als biologisches Korrelat in verschiedenen Stichproben mit häufigen Alpträumen (Teilnehmende mit häufigen Alpträumen, aber ohne schwere Komorbiditäten sowie Personen mit Borderline-Persönlichkeitsstörung und häufigen Alpträumen) eine wichtige Rolle spielt und Veränderlichkeit nach Interventionen zeigt, ii) IRT neben einer Reduktion der Alptraumsymptome erfolgreich bei der Verringerung der Gamma-Aktivität und des psychologischen Arousals ist, und iii) die Reaktivierung von entspannungsassoziierten Inhalten die Spindelaktivität beeinflusst und sogar mit Veränderungen der subjektiven Durchschlafstörungen verbunden ist. Dies deutet darauf hin, dass die Reaktivierung von entspannungsassoziierten Inhalten eine vielversprechende neue Technik zur Veränderung von Hyperarousal ist. Zukünftige Forschung

sollten sich daher auf weitere Versuche konzentrieren, kortikales Hyperarousal durch Stimulationsmethoden oder durch Reaktivierung von IRT experimentell zu manipulieren, und sollte auch andere Faktoren des integrativen Modells der Alptraum-Ätiologie, insbesondere die Furchtlöschung, einbeziehen.

1. General Introduction

"No malady that causes mortal distress to the sufferer, not even seasickness, is viewed by medical science with such complacent indifference as the one which is the subject of this book." (Jones, 1931, *On the Nightmare* p. 13).

The malady Jones refers to are nightmares, described by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association (APA), 2013) and International Classification of Sleep Disorders (American Academy of Sleep Medicine, AASM, 2014) as "extended, extremely dysphoric" dreams that "usually involve efforts to avoid threats to survival, security, or physical integrity". It is estimated that about 5 – 8 % of the general population suffers from regular nightmares (Schredl, 2016) that can either be idiopathic, i.e., arising spontaneously or from an obscure or unknown cause or be related to a traumatic event. The prevalence is even higher in psychiatric patients (Swart, Van Schagen, Lancee & Van Den Bout, 2013) and nightmare occurrence has been associated with reduced daytime functioning (Krakow, 2006), worse outcomes concerning academic performance (Wiechers, Schlarb, Urschitz, Eggebrecht, Schlaud & Poets, 2011), mental distress (Blagrove, Farmer & Williams, 2004) and even increased suicidality (Lemyre, Bastien & Vallières, 2019). Although the introductory statement on indifference from the medical field is no longer completely valid and there are treatment options for nightmares, these options are often not available to all individuals who could potentially profit from them. This is mainly due to treatment often focusing on other symptoms, e.g. in the treatment of depression or even posttraumatic stress disorder (PTSD). This thesis presents results from three polysomnographic studies investigating the variability in biological correlates of nightmares and the effects of different interventions on several patient populations. The aim of this research is to deepen our understanding of physiological and affective mechanisms of nightmares and nightmare therapy and, ultimately, improve treatment options for nightmares.

1.1 Physiological correlates of nightmares and nightmare etiology

Nightmares are not only defined by aversive subjective experiences, but they are also associated with several physiological changes. Identifying physiological markers associated with nightmares can enhance the assessment of symptom severity and treatment outcomes and also contribute to the development of etiological models of nightmares.

1.1.1 Potential physiological correlates of nightmares

Although nightmares are difficult to study in a sleep lab environment since they tend to occur less often and cause less distress there than in domestic sleep environments (Paul, Alpers, Reinhard & Schredl, 2019), there is a growing body of literature comparing the sleep of individuals with frequent nightmares to healthy controls. Findings can be divided into differences in sleep architecture, microstructure, and autonomic arousal. It is, however, highly likely that they share underlying causal mechanisms.

1.1.1.1 Different domains of potential physiological correlates

Macrostructure. Investigating the patterns of sleep continuity and sleep architecture in people with frequent nightmares has led to differing results so far. Several studies (Simor, Horváth, Gombos, Takács & Bódizs, 2012; Woodward, Arsenault, Murray & Bliwise, 2000) found reduced sleep efficiency driven by both increased sleep onset latency and wake after sleep onset in nightmare sufferers. When looking at the distribution of sleep stages, there is some evidence for differences in N2 latency for

frequent nightmare recallers (Picard-Deland, Carr, Paquette, Saint-Onge, & Nielsen 2018) and increased N1 and rapid-eye-movement (REM) sleep duration with reduced slow wave sleep (SWS) duration in subjects with frequent nightmares (Simor et al., 2012). However, Paul et al. (2015) did not find any differences in sleep architecture and overall results concerning macrostructure vary between studies. This could in part be due to a discrepancy between subjective and objective sleep measurements, as has also been observed in insomnia (Xu, Cai, Mai, Liang, Huang & Yang, 2022) with insomnia, mostly assessed by subjective measures, often co-occurring with frequent nightmares (Delage, Côté, Journault, Lemyre & Bastien 2024). Another explanation could be that nightmares only impact sleep architecture when symptoms are very severe, e.g. in Woodward et al. (2000) who studied nightmares in individuals with PTSD. This conclusion is also backed by a review by Spoormaker and colleagues (2006) stating that most changes in sleep architecture of individuals with frequent nightmares were more pronounced in those with traumatic nightmares.

Microstructure. Sleep is not only characterized by a succession of sleep stages and wake phases, but there are also both persistent and transient patterns of spectral activity that can be linked to nightmares. Experiencing nightmares is closely linked to how often nightmares are remembered and indeed, several studies found altered spectral activity associated with memory processes during sleep (see 1.4 Targeted memory reactivation). Frequent nightmare recallers have been found to have a lower-than-normal density of slow spindles (10 – 12.79 Hz) and higher density of fast spindles (12.8 – 16 Hz), which was related to increased dream fear and decreased positive emotions (Picard-Deland et al., 2018). Moreover, frequent nightmare recall has been associated with higher theta activity during REM and higher beta activity during non-rapid eye movement sleep (NREM), which is in turn linked to viewing of fearful stimuli with threat-induced anxiety (Marquis, Paquette, Blanchette-Carrière, Dumel, & Nielsen, 2017).

Not all changes in spectral activity are related to nightmare recall. Another factor that has been found repeatedly is spectral activity patterns connected to increased arousal, such as a different distribution of cyclic alternating patterns (CAP) that indicate unstable sleep depth and increased arousal (Simor, Bódizs, Horváth, & Ferri 2013). High frequency electroencephalographic (EEG) activity in the beta (Marquis et al., 2017) and gamma band has also been implicated in frequent nightmares, especially in pre-REM sleep intervals (Blaskovich, Reichardt, Gombos, Spoormaker & Simor 2020). These changes in spectral activity have the potential to disrupt sleep even below the threshold of changing sleep architecture.

Autonomic arousal. Nightmare-related arousal is not contained to brain activity, as it is distributed in the body via the somatic and, most importantly, via the autonomous nervous system. The former can be displayed in elevated periodic limb movement indices (Germain & Nielsen, 2003) and some studies report increased muscle tone (Simor, Körmendi, Horváth, Gombos, Ujma & Bódizs, 2014) related to nightmares, whereas other studies failed to find effects on electromyographic (EMG) measures (Mäder et al., 2023; Davis, Rhudy, Pruiksma, Byrd, Williams, McCabe & Bartley, 2011). For autonomic arousal, changes in heart rate and heart rate variability (HRV) are reported often (e.g. Paul et al., 2019; Tomacsek, Blaskovich, Király, Reichardt & Simor, 2024) with high frequency (HF) and low frequency (LF) being the most commonly reported parameters, as they indicate parasympathetic and sympathetic activity respectively. Another heart rate related measure are heartbeat evoked potentials in EEG-activity during REM sleep, which were found to differ in some studies of individuals with nightmare disorder when compared to healthy controls (Perogamvros, Park, Bayer, Perrault, Blanke & Schwartz, 2019) but not in others (Bogdany, Perakakis, Bódizs, & Simor 2022). Moreover, increased skin conductance, an indicator of sympathetic activity, has been associated with nightmare occurrence in various studies

(Mäder et al., 2023; Tanev, Orr, Pace-Schott, Griffin, Pitman & Resick, 2017). Changes in breathing patterns have been described as well (Li, Zhang, Li & Wing, 2010). Notably, nightmares and sleep apnea seem to be closely related, with individuals with sleep apnea reporting more nightmares than individuals with healthy breathing patterns and sleep apnea being a common co-morbidity of PTSD which often includes traumatic nightmares (Krakow et al., 2004).

Broadening the perspective of arousal, several studies also investigated the hormonal correlates of nightmares and arousal. The hypothalamic-pituitary-adrenal axis, with levels of cortisol and other metabolites have been studied in several samples, and a blunted cortisol awakening response has been found in participants with frequent nightmares (Nagy, Salavecz, Simor, Purebl, Bódizs, Dockray & Steptoe, 2015) and after nightmare occurrence compared to neutral dreams (Hess, Schredl, Gierens & Domes, 2020).

1.1.1.2 Overlap with physiological correlates in related disorders

Broadening the scope towards other (related) disorders, there are several overlaps in physiological correlates. Nightmares as a sleep disorder are closely related to insomnia, which is also reflected in common biomarkers such as increased cortical hyperarousal and difficulties with sleep continuity (Riemann, Spiegelhalder, Feige, Voderholzer, Perlis, & Nissen, 2010). In insomnia, increased cortical hyperarousal has been linked to sleep misperception (Xu et al., 2022) and could thus be considered a causal factor in paradoxical insomnia.

Another conceptually closely related disorder is PTSD. It shares many characteristics in sleep architecture with nightmares and even exacerbates some of them, such as increased N1 and REM as well as reduced SWS and increased cortical and autonomous arousal (Phelps, Kanaan, Worsnop, Redston, Ralph & Forbes, 2018; Miller, Brownlow, Woodward & German, 2017). This might, in part, be explained by co-morbidity, as nightmares and sleep disturbance are core symptoms of PTSD and could therefore cause similar sleep disturbances. Idiopathic and traumatic nightmares do however differ in content and etiology which is, in part, reflected in differences in physiological measures. People suffering from posttraumatic nightmares showed more nocturnal awakenings than those suffering from idiopathic nightmares (Germain & Nielsen, 2003) and might be more likely to have worse sleep efficiency as a result (Woodward et al., 2000). Thus, the difference in physiological correlates between traumatic and idiopathic nightmares might be rather quantitative than qualitative. This demonstrates how idiopathic nightmares and PTSD share etiological factors such as difficulties in fear extinction (Gieselmann et al., 2019) and noradrenergic activity leading to increased arousal during sleep and waketime (Krystal & Neumeister, 2009).

The arousal aspect during sleep is also present in anxiety disorders such as social anxiety disorder (Sachs, Anderer, Dantendorfer, & Saletu, 2004). For affective disorders, there is considerably less overlap as they can influence sleep in various directions from hypersomnia to insomnia (Freeman, Sheaves, Waite, Harvey & Harrison, 2020). Depression, however, has been connected to shorter REM latency and longer REM duration (Wichniak, Riemann, Kiemen, Voderholzer & Jernajczyk, 2000) and there is evidence of increased cortical hyperarousal during sleep in individuals with major depressive disorder (Lin, Du, Xia, Xiao & Wang, 2023). In the realm of personality disorders, a meta-analysis by Winsper et al. (2017) on borderline personality disorder (BPD) indicated significant differences between BPD and healthy control groups concerning sleep continuity, albeit mostly in subjective reports and not necessarily in objective data. There were no findings regarding microstructure during sleep, but vigilance seems to be increased during daytime (Kramer, Sander, Bertsch, Gescher, Cackowski, Hegerl & Herpertz, 2019). Finally, it is worth noting that individuals with BPD report high rates of nightmares,

which could help explain the changes in sleep architecture (Winsper, Tang, Marwaha, Lereya, Gibbs, Thompson & Singh, 2017).

In all the disorders discussed here, the similarities in physiological correlates can, in part, be explained by a direct common factor like increased hyperarousal but also by indirect effects of increased nightmare occurrence, especially in PTSD and BPD, as well as sleep disturbance in general.

1.1.2 Etiology of nightmares

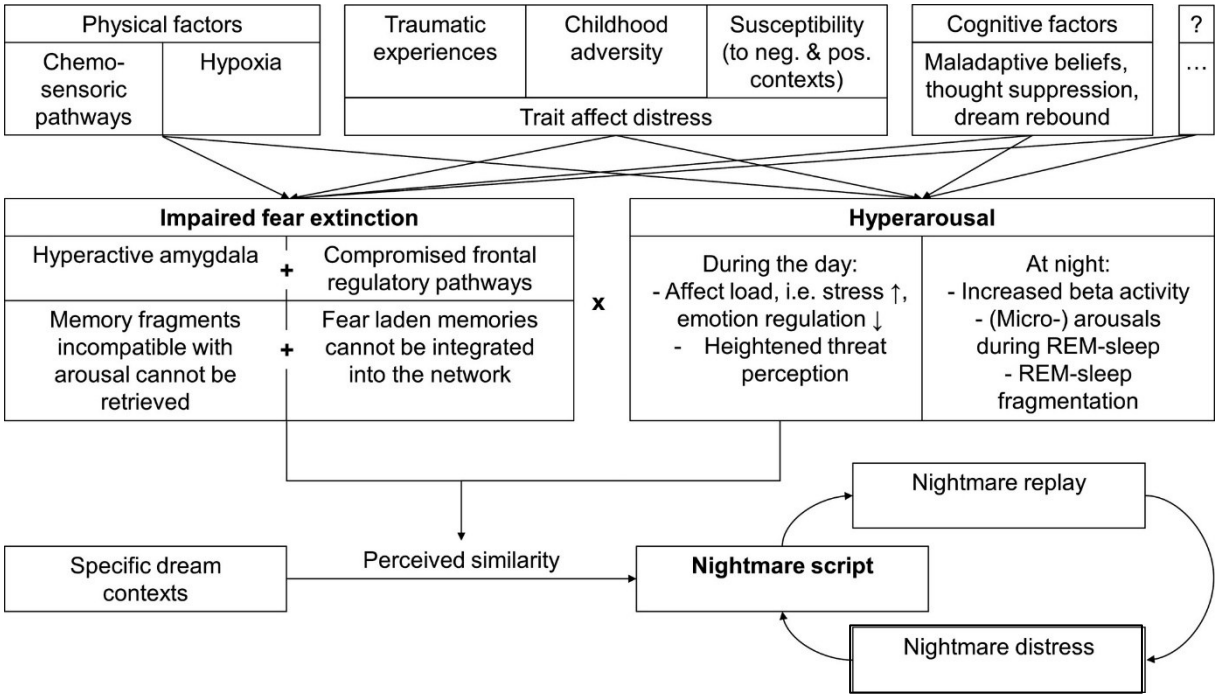
Early etiology models from the psychodynamic tradition conceptualized nightmares as an expression of repressed urges (Freud, 1900; Jones, 1931) or unresolved conflicts (Jung, 1974). Later, the focus shifted towards explaining nightmares as a (failed) attempt to master repressed anxiety (Greenberg, Pearlman & Gampel, 1972) or traumatic experiences (Lansky & Bley, 1995) and researchers began to include a physiological background, cf. the REM desomatization hypothesis (Fisher, Byrne & Edwards, 1970). It states that REM dreaming modulates anxiety by autonomic deactivation during REM sleep and that nightmares occur 'when the anxiety exceeds a certain threshold and the REM desomatization mechanism breaks down, allowing autonomic activation [hyperarousal] to occur' (Nielsen & Levin, 2007), which would imply that measures of hyperarousal are biological correlates or outcomes of that impaired desomatization process. Solms (1995) then implicated the meso-cortico-limbic dopaminergic system in dream and nightmare generation.

From the 1990s onwards, on the one hand, some models postulated the potential benefits of nightmares from a preparatory-evolutionary standpoint (Revonsuo, 2000) or from an emotion regulation perspective (Hartmann, 1998). On the other hand, new risk factors for nightmare experience were identified such as higher boundary permeability (Hartmann, Elkin & Garg, 1991), i.e., a personality trait of being more emotionally sensitive and reactive towards environmental stimuli, and childhood adversity (Nielsen, 2017) which is thought to increase fear sensitivity and impair fear extinction leading to more frequent nightmares. The proposed neural mechanisms behind fear extinction during dreams are described as follows by Nielsen & Levin (2007) in their affective network dysfunction model: dream contents are retrieved from the anterior hippocampus, relayed to the amygdala for further processing of fear while regulatory influence from medial prefrontal cortex and dorsal and rostral anterior cingulate cortex creates fear extinction memories and aims to keep arousal levels at tolerable levels. If this process fails, increased arousal is generated by caudate nucleus stimulation of the brainstem and hypothalamus.

The integrative model of nightmare etiology (Gieselmann et al., 2019) proposes an interplay between impaired fear extinction and hyperarousal with several predisposing factors such as childhood adversity, trauma and thin boundaries and maintaining factors such as maladaptive beliefs and emotion regulation in the background (Figure 1, model from Gieselmann et al., 2019). Together these factors interact to activate a nightmare script during normal dreaming, while the nightmare replay increases arousal and distress and maintains the nightmare experience. In the context of this model, hyperarousal, as in a failure to downregulate noradrenergic activity during REM, could impair crucial aspects of emotional processing in this sleep stage (Walker & van der Helm, 2009) as well as fear extinction thus helping to generate and maintain nightmares. Hence, increased autonomous or cortical hyperarousal could be the measurable output of a maladaptive fear extinction process. Interestingly, Van Someren (2021), proposed a similar arousal model for insomnia etiology in which a failure to downregulate emotional arousal during REM sleep results in increased residual noradrenergic activity.

Figure 1.1

Integrative model of nightmare etiology



Note. Model from Gieselmann et al., 2019

1.2 Treatment options for nightmares

Since Ernest Jones' day (1931), more treatment options for nightmares have become available that target various components of the previously discussed etiology models. There is a considerable overlap with psychotherapeutic and psychopharmacological treatment approaches for nightmares with those for anxiety disorders and PTSD. This mirrors conceptual similarities and co-morbidities between the disorders. However, there are some approaches unique to nightmares, such as imagery rehearsal therapy (IRT) (Krakow et al., 2001) and lucid dreaming (Zadra & Pihl, 1997).

1.2.1 Pharmacological treatment

Pharmacological treatment for nightmares has almost exclusively been studied in PTSD-related nightmares; therefore, recommendations for pharmacological treatment are limited to this type of nightmares (Morgenthaler et al., 2018). There are several types of medication focusing on reducing arousal (Gupta, Popli, Bathurst, Hennig, Droney & Keller 1998) and / or altering sleep architecture (Miyazaki, Uchida, Mukai & Nishihara, 2004) with various mechanisms of action that have been researched in this context. The biggest group are sedatives such as atypical antipsychotic medications (Stanovic, James & Vandervere, 2001; Lambert, 2006) as well as benzodiazepines. Their modes of action include medications influencing α-2 adrenergic receptors and thus sympathetic nervous system activity such as clonidine (Miyazaki et al., 2004) or prazosin (Ortuno, Seda, Welsh, Halbower & Edinger, 2013) and those influencing the GABA system. Antidepressants with serotonergic and noradrenergic mechanisms of action have also been used, even nabilone, a synthetic cannabinoid receptor agonist (Jetly, Heber, Fraser & Boisvert, 2015). None of these medications received a level of recommendation equal to IRT, an intervention that will be discussed in more detail below, but there is some level of evidence that supports the use of "atypical antipsychotics […], clonidine, cyproheptadine,

fluvoxamine, gabapentin, nabilone, phenelzine, prazosin, topiramate, trazodone, and tricyclic antidepressants" (Morgenthaler et al., 2018, p.1043) in PTSD-related nightmares with prazosin also receiving recommendations for nightmare disorder.

1.2.2 Psychotherapy for nightmares

Psychotherapeutic approaches for nightmares have borrowed techniques from anxiety therapy, mainly exposure therapy in various forms (Davis & Wright, 2007), from PTSD treatment such as Eye Movement Desensitization and Reprocessing (Silver, Brooks & Obenchain, 1995), as well as relaxation or cognitive-behavioral therapy for insomnia (Miller, Brownlow & Gehrman, 2020). While the latter focus on reducing sleep disturbance and arousal caused by nightmares, exposure therapy and EMDR directly engage with the nightmare content. Exposure therapy can be conceptualized as remedying impaired fear extinction and cortical arousal (Paredes & Morilak, 2019), which is crucial to the etiology of both PTSD (Suarez-Jimenez et al., 2019) and nightmare disorder (Gieselmann et al., 2019). However, since the 1990s, nightmare-specific approaches have been developed. Both lucid dreaming and IRT aim to alter nightmare content. Lucid dreaming, i.e., realizing that one is currently dreaming, can be utilized to change the course of the nightmare to less aversive content (Spoormaker & van den Bout, 2006). As reaching lucidity requires training and / or a natural propensity to do so, modifying nightmare content during wake as in IRT (Krakow et al., 2001) seems more scalable for populations suffering from frequent nightmares.

1.2.2.1 Imagery rehearsal therapy

When IRT was first developed, the aim was to find an effective, not too confrontational intervention for traumatic and idiopathic nightmares. It focused on "nightmares as a learned sleep disorder" and as a "symptom of a damaged imagery system" (Krakow & Zadra, 2006, p.49). The course of the intervention gradually builds up from psychoeducation on sleep disturbances caused by nightmares and the potential benefits they might have had for the acute processing of a traumatic event to the chronification of nightmares and the use of imagery to ultimately alter the course of the nightmare. In this rescripting process, patients first generate a script of a typical nightmare they have. Then, they identify typical and negative elements of the nightmare and rescript them in a way that the typical elements remain while the negative elements are altered to become neutral or even positive in a way that is plausible to the patient. The rescripting is usually guided by a therapist at first; later patients are often able to rescript nightmares themselves. For example, an individual could have the repeating nightmare of running through a dark forest while being chased by a man with a knife. Typical elements that might be kept could be the forest setting as well as the sense of moving through the forest. The negative elements of darkness and the man with the knife and being chased could, however, be rescripted to become a light, summery forest in which the patient takes a leisurely stroll and encounters a deer. Since its development, IRT has been evaluated in a large number of randomized-controlled studies, and meta-analyses found moderate (Yücel, van Emmerik, Souama & Lancee, 2020) to large (Casement & Swanson, 2012) effects on nightmare frequency, sleep quality and PTSD symptoms in case traumatic nightmares were included in the studies. Therefore, IRT is the only intervention receiving the highest degree of recommendation and is hence considered the 'gold standard' in the treatment of nightmares (Morgenthaler et al., 2018).

During the last decade, more research has been conducted on the active components of IRT. Even though exposure therapy is not the main focus of IRT (Krakow & Zadra, 2006), it can occur to some degree while altering nightmare content. However, exposure does not seem to be a necessary component of IRT (Pruiksma, Cranston, Rhudy, Micol & Davis, 2018) and a non-inferiority trial by Kunze and colleagues (2017) revealed that both an exposure and a rescripting focused intervention led to reduced

nightmare frequency and distress. Lately, short form protocols of IRT have been employed (Schwartz, Clerget & Perogamvros, 2022) which skipped over most of the psychoeducation components and focused on the actual rescripting part of the intervention with special emphasis on at-home practice. The research on active components of IRT and the prominence of the actual rescripting connect well to the proposed mechanisms of action in IRT. As it was proposed by Krakow and Zadra (2006), patients do seem to experience an increased sense of mastery by rescripting their formerly uncontrollable nightmare with the use of their imagination, which has since been suggested to be a major mechanism of action in IRT (Rousseau, Dubé-Frenette & Belleville, 2018). Other potential mechanisms of action hark back to the etiology models of nightmares (Gieselmann et al., 2019). Similar to the previously mentioned exposure therapy, IRT might also help improve fear extinction and emotional processing. This could happen during daytime via modifying cognitions related to the nightmare, thus preventing avoidance of the nightmare content and decreasing arousal (Germain & Nielsen, 2003). Or one could also assume a more indirect effect of IRT on anxiety- and trauma-related symptoms through improving REM sleep, which is associated with a suppression of central adrenergic neurotransmitters while simultaneously activating amygdala-hippocampal networks (van der Helm, Yao, Dutt, Rao, Saletin & Walker, 2011). This is thought to de-potentiate previous affective experiences, thus further promoting emotional processing by providing 'overnight therapy' (Walker & van der Helm, 2009) and decrease arousal.

Overall, IRT is a well-established intervention for nightmares and there are several hypotheses on its mechanisms of action. However, there are few studies (cf. Davis et al., 2011) to date that include physiological correlates in intervention studies and thus little is known about the sensitivity-to-treatment or variability of these correlates. Moreover, several physiological phenomena, such as fragmented REM sleep or hyperarousal, have been implicated in etiology models and mechanisms of action, but as their variability has rarely been measured in experimental or intervention studies, their actual causal role remains unclear.

1.3 Targeted memory reactivation

Whereas emotional processing is one of the most important functions of sleep (Walker & van der Helm, 2009), memory consolidation certainly is another (Born & Wilhelm, 2012). SWS is crucial to that process, with newly encoded, unstable memories being transferred from temporary to more long-term, stable storage mostly in the neocortex via reactivation of the memory trace. On a neural level, up-states of slow oscillations are coupled with hippocampal sharp-wave ripples and thalamo-cortical spindles. As research in the last decades has shown, memory consolidation is not an enclosed process but can be manipulated by presenting external cues during sleep that have previously been associated with the content at encoding in a process called targeted memory reactivation (TMR) (Schreiner & Rasch, 2015). TMR has been used to influence consolidation of various memory contents, such as verbal (Schreiner & Rasch, 2015) or visio-spatial (Rasch, Büchel, Gais & Born, 2007) semantic memory content but also broader concepts such as creativity (Ritter, Strick, Bos, Van Baaren & Dijksterhuis, 2012) or episodic memories (Fernández, Picco, Beron, Bavassi, Campos, Allegri & Pedreira, 2022).

Psychotherapy can also be conceptualized as learning new concepts and altering or re-consolidating memories relevant to the problem or disorder addressed in psychotherapy. It has already been established that sleep after a psychotherapy session, such as exposure therapy (Kleim, Wilhelm, Temp, Margraf, Wiederhold & Rasch, 2013), can enhance therapy outcome, possibly by improving consolidation processes. In recent years, this research has been expanded by using TMR to further augment psychotherapy outcomes. Some studies, including one by Schwartz and colleagues (2022) that used TMR to boost an IRT intervention in individuals with nightmare disorders, found that TMR improved therapy outcomes. Moreover, it seems that it is not only possible to reactivate semantic

concepts like contents of a therapy session but also concepts like relaxation that even caused changes in spectral activity during sleep (Beck, Loretz & Rasch, 2021). However, TMR in therapy contexts has not always been successful (Rihm, Sollberger, Soravia & Rasch, 2016) or has at least not been able to (successfully) influence all desired outcome measures (Borghese, Henckaerts, Guy, Perez Mayo, Delplanque, Schwartz, & Perogamvros et al., 2022). One possible explanation for these varying results might be that the interventions to be enhanced by TMR were already too effective on their own, such as exposure therapy, hence creating a ceiling-effect. Another possibility is that the success of TMR is influenced by its exact application, i.e., which cues were used and coupled with which part of the intervention (Rihm et al., 2016) and when exactly the reactivation took place, e.g. in REM vs NREM sleep (Borghese et al., 2022). Nevertheless, TMR offers a route to apply interventions for nightmares directly during sleep, that might even influence biological correlates.

While the type of reactivated content is one factor, the type of cues used certainly is another. Since the beginning of TMR research, several types of cues have been utilized that fulfill the requirements of a) being able to be processed by the sleeping brain to some degree (Atienza, Cantero & Escera, 2001) and b) not disturbing sleep at the same time (Carskadon & Herz, 2004). So far, the cues that have been used the most often have been auditory cues such as simple sounds (Rudoy, Voss, Westerberg & Paller, 2009), melodies (Antony, Gobel, O'Hare, Reber, & Paller 2013) or words (Beck, Loretz & Rasch, 2021) as well as olfactory cues (Rasch, Büchel, Gais & Born, 2007). There are some advantages to using olfactory cues, as they are less disruptive than auditory cues both while encoding the content with the cue, which is especially important in psychotherapy contexts and during reactivation while participants are sleeping (Carskadon & Herz, 2004). The method of odor presentation chosen for study 3 consequentially was the "Essence" olfactory device that allowed for the subliminal, intensity and frequency-controlled presentation of odors (Amores Fernandez, 2016) and will be described further in the respective chapter.

1.4 Research questions

Having laid out current findings on physiological correlates of nightmares, etiology models, interventions and potential further research methods, the following pattern emerges from the current state of research. On the one hand, several physiological correlates of nightmares have been described so far, such as changes in sleep architecture (Simor et al., 2012), cortical hyperarousal (Blaskovich et al., 2020), changes in spindle activity (Picard-Deland et al., 2018) or increased autonomic arousal (Paul et al., 2019). These correlates have also been found in related disorders such as insomnia (Riemann et al., 2010) or PTSD (Phelps et al., 2018) and have been integrated into etiology models for nightmares, most notably the affective network dysfunction model by Nielsen and Levin (2007) and the integrative model of nightmare etiology (Gieselmann et al., 2019). On the other hand, there are various successful nightmare interventions, especially IRT, available to date (Morgenthaler et al., 2018), but little is known if and how physiological correlates react to treatment. This limits the understanding of the causal mechanisms proposed in etiology models and might impede development of further treatment options. This thesis summarizes three studies that examine the sensitivity to treatment of biological correlates of nightmares, especially cortical hyperarousal, to IRT and to the reactivation of a relaxation exercise targeting cortical hyperarousal. The studies include samples of individuals with frequent nightmares from different patient populations and utilize polysomnography (PSG) or high-density EEG-measurements.

The first part of the thesis centers on physiological correlates of nightmares as a partial replication of previous findings, and the effects of IRT on these correlates to extend on the existing literature. Using an 8-week IRT group treatment for participants with frequent nightmares whose sleep was compared to

age and gender matched healthy controls, study 1 addresses, how physiological correlates differ between nightmare sufferers and healthy controls and how the intervention influences nightmare symptoms and physiological correlates. In study 2, a similar paradigm is used to investigate the effects of IRT as an add-on to inpatient treatment for individuals with BPD. Both studies expand on the effects of IRT, potential mechanisms behind it and how they are reflected in sensitivity-to-treatment of biological correlates.

Uncovering potential mechanisms of IRT and biological correlates of nightmares can be improved by attempting to experimentally manipulate these biological correlates directly, which can increase understanding and ultimately further the development of new treatment options. In the second part of the thesis (study 3), I investigate the effects of a relaxation exercise reactivated with TMR in an attempt to directly influence cortical hyperarousal in participants with frequent nightmares. Furthermore, I investigate whether the reactivation of the relaxation exercise has an influence on nightmare frequency and other related symptoms. The results of these studies bring us one step closer to understanding the role of cortical hyperarousal in the etiology of nightmares and to improve treatment options in the future.

2 Study 1: Cortical hyperarousal in individuals with frequent nightmares[1]

2.1 Abstract

Nightmares are common among the general population and psychiatric patients and have been associated with signs of nocturnal arousal such as increased heart rate or increased high-frequency EEG activity. However, it is still unclear whether these characteristics are more of a trait occurring in people with frequent nightmares or rather indicators of the nightmare state. We compared participants with frequent nightmares (NM) (n = 30) and healthy controls (n = 27) who spent four nights in the sleep laboratory over the course of eight weeks. The nightmare group received six sessions of IRT, the gold-standard of cognitive-behavioral therapy for nightmares, between the second and the third night. Sleep architecture and spectral power were compared between groups and between nights of nightmare occurrence and nights without nightmare occurrence in the NM group. Additionally, changes before and after therapy were recorded. NM participants showed increased beta (16.25–31 Hz) and increased low gamma (31.25–35 Hz) power during the entire night compared to healthy controls, but not when comparing nights of nightmare occurrence to those without. Moreover, low gamma activity in REM sleep was reduced after therapy in NM participants. Our findings indicate that cortical hyperarousal is more of a trait in people with frequent nightmares within a network of other symptoms, but also malleable by therapy. This is not only a new finding for IRT but could also lead to improved treatment options in the future that directly target high-frequency EEG activity.

Keywords: nightmares, arousal, IRT, EEG

2.2 Introduction

Nightmares are very common among the general population and even more so in psychiatric patients (Schredl, 2009). They are related to sleep disturbances (Lancee, Spoormaker & Van Den Bout, 2010) and can contribute to impaired daytime functioning (Nadorff, Titus & Pate, 2019). Moreover, they are comorbid with many other disorders such as depression (Agargun et al., 2007), anxiety disorder (Nadorff, Lambdin & Germain, 2014) and have even been linked to increased suicide risk (Sjöström, Wærn & Hetta, 2007).

Much research on nightmares, their frequency and impact has been based on subjective reports. In addition to that, there has been a growing interest in finding physiological correlates of nightmares in the last two decades. One of the first potential ones to be examined was sleep macrostructure. Some studies have demonstrated differences in sleep continuity, with participants with frequent nightmares showing worse sleep efficiency and more wake after sleep onset (Woodward, Arsenault, Murray, & Bliwise, 2000) and sleep architecture with longer stage 1 sleep, longer stage 2 sleep latency and shorter SWS duration (Simor, Horváth, Gombos, Takács & Bódizs, 2012). However, other studies failed to find these differences in sleep continuity (Blaskovich, Reichardt, Gombos, Spoormaker, & Simor, 2020) or sleep architecture (Germain & Nielsen, 2003; Paul, Schredl, & Alpers, 2015).
Sleep microstructure has also been studied regarding nightmare characteristics.

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For example, Simor and colleagues (2013) found differences in CAPs with a significantly lower percentage of CAP A1 and higher rates of A2 as well as a trend of an increased number of A3 subtypes in people with frequent nightmares compared to healthy controls. Picard-Deland et al. (2018) found lower than normal density of slow spindles in most EEG derivations, a higher density of fast spindles in frontal derivations, and an elevated fast spindle oscillatory frequency of "faster fast" spindles mainly in central derivations people with frequent nightmares compared to healthy controls. Additionally, slow spindle density was positively correlated with dreamed fear and nightmare word count and negatively correlated with dreamed positive emotion. Most recently, Blaskovich et al. (2020) found increased cortical hyperarousal, i.e., increased beta and gamma EEG activity, in participants with frequent nightmares, especially in the 10-minute interval before REM sleep.

Autonomous arousal has also been studied as a nightmare characteristic for a considerable period of time (Fisher, Byrne, Edwards et al., 1970). Elevated periodic limb movement indices have been found in people with frequent nightmares (Spoormaker, Schredl, & van den Bout, 2006), as well as differences in heart rate and HRV (Paul, Alpers, Reinhard & Schredl, 2019) These parameters have been used both in association with actual nightmare occurrence (Phelps, Kanaan, Worsnop, Redston, Ralph & Forbes, 2018) and in comparing people with frequent nightmares to healthy controls (Paul et al., 2019).

The inconsistent findings on physiological correlates of nightmares, e.g. regarding differences in sleep architecture may in part be explained by general methodological issues: More specifically, there is evidence for nightmares occurring less often in a sleep laboratory environment, thus study designs mostly focus on comparing people with frequent nightmares to healthy controls in more of a 'trait-approach' while only a few (Phelps et al., 2018; Paul et al., 2019) include actual nightmare occurrence as an additional 'state-approach'.

Despite the inconsistencies in previous research on physiological correlates of nightmares, studying them in both trait- and state approach is crucial to increase our understanding of nightmares. Physiological measures can be helpful in monitoring treatment success, as has been done with actigraphy in cognitive behavioral therapy for insomnia (Talbot, Maguen, Metzler, Schmitz, McCaslin, Richards & Neylan, 2014). To the authors' knowledge, the outcome of one of the most common cognitive behavioral treatments for nightmares, IRT (Krakow, Hollifield, Johnston, Koss, Schrader, Warner & Prince, 2001), has not been monitored with physiological measures so far. In addition to monitoring outcome of already existing treatments, Physiological correlates can also inform the development of new treatment options.

The aims of this study are i) discerning which physiological correlates occurring in nightmares, especially cortical and autonomous hyperarousal, are more indicative of the nightmare state itself and which are rather a trait of people with frequent nightmares and ii) investigating whether any of these physiological measures change after successful treatment with IRT.

2.3 Methods and Materials

2.3.1 Participants

Participants were recruited by advertisement in local newspapers and on the radio, postings in public places (e.g., supermarkets, libraries) and at the University of Luebeck. Participants with frequent nightmares were additionally approached via a mailing list of local psychotherapists and directly addressed by the study therapist at the outpatient clinic of the *Universitätsklinikum Schleswig-Holstein*. They were aged between 18 and 67 and fluent in German. Participants in the nightmare and control

group were screened for psychiatric conditions, for depression, substance abuse, anxiety, obsessive-compulsive disorder and eating disorder symptoms as well as retrospective subjective sleep quality in an in-person interview based on DSM criteria. The presence of any psychiatric disorder was an exclusion criterion for the control but not for the nightmare group. Participants with frequent nightmares were required to (1) have at least one nightmare a week, (2) not take any benzodiazepines, antidepressants or other medication affecting sleep and (3) abstain from alcohol for at least a week. Healthy controls were required to (1) not suffer from any somatic illness and (2) not take any medication, smoke or take drugs. All participants were asked to abstain from alcohol and caffeine on the days of PSG measurements.
The study was approved by the university's ethics committee. All participants provided written informed consent after having been given a complete description of the study protocol. Participants were compensated financially for the nights spent in the laboratory.

The initial sample consisted of 30 participants with frequent nightmares and 16 age and gender matched healthy controls. Later, 11 further healthy, age-matched controls from other studies were included in the analyses. The sample consisted of 43 women and 14 men, mean age was 36.3 (SD = 14.28). There were no differences in age ($t(54) = 0.375$, $p > 0.7$) or gender distribution ($X^2(1,57) = 1.011$, $p > 0.3$) between groups. Participants with frequent nightmares mostly suffered from nightmares since childhood (n = 11) or for at least 10 years (n = 6). On a 5-point Likert scale, 15 participants rated their degree of suffering from nightmares as "strong" and 5 participants even reported a "very strong" degree of suffering. The majority of the sample remembered nightmare content often or always. Half of the participants reported an identical or almost identical repetition of the nightmare. The majority of participants linked their nightmares to their biography (18 out of 30) and one participant in the nightmare group was diagnosed with PTSD. We did not differentiate between idiopathic and traumatic nightmares. 14 of the participants with frequent nightmares reported to have a nightmare in at least one of the sleep lab nights allowing for a within-subject comparison of 19 nightmare and no nightmare nights.

2.3.2 Materials

2.3.2.1 Questionnaires

Participants completed questionnaires to assess current and childhood posttraumatic symptoms with the Impact of Event Scale–revised, IES-R (Weiss, 1997) and Childhood Trauma Questionnaire, CTQ (Bernstein & Fink, 1998), depressive symptoms with Beck's Depression Inventory, BDI-II (BDI-II, Beck & Steer, 1993), anxiety symptoms with the Beck's Anxiety Inventory, BAI (Beck, Steer & Brown, 1996) and general psychological symptom burden symptom checklist, SCL-90-S (Franke, 2014). Nightmare experience was assessed by a customized questionnaire that assessed nightmare frequency, time of nightmare onset, nightmare content, ability to remember nightmares and distress caused by nightmares (Supplementary material 2.A). Additionally, subjective sleep quality was measured with evening and morning protocols that assessed tiredness during daytime, concentration, mood, sleep quality and relaxation during sleep lab nights, and in retrospect for two weeks with the Pittsburgh Sleep Quality Index, PSQI (Buysse, Reynolds, Monk, Berman & Kupfer, 1989). Additionally, emotion regulation was assessed with the Emotion Regulation Questionnaire, ERQ (Gross & John, 2003) and EMOCheck (Berking & Znoj H, 2008).

2.3.2.2 Polysomnography

Participants were fitted with 6 EEG electrodes (Fz, F4, C3, C4, Cz, O2, and Oz) according to the 10–20 system, referenced to linked mastoid (A1 and A2) electrodes. We used EMG electrodes placed on the chin, as well as electrooculography (EOG) and electrocardiography (ECG) according to AASM (Berry et al., 2020). During adaptation night, periodic limb movements were measured with two EMG

electrodes attached to the tibialis muscle and potential sleep apnea events were recorded via nasal airflow. None of the participants were subsequently diagnosed with periodic limb movements of sleep or sleep apnea and thus continued further recordings of the study. Data was recorded with SOMNOscreen™ plus (Somnomedics, Randersacker, Germany). Impedances were below 4 kΩ. Sampling rate was 256 Hz. The device has inbuilt 0.2 – 35 Hz filters for EEG and EOG and 0.2 – 150 Hz filters for EMG and ECG channels.

2.3.2.3 Sleep macrostructure and spectral power analysis

Sleep stages were scored manually according to AASM criteria (Berry et al., 2020) by two experienced sleep lab technicians. Further preparations and spectral power analysis were made with the FieldTrip (Oostenveld, Fries, Maris & Schoffelen, 2011) toolbox. Recordings were visually inspected on a 30-second basis and channels with muscle- and technical-related artifacts were discarded. Artifact-free, 50% overlapping, 8.192-second epochs were Hanning-tapered and Fast Fourier Transformed (FFT) in order to calculate absolute power spectral densities for each frequency bin between 1.25 Hz and 35 Hz for NREM (Stage 2 and Stage 3) and REM sleep periods, separately. The specific window length was chosen as it is common procedure in FFT analysis (Ngo, Martinetz, Mölle & Born, 2013) that offers the ability to detect more transient phenomena such as sleep spindles or slow oscillations while offering a high resolution for long-lasting frequency bands. A 50 % overlap and Hanning-tapered windows allowed for analysis of the entire dataset of interest without creating edge artifacts. Pre-REM periods were defined as 10-minute intervals of NREM sleep directly before the onset of the first two REM periods. Accordingly, post-REM periods included similar 10-minute NREM epochs following the end of the first two REM periods. The frequency bin boundaries were chosen as a replication of Blaskovich et al. (2020), however due to inbuilt filters in the recording device recording of the gamma band was only possible up to 35 Hz instead of 45 Hz, therefore findings on gamma activity will be referred to as "low gamma activity". Band-wise spectral power was extracted by summing up bin-wise values into the traditional frequency ranges of delta (1.25–4 Hz), theta (4.25–8 Hz), alpha (8.25–13 Hz), sigma (13.25–16 Hz), beta (16.25–31 Hz) and low gamma (31.25–35 Hz) bands and averaged across all channels.

2.3.2.4 Heart rate variability

For HRV analysis, which was conducted with HRVtool, the last five minutes of REM phases were selected, following the approach of Paul et al. (2019). Artifacts were identified and corrected manually before extracting parameters of time (Heart Rate, Mean R-R interval, standard deviation of normal-to-normal interval (SDNN), root mean square of successive differences (RMSSD) and percentage of consecutive normal-to-normal intervals that differ by more than 50 milliseconds (pNN50)) and frequency domain (LF: 0.04 – 0.15 Hz, HF: 0.15 – 0.4 Hz, LF/HF ratio).

2.3.2.5 Intervention

Participants with frequent nightmares attended six sessions of imagery rehearsal group therapy (Thünker & Pietrowsky, 2010). Groups typically included 6 – 8 patients at a time and were conducted by an experienced clinical psychologist. During therapy, patients first analyzed their nightmares for typical and negative elements with the help of the therapist. They were then instructed to find an alternative to the negative elements to make the dream less frightening or disgusting and then regularly imagine the alternative dream script before bedtime. Additionally, patients received psychoeducation on nightmares, information on sleep hygienic behavior and learned a relaxation technique (progressive muscle relaxation or autogenic training).

2.3.3 Procedure

Participants spent four nights in the sleep lab, the first two prior to the nightmare group starting their six weeks of imagery rehearsal group therapy (Thünker & Pietrowsky, 2010). The first night served as an adaptation night and to test for medical conditions such as sleep apnea and restless legs syndrome. Third and fourth PSG nights took place about eight weeks after the first measurements when the nightmare group had finished therapy. Participants filled in questionnaires at second and fourth PSG nights.

2.3.4 Statistical analyses

Statistical analyses were carried out with Statistical Package for the Social Sciences (SPSS). For every test, we checked for violation of assumptions such as normality beforehand using Kolmogorov-Smirnov and Shapiro-Wilks tests. Differences in sleep architecture and psychometric measures between participants with frequent nightmares and controls at the second PSG night, i.e. before the nightmare group started IRT, were evaluated by independent samples t-tests, differences within the nightmare group (nightmare vs. no nightmare nights and pre vs. post therapy) were evaluated by dependent samples t-tests. Šidák correction was used to correct for multiple comparisons. Band-wise spectral power differences between participants with frequent nightmares and control participants, nightmare and no nightmare nights and before and after therapy were examined by 2(Group, Nightmare occurrence or Time) x 3(location) Analyses of Variance (ANOVA) for each frequency band separately. Electrode locations (frontal: F4 and Fz; central: C3, C4 and Cz; occipital: Oz and O2) were included to increase precision of results. In order to examine pre-REM and post-REM periods between nightmare and control participants more closely, we tested a 2 × 3 × 2 ANOVA mixed model including Phase (pre-REM, post-REM) and location (frontal, central, occipital) as within-subject factors, and Group (participants with frequent nightmares, control participants) as a between-subject factor. For heart rate analysis, an outlier correction of any values ± 2 SD was applied. Then, one-way ANOVAs were calculated for the last five minutes of REM sleep which were aggregated over as many sleep cycles as were available in the respective night.

2.4 Results

2.4.1 Comparison between nightmare participants and healthy controls

2.4.1.1 Psychometric characteristics, sleep architecture and subjective sleep quality

Participants with frequent nightmares showed higher levels of depression, anxiety, hyperarousal, childhood trauma and negative affect as compared to healthy controls (all ps ≤ 0.002, see Table 2.1 for descriptives). Group differences in traditional parameters of sleep architecture were calculated and are summarized in Table 2.2 together with measures of subjective sleep quality. Nightmare participants reported to have worse mood to the first experimental night in the sleep laboratory ($p = 0.002$) and lower subjective sleep quality in the two weeks before the intervention as indicated by the PSQI ($p < 0.001$). Other differences did not remain significant after correction for multiple testing.

Table 2.1

Psychometric Characteristics of nightmare (NM) and control group (CTL)

		NM *n* = 25	CTL *n* = 16	
		M(SD)	*M(SD)*	*p*
Psychological Symptom Severity				
BDI-II		**20.48(12.26)**	**2.00(3.20)**	**<0.001***
BAI		**17.31(10.60)**	**2.81(2.88)**	**<0.001***
SCL-90 S total		58.88(12.30)	38.60(9.09)	0.194
IES-R				
	Intrusions	19.27(9.74)	9.67(3.21)	0.121
	Avoidance	21.38(10.32)	2.93(2.57)	0.119
	Hyperarousal	**14.35(13.02)**	**1.33(0.58)**	**0.001***
CTQ				
	Emotional Neglect	**16.63(7.86)**	**5.00(0.00)**	**<0.001***
	Sexual Abuse	**9.08(5.18)**	**7.47(1.55)**	**<0.001***
	Physical Abuse and Neglect	14.56(7.09)	6.67(1.95)	0.013†
	Emotional Abuse	**13.83(5.47)**	**0.73(1.10)**	**<0.001***
	Denial	**0.04(0.20)**	**4.95(1.29)**	**<0.001***
Emotion Regulation				
EMOCheck				
	Positive Affect	1.78(0.82)	2.98(0.54)	0.021†
	Negative Affect	**1.28(0.78)**	**0.33(0.28)**	**0.002***
	Emotional Competence	2.3(0.68)	3.19(0.52)	0.522
ERQ				
	Reappraisal	3.51(1.21)	4.98(1.29)	0.515
	Suppression	3.77(1.47)	3.02(1.06)	0.081

Note. * = $p < 0.003$ (Šidák adjusted *p*-value), † = $p < 0.05$

Table 2.2

Objective and Subjective Sleep Parameters in nightmare (NM) and control group (CTL)

	NM *n* = 26	CTL *n* = 27	
	M(SD)	*M(SD)*	*p*
Polysomnography data			
SE	89.94(8.25)	93.59(3.69)	0.041†
TST	442.61 (27.49)	451.37(32.10)	0.292
WASO	2.78 (6.57)	-6.25(56.57)	0.423
SL	18.40(18.40)	18.55(56.45)	0.990
MA total	56.5(19.81)	53.33(23.32)	0.597
MA REM	11.62(6.69)	11.74(5.68)	0.942
REM duration	87.38(31.27)	93.36(15.59)	0.380
N1 duration	24.3(12.08)	22.81(9.65)	0.621
N2 duration	221.8(38.47)	231.07(42.74)	0.411
N3 duration	83.69(46.67)	86.17(32.54)	0.823
REM density	13.57(6.2)	9.89(4.93)	0.020†
Subjective Sleep Quality			
Tiredness during Daytime	3.79(0.88)	2.48(1.15)	0.066
Concentration	3.34(0.73)	2.5(0.78)	0.004†
Mood	**2.87(1.01)**	**2.1(0.58)**	**<0.001***
Sleep Quality	3.13 (1.2)	2.24(0.94)	0.009†
Relaxation	3.35(0.83)	2.18(0.86)	0.018†
Retrospective Subjective Sleep Quality			
PSQI	**12.00(4.57)**	**2.58(1.62)**	**<0.001***

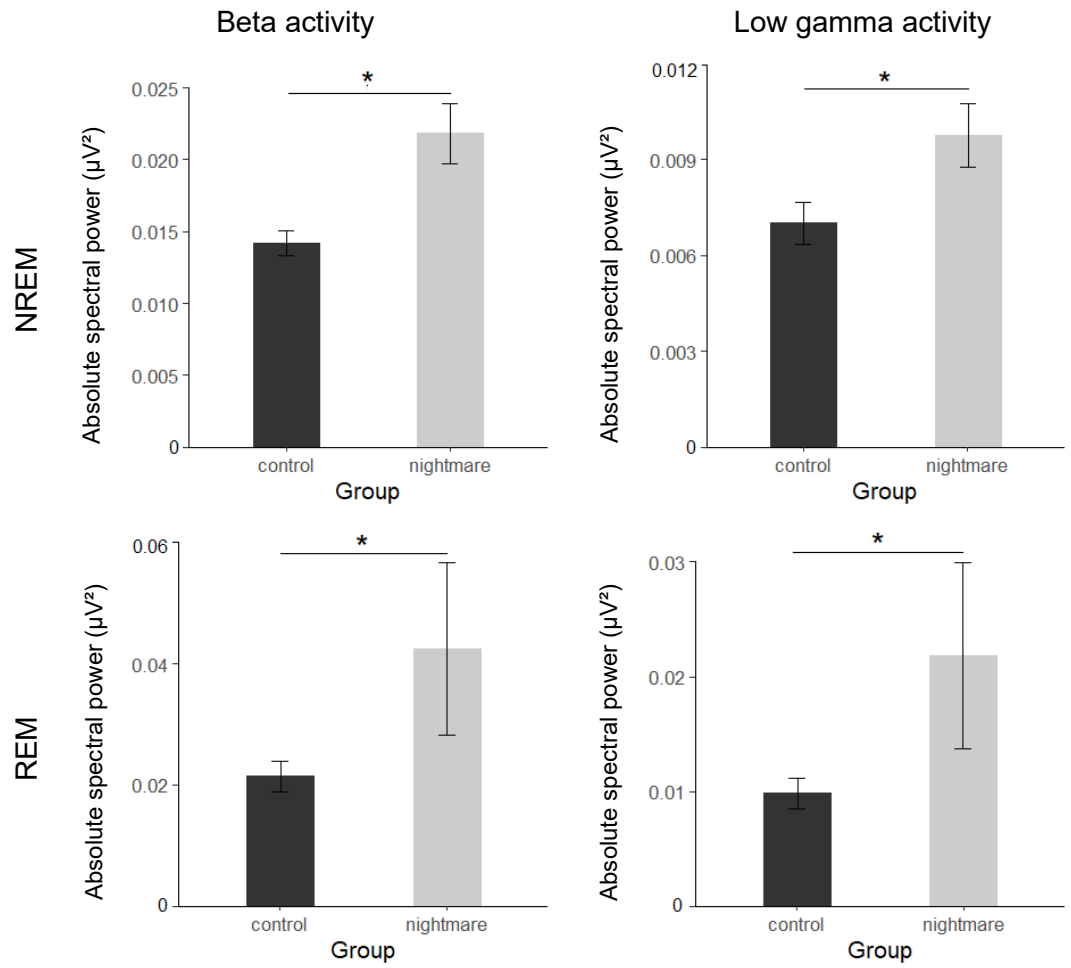
Note. * = $p < 0.002$ (Šidák adjusted *p*-value); † = $p < 0.05$. Measures of polysomnography and self-reported sleep quality measures in the nightmare (NM) and control group (CTL) at baseline.

2.4.1.2 Differences in spectral power: NREM and REM during the whole night

In order to examine differences between participants with frequent nightmares and healthy controls, we first compared absolute spectral power between groups using 2 (group) x 3 (location) ANOVAs for each frequency band. There were no significant effects of group from the delta to the sigma band (all ps ≥ 0.057). Participants with frequent nightmares as compared to healthy controls showed higher EEG oscillatory activity in the beta frequency band (16.25 –31 Hz) in both, NREM and REM sleep as indicated by significant main effect of group (NREM: $F(1,46) = 6.877$, $p = 0.012$, $np^2 = 0.130$; REM: $F(1,46) = 7.332$, $p = 0.009$, $np^2 = 0.137$, Figure 2.1). The significant effect of group was also present in the low gamma band (31.25 – 35 Hz; NREM: $F(1,44) = 8.222$, $p = 0.006$, $np^2 = 0.157$; REM: $F(1,46) = 5.931$, $p = 0.019$, $np^2 = 0.114$, Figure 2.1). This effect was not modulated by the electrode position (all $p \geq 0.121$ for interaction group x location).

Figure 2.1

Beta and low gamma activity between nightmare and control group



Note. Absolute spectral power in the beta (16.25 – 31 Hz, left) and low gamma band (31.25 – 35 Hz, right) in NREM (top) and REM sleep (bottom) for control group (black bar) and nightmare group (grey bar). *p<0.05.

2.4.1.3 Differences in spectral power: Pre- and post-REM spectral power

Previous findings (Blaskovich et al., 2020) indicate that the transitional period from NREM to REM sleep is especially important for the study of cortical hyperarousal. Therefore, we compared the 10-minute intervals before and after REM separately in a 2 (group) x 2 (time: pre / post REM) x 3 (location) for the beta and gamma band. Beta and low gamma activity did not differ between pre- and post-REM periods (ps ≥ 0.064 for time x group, location x time interactions and time x group x location interactions).

2.4.1.4 Heart rate variability

There was a trend for heart rate when comparing the nightmare and the control group ($F(41,1)= 2.125$, $p = 0.094$, $\eta^2 = 0.067$) with the nightmare group showing increased heart rate in the last five minutes of REM. Participants with frequent nightmares and healthy controls did not differ on any of the other HRV parameters when comparing the last five minutes of REM sleep ($p = 0.808$).

Table 2.3

Objective and Subjective Sleep Parameters in nightmare (NM) and no nightmare nights (no NM)

	NM *n* = 19	no NM *n* = 19	
	M(SD)	*M(SD)*	*p*
Polysomnography data			
SE	88.23(6.65)	88.34(8.12)	0.752
TST	413.74(42.63)	411.38(42.64)	0.909
WASO	33.53(26.64)	30.18(28.73)	0.800
SL	21.03(12.16)	21.31(12.93)	0.588
MA total	59.42(24.57)	57.00(23.6)	0.023[b]
MA REM	12.74(7.92)	13.53(9.07)	0.066
REM duration	83.14(31.18)	75.93(23.67)	0.580
N1 duration	30.35(13.34)	27.24(13.35)	0.315
N2 duration	224.45(29.67)	226.33(30.7)	0.904
N3 duration	74.52(32.73)	81.79(38.54)	0.090
REM density	14.21(6.32)	13.26(6.65)	0.471
Subjective Sleep Quality			
Tiredness during Daytime	4.21(1.58)	3.47(1.71)	0.080
Concentration	4.00(1.49)	3.53(1.35)	0.042[b]
Mood	3.95(1.22)	3.63(1.46)	0.739
Sleep Quality	3.05(1.18)	3.37(1.12)	0.124
Relaxation	4.00(1.15)	3.74(1.28)	0.213

Note. [b] = $p < 0.05$. Measures of polysomnography and self-reported sleep quality measures in the nights with nightmare occurrence (NM) and no nightmare occurrence (no NM) within subjects in the nightmare group.

2.4.2 Comparison between nightmare and no nightmare nights within the nightmare group

2.4.2.1 Sleep architecture and subjective sleep quality

There were more movement arousals and a lower rating of concentration in nightmare nights compared to no nightmare nights. However, these differences did not survive correction for multiple testing (Table 2.3).

2.4.2.2 Differences in spectral power: NREM and REM during the whole night

In order to compare spectral activity between nightmare and no nightmare nights, we first compared absolute spectral power between nightmare and no nightmare nights in 2 (Nightmare occurrence) x 3 (location) ANOVAs for each frequency band and for REM and NREM periods separately. Nights in which a nightmare occurred did not differ from nights without nightmares in any of the frequency bands (all main effects and interactions for REM and NREM ps $\geq$ 0.084).

2.4.2.3 Heart rate variability

There were no significant differences between the last five minutes of REM sleep when comparing nightmare and no nightmare nights in any of the analyses (all ps ≥ 0.451).

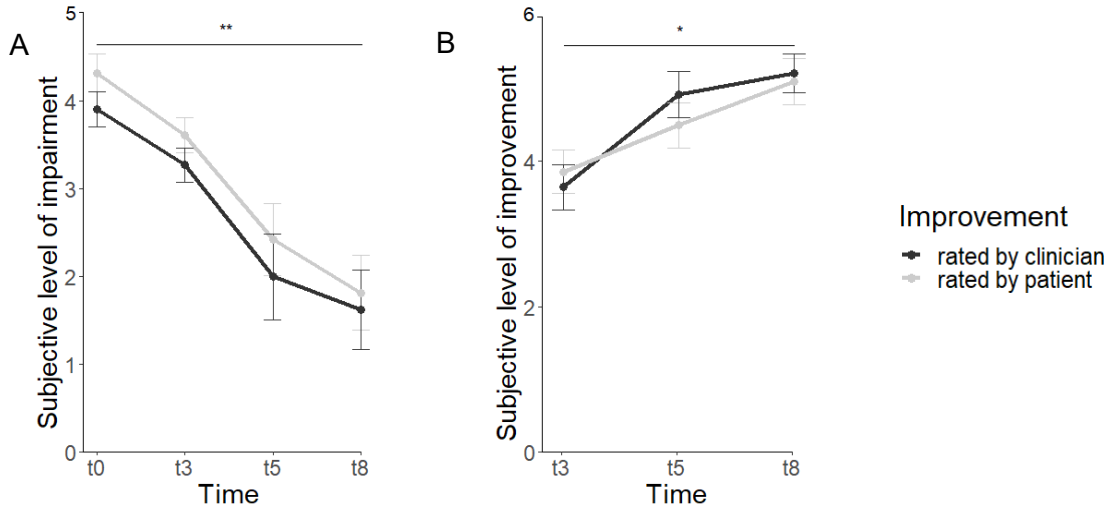
2.4.3 Comparison within participants with frequent nightmares pre and post therapy

2.4.3.1 Psychometric characteristics, sleep architecture and subjective sleep quality

Over the course of therapy, impairment by nightmare symptoms was reduced significantly in both patient ($F(8,3)=15.942$, $p = 0.001$, $np^2 = 0.857$) and clinician ratings ($F(8,3)=17.243$, $p = 0.001$, $np^2 = 0.866$). Patients' ($F(9,2)=7.610$, $p = 0.012$, $np^2 = 0.628$) and clinicians' rating ($F(9,2)=6.033$, $p = 0.022$, $np^2 = 0.573$) of the improvement of nightmare symptoms was also significant (Figure 2.2). In participants with frequent nightmares, neither sleep architecture nor subjective sleep quality did change from pre- to post-therapy (all ps ≥ 0.069, Table 2.4). There was a trend towards reduced anxiety as indicated by the BAI ($t(12) = -2.80$; $p = 0.015$), that did not survive correction for multiple testing (Table 2.5).

Figure 2.2

Impairment by and improvement of nightmare symptoms



Note. Subjective ratings of impairment by (A) and improvement of (B) of nightmare symptoms before therapy (t0), after the third session (t3), after the fifth session (t5) and after the completion of therapy (t8). Ratings were made by clinicians (black line) and patients (grey line) on a 7-point Likert scale. *p<0.05; **p<0.01.

Table 2.4

Objective and Subjective Sleep Parameters pre and post therapy

	pre *n* = 17	post *n* = 17	
	M(SD)	*M(SD)*	*p*
Polysomnography data			
SE	88.06 (9.62)	89.95(8.65)	0.490
TST	445.99 (29.37)	441.03(24.14)	0.602
WASO	3.57 (8.24)	4.27(12.70)	0.856
SL	21.84(14.45)	18.08(15.25)	0.241
MA total	54.82(14.68)	67.00(31.51)	0.145
MA REM	12.70(7.85)	15.71(8.67)	0.249
REM duration	94.15(30.69)	91.16(15.99)	0.694
N1 duration	24.43(11.74)	23.62(12.41)	0.763
N2 duration	222.09(35.82)	221.71(35.64)	0.980
N3 duration	75.03(53.00)	79.79(41.01)	0.578
REM density	15.06(6.58)	13.53(6.98)	0.416
Subjective Sleep Quality			
Tiredness during Daytime	4.06(0.73)	3.71(1.05)	0.371
Concentration	3.33(0.85)	3.24(1.25)	0.779
Sleep Quality	3.41 (0.61)	3.73(1.40)	0.412
Restedness	3.58(1.01)	3.75(1.22)	0.635
Retrospective Subjective Sleep Quality			
PSQI	10.38(4.74)	7.54(4.70)	0.069

Note. Measures of polysomnography and self-reported sleep quality measures in the nightmare group (NM) before and after completing six sessions of IRT.

Table 2.5

Psychometric Characteristics of nightmare participants pre and post therapy

	pre *n* = 17	post *n* = 17	
	M(SD)	*M(SD)*	*p*
Psychological Symptom Severity			
BDI-II	19.77(11.98)	15.73(12.77)	0.078
BAI	18.79(11.22)	14.11(10.60)	0.015[b]
SCL-90 S total	59.75(16.16)	59.38(12.39)	0.861
Emotion Regulation			
EMOCheck			
Positive Affect	2.03(0.80)	2.00(1.11)	0.936
Negative Affect	1.38(0.99)	1.14(0.73)	0.265
Emotional Competence	2.45(0.84)	2.53(0.97)	0.737
ERQ			
Reappraisal	3.51(1.38)	4.03(1.57)	0.112
Suppression	4.07(1.29)	3.85(1.16)	0.232

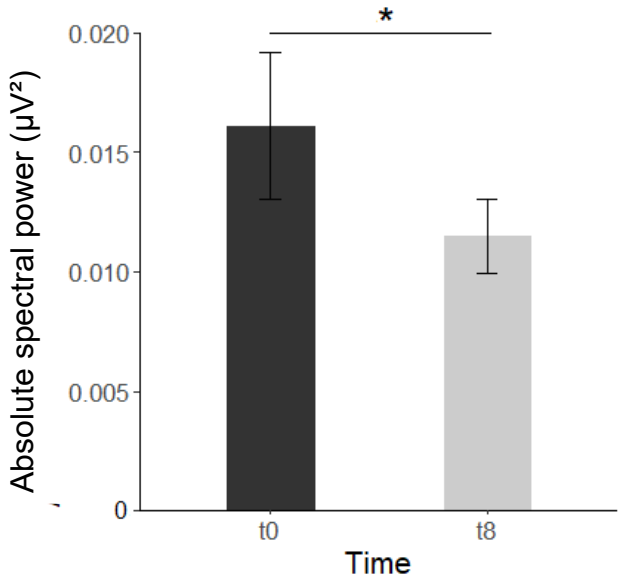
Note. [b] = $p < 0.05$. Psychological symptoms and measures of emotion regulation in the nightmare group (NM) before and after completing six sessions of IRT.

2.4.3.2 Differences in spectral power: NREM and REM during the whole night

To assess changes in spectral power before and after therapy, we calculated 2 (time) x 3 (location) ANOVAs for each frequency band in NREM and REM sleep. In NREM sleep, spectral power did not change when comparing before and after six weeks of psychotherapy (all ps ≥ 0.189). In REM sleep however, there was a significant effect of time with regard to low gamma activity ($F(15,1) = 6.529$, $p = 0.022$, $np^2 = 0.303$) with gamma activity being higher before than after therapy (Figure 2.3). There were no significant interactions between time and electrode position (all ps ≥ 0.103).

Figure 2.3

Low gamma activity in REM sleep before and after IRT



Note. Absolute spectral power in the low gamma band (31.25 – 35 Hz, right) in the nightmare group at t0 before therapy (black bar) and at t8 after therapy was completed (grey bar). *p<0.05.

2.4.3.3 Heart rate variability

There was no significant effect of time on any HRV parameters in the last five minutes of REM sleep (all ps > 0.361).

2.4.4 The role of co-morbidities in the nightmare group

As the nightmare group was heterogeneous concerning symptom load and co-morbidities, we calculated additional correlations between symptom scores (BDI-II, BAI, IES-R and CTQ) and beta and low gamma activity in the nightmare group. In NREM sleep, there were significant correlations of BAI scores with beta activity over all locations (all ps < 0.029) as well as frontal ($r = 0.507$, $p = 0.016$) and central low gamma activity ($r = 0.519$, $p = 0.013$). In REM sleep, IES-R was correlated with frontal gamma activity ($r = 0.609$, $p = 0.047$). However, all these correlations did not survive the correction for multiple testing (Šidák-corrected p-value = 0.0021). As the BAI also was the only symptom measure that showed a trend towards changing after therapy, we correlated the change scores of low gamma in REM sleep with changes on the BAI. There was a significant correlation of changes in frontal gamma with changes in BAI ($r = 0.607$, $p = 0.021$) that also did not survive correction for multiple testing (Šidák-corrected p-value = 0.016).

We also analyzed whether participants in the nightmare group having a psychiatric comorbidity had an influence on their beta and low gamma activity in between subject univariate ANOVAs. There were no significant differences between the group with and without any comorbidities in any of the frequency bands for both NREM and REM sleep (all p > 0.265). Moreover, we repeated the group comparison between participants with frequent nightmares and healthy controls including only the participants from the nightmare group without psychiatric comorbidities. The differences in beta activity in both NREM ($F(24,1) = 10.991$, $p = 0.003$, $\eta^2 = 0.314$) and REM ($F(32,1) = 7.936$, $p = 0.008$, $\eta^2 = 0.199$) remained

significant. For low gamma activity, the difference between groups remained significant in REM sleep ($F(32,1) = 4.821$, $p = 0.035$, $\eta^2 = 0.131$).

2.5 Discussion

In this study, we investigated which nightmare characteristics, especially cortical and autonomous hyperarousal, are more indicative of the nightmare state itself, which are rather a trait of people with frequent nightmares and whether any of these measures change after successful treatment with IRT. We found significantly higher beta- and low gamma activity in REM and NREM during the whole night in the nightmare as compared to the control group, but not when comparing nightmare with no nightmare nights in participants with frequent nightmares. During IRT, impairment by nightmare symptoms significantly declined in both patients' and clinicians' ratings. Moreover, low gamma activity in REM in the nightmare group was significantly lower after IRT compared to before the intervention.

The results of increased EEG activity in the beta and gamma band in nightmare patients as compared to controls are in line with the idea that cortical hyperarousal is also central to nightmares, especially in NREM sleep (Blaskovich et al., 2020; van der Wijk, Blaskovich, Farahzadi & Simor, 2020). A potential source of cortical hyperarousal has already been identified with previous research pointing to increased left anterior cingulate cortex and right inferior parietal lobule activity, which has also been associated with other measures of physical and psychological arousal in nightmare sufferers (Shen et al., 2016).

Besides the increased EEG activity in the beta and gamma range in participants with frequent nightmares as compared to controls, we found no difference in these frequency bands between nights with and without nightmares within nightmare patients. This suggests that the differences probably tend to be more the result of a trait rather than a state. In previous research on nightmare biomarkers in general (Simor et al., 2012), and on cortical hyperarousal in nightmares in particular (Blaskovich et al.; van der Wijk et al., 2020) study designs favored either group comparisons or online nightmare recordings without group comparisons (Phelps et al., 2018). So far, only Paul et al. chose a design that allowed for state vs. trait comparison, albeit with HRV measurements (see following paragraph). Another difficulty in earlier studies was that nightmares tend to occur less often in the sleep lab, making this study with 19 pairs of nightmares and no nightmare nights a good opportunity for discerning trait vs. state.

With cortical hyperarousal skewing more towards the trait side in our dataset and the presence of anxiety and other symptoms in our sample, more questions are opened towards the origins of this trait and potential commonalities and interactions with other disorders. Network approaches, as have been recently proposed by Sheaves et al. (2022), seem to be a promising new avenue of research in that direction. Cortical hyperarousal, potentially together with impaired fear extinction (Gieselmann et al., 2019), might be a crucial part of a network connecting nightmares, negative affect and anxiety. Future studies should investigate both long-term symptom development in symptom clusters and the effect of symptom-specific interventions to uncover potential causalities and networks. This could further strengthen the transdiagnostic quality of cortical hyperarousal, having already been found in PTSD (Wang, Ramakrishnan, Laxminarayan, Dovzhenok, Cashmere, Germain & Reifman, 2020) social phobia (Sachs, Anderer, Dantendorfer & Saletu, 2004) and in comorbid (Kwan, Baek, Chung, Kim & Choi, 2018) and idiopathic insomnia (Zhao et al., 2021). This connection is further supported by the correlation between anxiety and changes in anxiety with high frequency EEG activity and their changes after IRT. It is important to note that the degree of suffering caused by nightmares points to potential daytime impairment in the nightmare group, which is potentially more severely impacted than in other studies and suggests a diagnosis of nightmare disorder in a substantial number of participants. However, nightmare symptom severity (measured with the item degree of suffering on the nightmare questionnaire) and presence of

comorbidities were not related to high frequency EEG activity in the nightmare group. Additionally, degree of suffering might be the more clinically relevant criterion in assessing and diagnosing nightmares (Gieselmann et al., 2019) and a moderate to high degree of suffering is to be expected in this more naturalistic help provide a more realistic sample of nightmare sufferers willing to seek treatment for their nightmares. Furthermore, in contrast to previous studies we did not differentiate between idiopathic and traumatic nightmares. As there is evidence for cortical hyperarousal during sleep both in person with frequent idiopathic nightmares (Blaskovich et al., 2020) and in PTSD patients with nightmares (Wang et al., 2020), possible differences between idiopathic and traumatic nightmares regarding cortical hyperarousal should be quantitative rather than qualitative. Cortical hyperarousal might also explain the gap between subjective and objective sleep quality between groups (see Table 2), as it has been used as a possible explanation in insomnia as well (Xu, Cai, Mai, Liang, Huang & Yang, 2022). Broadening the view from the role of cortical hyperarousal as a transdiagnostic factor, this process might be related to difficulties in memory consolidation during sleep (Puetz et al., 2011) but also with increased dream (Moyne et al., 2022) and nightmare recall (Marquis, Paquette, Blanchette-Carrière, Dumel & Nielsen, 2017). Moreover, beta (Moyne et al., 2022; Scarpelli et al., 2017) and gamma activity (Scarpelli, Alfonsi, Gorgoni & De Gennaro, 2022) have been associated with processing of emotional information and a transcranial direct current stimulation (tDCS) induced excess of gamma activity during sleep has been associated with worse mood during the next morning (Marshall, Kirov, Brade, Mölle & Born, 2011). Tying these findings together, increased beta- and gamma activity seems to be present in non-pathological processes like dream recall and emotion processing but could potentially go wrong in nightmares by causing persisting negative affect and arousal and facilitating nightmare recall.

When looking at the 10-minute intervals pre- and post-REM, cortical hyperarousal persisted in the post REM phase as well. This is in contrast to the findings of Blaskovich et al. (2020) who reported that the difference in cortical hyperarousal between groups disappeared after REM sleep. As the transition to REM sleep has not been broadly studied yet in the nightmare context, these results are difficult to interpret. A possible explanation is that this difference might be due to higher psychological symptom severity in our sample, esp. concerning higher depression and anxiety levels (see Table 2.1), thus potentially leading to higher levels of cortical hyperarousal that is not alleviated after REM sleep.

In our study we found no differences in any measures of HRV. In previous studies changes in autonomous arousal seemed to be more closely related to nightmare occurrence (Paul et al., 2019; Phelps et al., 2018) but no significant effects could be detected in this study. This might be mainly due to the way nightmare occurrence was sampled in our study, where it was only reported the morning after, compared to Paul et al. (2019) who made participants record nightmare experience as soon as they woke up from a nightmare or a non-nightmare dream. Future studies should therefore utilize online recording of nightmares and measures of both cortical and autonomous arousal to further investigate the notion that cortical arousal is indeed more of a trait in nightmare sufferers while autonomous hyperarousal seems to be more indicative of the nightmare state.

The intervention the nightmare group received both led to changes on the symptom and the physiological level when comparing pre and post therapy. The changes on the nightmare symptoms are in line with what could be expected from an IRT intervention, given that it is the gold-standard for nightmare interventions (Morgenthaler et al., 2018). The reduction in low gamma activity after the intervention, however, is a more novel finding, as studies on IRT usually do not include data from spectral analysis. This is an especially interesting finding as it points to cortical hyperarousal being malleable by intervention despite being a trait-like phenomenon in people with frequent nightmares. As these changes were however more of a by-product of the successful treatment with IRT, an important next step to better

understand the role of cortical hyperarousal in nightmares, and potentially in other disorders, would be studies which directly experimentally manipulate cortical hyperarousal. TDCS in the theta band has already shown to increase gamma activity in healthy participants (Marshall et al., 2011) but as this experimental manipulation also led to worse mood, it might not be that suitable for therapeutic purposes. Delta activity has already been targeted with open loop audiovisual stimulation (AVS) and improved subjective sleep quality in patients with insomnia-related cortical hyperarousal (Fries, Scheeringa & Oostenveld, 2008) but that stimulation did neither target nor affect high frequency activity. Thus, studies that experimentally manipulate cortical hyperarousal in people with frequent nightmares might not only help with better understanding of underlying processes but also with the development of treatment options.

2.5.1 Limitations

As briefly mentioned, when discussing the results on HRV, a major limitation of the study design was that nightmare occurrence was only recorded retrospectively in the morning and not whenever the participants awoke at night directly after a nightmare, as was done by Paul et al. (2019). Even though this allowed for less disturbed sleep for the participants, it also meant that physiological data, especially spectral power, and measures of autonomous hyperarousal, could not be analyzed more closely around an actual nightmare occurrence. Moreover, not every awakening, particularly from REM, could be traced back to a nightmare occurrence with certainty, further complicating a more fine-grained analysis. This especially impedes the interpretation of differences between nightmare and no nightmare nights as transient phenomena around actual nightmare occurrence might not have been detected when comparing data of the entire night.

The second limitation to this study is the measurement of gamma activity, which was limited to 35 Hz due to an in-built filter in the recording device so not all effects in the gamma band might have been detected. However, as problems with artifacts in high frequency bands are very likely (Muthukumaraswamy, 2013) using data from frequency bands higher than 30 or 35 Hz might not be advisable anyway.

A major limitation when interpreting the effects of IRT on EEG activity is the lack of a randomized control group that also suffered from nightmares but did not receive an intervention. This only allows for a comparison of symptoms and EEG activity before and after the intervention within the intervention group. While a reduction in subjective parameters such as anxiety could also be explained by expectancy effects (Hjorth et al., 2021), the pre-post difference on an objective measure such as gamma activity is more likely an effect of the intervention. The correlation of changes in anxiety symptoms and frontal gamma activity further supports this assumption. Nevertheless, future studies need to include a control group of nightmare patients who do ideally receive a minimal intervention that does not target nightmares or related symptoms. Another consideration in that regard is that our design does not allow us to discern which component of the intervention, i.e., dream rescripting specifically, relaxation, psychoeducation etc., contributed to the changes in symptoms. Future research using randomized controlled designs should also evaluate the effective components of IRT on EEG activity.

2.5.2 Conclusion

Cortical hyperarousal seems to be the central parameter identified in this study and is more likely to be a trait occurring in nightmare sufferers than an indicator of the nightmare state. Additionally, it is possibly malleable by successful therapy. More research is needed as to which mechanisms are behind

cortical hyperarousal in nightmares, its potential role in broader symptom networks, and how it might be used in the development of new treatment options.

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2.7 Figure and table legends

2.8 Supplementary Materials

Supplementary material 2.A: Nightmare questionnaire

Dear patients,

Nightmares are defined as a "dream experience filled with fear and anxiety with detailed memory of dream content ". Common themes are persecution, being attacked or hurt by other humans or animals, threat to own life or life of others up to murder, furthermore severe illness or committing violent acts toward others.

Demographic data

Patient's initials:

Age in years:

Gender: ◯ female ◯ male

Education level:

◯ No diploma ◯ 8 to 9 years of schooling

◯ 10 years of schooling ◯ 12 to 13 years of schooling

◯ University graduate ◯ Still in school

Do you smoke? ◯ never ◯ rarely ◯ regularly

How much do you smoke? Per day: ……cigarettes

Do you drink alcohol? ◯ never ◯ rarely ◯ regularly

Which types of alcohol? ◯ beer ◯ wine ◯ hard liquor

◯ mixed ◯other:……

Which medications are you currently taking? (Please fill in name and dose)

…… ……

…… ……..

Do you suffer from a physical illness?

◯ no
◯ yes If so, which one(s)?.....

Questionnaire about nightmares

Pat.-Nr.: ……

Dear patients,

on the following pages you find a number of questions concerning nightmares. Please read each question carefully and determine, to what extent you experienced distress and disturbances by these dreams.

1. Have you ever experienced nightmares?

◯ no
◯ yes

2. If yes, do they occur more than once a month?

◯ no
◯ yes

If you answered one of these questions with **no** you are finished with this questionnaire now. Please return the questionnaire to your attending physician. Thank you very much!

---

3. How often do you have nightmares?
   … per week
   … per month

Additional remarks about nightmare frequency:……

4. Since when have you had nightmares?

◯ …since childhood
◯ …for more than 20 years
◯ …for at least 10 years
◯ …for at least 5 years
◯ …for at least 1 year
◯ …for at least 6 months
◯ …for at least 3 months

◯ …for at least 1 month
◯ …for less than a month

5. How often do you vividly remember your dreams after you wake up?

never	sometimes	often	very often	always
◯	◯	◯	◯	◯

6. Do your dreams repeat themselves in an almost identical manner?

◯ no
◯ yes

7. Do the themes of your dreams repeat themselves while details and settings change?

◯ no
◯ yes

8. Which themes occur in your nightmares? (Multiple answers are possible)
I am…

◯ … being chased.
◯ … being attacked / assaulted (beaten, raped, stabbed, etc.).
◯ … locked up and cannot escape.
◯ … frozen / paralysed with fear
◯ … falling into an abyss.
◯ … unable to move.
◯ … drowning.
◯ … witnessing an injustice and cannot intervene.
◯ … being killed.
◯ …seeing myself die.
◯ …losing control of a vehicle.
◯ …failing at an exam.
◯ …unable to breathe
◯ …killing someone.
◯ … witnessing an injustice and cannot help.
◯ …ill / a loved one is severely ill.
◯ …running but not getting anywhere.

Other themes:

◯ …flooding
◯ …war / war injuries
◯ …tornadoes
◯ …earthquakes
◯ …insects, spiders

◯ …animals in general
◯ …fire
◯ …monsters / ghosts
◯ …aliens / UFOs
◯ …accidents

9. Do you think there is a connection to traumatic experiences in your biography?

◯ no
◯ yes

10. Do your nightmares constitute a coherent story?

◯ no
◯ yes
◯ sometimes

11. Do your nightmares constitute single impressions without a coherent story?

◯ no
◯ yes
◯ sometimes

12. After waking up from a dream, are you rather …(Multiple answers are possible)

◯ …oriented quickly
◯ …disoriented / confused
◯ …awake
◯ …tired
◯ …other:
……..
……..
……
……
……

13. How much do you suffer from your nightmares or the sleep disturbance caused by nightmares?

not at all	rarely	occasionally	strongly	very strongly
◯	◯	◯	◯	◯

14. Have you ever tried anything to reduce your nightmares?

◯ no
◯ yes

If yes: what exactly have you done to reduce the nightmares?
……
……
……
……
……
……

15. Do you see a connection to other physical illnesses you might have?

◯ no
◯ yes

If yes: please describe!
……
……
……
……
……
……..

16. Do you see a connection to any medication you are taking / have taken?

◯ no
◯ yes

If yes: please describe!
……
……
……
……

17. Do you see a connection to any illicit drugs you are taking / have taken?

◯ no
◯ yes

If yes: please describe!
……
……
……
……

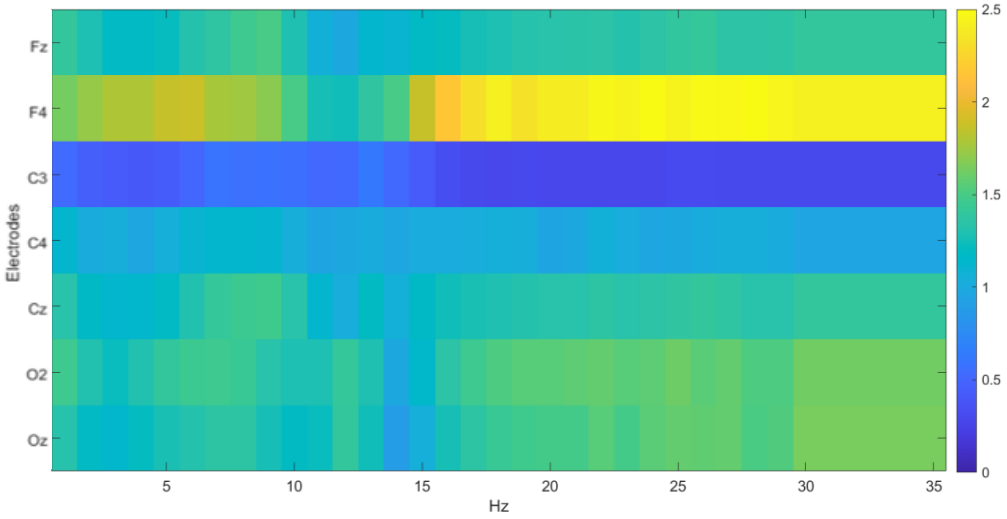
18. Do you have any other explanation for your nightmares? (Please describe)

……
……
……
……
……

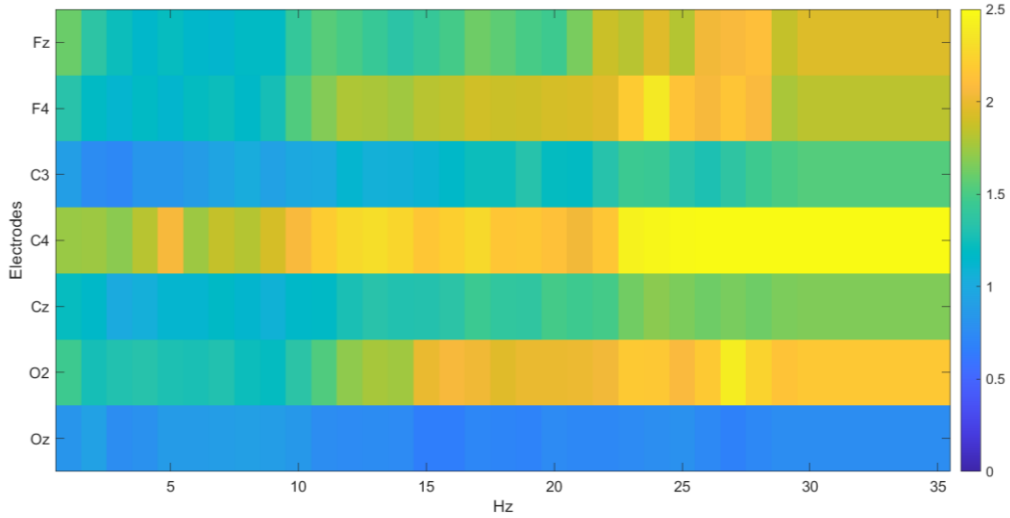
Thank you very much! We will get back to you in the next few days.

Supplementary materials 2.B: Absolute power spectral differences in NREM (A) and REM sleep (B)

(A)



(B)



*Note***.** Differences in absolute spectral power between NM participants and controls during NREM and REM sleep. Colormap represents absolute spectral power ratio (NM/CTL) in NREM and in REM sleep for each frequency bin and every EEG channel.

3 Study 2: Imagery rehearsal therapy for the treatment of nightmares in individuals with borderline personality disorder – a pilot study[2]

3.1 Abstract

Insomnia and nightmares are present in up to 45 % of individuals with BPD and can contribute to challenges with emotion regulation, low sleep quality, dream anxiety, increased arousal and self-control. Despite their prevalence, nightmares are usually not addressed in classical BPD treatment. IRT is considered first in line treatment for nightmares, however, there are no studies to date that investigate its effects in individuals with BPD. Here we investigated a) whether IRT can be used to treat nightmares in individuals with BPD and b) whether there is an additional benefit of the intervention on symptoms associated with BPD. In a between-subjects design, 22 individuals with BPD completed eight sessions of group-IRT as an add-on to their inpatient treatment and were compared to 22 gender and age matched control participants regarding nightmares, trauma, depression and anxiety symptoms. Nightmare symptoms improved significantly during the intervention as indicated by subjective ratings. Moreover, participants in the IRT group showed a more pronounced decrease in intrusions, hyperarousal and anxiety compared to the control group. This pilot study gives a first glimpse into the feasibility and benefits of IRT in individuals with BPD. Our findings suggest that IRT may not only help treat nightmare symptoms but also reduce anxiety and trauma symptoms in BPD. Future studies should include randomized controlled trials of IRT in individuals with BPD with larger sample sizes and PSG in both groups.

3.2 Introduction

BPD occurs in about 0.7 to 3.5 % of the general population and they make up between 9 – 18 % of all individuals in psychiatric inpatient and outpatient settings (Doering, 2019). Its diagnostic criteria, according to the DSM-5 (APA, 2013), include instability in identity, self-direction and interpersonal relationships, negative affectivity, disinhibition, and hostility. It is associated with challenges to safety (DeShong & Tucker, 2019). There is a wide variety of comorbidities associated with BPD such as substance use disorders, eating disorders, depression, or PTSD (Ford & Courtois, 2014).

Sleep disturbances have been reported in 5 to 45 % of individuals with BPD (Vanek et al., 2021) but are not studied as often as other comorbidities of BPD (Semiz, Basoglu, Ebrinc & Cetin, 2008). Sleep disturbances in BPD include insomnia (Vanek et al., 2021; Plante et al., 2013), disturbance of circadian rhythm, such as delayed sleep phase syndrome (Jenkins et al., 2022) as well as nightmares, dream anxiety and dysphoric dreams (Selby, Ribeiro & Joiner, 2013; Simor et al. 2010). With regard to objective sleep disturbances a lower sleep quality, decreased sleep duration, REM sleep latency and NREM sleep duration, sleep fragmentation, increased sleep latency and REM sleep duration as well as paradoxical insomnia was reported in individuals with BPD (Hafizi et al., 2013, Oltmanns & Oltmanns, 2015).

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[2] This chapter has been published as: **Sayk, C**., Koch, N., Stierand, J., Timpe, F., Ngo, H. V. V., Wilhelm, I., & Junghanns, K. (2025). Imagery rehearsal therapy for the treatment of nightmares in individuals with borderline personality disorder–A pilot study. *Journal of Psychiatric Research*, *182*, 34-41**.** I analyzed the data, wrote and revised the manuscript and was responsible for data visualization.

According to a meta-analysis by Winsper and colleagues (2017), individuals with BPD as compared to healthy controls had decreased sleep continuity, less SWS, shorter REM latency and higher REM density. Interestingly, these differences seem to be independent of co-morbid depression and PTSD symptoms (Schredl et al., 2012, Harty et al., 2010) and have been shown to indicate recovery status with recovered individuals having better subjective sleep quality and shorter sleep latency (Plante et al., 2013). The findings by Plante and colleagues (2013) indicate a strong bidirectional relationship between sleep disturbances and BPD. Indeed, sleep disturbances are highly correlated with BPD symptoms (King et al., 2024) and affect and cognition during the day in individuals with BPD (Simor & Horvath, 2013). Nightmares especially seem to increase challenges with emotion regulation, especially fear extinction (Gieselmann et al., 2019), low sleep quality, dream anxiety, increased arousal and reduced self-control (Behloradova et al., 2023). Nightmares can even precede the development of personality disorders, might constitute a risk factor in their development (Morales-Muños et al.,2021; Lereya et al., 2017) and are associated with long-term outcomes such as lower education level and unemployment, (Semiz et al., 2008) and dissociative symptoms (Lemyre et al., 2019) in individuals with BPD. Furthermore, nightmares and related sleep problems have been found to be related to challenges with safety (Andrews et al., 2020; Scamaldo et al., 2022), even though nightmares do not mediate between BPD symptoms and these challenges (DeShong & Tucker, 2019). They can contribute to negative emotion and rumination cascades in individuals with BPD which can in turn lead to substance use, binge eating, fighting, or self-injury (Selby et al., 2013).

Difficulties with self-regulation have been proposed as a potential mechanism to explain the relationship between sleep disturbances and BPD symptoms (e.g., Harty et al., 2010). In the emotional cascade model (Selby et al., 2013), cascades of increased emotional arousal during the day carry over to increased cognitive activity and arousal during sleep, which in turn contribute to increased nightmares and difficulties managing daily tasks in the subsequent day. While emotion and self-regulation during daytime is at the core of dialectical behavior therapy (DBT) (Linehan, 2018) or schema therapy (Martin & Young, 2010) for individuals with BPD, sleep disturbances in general and nightmares in particular are usually not directly addressed in treatment, despite several studies calling for such interventions to be implemented (Semiz et al., 2008; Schredl, 2016; Huỳnh et al., 2016; King et al., 2024).

IRT is a cognitive-behavioral intervention with an "educational restructuring element, focused on helping the nightmare sufferer to consider their disturbing dreams as a learned sleep disorder […] and an imagery training element, which teaches patients how to implement a specific set of imagery steps to decrease nightmares" (Krakow & Zadra, 2010, p. 290). It is considered first in line treatment for nightmare disorder (Morgenthaler et al., 2018) and has been successful in treating idiopathic nightmares, nightmares in individuals with depression (Thünker & Pietrowsky, 2012) and posttraumatic nightmares (Yücel et al., 2020). Apart from increased mastery and self-efficacy due to learning to control dream content, one of the main proposed mechanisms behind IRT is an improvement in both day- and nighttime emotional processing (Rousseau & Belleville, 2018). More specifically, the rescripting of the nightmare allows individuals to integrate new information that makes them feel safe and in control into their nightmare script (Davis et al., 2007), which promotes improved fear extinction and emotion regulation. This improved emotion regulation is thought to occur during daytime and at night, especially during REM sleep which is closely related to emotional processing and 'overnight therapy' (Walker & van der Helm, 2009). These improvements in fear structures, safety learning (Davis et al., 2007) and emotional processing during REM sleep could be greatly beneficial to individuals with BPD. Yet, there are no studies to date that investigate the effects of IRT in individuals with BPD, except for a case study of imagery rehearsal based art therapy (Kehr & Haeyen, 2023) which also emphasized the benefits of this

therapeutic method on emotional processing. This might be due to individuals with BPD and their therapists focusing on other therapy goals, such as ensuring personal safety and fostering a strong therapeutic alliance first (Linehan, 2018) which makes it harder to implement an additional nightmare therapy in both inpatient and outpatient settings. However, Ellis et al. (2019) conducted a first study on the efficacy of IRT in a mixed psychiatric inpatient sample with promising results.

The aim of the present study was thus primarily to investigate whether IRT can be used to successfully treat nightmares and improve sleep in individuals with BPD and secondary, whether, in addition to improvement in nightmares, IRT is also associated with improvement in psychiatric symptoms, such as anxiety, depression or difficulties in emotion regulation that are typically associated with BPD.

3.3 Methods and Materials

3.3.1 Participants

Individuals with frequent nightmares were recruited from inpatient treatment for BPD at *Universitätsklinikum Schleswig-Holstein Lübeck*. They were aged between 18 and 67, mean age was 32.37 (SD = 11.20) and fluent in German. The majority of the sample (n = 52 of 55) was female. BPD diagnosis and potential comorbidity with PTSD were confirmed with the structured clinical interview for DSM (First & Gibbon, 2004). Information on current medication and potential somatic comorbidities were taken from clinic records. Most participants in both groups had several somatic and psychiatric comorbidities other than PTSD and BPD. Participants were excluded when they were (1) currently having a psychotic episode and (2) currently addicted to or withdrawing from alcohol, benzodiazepines or illicit drugs. Most participants took various psychotropic medications, which we tried to keep constant throughout the course of the study.

The original sample consisted of 33 participants in the IRT group of which 11 participants dropped out of the study at different time points (see supplementary material 3.A). These participants explored other options and preferences for care and therefore also chose to no longer participate in the study. The participants that dropped out did not differ significantly in demographics, nightmare and psychological symptoms or emotion regulation compared to those remaining in the study (all ps $\geq$ 0.081), nor did they differ in total number of psychiatric and somatic comorbidities (all ps $\geq$ 0.531). Most participants in both groups had several somatic and psychiatric comorbidities other than PTSD and BPD (see supplementary material 3.B for descriptive statistics). 22 age and gender matched controls that received treatment-as-usual (TAU) (including DBT-focused individual and group therapy and optimization of psychiatric medication) were matched retrospectively to the participants in the intervention group that completed the intervention. There were no differences in age, gender, or other psychological symptoms between groups except for participants in the IRT group reporting a higher degree of suffering from nightmares and a slightly higher number of co-morbidities.

The study was approved by the university's ethics committee. All participants provided written informed consent after having been given a complete description of the study protocol. Participants were compensated financially for the nights spent in the laboratory.

Table 3.1

Psychometric Characteristics of intervention (IRT) and control group (CTL) pre therapy

	IRT completers *n* = 22	CTL *n* = 22
	M(SD)	*M(SD)*
Demographics		
Age	29.91(9.61)	34.52(13.13)
Gender (% female)	100	100
PSQI	12.79(3.64)	13.81(3.51)
Nightmare characteristics		
Frequency per Week	4.44(1.54)	4.07(1.98)
Symptom Onset	2.18(1.53)	2.05(1.75)
Memory Frequency	3.73(1.07)	3.29(1.19)
Identical Repetition	0.68(0.47)	0.48(0.51)
Relation to Biography	0.82(0.39)	0.76(0.44)
Degree of Suffering	4.18(0.66)	3.57(0.87)
BDI-II	40.33(10.32)	41.14(10.87)
BAI	30.29(14.75)	32.25(11.89)
SCL-90 S total	70.3(7.33)	72.17(5.92)
Intrusions	25.92(10.72)	27.06(7.21)
Avoidance	24.62(8.48)	26.47(9.19)
Hyperarousal	22.62(8.99)	24.29(7.94)
CTQ		
Emotional Neglect	16.88(5.52)	15.73(6.27)
Sexual Abuse	10.9(7.15)	12.37(8.18)
Physical Abuse and Neglect	21.31(9.56)	21.67(11.28)
Emotional Abuse	17.34(6.09)	16.36(6.65)
Positive Affect	0.82(0.45)	0.91(0.63)
Negative Affect	2.50(0.79)	2.47(0.69)
Emotional Competence	1.55(0.74)	1.52(0.67)

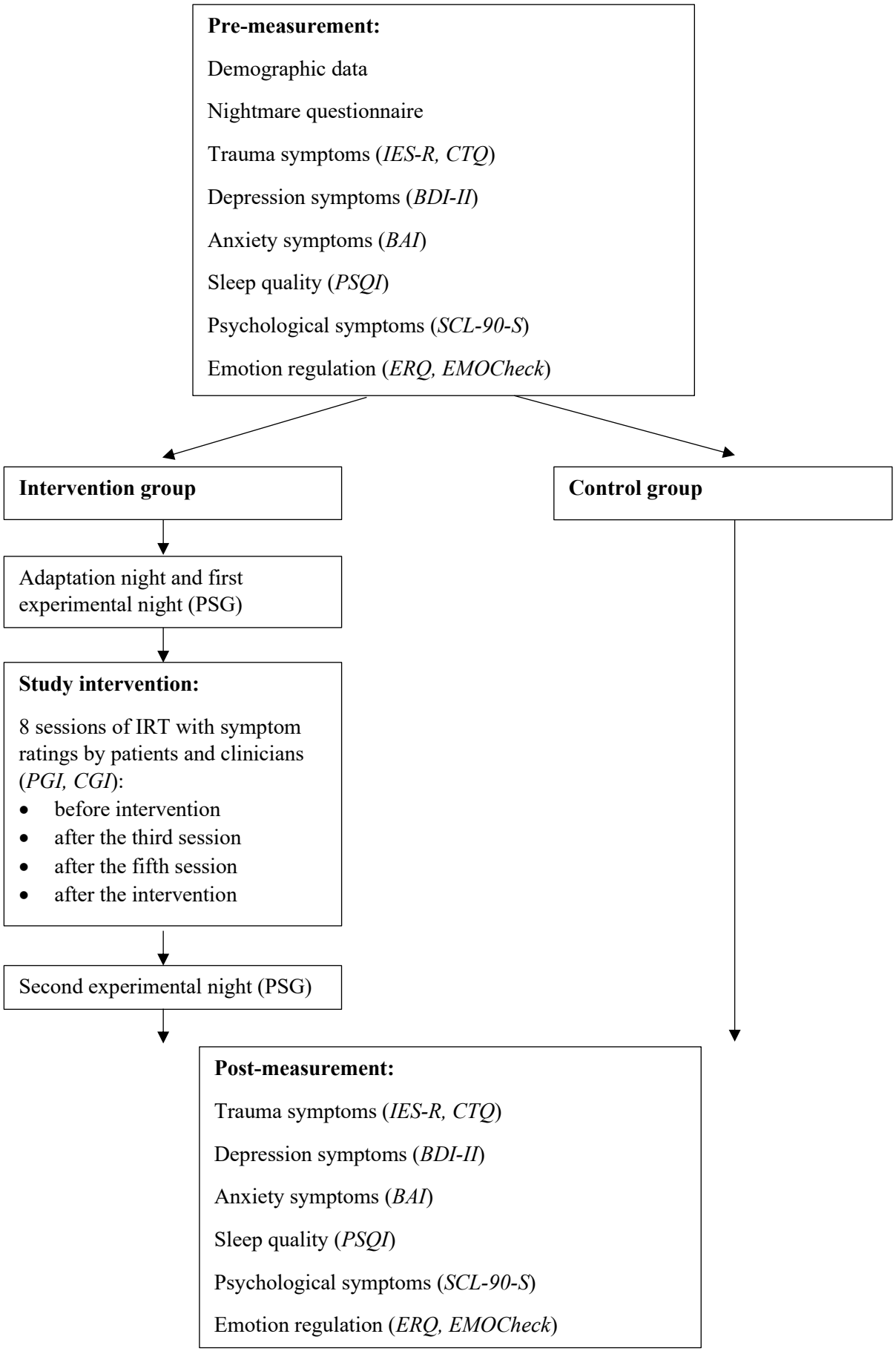
Reappraisal	3.52(1.18)	3.75(0.98)
Suppression	4.65(1.48)	4.81(1.12)

3.3.2 Materials

Questionnaires. Participants completed questionnaires to assess current and childhood posttraumatic symptoms with the IES-R (Weiss, 1997) at pre and post measurement and CTQ (Bernstein & Fink, 1998) at pre measurement, depressive symptoms with BDI-II (Beck, Steer & Brown, 1987), anxiety symptoms with the BAI (Beck & Steer, 1988) and general psychological symptom burden SCL-90-S (Franke, 2016) at pre and post measurement. Emotion regulation was assessed with the ERQ (Gross & John, 2003) and EMO Check (Berking & Znoj, 2008) also at pre and post. Nightmare experience was assessed by a customized questionnaire (published in Sayk et al., 2024) that encompassed items on nightmare frequency, symptom onset, memory of nightmares, nightmare topics including identical repetition of a specific nightmare, relation of the nightmares to individuals' biography and the degree of suffering caused by the nightmares at premeasurement. Additionally, subjective sleep quality was assessed with evening and morning protocols of sleep lab nights and in retrospect for two weeks with the PSQI (Buyssee, Reynolds, Monk, Berman & Kupfer, 1989) at pre and post measurement. Symptom development was consistently assessed using the Patient Global Impression (PGI) scale and the Clinical Global Impressions (CGI) scale (Guy, 1976) in the intervention group only, before therapy, after the third session, after the fifth session and after the intervention was complete. It was not evaluated in the TAU group. Both scales include one item assessing the impairment caused by nightmare symptoms and one item assessing the improvement of symptoms from the participants' perspective (PGI) and the clinicians' perspective (CGI) and served as our primary outcome measure for nightmare symptoms. All questionnaires except for the CGI were self-reported symptom scales. A detailed graph which measures were employed when can be found in Figure 3.1. Items of the PGI and CGI scales can be found in the supplementary materials (supplementary material 3.C).

Figure 3.1

Timepoint of measurements during the course of the study



Polysomnography. Participants were fitted with 7 EEG electrodes (Fz, F4, C3, C4, Cz, O2, and Oz) according to the 10–20 system, referred to the mathematically linked mastoid (A1 and A2) electrodes. We used EMG placed on the chin, as well as EOG and ECG according to AASM. Data was recorded with SOMNOscreen™ plus (Somnomedics, Randersacker, Germany). Impedances were kept below 4 kΩ. Sampling rate was 256 Hz. The device has inbuilt 0.2 – 35 Hz filters for EEG and EOG and 0.2 – 150 Hz filters for EMG and ECG channels.

Sleep macrostructure and spectral power analysis. Sleep stages were scored manually according to AASM criteria (Berry et al., 2017) by two experienced sleep lab technicians. Recordings were visually inspected on a 30-second basis and channels with muscle- and technical-related artifacts were discarded. Artifact-free, 50% overlapping, 8.192-second epochs were Hanning-tapered and Fast Fourier Transformed with FieldTrip (Oostenfeld, Fries, Maris & Schoffelen, 2011) in order to calculate absolute power spectral densities for each frequency bin between 1.25 Hz and 35 Hz for NREM (Stage 2 and Stage 3) and REM sleep periods, separately. Band-wise spectral power was extracted by summing up bin-wise values into the traditional frequency ranges of delta (1.25–4 Hz), theta (4.25–8 Hz), alpha (8.25–13 Hz), sigma (13.25–16 Hz), beta (16.25–31 Hz) and low gamma (31.25–35 Hz) bands and averaged across all channels.

Intervention. The IRT group attended eight sessions of imagery rehearsal group therapy (Thünker & Pietrowsky, 2012) as an add-on to their inpatient treatment (treatment as usual, TAU), which is described in more detail below. Groups typically included 6 – 8 participants at a time and were conducted by an experienced clinical psychologist. IRT sessions were usually scheduled weekly and integrated into their treatment plan during the inpatient program. During therapy, participants first analyzed their nightmares for typical and negative elements with the help of the therapist. They then found an alternative ending to the nightmare and repeatedly imagine the alternative dream script regularly before bedtime. Additionally, participants received information on sleep hygienic behavior and learned a relaxation technique (progressive muscle relaxation or autogenic training).

Treatment-as-usual. Both groups were part of a 12-week inpatient treatment program that was based on DBT. This consisted of two weekly DBT-based group sessions and one DBT-based individual psychotherapy session. In addition to that, participants attended occupational and physiotherapy sessions and participated in mindfulness, creativity and movement groups.

3.3.3 Procedure

Participants in the IRT group spent three nights in the sleep lab in total, the first two prior to starting their six weeks of imagery rehearsal group therapy (Thünker & Pietrowsky, 2012). The first night served as an adaptation night and to test for medical conditions such as sleep apnea and restless legs syndrome. If a diagnosis was made, participants could remain in the study but were referred to further treatment if necessary. The last PSG night took place about eight weeks after the first measurements when the intervention group had finished IRT. Participants filled in questionnaires at second and third PSG nights. The TAU group filled in the same questionnaires, except for PGI and CGI, as the intervention group at the beginning and at the end of their twelve-week inpatient treatment.

3.3.4 Statistical analyses

Statistical analyses were carried out with SPSS. Differences in sleep architecture, spectral power in single electrodes and frequency bands were evaluated by dependent samples t-tests within the intervention group. Šidák correction was used to correct for multiple comparisons for the primary outcome, nightmare symptoms and sleep quality, whereas, in line with recommendations from Li et al. (2017), the analysis of the secondary outcome measures, such as psychological symptoms and emotion regulation were considered exploratory and therefore not warranting adjustment for multiple testing. Due to the exploratory nature of this pilot study, especially of the secondary hypothesis, a per-protocol analysis was used that only compared participants with complete datasets. Nightmare symptoms during therapy were analyzed with separate repeated measure ANOVAs with the factor Time (first session, third session, fifth session and post therapy) in the intervention group. Band-wise spectral power differences in the intervention group pre and post therapy were examined by repeated measure 2x7 ANOVA with the factors Time (pre IRT, post IRT) and Electrodes (Fz, F4, C3, C4, Cz, O2, and Oz) for each frequency band and for NREM and REM sleep separately.

Development of psychological symptoms, subjective sleep quality and emotion regulation in the intervention and control group were analyzed with a 2x2 mixed model ANOVA including Time (pre, post therapy) as within subject factor and Group (IRT group, TAU group) as between subject factors.

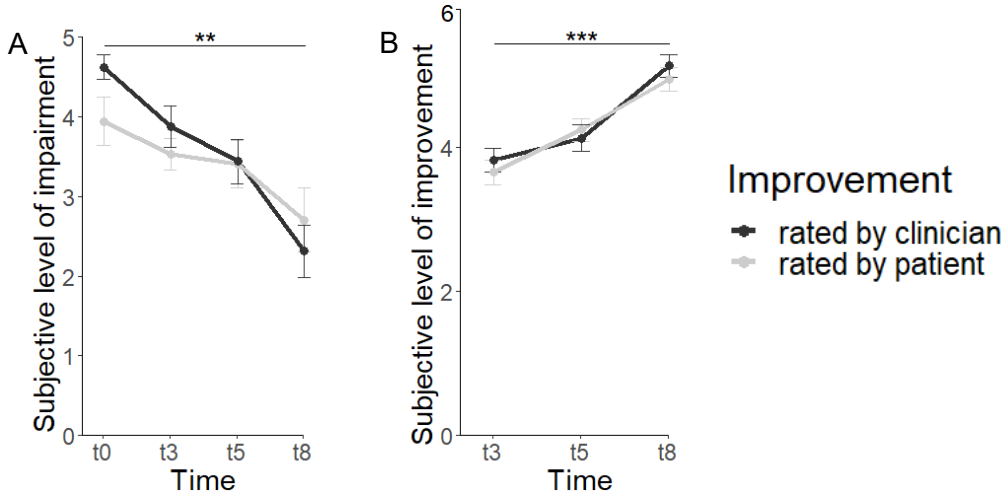
3.4 Results

3.4.1 Nightmare symptoms and sleep in the intervention group

Nightmare symptoms. In both participant and clinician ratings, impairment through nightmares decreased significantly during treatment (participants: $F(14,3) = 5.808$, $p = 0.009$, $\eta p^2 = 0.554$; clinicians: $F(13,3) = 22.585$, $p < 0.001$, $\eta p^2 = 0.839$). Moreover, participants and clinicians reported significant improvement of nightmare symptoms (participants: $F(15,2) = 16.582$, $p < 0.001$, $\eta p^2 = 0.689$; clinicians: $F(14,2) = 14.770$, $p < 0.001$, $\eta p^2 = 0.689$; Figure 3.2).

Figure 3.2

Nightmare symptoms over time in the intervention group



Note. A) Impairment (from 6 = extremely severe illness to 0 = no impairment at all) and B) improvement (from 0 = much worse to 6 = greatly improved) ratings of nightmare symptoms by patients (grey line) and clinicians (black line) in the intervention group before therapy (t0), after the third session (t3), after the fifth session (t5) and after the intervention was complete (t8). *p<0.013 (Šidák-corrected p-value), **p<0.01, ***p<0.001

Sleep macrostructure and spectral power. There were no significant differences regarding sleep architecture in the intervention group before and after IRT (all ps ≥ 0.555; see Table 3.2). Subjective sleep quality in sleep lab nights did not change significantly either (all ps ≥ 0.09). The only significant difference was related to retrospective subjective sleep quality measured with the PSQI ($t(14) = 3.850$, $p = 0.002$) which showed an improvement during treatment. There was no change in any of the EEG frequency bands from before to after therapy, neither in REM sleep nor in NREM sleep (all ps ≥ 0.560 for main of effects of time and interactions time x electrode). Post-hoc power calculations revealed a power of $1 - \beta \leq 0.007$ for the analysis of the objective sleep data (see supplementary material 3.E) indicating that a much larger sample size would have been required to see significant difference, if they actually existed.

Table 3.2

Objective and Subjective Sleep Parameters in IRT group pre and post therapy

	pre *n* = 19	post *n* = 19	
	M(SD)	*M(SD)*	*p*
Polysomnography data			
Sleep Efficiency	91.02(4.53)	91.12(5.72)	0.926
Total Sleep Time	413.78(40.1)	419.43(35.33)	0.610
Wake after Sleep Onset	10.33(15.32)	8.44(14.11)	0.555
Sleep Latency	17.09(12.83)	17.11(11.95)	0.996
Movement Arousal total	63.16(51.62)	61.42(28.86)	0.854
MA REM	12.15(11.91)	12.73(11.21)	0.867
REM duration(minutes)	88.17(34.97)	92.69(37.38)	0.670
N1 duration (minutes)	28.02(24.34)	27.66(14.01)	0.939
N2 duration (minutes)	201.35(44.91)	207.93(28.02)	0.607
N3 duration (minutes)	94.21(38.68)	91.05(36.86)	0.688
REM density	16.26(8.36)	16.47(8.74)	0.917
Absolute Spectral Power (μV^2)			
NREM			
delta (1.25 – 4 Hz)	5.17 (2.81)	5.45 (3.44)	0.560
theta (4.25 – 8 Hz)	0.74 (0.39)	0.76 (0.41)	0.684
alpha (8 – 13 Hz)	0.31 (0.15)	0.31 (0.11)	0.899
sigma (13.25 – 16 Hz)	0.15 (0.08)	0.16 (0.06)	0.671
beta (16.25 – 31 Hz)	0.03 (0.03)	0.03 (0.01)	0.879
low gamma (31.25 – 35 Hz)	0.02 (0.02)	0.02 (0.01)	0.838
REM			
theta (4.25 – 8 Hz)	0.40 (0.25)	0.42 (0.19)	0.798
alpha (8 – 13 Hz)	0.13 (0.07)	0.14 (0.06)	0.805
sigma (13.25 – 16 Hz)	0.06 (0.03)	0.06 (0.02)	0.958
beta (16.25 – 31 Hz)	0.03 (0.02)	0.03 (0.02)	0.842
low gamma (31.25 – 35 Hz)	0.01 (0.01)	0.01 (0.01)	0.655
Subjective Sleep Quality			
Tiredness during Daytime	4.21(1.58)	3.47(1.71)	0.090
Concentration	4.00(1.49)	3.53(1.35)	0.176
Mood	3.95(1.22)	3.63(1.46)	0.461

Sleep Quality	3.05(1.18)	3.37(1.12)	0.301
Restedness	4.00(1.15)	3.74(1.28)	0.438
Retrospective Subjective Sleep Quality			
PSQI	**13.60(2.99)**	**10.00(4.84)**	**0.002***

Note. * = $p < 0.002$ (Šidák adjusted p-value); † = $p < 0.05$

3.4.2 Comparison between intervention and treatment-as-usual group

At baseline in the 2(group) x 2(time) ANOVA (descriptive statistics in Table 3.3), IRT and TAU group did not differ in terms of psychological symptoms, retrospective subjective sleep quality and emotion regulation (all ps for the group main effect in the 2x2 ANOVA ≥ 0.061). There was a significant improvement of subjective sleep quality over time in both groups as indicated by the PSQI (main effect of time $F(32,1) = 4.481$, $p = 0.042$, $\eta p^2 = 0.123$). Moreover, depressive symptoms and negative affect showed a significant reduction from pre- to post-treatment (main effect of time for depressive symptoms: $F(38,1) = 14.196$, $p = 0.001$, $\eta p^2 = 0.272$, negative affect: $F(33,1) = 10.099$, $p = 0.003$, $\eta p^2 = 0.234$), while positive affect increased ($F(33,1) = 5.101$, $p = 0.031$, $\eta p^2 = 0.134$) (see Table 3.3). We also found a significant main effect in anxiety symptoms ($F(36,1) = 5.711$, $p = 0.022$, $\eta p^2 = 0.137$), intrusions ($F(28,1) = 7.177$, $p = 0.012$, $\eta p^2 = 0.204$) and hyperarousal ($F(28,1) = 13.631$, $p = 0.001$, $\eta p^2 = 0.327$), that was qualified by a significant interaction between time and group. The IRT group as compared to the TAU group (Supplementary material 3.D) showed a significantly larger reduction in anxiety symptoms and hyperarousal and a marginally larger reduction in intrusions (time x group interaction: anxiety symptoms: $F(36,1) = 5.298$, $p = 0.027$, $\eta p^2 = 0.128$; hyperarousal ($F(28,1) = 9.793$, $p = 0.004$, $\eta p^2 = 0.259$; intrusions: ($F(28,1) = 3.874$, $p = 0.059$, $\eta p^2 = 0.122$). Post-hoc t-test indicate that level of anxiety, hyperarousal and intrusion was lower after treatment in the IRT as compared to the TAU group ($\bar{x}_1$(IRT) - $\bar{x}_2$(TAU)) (T1 anxiety: $t(39) = -2.768$, $p = 0.009$, T1 intrusions: $t(31) = -2.125$, $p = 0.042$, T1 hyperarousal: $t(31) = -3.168$, $p = 0.003$). While symptom severity decreased significantly in the IRT group this was not the case in the TAU group (IRT group pre minus post: anxiety: $t(17) = 2.819$, $p = 0.012$, intrusions: $t(12) = 2.491$, $p = 0.028$, hyperarousal: $t(12) = 3.342$, $p = 0.006$; TAU group pre minus post: anxiety: $t(19) = 0.075$, $p = 0.941$, intrusions: $t(16) = 0.698$, $p = 0.495$, hyperarousal: $t(16) = 0.701$, $p = 0.493$; see Figure 3.3).

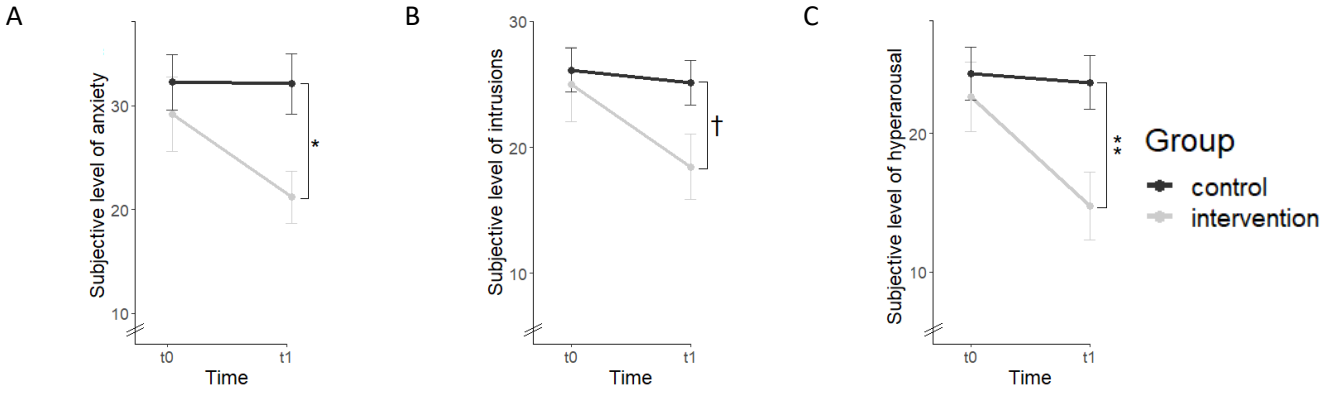
Table 3.3

Subjective sleep quality, psychological symptoms and emotion regulation in the intervention (IRT) and control group (CTL) pre and post therapy

	IRT *n* = 22		CTL *n* = 22	
	M(SD)		*M(SD)*	
	pre	post	pre	post
Subjective sleep quality (PSQI)	12.78(3.75)	10.72(2.56)	13.81(3.51)	12.87(2.60)
Psychological Symptom Severity				
BDI-II	39.17(10.71)	32.28(15.22)	41.14(10.87)	34.18(14.84)
BAI	29.17(15.14)	21.17(10.77)	32.25(11.89)	32.10(12.96)
SCL-90 S total	69.63(8.06)	67.56(6.21)	72.17(5.92)	69.08(9.13)
IES-R				
Intrusions	25.92(10.72)	19.38(9.27)	27.06(7.21)	26.06(7.23)
Avoidance	24.62(8.48)	22.62(6.37)	26.47(9.19)	25.29(8.36)
Hyperarousal	22.62(8.99)	14.77(8.84)	24.29(7.94)	23.65(7.96)
Emotion regulation				
EMOCheck				
Positive Affect	0.82(0.45)	1.11(0.70)	0.91(0.63)	1.11(0.83)
Negative Affect	2.50(0.79)	2.03(0.72)	2.47(0.69)	2.27(0.78)
Emotional Competence	1.55(0.74)	1.61(0.95)	1.52(0.67)	1.78(0.62)
ERQ				
Reappraisal	3.52(1.18)	3.48(1.39)	3.75(0.98)	4.03(1.14)
Suppression	4.65(1.48)	4.60(1.31)	4.81(1.12)	4.56(1.36)

Figure 3.3

Symptom development over time between groups for anxiety, intrusions and hyperarousal scores



Note. Symptom development in the intervention group (grey line) and in the control group (black line) for anxiety (A), measured with the BAI, intrusions (B), measured with the first IES-R subscale and hyperarousal (C), measured with the third IES-R subscale before the intervention period (t0) and after the intervention period (t1). †p<0.1, *p<0.05, **p<0.01.

3.5 Discussion

This study investigates the effects of IRT in individuals with BPD on nightmare symptoms, sleep quality and other psychological symptoms. Apart from a significant reduction in nightmare symptoms and an improvement in subjective sleep quality as indicated by the PSQI none of the sleep parameters significantly changed across time in the IRT group. In further exploratory analyses, IRT as compared to TAU yielded larger reductions in anxiety and trauma-related symptoms in individuals with BPD. This is the first study showing that IRT is beneficial in treating individuals with BPD, thus extending the results of previous studies demonstrating efficacy of this intervention for treating idiopathic nightmares, nightmares in individuals with depression (Thünker & Pietrowsky, 2012) and posttraumatic nightmares (Yücel et al., 2020).

Changes in nightmare symptoms in the IRT group and an improvement in subjective sleep quality were not paralleled by changes in objective sleep data. It is worth mentioning that sleep parameters in the intervention group were already within the normal range at baseline, so additional changes in objective sleep data might not be expected. In addition, a discrepancy between subjective and objective sleep quality is often found and can very likely be attributed to an inaccurate sleep perception in people with sleep disorders (Xu et al., 2022). Lastly, another important factor is the psychotropic medications almost all participants were taking that possibly altered sleep and masked differences in sleep parameters. Future studies should therefore include ambulatory sleep and nightmare assessments over multiple nights in both intervention and control groups. This could also alleviate potential differences in sleep in this sensitive group caused by sleeping in a sleep lab environment.

Our findings on greater reductions in anxiety and trauma-related symptoms when comparing pre to post IRT values are in line with previous research showing effects of IRT not only on nightmare symptoms per se but also on anxiety (Hansen et al., 2013) and PTSD symptoms (Casement & Swanson, 2012). A possible explanation for the transfer effects lies in one of the proposed mechanisms behind

IRT as collected in a review by Rousseau & Belleville (2018). More specifically, apart from increased self-efficacy through mastering dream content, IRT might also help improve emotional processing. This could happen directly during daytime via modifying cognitions related to the nightmares, helping to interact with the nightmare content in a safe and supportive way and decreasing arousal (Germain & Nielsen, 2003). These modified cognitions could thus contribute to improved safety learning, fear extinction and emotion regulation in general. This could be especially helpful for individuals with BPD, as it could help them break emotional cascades as postulated by the model of Selby and colleagues (2013). One could also assume a more indirect effect of IRT on anxiety- and trauma-related symptoms through improving REM sleep. REM sleep is associated with a suppression of central adrenergic neurotransmitters while simultaneously activating amygdala-hippocampal networks (van der Helm et al., 2011). This is thought to de-potentiate previous affective experiences, thus further promoting emotional processing by providing 'overnight therapy' (Walker & van der Helm, 2009, Germain, 2013). Future research should focus on the mechanisms influencing daytime and night-time symptoms through IRT, especially with regards to emotional processing (Rousseau & Belleville, 2018) as this could help to further develop interventions for individuals with BPD and should take the broader benefits of reduced nightmares, such as potentially reduced challenges with safety into account (King et al., 2024).

3.5.1 Limitations

This study has a number of limitations: In the context of this pilot study, randomization of participants to the conditions was not possible, instead participants in the intervention group opted to participate in IRT as an add-on to their treatment and the control group was matched retrospectively. A major problem related to such non-randomized assignment of participants is that it can lead to group differences that already exist before the intervention. In fact, the intervention group reported higher levels of distress at baseline. However, the degree of suffering was not correlated with any changes in nightmare symptoms, anxiety, intrusions or hyperarousal. Furthermore, there were no baseline differences in the outcome variables that showed a group difference after treatment. Thus, we assume that the effects are very likely not due to possible pre-existing differences between groups that could have emerged because of the non-randomized design.

The fact that all dropouts came from the intervention group could lead to the assumption that IRT is not as feasible. It is, however, worth noting that only three dropouts can be directly traced back to aspects of the study. This concerned three participants in the intervention group that did not participate in the post-measurement PSG. For the others, the overall treatment program was not a good fit at the time of the study, and they made other decisions about their care. Moreover, dropout rates for studies with individuals with BPD in an outpatient setting have been reported to be around 20 % (Arntz et al., 2022). Therefore, the higher drop-out rates in an inpatient setting might be expected and not necessarily indicative of the unsuitability of the intervention for these individuals. Nonetheless, future studies should monitor reasons for dropouts more closely and include qualitative reports of participants' experiences with the study intervention.

Another aspect that limits the interpretation of our findings is that not all changes in overall symptoms and emotion regulation can solely be traced back to the IRT intervention as both groups received the same inpatient care between pre- and post-measurement and changes in nightmare symptoms were not measured over time in the control group.

An additional limitation concerns the sleep data, which is also only available for the intervention group. This should be amended in future studies in order to better discern the effects of time, treatment as usual and the intervention as well as interactions between time and intervention.

3.5.2 Conclusion

Our findings indicate that IRT may not only reduce nightmares and sleep problems in individuals with BPD but also has the potential to reduce other typical symptoms such as anxiety, intrusions and hyperarousal these individuals experience. Thus, IRT may be a potential add-on treatment to support the psychotherapeutic treatment of individuals with BPD. It can be implemented as group or individual therapy in outpatient or inpatient settings. Although preliminary due to the above-mentioned methodological limitations we hope that our findings may encourage future research investigating the effect of IRT in individuals with BPD as well as individuals with other psychiatric symptoms and nightmares in randomized controlled trials including long-term measurement of nightmares, sleep and psychiatric symptoms.

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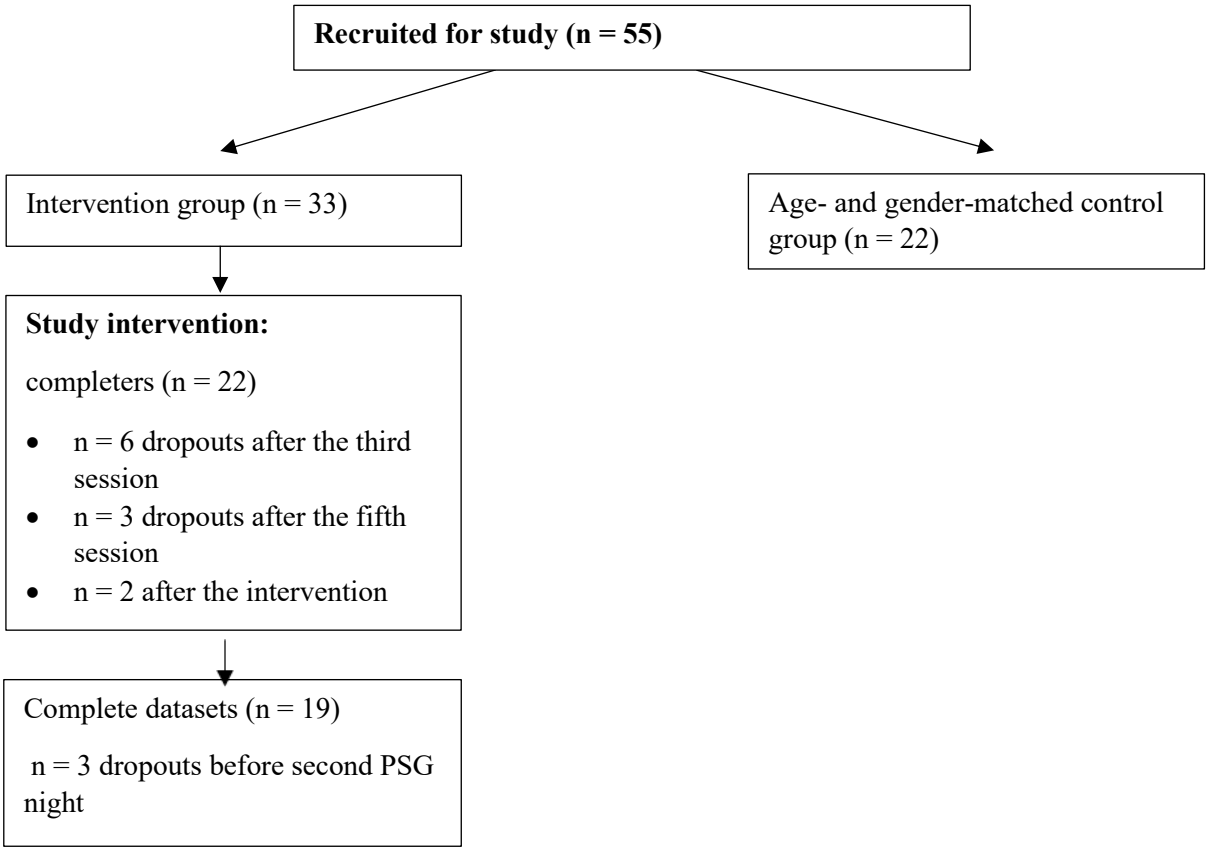
3.7 Legend of Tables and Figures

3.8 Supplementary materials

Supplementary material 3.A: Dropouts from the study sample over time



Supplementary material 3.B

Cumulative frequencies of psychiatric and somatic comorbidities in the study sample

	Intervention group completers (dropouts)	Control group
Psychiatric comorbidities		
Affective disorders		
MDD[1)]	n = 6(2)	n = 11
Dysthymia	-	n = 2
Zyclothymia	-	n = 1
Anxiety disorders		
Social phobia	n = 2	n = 4
Panic disorder & agoraphobia	n = 0(1)	-
GAD[2)]	-	n = 1
PTSD	n = 11	-
Eating disorders		
Anorexia	-	n = 7
Bulimia	-	n = 3
Binge-eating disorder	-	n = 1
Not-otherwise specified	n = 4(1)	n = 4
Substance use disorder	n = 3	n = 2
ADHD[3)]	n = 1	n = 1
other / unspecified	n = 2(10)	n = 1
Somatic comorbidities		
Cardiovascular conditions	n = 4(1)	n = 2
autoimmune and allergic conditions		
asthma	n = 6(1)	n = 3
IBS[4)]	n = 3	n = 1
Hypothyroidism	n = 0(1)	n = 1
Insuline resistence / diabetes	n = 1(1)	n = 1
Atopic dermatitis / psoriasis	n = 1	n = 1
Multiple sclerosis	-	n = 1
Orthopedic conditions	n = 3(4)	n = 2
Chronic pain conditions	n = 3(1)	n = 1
Other	n = 3(3)	n = 1

Note. [1)]MDD = major depressive disorder; [2)]GAD = generalized anxiety disorder; [3)]ADHD = attention deficit hyperactivity disorder; [4)]IBS = irritable bowel syndrome. Note that number of co-morbidities for the dropouts (in brackets) is not included in the number of co-morbidities for completers (number before brackets).

Supplementary material 3.C: PGI and CGI

PGI (Patient Global Impression)

Pat. -Code : Date :

Therapy session:

How much do your nightmares and their consequences impair your overall quality of life?

not impaired at all	
borderline impaired	
only slightly impaired	
moderately impaired	
significantly impaired	
severely impaired	
extremely severely impaired	

Please rate the overall change in your nightmares as they are now compared to when you started treatment. (One cross only, please.)

very much improved	
much improved	
little improved	
unchanged	
slightly worse	
much worse	
very much worse	

CGI (Clinical Global Impression)

Pat.-Code: Date:

Therapy session:

Consider all your experience with this type of patient and indicate your assessment of the patient's current level of impairment by their symptoms during the past week.

Patient is not ill at all	
Patient is a borderline case of psychiatric illness	
Patient is only slightly ill	
Patient is moderately ill	
Patient is clearly ill	

Patient is severely ill	
Patient belongs to the extremely seriously ill	

Please assess the overall change in condition. Please compare the patient's current condition with that at the start of the study and indicate the extent to which the patient's clinical picture has changed. (Please only one cross.)

Condition is much better	
Condition is better	
Condition is only slightly better	
Condition is unchanged	
Condition is slightly worse	
Condition is much worse	
Condition is a lot worse	

Supplementary material 3.D

Main effects and interactions on outcome measures compared between intervention and control group and pre and post measurement

	main effects		interaction
	group	*time*	*group x time*
Subjective sleep quality (PSQI)	.061	**.042***	.435
Psychological Symptoms			
BDI-II	.606	**.001****	.986
BAI	.072	**.022***	**.027***
SCL-90 S total	.421	.069	.710
IES-R			
Intrusions	.176	**.012***	.059
Avoidance	.395	.312	.792
Hyperarousal	.076	**.001****	**.004***
Emotion regulation			
EMOCheck			
Positive Affect	.843	**.031***	.682
Negative Affect	.667	**.003****	.231
Emotional Competence	.741	.243	.462
ERQ			
Reappraisal	.284	.537	.416
Suppression	.879	.580	.698

Supplementary material 3.E

Post-hoc power calculations for the primary outcome measures

Impairment through nightmares & symptom improvement rated by patients (PGI) and clinicians (CGI)

	Šidák adjusted *p*-value	effect size (η_p^2)	power ($1 - \beta$)
Impairment by symptoms			
PGI	0.013	0.554	1.00
CGI	0.013	0.839	1.00
Improvement of symptoms			
PGI	0.013	0.689	1.00
CGI	0.013	0.689	1.00

Objective and Subjective Sleep Parameters in IRT group pre and post therapy

	Šidák adjusted *p*-value	effect size (*dz*)	power ($1 - \beta$)
Polysomnography data			
Sleep Efficiency	0.002	0.019	0.002
Total Sleep Time	0.002	0.149	0.006
Wake after Sleep Onset	0.002	0.128	0.005
Sleep Latency	0.002	0.001	0.002
Movement Arousal total	0.002	0.038	0.002
MA REM	0.002	0.050	0.002
REM duration(minutes)	0.002	0.124	0.005
N1 duration (minutes)	0.002	0.017	0.002
N2 duration (minutes)	0.002	0.167	0.007
N3 duration (minutes)	0.002	0.083	0.003
REM density	0.002	0.024	0.002
Absolute Spectral Power (μV^2)			
NREM			
delta (1.25 – 4 Hz)	0.002	0.088	0.003
theta (4.25 – 8 Hz)	0.002	0.049	0.002
alpha (8 – 13 Hz)	0.002	0.000	0.002
sigma (13.25 – 16 Hz)	0.002	0.138	0.005
beta (16.25 – 31 Hz)	0.002	0.000	0.002
low gamma (31.25 – 35 Hz)	0.002	0.000	0.002
REM			
theta (4.25 – 8 Hz)	0.002	0.088	0.003

alpha (8 – 13 Hz)	0.002	0.152	0.006
sigma (13.25 – 16 Hz)	0.002	0.000	0.002
beta (16.25 – 31 Hz)	0.002	0.000	0.002
low gamma (31.25 – 35 Hz)	0.002	0.000	0.002
Subjective Sleep Quality			
Tiredness during Daytime	0.002	0.448	0.083
Concentration	0.002	0.329	0.033
Mood	0.002	0.235	0.014
Sleep Quality	0.002	0.277	0.021
Restedness	0.002	0.213	0.011
Retrospective Subjective Sleep Quality			
PSQI	**0.002**	**0.851**	**0.552**

4. Study 3: Reactivating a relaxation exercise during sleep to influence cortical hyperarousal in people with frequent nightmares[3]

4.1 Abstract

Introduction

Cortical hyperarousal during sleep, i.e. increased high-frequency EEG activity, is a transdiagnostic feature across mental health disorders, including anxiety, insomnia, PTSD and nightmare disorder. Although it has been discussed as a viable target of intervention, specific treatment options are not yet available. We tested whether exposure to relaxation-associated odor cues during sleep (TMR) would reduce cortical hyperarousal, as indicated by lower beta (16.25 – 31 Hz), gamma (31.25 – 45 Hz), spindle activity and nightmare occurrence in participants with frequent nightmares.

Methods

Twenty-five (21 female, mean age (SD) = 24.94(5.01)) participants with at least one nightmare per week received a deep breathing relaxation intervention for one week coupled with an odor. On two subsequent nights in the sleep laboratory, the associated odor, or a control odor were presented in randomized order in a within-subjects design.

Results

We found that exposure to relaxation-associated odor cues during sleep did not affect beta or gamma activity while spindle count and density were significantly reduced. The reduction in spindle count during reactivation nights was correlated with reduced subjective reports of wake-after-sleep-onset. There was no additional impact on nightmare symptoms.

Discussion

Our data suggests that the reactivation of relaxation-associated states with odor cues during sleep may be a viable treatment strategy to reduce cortical hyperarousal. Future studies should implement multiple nights of reactivation and include different patient groups with cortical hyperarousal to test the transdiagnostic potential of this new intervention.

4.2 Introduction

Cortical hyperarousal can be defined as increased high-frequency EEG activity during sleep, especially in the beta and gamma bands (Blaskovich et al., 2020), but also in high-frequency spindle activity (Picard-Deland et al., 2018). It occurs in multiple disorders such as insomnia (Zhao et al., 2021), PTSD (Wang et al., 2020) and depression (Lin et al., 2023) and could therefore be considered a transdiagnostic feature of the abovementioned disorders. In addition, (cortical) hyperarousal is associated with symptom pathways and severity. Briere et al. (2015) found for example, that hyperarousal is predictive of suicidality in PTSD patients.

[3]This chapter is currently under review as: **Sayk C.**, Probst, A., Lange, F., Eickemeier, S., Amores, J., Ngo, H.-V.V., Ehsanifard, M., Junghanns, K. & Wilhelm, I. (2024). Reactivating a relaxation exercise during sleep to influence cortical hyperarousal in people with frequent nightmares. Manuscript submitted for publication. I was involved in designing the study and responsible for data collection. I analyzed the data, wrote the manuscript and was responsible for data visualization.

Likewise, psychological hyperarousal symptoms, including sleep disturbances, are often residual symptoms even after successful PTSD treatment (Kovacevic et al., 2023; Larsen et al., 2019; Miles et al., 2022; Schnurr & Lunney, 2019) and can thus be considered as insufficiently targeted by standard treatment protocols. Cortical hyperarousal has been implicated in etiology models of insomnia (Levenson et al., 2015; Riemann et al., 2015), nightmare disorder (Gieselmann et al., 2019) and PTSD (Krystal & Neumeister, 2009). In the latter it has been linked to increased locus coeruleus and noradrenergic activity which are considered a potential source for this type of spectral activity (Kelmendi et al., 2015). Van Someren (2021) proposed that cortical hyperarousal could be caused by fragmented REM sleep, that fails to downregulate noradrenergic tone as would occur in healthy REM sleep to facilitate emotional processing (Goldstein & Walker, 2014). Both fragmented REM sleep and cortical hyperarousal are thought to be influenced by a mixture of genetic predisposition and early childhood adversity (Muscatello et al., 2020). However, most findings on cortical hyperarousal and psychiatric symptoms are correlational so far (e.g. Blaskovich et al., 2020) and it has been difficult to determine whether it is the outcome of fragmented REM sleep, a byproduct or even the cause of fragmented REM sleep. It has been argued for example, that nocturnal cortical hyperarousal, which is closer to wake-like EEG activity, might cause higher responsiveness to external cues and thus disrupt sleep (Xu et al., 2022).

Taken together (cortical) hyperarousal is a relevant transdiagnostic feature that may not only be a relevant biological mechanism but also a target for novel interventions. However, interventions that specifically target cortical hyperarousal and could thus help us to better understand its role and develop new treatment options are not available yet.

There are several options for the manipulation of cortical hyperarousal that were considered for this study. Cortical stimulation, such as tDCS, can be used to influence high-frequency spectral activity (Kayarian, Jannati, Rotenberg & Santarnecchi, 2020). However, stimulation usually leads to an increase in the targeted frequency band which would be counterproductive to the desired direction of the intervention. Relaxation exercises such as deep breathing or progressive muscle relaxation can influence high-frequency EEG-activity (Kim, Rhee & Kang, 2014; Lee, Bhattacharya, Sohn & Verres, 2012) and thus have the potential to reduce cortical arousal. The effects of relaxation exercises on EEG-activity mostly pertain to effects observed during the actual exercise (Jacobs & Friedman, 2004) or to wake-EEG in the follow-up (e.g. Cheng et al., 2018), it is, however, still unclear how these effects can be translated to target cortical hyperarousal during sleep. TMR (Oudiette & Paller, 2013) is a method that can be used to reactivate memory contents via an (often auditory or olfactory) cue during sleep that has been associated with the cue at encoding (Born & Wilhelm, 2012). Beck et al. (2021) could show that cueing with relaxation-associated words altered spectral activity. It therefore may have the potential of transferring the effects of a relaxation exercise on cortical hyperarousal to brain activity during sleep.

As mentioned above, cortical hyperarousal is increased in patients who suffer from frequent nightmares. More specifically, Blaskovich and colleagues (2020) found increased beta- and gamma activity, especially shortly before entering REM-sleep, in subjects with frequent nightmares. Additionally, individuals with frequent nightmares exhibited increased fast spindle activity compared to a control group (Picard-Deland et al., 2018). Recent findings from our lab corroborate this. A group of nightmare patients, who received IRT (Thünker & Pietrowsky, 2021) to treat nightmares, showed increased cortical arousal compared to healthy controls, independent of actual nightmare occurrence during the measurement (Sayk, Saftien, Koch, Ngo, Junghanns & Wilhelm, 2024). Moreover, when comparing EEG-activity before and after the intervention, there was a trend towards lower gamma activity after IRT, which again points to the important role of cortical hyperarousal in nightmare

etiology. However, these findings are correlational and interventions that directly target cortical hyperarousal, such as a deep-breathing relaxation exercise, and include an experimental manipulation are still lacking. This is especially important given the transdiagnostic aspect of cortical hyperarousal and the potential of interventions that target it.

The primary goal of this study was to investigate whether reactivating a relaxation exercise in participants with frequent nightmares that has been practiced for one week led to 1) a reduction of cortical hyperarousal during sleep as indicated by beta, gamma and spindle activity and 2) a reduction in nightmare symptoms.

4.3 Methods and Materials

4.3.1 Participants

Participants were mainly recruited from the undergraduate student body at the University of Luebeck, Germany. They were required to be between 18 and 35 years old, have at least one nightmare a week, not to suffer from any other psychiatric or somatic illness or other sleep disorders and not to take any sleep-altering medication.

The study was approved by the university's ethics committee. All participants provided written informed consent after they were given a complete description of the study protocol. Participants were compensated financially (some received part of the compensation in the form of course credits) for study participation.

The initial sample consisted of 29 participants with frequent nightmares. Four participants dropped out of the study after adaptation night due to inability to sleep in the sleep lab. The majority of the sample (n = 21) was female, mean age was 23.58 (SD = 4.6). Participants mostly suffered from nightmares since childhood (n = 5) or for at least 10 years (n = 11). On a 5-point Likert scale, 20 participants rated their degree of suffering from nightmares as "moderate" and 5 participants reported a "strong" degree of suffering. Most of the participants remembered nightmare content very often or always. Six of the participants reported an identical or almost identical repetition of one nightmare, and nine participants reported their nightmares to relate to their biography. Participants on average had healthy sleep according to the PSQI, average sleep reactivity and average suggestibility, i.e. the tendency to react to hypnotic suggestions and absorption levels, i.e. imaginative involvement and the tendency to become mentally absorbed in everyday activities (see also Table 4.1).

Table 4.1

Demographic and psychometric characteristics of sample at baseline

	M(SD)
Demographics	
Age	23.58(4.6)
Gender (% female)	72 %
Sleep quality and reactivity	
PSQI[1)]	6.21(1.69)
FIRST[2)]	2.64(0.49)
Suggestibility	
TAS[3)]	6.24(17.85)
HGHS:5G[4)]	2.27(1.66)
Nightmare characteristics	

Frequency (per month)	9.03(4.48)
Frequency (per week)	2.00(0.79)
Nightmare onset ≥ 10 years (% of sample)	55.2
Memory of nightmares: very often / always (% of sample)	72.4
Identical Repetition (% yes)	20.7
Degree of Suffering	3.00(0.58)

Note. [1)]PSQI = Pittsburgh Sleep Quality Inventory; [2)]FIRST = Ford Insomnia Response to Stress Test; [3)]TAS = Tellegen Absorption Scale; [4)]HGHS-5:G = the Harvard Group Scale of Hypnotic Susceptibility 5-Item Short-Version.

4.3.2 Materials

Questionnaires. Nightmare symptoms were assessed with a customized questionnaire, at baseline and after the intervention week including nightmare frequency, time of nightmare onset, nightmare content, ability to remember nightmares and distress caused by nightmares (see Sayk et al., 2024). Subjective sleep quality was measured with the *Schlaffragebogen A*, SF-A/R (Görtelmeyer, 2011) during sleep lab nights, and retrospectively using the PSQI (Buyssee, Reynolds, Monk, Berman & Kupfer, 1989) at baseline and after the intervention week. Additionally, at baseline, sleep reactivity was assessed with the Ford Insomnia Response to Stress Test (FIRST) (Drake et al., 2004) and suggestibility and absorption were measured with the Harvard Group Scale of Hypnotic Susceptibility 5-Item Short-Version (HGSHS-5: G) (Riegel et al., 2021) and Tellegen Absorption Scale (TAS) (Tellegen, 1992) respectively. During the relaxation and control task, participants repeatedly rated their current affective state with a short version of the Positive and Negative Affect Schedule (PANAS) (Breyer & Bluemke, 2016).

Polysomnography. Participants were fitted with 64 electrode EEG caps (ActiChamp, Brain Products, Gilching, Germany) referred to the left mastoid (M1) and ground electrode. We used EMG placed on the chin, as well as EOG and ECG measurements. Data was recorded with Brain Vision Recorder (Brain Products, Gilching, Germany). Impedances were below 10 kΩ. Sampling rate was 500 Hz.

Sleep Scoring and spectral power analysis. Sleep stages were scored manually according to AASM criteria (Berry et al., 2020) by two experienced sleep lab technicians. Recordings were visually inspected on a 30-second basis and channels with muscle- and technical-related artifacts were discarded. Additionally, for the computer task EEG data, eye movement artifacts were removed with independent component analysis (ICA). Artifact-free, 50% overlapping, 8.192-second epochs were Hanning-tapered and Fast Fourier Transformed in order to calculate absolute power of spectral densities for each frequency bin between 1.25 Hz and 45 Hz for NREM (Stage 2 and Stage 3) and REM sleep periods, separately. Spectral power was calculated for the EEG task, the whole night, for odor-on and odor-off periods separately and for 10 minutes pre- and post-REM. Pre-REM periods were defined as 10-minute intervals of NREM sleep directly before the onset of the first two REM periods. Accordingly, post-REM periods included similar 10-minute NREM epochs following the end of the first two REM periods. Band-wise spectral power was extracted by summing up bin-wise values into ranges of beta (16.25–31 Hz) and gamma (31.25–45 Hz) bands for sleep EEG data and alpha (8.25–13 Hz), beta (16.25–31 Hz) and gamma (31.25–45 Hz) bands for EEG data gathered during the computer task. Additionally, spindle count, density, amplitude and threshold were calculated for stage 2 and 3 of NREM sleep in the frequency band between 12 and 16 Hz.

Olfactometer. Odors were presented using an olfactometer "Essence" (Amores, 2016), that was placed in a holder directed at the participant's face at 50 cm distance. Odor presentation started when the participants first reached SWS and stopped 30 minutes before their scheduled wake-up time or when they showed signs of waking up before that on the PSG. Odors were presented in 20 millisecond bursts every 55 seconds that were arranged in four-minute loops of odor-on and odor-off periods.

Intervention and control task. The relaxation exercise used in this study was a custom-made 15-minute deep breathing exercise that enabled the participants to practice deep, diaphragmatic breathing and relax. On average, participants rated the ability to follow the instructions for the relaxation exercise to be high (M = 4.04, SD = 1.03) as well their ability to engage with the exercise at first trial (M = 4.01, SD = 0.97) on a 5-point Likert scale. For the week of relaxation exercise, 18 participants reported to have practiced daily, while those who did not practice daily missed 2.86 (SD = 2.03) days of practice on average. Mean ratings of understanding of and engagement with the exercise were 4.37 (SD = 0.71) and 4.16 (SD = 0.7) respectively.

As a control task, that was presented as a part of the computer task at the evening of the adaptation night and of the first experimental night, participants listened to texts about polar research that had the same length as the relaxation exercise. The audio of the relaxation exercise and the control texts were both recorded in the voice of a member of the research group who was otherwise not involved in any interactions with the participants.

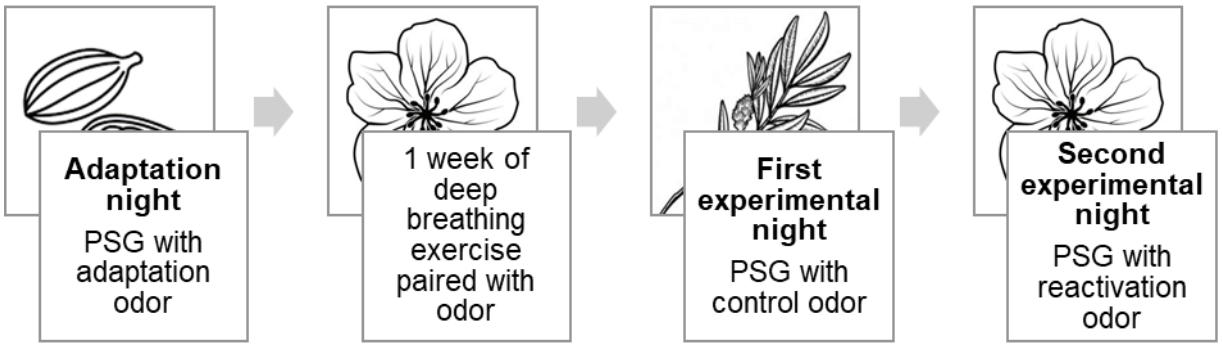
4.3.3 Procedure

Participants spent three nights in the sleep lab (Figure 1). They were screened for eligibility in a telephone interview and if all inclusion and exclusion criteria were met. The first set of questionnaires were completed via an online link before coming to the sleep laboratory for their adaptation night. There they rated four odors concerning pleasantness, familiarity, and intensity. The two odors that were rated to be the least familiar but the most pleasant and intense were chosen as relaxation-associated and control odor respectively for that participant. Afterwards, they were fitted with EEG, EOG, EMG, ECG and skin conductance response (SCR) electrodes before completing a computer task using PsychoPy 3.1 (Peirce, Hirst & McAskill, 2022). During this computer task, participants completed the relaxation and control task which were both followed by a 2 x 2 minutes block design of eyes open and eyes closed to

assess the aftereffect of both tasks. Levels of relaxation as well as positive and negative affect were measured at baseline and after each task. The relaxation and the control task were presented in randomized order across participants and nights (adaptation night and first experimental night). Then SCR electrodes were removed, and they went to bed at their usual bedtime where an adaptation odor was presented with a diffusor for the whole night. In the morning, participants downloaded the audio of the relaxation exercise on their phones, received a diffusor with their relaxation-associated odor and were instructed to practice the relaxation exercise daily for the next seven days while activating the diffusor. After that week they completed another set of online questionnaires and returned to the sleep laboratory for the first of two experimental nights where they completed the computer experiment again. This time, the olfactometer (Amores, 2016) was activated when the participants first reached stable SWS. The order in which the odors were presented in the first and second experimental night was randomized between subjects. The last experimental night with odor presentation took place another 2 – 7 days after the first experimental night (see Figure 4.1 for an exemplary procedure as one participant would have gone through it).

Figure 4.1

Experimental Procedure



Note. Schematic of the study procedure and use of odors (pictures depict an exemplary selection of plant fragrances used during the study). At adaptation night, a reactivation and a control odor are chosen according to participant's rating. Participants paired the odor with practicing the deep breathing exercise for a week then came back for two experimental nights where the either the reactivation or a control odor were presented in randomized order.

4.3.4 Statistical analyses

Statistical analyses were carried out with SPSS and FieldTrip (Oostenveld, Fries, Maris & Schoffelen, 2011). Differences in sleep architecture were evaluated by dependent samples t-tests. Šidák correction was used to correct for multiple comparisons. Differences in band-wise spectral power for the computer task, the whole night, odor-on vs. odor-off periods and 10 minutes pre- and post-REM were tested with cluster-based permutation tests. The same tests were used for sleep spindle characteristics. For the computer task, there were subsequent 2 x 2 task (relaxation, control) and time (pre and post) analysis for the beginning (2nd to 6th minute) and end (8th to 12th minute) as well as 2(task: relaxation and control) x 2 (time: pre and post) x 2 blocks (eyes open, eyes closed) ANOVAs for the two minute blocks of eyes open and eyes closed after the control and the relaxation task. Changes in questionnaires before and after the intervention week were calculated with repeated-measure ANOVAs and correlation of questionnaire data and physiological data were calculated with correlation analysis.

4.4 Results

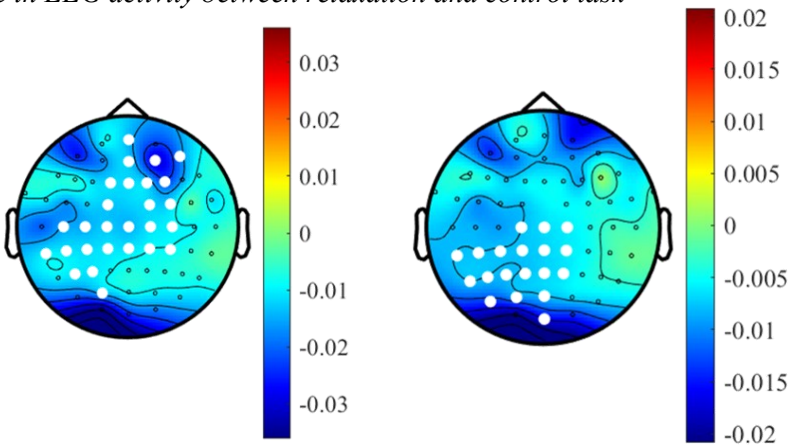
4.4.1 Effects of the relaxation exercise and its reactivation

4.4.1.1 Effects during the relaxation exercise

Spectral activity during the relaxation exercise. When comparing the spectral activity between the relaxation and control tasks, there was a significant difference in the beginning of the tasks (2nd to 6th minute) with significantly less beta and gamma activity in the relaxation than in the control task (figure 4.2). These effects did not persist in the end (8th to 12th minute) of the tasks. There were no significant effects of time or any significant interactions between the factors task and time. In the blocks of eyes opened and closed after the tasks, there was a significant effect of eyes open vs. closed in the alpha and beta band over both tasks and time points with spectral activity being higher in the eyes closed compared to the eyes open. There were no effects of task, time or significant interactions

Figure 4.2

Difference in EEG activity between relaxation and control task

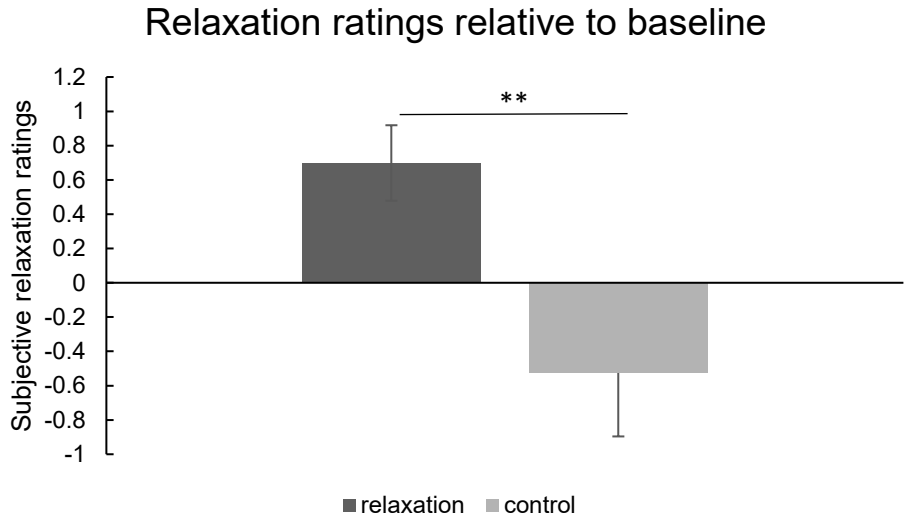


Note. Differences in beta (16.25 – 31 Hz, left) and gamma (31.25 – 45 Hz, right) activity in the beginning of the relaxation and control task. Significant electrode clusters ($p < 0.05$) are marked in white.

Effects during relaxation exercise on subjective relaxation ratings. For the relaxation ratings (figure 4.3), subjectively rated relaxation relative to baseline was significantly higher after the relaxation task than after the control task ($F(24,1) = 13.206$, $p = 0.001$, $\eta p^2 = 0.355$). There were no significant effects of time when comparing pre and post intervention week measurements nor significant interactions between task and time of measurement. For the PANAS ratings, there was a significant effect of time on both positive and negative affect ($F(21,1) = 18.479$, $p = 0.001$, $\eta p^2 = 0.468$) with affect ratings generally being lower at the post than at the pre measurement. There were no significant effects of affect or task and no significant interactions.

Figure 4.3

Relaxation ratings relative to baseline



4.4.1.2 Effects of the reactivation

Effects of the reactivation on sleep architecture. The comparison of sleep architecture between nights with the reactivation odor and the control odor (Table 4.2) yielded no significant results.

Table 4.2

Sleep architecture during nights with the reactivation and the control odor

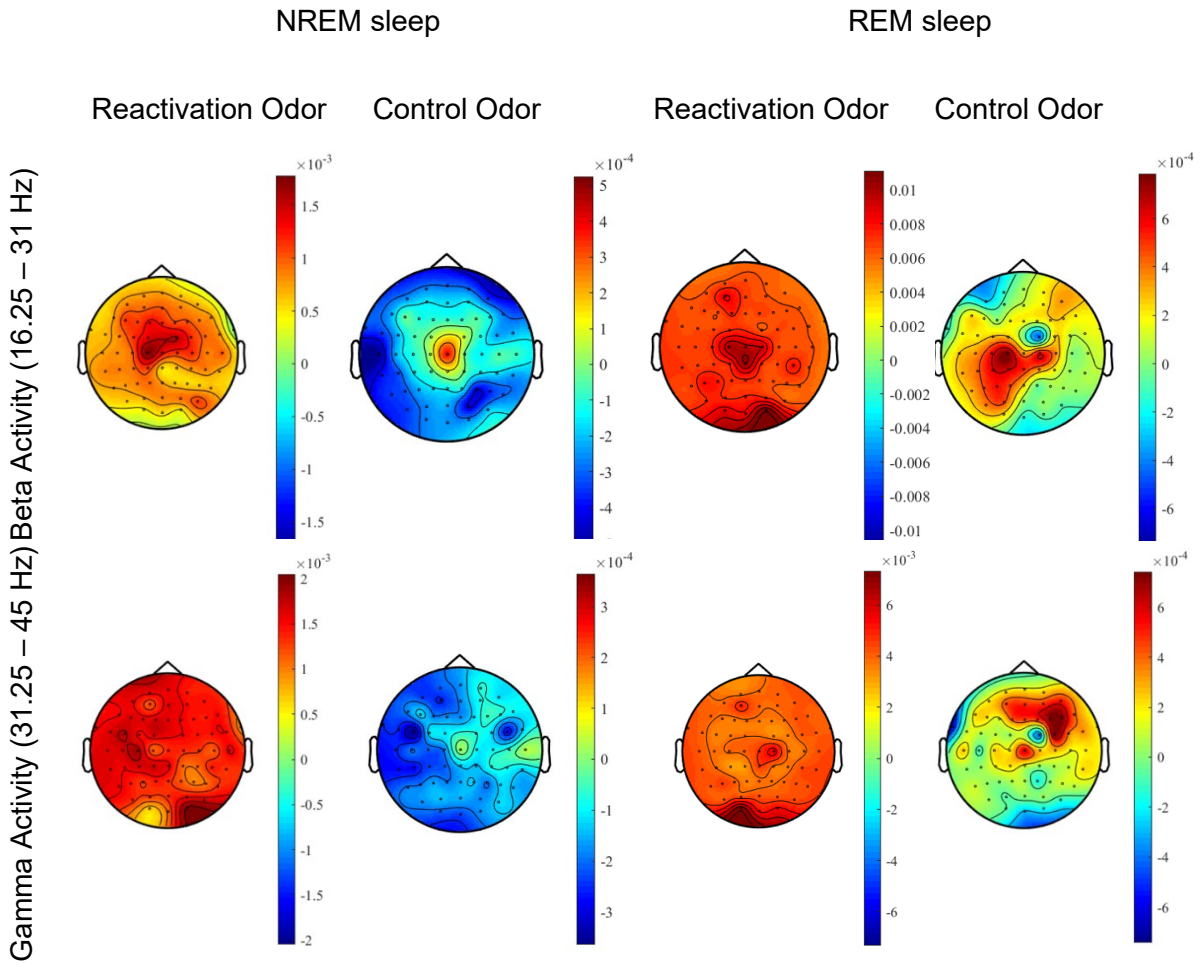
	Reactivation odor	**Control odor**	
	M(SD)	*M(SD)*	*p*-value
Total sleep time (minutes)	435.46 (62.47)	447 (61.7)	0.285
Sleep efficiency (%)	91.35 (6.61)	90.96 (9.64)	0.776
N1 duration (%)	4.73 (2.42)	5.09 (2.57)	0.357
N2 duration (%)	52.02 (7.31)	52.63 (8.96)	0.622
N3 duration (%)	16.88 (5.29)	17.46 (5.8)	0.371
REM duration (%)	21.16 (3.85)	20.75 (5.52)	0.978
REM density	480.94 (263.93)	375.33 (172.18)	0.019†
Awakening during REM	2.00 (1.61)	1.83 (1.86)	0.681
Movement Arousal REM	11.5 (4.64)	8.5 (4.65)	0.012†

Note. * = $p < 0.0056$ (Šidák adjusted p-value), † = $p < 0.05$

Effects of reactivation on spectral activity and spindle characteristics. When comparing spectral activity in reactivation and control nights for the entire night (for NREM and REM sleep separately), there were no significant differences in any of the frequency bands. Comparing odor on and off periods within the reactivation nights did not reveal any differences in the beta and gamma band neither during NREM nor REM sleep (Figure 4.4). Lastly, when examining spectral activity during the 10 minutes pre and post REM as has been done in previous studies (Blaskovich et al., 2020), there were neither significant differences for odor nor any significant interactions of odor with pre or post REM interval.
Spindle count (Figure 4.5 C) and density (Figure 4.5 B) were significantly lower in reactivation nights than in control nights. There were no significant differences for spindle amplitude (Figure 4.5 A) and spindle threshold (Figure 4.5 D).

Figure 4.4

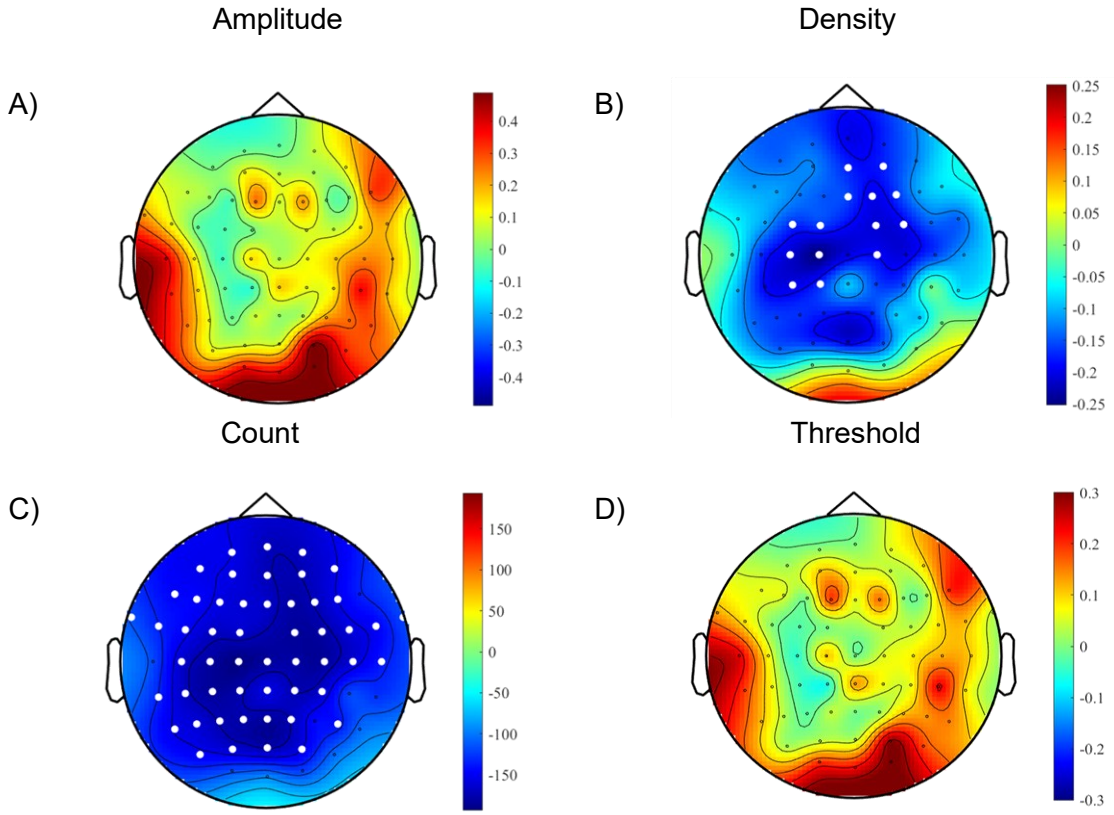
Beta and Gamma activity in NREM and REM sleep with and without reactivation



Note. Absolute spectral power in the beta (16.25 – 31 Hz, top) and gamma band (31,25 – 45 Hz, bottom) with the difference in activity between the reactivation or the control odor on and off. Absolute spectral power in the beta (16.25 – 31 Hz, top) and gamma band (31,25 – 45 Hz, bottom) did not differ between odor on and odor off periods neither for reactivation odor nor control odor.

Figure 4.5

Spindle Activity (12 – 16 Hz) in reactivation nights vs control nights



Note. Spindle parameters (12 – 16 Hz) between nights with the reactivation odor and nights with the control odor with significant electrode clusters marked in white (p-alpha < 0.05). Spindle count (C) and density (B) were lower when the reactivation odor was presented.

4.4.2 Effects on nightmare symptoms

Effects of relaxation exercise on nightmare symptoms and sleep quality. One week of practicing the relaxation exercise at home did neither affect subjectively rated retrospective sleep quality as indicated by the PSQI nor nightmare frequency nor the level of distress caused by nightmares (all ps ≥ 0.417 for the comparison of the measurement before and after the week of practice; Table 4.3).

Table 4.3

Sleep quality and nightmare symptoms before and after one week of relaxation intervention

	pre	**post**	
	M(SD)	*M(SD)*	*p*-value
PSQI[1)] (sleep quality)	6.13 (1.68)	6.94 (1.89)	0.846
Nightmares / week	2.00 (0.79)	2.13 (1.33)	0.589
Degree of suffering	3.00 (0.57)	2.88 (0.97)	0.417

Note. [1)]PSQI = Pittsburgh Sleep Quality Inventory

In addition to this retrospective assessment of nightmare characteristics and sleep quality during one week of relaxation exercise, we investigated the direct effect of reactivation in the sleep lab on these parameters. A comparison of nightmare occurrence, sleep quality, and both negative and positive affect between nights with the reactivation odor and those with the control odor revealed no significant differences. (all ps ≥ 0.249) (Table 4.4).

Table 4.4

Comparison between nights with reactivation and control odor

	Reactivation odor	**Control odor**	
	M(SD)	*M(SD)*	*p*-value
Subjective sleep quality (SF-A/R)[1)]			
sleep quality	2.59 (0.66)	2.47 (0.69)	0.484
trouble falling asleep	3.68 (0.98)	3.72 (0.98)	0.870
trouble staying asleep	3.24 (1.25)	3.5 (1.11)	0.249
sleep depth	3.47 (0.58)	3.32 (0.84)	0.460
relaxation after sleep	3.38 (0.45)	3.31 (0.67)	0.642
Nightmare occurrence (%)	25	41	0.459

Note.[1)] SF-A/R = *Schlaffragebogen A*

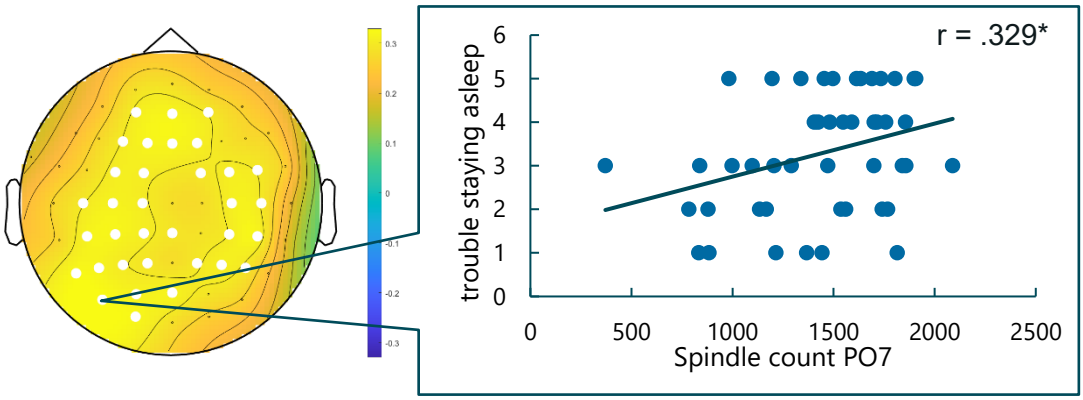
4.4.3 Correlations between physiological and behavioral data

For all significant differences on neural measures (i.e. beta and gamma activity during the relaxation task and spindle count and density during reactivation in sleep), we tested whether they correlated with any of the related behavioral data, which consisted of subjective relaxation and affect

ratings during the relaxation task and subjective sleep quality for reactivation and control nights. For the relaxation task, there were no significant correlations between neural and behavioral data. However, spindle count was positively correlated with trouble staying asleep so that a higher spindle count was associated with longer subjectively reported wake after sleep onset (Figure 4.6).

Figure 4.6

Correlation of spindle count and trouble staying asleep



Note. Correlation of subjectively rated wake after sleep onset and spindle count with scatterplot for PO7 electrode. Significant electrode clusters are marked in white (p-alpha < 0.05).

4.5 Discussion

The main goal of this randomized controlled study was to determine whether a week of relaxation exercise, which was reactivated during sleep using odors, reduces cortical hyperarousal as indicated by beta, gamma and spindle activity and reduces nightmare symptoms. While the relaxation task led to reduced beta and gamma activity during the exercise, this effect did not directly translate to the reactivation of the relaxation task, i.e. there was no effect of the reactivation on beta and gamma activity during sleep. However, the reactivation led to reduced spindle count and density, with spindle count being positively correlated with subjectively rated trouble staying asleep. No further effects on nightmare symptoms could be observed.

Consistent with previous studies (Cheng et al., 2018), the effects of the relaxation exercise on cortical hyperarousal and subjective ratings of relaxation while the participants were performing the task demonstrate that the deep breathing exercise functioned as expected. However, retrospective ratings of sleep quality and nightmares did not improve after practicing the relaxation exercise. Pruiksma and colleagues (2018) could show that a treatment focused on reducing arousal, which included relaxation exercises, reduced nightmare frequency and improved sleep quality in a way that was not inferior to a treatment arm including exposure and rescripting. However, studies that attempt to disentangle/decipher the effective components of nightmare treatments in general and the role of relaxation exercises in particular are still missing (Gieselmann et al. 2019). Therefore, it is difficult to determine the effects the deep breathing exercise in the dosage used in this study can have. One major difference to the study by Pruiksma et al. (2016) is indeed dosage. Their intervention lasted three weeks compared to just one week which could explain the lack of effects on nightmare symptoms and sleep quality found in our study.

While a reduction in beta and gamma activity was observed during the relaxation exercise, reactivating the relaxation exercise during the night did not lead to a corresponding reduction in these frequency bands. One reason for that might be that baseline beta and gamma activity in our sample could have been not as high as in previous studies (Blaskovich et al., 2020; Sayk et al., 2024) and thus a further reduction through reactivation was not feasible. As the approach of this study is still very new and there is very little research on altering beta and gamma activity during sleep, it might also be that our approach was not well-suited to directly target these frequency bands and effects are instead displayed in spindle activity, which is discussed in more detail below.

While beta and gamma activity were not influenced by the reactivation, spindle count and density were reduced in reactivation nights. At first glance, these results appear to be unexpected, as they do not align with findings from previous reactivation studies, some of which report an increase in spindle activity in response to reactivation (Ngo et al., 2015). However, these studies differ significantly from ours in that they reactivated semantic contents, such as learned words, in healthy controls, rather than the content of a relaxation exercise in individuals suffering from frequent nightmares. Our results fit well within the emerging picture provided by findings on the relationship between spindle activity, arousal, and mental disorders characterized by heightened arousal. For example, Picard-Deland and colleagues (2018) found elevated fast spindle activity in subjects with frequent nightmares compared to healthy controls, and linked altered spindle activity to dream content, fear during dreams as well as anxiety and depression. When broadening the picture, similar findings have been presented for PTSD in a review by Natraj and Richards (2023), that linked increased fast spindle activity to PTSD symptoms and suggested this increase to be caused by an increase in arousal. They propose this increased spindle activity could be an expression of unsuccessful over-consolidation of a traumatic event. It is therefore possible that a similar maladaptive over-consolidation may occur in the context of nightmare disorders (van der Heijden et al., 2021).

Taken together, it seems likely that a) increased spindle activity is a nightmare related form of cortical hyperarousal that could have been present in our study sample as well and b) that this form of cortical hyperarousal was indeed influenced by the reactivation of the relaxation exercise. The positive correlation between spindle count and troubles staying asleep could suggest that a breathing exercise not only reduces nightmare-related spindle activity (i.e. cortical hyperarousal) but also potentially improves subjective sleep quality.

Aside from our findings suggesting a correlational link between spindle activity and subjective sleep quality, we found no general effects of reactivation on any behavioral measures during reactivation in the sleep lab. More specifically, neither nightmare symptoms nor subjective or objective sleep quality was directly affected by the reactivation. Several factors might account for these lacking effects. First, the only time the reactivation occurred was in the sleep laboratory environment and research has shown that nightmare experience in the sleep lab is less severe and emotional than in the home sleep environment (Paul et al., 2019). Therefore, it could be advisable to measure the effects of reactivation for more than one night and outside a sleep laboratory in future studies. Other than the laboratory environment, the amount of reactivation could have been an issue that should especially be considered when trying to expand this type of intervention to other disorders than nightmare disorder that involve cortical hyperarousal. Since we only reactivated the relaxation exercise for one night, this might not have been a long enough amount of reactivation. This becomes more apparent when taking into account other studies that reactivated psychotherapeutic interventions, as the successful ones tend to have longer amounts of reactivation. For instance, a recent study by Schwartz and colleagues (2022) who reactivated

IRT by using auditory cues for a period of two weeks found significant effects of the reactivation, whereas Rihm et al. (2016) who reactivated exposure therapy for specific phobias using an odor cue for one night did not find additional effects on anxiety symptoms. Interestingly, they did, however, report changes in spectral activity after the reactivation which, taken together with our findings, might suggest that changes in spectral activity could precede behavioral or symptom changes in a reactivation context.

Future studies should therefore consider longer reactivation periods. Moreover, timing and type of intervention could be optimized so that the intervention targets both cortical hyperarousal and has the potential to influence specific symptoms, such as IRT for nightmares. Due to its transdiagnostic nature, TMR-based interventions that target cortical hyperarousal should be trialed in other disorders next, such as insomnia, PTSD or anxiety disorders. Lastly, one other route for future research could be drawn from Paul and colleagues (2019), who found that changes in autonomic arousal were directly related to nightmare occurrence. If a stable pattern of nightmare specific autonomic arousal was found, reactivation could be made even more targeted with the online detection of nightmare biomarkers and subsequent direct reactivation of an effective intervention.

4.6 Conclusion

The reactivation of a deep breathing relaxation exercise in participants with frequent nightmares did partly influence cortical hyperarousal but not nightmare symptoms. However, the decrease in spindle count and density suggests that a partial increase in relaxation and decrease in nightmare-related neuronal activity occurred. As these mixed results could have been caused by type of intervention and length of the reactivation, future studies should explore longer reactivation periods and different intervention options to influence cortical hyperarousal in multiple disorders.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

4.7 Sources

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4.8 Legend of Tables and Figures

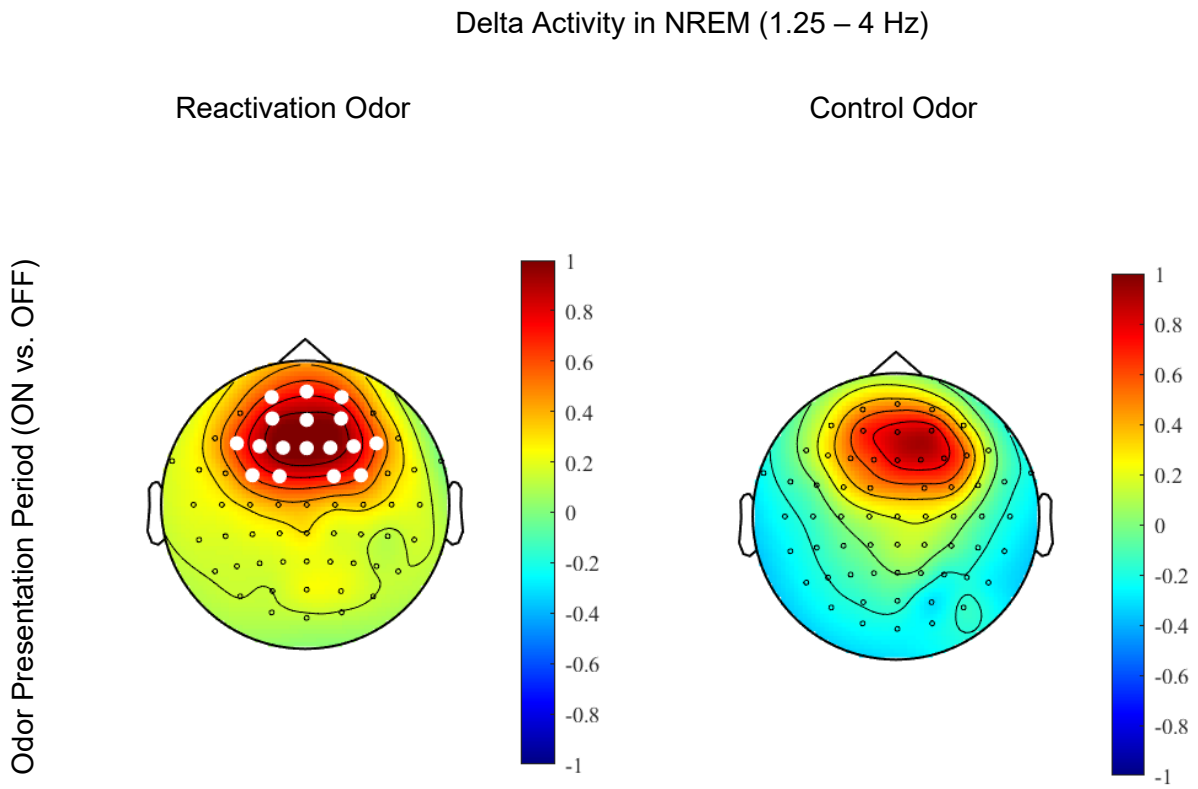
4.9 Supplementary materials

Supplementary material 4

Delta activity in NREM was significantly higher when the reactivation odor was present compared to when it was not, while this difference was not significant for the control odor and there was no significant interaction of odor on and off periods and type of odor. The effect was located in a cluster of frontal and central electrodes (see Figure 4.A). A similar pattern was present in alpha activity during REM sleep, with alpha activity being higher during odor on phases of the reactivation odor than during the odor off phases this difference also was neither significant for the control odor nor was there a significant interaction of odor on and off periods and type of odor. The significant electrode cluster was in a parieto-occipital location (see Figure 4.B). However, these effects in the alpha and delta band were also present when comparing odor on and odor off periods across both odors. The differences in delta and alpha activity were not correlated to any measures of sleep quality, relaxation or negative and positive affect. There were no other significant effects during sleep for any other comparison or frequency band.

Figure 4.A

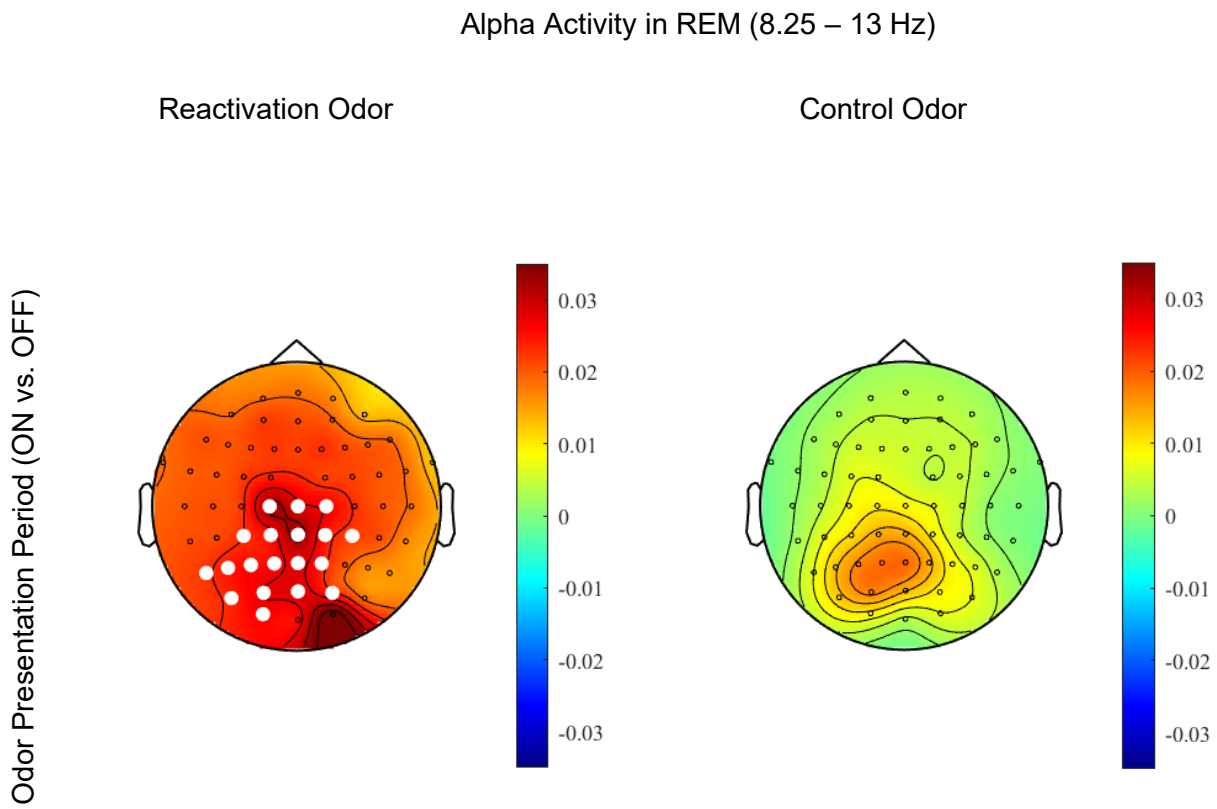
Delta activity in NREM sleep with and without reactivation odor.



Note. Spectral Power differences in the delta band (1.25 – 4 Hz) between odor ON and odor OFF periods in the reactivation odor and the control odor with significant electrode clusters marked in white (p-alpha < 0.05). Delta activity was higher when the reactivation odor was presented.

Figure 4.B

Alpha activity in REM with and without reactivation odor



Note. Spectral Power differences in the alpha band (8.25 – 13 Hz) between odor ON and odor OFF periods in the reactivation odor and the control odor with significant electrode clusters marked in white (p-alpha < 0.05). Alpha activity was higher when the reactivation odor was presented.

5 General Discussion

This thesis reported three studies that investigated the variability in biological correlates of nightmares, especially cortical hyperarousal, in individuals with frequent nightmares in different samples. More specifically, the effects of IRT and TMR on biological correlates and nightmare symptoms were examined using PSG and high-density EEG-measurements.

Study 1 revealed that participants with frequent nightmares showed increased high frequency EEG activity compared to healthy controls, independent of actual nightmare occurrence and this increase was partly reduced after a successful IRT intervention. Study 2 focused on the feasibility of the same IRT intervention as an add-on to inpatient treatment for individuals with BPD and did not only demonstrate a significant reduction in nightmare symptoms, but also a decrease in daytime anxiety and hyperarousal symptoms that was more pronounced than in the control group. Finally, the experimental manipulation of cortical hyperarousal via the reactivation of a relaxation exercise in study 3 showed effects on spectral activity but not on nightmare symptoms.

5.1 Findings on and the relevance of (variability in) biological correlates of nightmares

As variability in biological correlates of nightmares was a central focus of this thesis, there are several findings from the studies it contains that not only replicate but add to the pre-existing knowledge and point out directions for further research.

5.1.1 Replication of previous findings on biological correlates

High-frequency EEG-activity. High-frequency EEG activity was found to be more trait-like in participants with frequent nightmares in study 1, as it was increased in participants with frequent nightmares when compared to healthy controls independent of actual nightmare occurrence. This, in part, replicated but also expanded on the findings of Blaskovich and colleagues (2020) who reported increased beta and gamma activity in the pre-REM interval in participants with frequent nightmares compared to healthy controls. It connects to findings of cortical hyperarousal in various other disorders, such as PTSD (Wang et al., 2020) and social anxiety (Sachs et al., 2004) when compared to healthy controls, might be involved in explaining paradoxical insomnia (Xu et al., 2022) and could thus constitute an important transdiagnostic factor that fits into the integrative model of nightmare etiology (Gieselmann et al., 2019). Spindle activity did not differ significantly between participants with frequent nightmares and healthy controls in study 1, in contrast to Picard-Deland et al. (2018) who found higher density of fast spindles and increased fast spindle oscillatory frequency in frequent nightmare recallers. This could be related to methodological issues, such as time of measurement, since study 1 investigated sleep during the night while Picard-Deland et al. (2018) studied morning naps or studied a slightly different sample with their focus on nightmare recallers. However, this could also be due to spindle activity, as opposed to other forms of high-frequency EEG activity, including several parameters that are less well studied to date in the context of trauma and distress (Natraj & Richards, 2023).

Movement arousals. An increased number of arousal events during sleep has also been cited as a physiological correlate of frequent nightmares in some studies (Blaskovich, Reicher, Gombos, Spoormaker & Simor, 2020), but not in others (Germain & Nielsen, 2003; Paul, Schredl & Alpers, 2015). In study 1, there was a trend towards more arousals in nightmare nights compared to those without nightmare occurrence but there was no difference in number of arousals between participants with frequent nightmares compared to healthy controls. Hence, it could be argued that findings on

arousal in the former studies were, in part, replicated. The results of study 1 might suggest that arousals are more closely linked to actual nightmare occurrence than to a trait of individuals with frequent nightmares. Yet, this aspect warrants further research.

Heart rate variability. There were no significant differences in any HRV measures when comparing participants with frequent nightmares to healthy controls (study 1). This might be due to sub-optimal placement of measurement intervals during sleep, despite the use of intervals from previous studies (Blaskovich et al., 2020; Paul et al., 2019). However, it is more likely that the failure to detect HRV differences is due to the properties of HRV as a biological correlate of nightmares. In studies that did find effects on HRV (Phelps et al., 2018; Paul et al., 2019), it was usually an effect of acute nightmare occurrence rather than a trait of participants with frequent nightmares. As none of the studies included in this thesis featured online nightmare assessment, due to concerns about the subjects' sleep quality, analysis of HRV around the actual nightmare was not possible. Overall, these findings are still observational and thus only allow for limited conclusions on their relevance for etiology models and causal mechanisms.

5.1.2 Sensitivity to treatment of physiological correlates

High-frequency EEG-activity. When examining high-frequency EEG-activity's sensitivity to treatment across all three studies in this thesis, a varied pattern emerges. While the IRT intervention in study 1 was associated with a reduction in gamma activity during REM sleep when comparing measurements pre and post intervention for participants with frequent nightmares, changes in cortical hyperarousal were not entirely reflected in the other two studies. In study 2, which found no differences at all in spectral activity when comparing pre and post intervention, this result might be due to medications normalizing sleep architecture in the study sample of individuals with BPD. In study 3, which was designed to directly influence cortical hyperarousal in otherwise healthy individuals with frequent nightmares, this lack of significant changes requires a different explanation. It is most likely that the intervention, i.e., the reactivation of a relaxation exercise with an associated odor, was not tailored enough to target beta and gamma activity as we might not know enough about the reactivation of mental states rather than the reactivation of semantic concepts yet. This becomes more apparent when examining differences in spindle activity which will be discussed next.

Spindle activity is especially interesting in that respect, as it has been implicated in nightmares before (Picard-Deland et al., 2018) and could be interpreted as another indicator of cortical hyperarousal that might even be susceptible to interventions. This was indicated by study 3, where spindle count and spindle density were reduced during the reactivation of a relaxation exercise. However, this was not reflected in the data from the other studies, which showed no changes in spindle activity in response to an intervention, potentially due to differences in study interventions and also EEG recording devices between studies. Nonetheless, spindle activity might be a potential new target for experimental manipulation and further exploration, especially since related disorders offer possible explanations for the role spindle activity might play in nightmares. On the one hand, van der Heijden and colleagues (2021) suggested increased spindle activity in PTSD might be a sign of memory over-consolidation. On the other hand, changes in spindle activity and thus their sleep protective function have been implicated in paradoxical insomnia (Şenel, Aydın, Aydın, Bayar & Karadeniz, 2021), similar to cortical hyperarousal (Xu et al., 2022).

Movement arousals. Movement arousals, or microarousals, constitute another physiological correlate that has been implicated in nightmares (Blaskovich, Reicher et al., 2020) and that was

investigated with regards to their treatment sensitivity in this thesis. The results in the studies at hand have been inconclusive. While there were no significant changes from before and after therapy in studies 1 and 2, study 3 in fact indicated increased arousals during reactivation of a relaxation exercise. The latter finding is unexpected, especially since the reactivation of the relaxation exercise in study 3 was supposed to decrease arousal. However, as reactivation of brain states is still in its infancy, more research is needed on how it actually affects brain states and other physiological correlates.

Heart rate variability. Looking at sensitivity to treatment in other biological correlates beyond cortical hyperarousal, such as HRV, results were even more varied. There were no significant differences in any HRV measures when comparing pre and post intervention in any of the studies. As discussed above, this could also be due to a combination of methodological issues and the state-like character of HRV in nightmares. If changes in HRV were indeed tied to actual nightmare occurrence and there were no nightmares during the experimental nights, they might not have been any detectable changes. Therefore, future studies of treatment sensitivity of HRV should include more measurements with online nightmare assessment to allow further conclusions.

Psychological correlates of arousal. Apart from physiological measures of arousal, there is also the possibility of measuring (changes in) psychological arousal, albeit during waketime. These measures are often part of PTSD questionnaires, such as the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1996) and can thus only indirectly be connected to (traumatic) nightmares and effects of nightmare interventions. Indeed, individuals with BPD in study 2, who received IRT as an add-on, reported reduced hyperarousal on the IES-R while the control group did not. As the other two studies did not include comparable measurements due to different sample compositions, it is difficult to determine how closely related these changes are to nightmare symptoms. Nonetheless, including measurements of psychological arousal should be included in future nightmare research, ideally in participants with idiopathic nightmares as well.

Conclusion. Despite the large variance across the different study samples, all of them displayed some changes in arousal, albeit on different measurements. While participants with frequent nightmares in study 1 displayed reduced gamma activity during REM sleep after the intervention and those in study 3 showed reduced spindle activity, participants in study 2 showed reduction of psychological arousal after IRT. This points to the robustness of variability in hyperarousal induced by two very different interventions and warrants further research across various measures of arousal and potential interventions.

5.1.3 Other measures of arousal to be considered in future studies

Considering the measures of arousal that were not used in the studies at hand, there are two that especially warrant further investigation with regard to their treatment sensitivity. While cortisol measurements or, in the case of study 1, analysis of cortisol data were not feasible, a blunted cortisol awakening response seems to be indicative of actual nightmare occurrence as well as a trait of individuals with frequent nightmares (Nagy et al., 2015; Hess et al., 2020) and should thus be included in future studies. Another measurement of arousal, that is easier to measure and analyze, is skin conductivity which seems to be more directly related to processing nightmare-related imagery (Rhudy, Davis, Williams, McCabe, & Byrd, 2008) and to actual nightmare occurrence (Paul et al., 2019). Therefore, skin conductivity could prove valuable for the online detection and administration of targeted interventions as will be discussed in more detail below.

Not only physiological correlates and their variability but also psychological measures of arousal beyond PTSD-specific questionnaires should be implemented in future research. This can be done with the aid of several nightmare questionnaires that offer the possibility of measuring subjective arousal related to nightmare experience, such as the Nightmare Behavior Questionnaire (NBQ, Pietrowsky & Köthe, 2003) with the items "I felt nervous and restless" or "I felt distressed", or the Van Dream Anxiety Questionnaire (VDAS, Ağargün et al., 1999) that includes both a scale on subjective experiences of physiological arousal and items like "During the past month, how often have you had feel yourself irritable [sic] or anxious in the morning because of your frightening dreams?" and "During the past month, how often have you had disturbances with your mood or psychological status because of your frightening dreams?". Other measures of sleep-related psychological arousal that could be further studied in this context apart from its use as covariate in study 3 include sleep reactivity, i.e. the tendency to react with sleep disturbance to stressful life events, pre-sleep arousal and fear of sleep. So far, sleep reactivity has mostly been investigated in the context of insomnia (Kalmbach, Cuamatzi-Castelan, Tonnu, Tran, Anderson, Roth & Drake, 2018), where it has been linked to increased cortical hyperarousal during sleep and as a risk factor for PTSD development (Reffi, Kalmbach, Cheng, & Drake, 2023). Similar findings have been reported for fear of sleep and pre-sleep arousal in individuals with PTSD (Werner, Danböck, Metodiev & Kunze, 2019). Given the close connection (via cortical hyperarousal) of these disorders with nightmares, it seems worthwhile to include sleep reactivity in future nightmare research alongside physiological measures. This could also help to investigate whether arousal in nightmares displays similar discrepancies between subjective and objective measures as those found in sleep quality in insomnia (Xu et al., 2022). Lastly, Wassing et al. (2016) could show that nocturnal mentation can be used as a proxy to measure REM fragmentation and hyperarousal which is in turn associated with poor emotional processing at night. As this links hyperarousal and impaired fear extinction, two core components of nightmare etiology (Gieselmann et al., 2019), integrating nocturnal mentation in future study designs could prove to be beneficial.

5.1.4 Epiphenomenon or causal mechanism?

Taken together, the findings strongly suggest that several physiological measures of hyperarousal, especially high frequency EEG activity, are associated with nightmares and show a degree of sensitivity to treatment. Moreover, they might constitute a transdiagnostic factor connecting nightmares to other disorders such as insomnia (Riemann et al., 2010) or PTSD (Wang et al., 2020). However, it is still not quite clear which role (cortical) hyperarousal plays exactly in nightmare etiology, since there were no direct effects of the experimental manipulation in study 3 on nightmare symptoms. The findings of study 1 do indeed suggest that cortical hyperarousal is not just an underlying and unchangeable epiphenomenon in individuals with frequent nightmares, as treatment with IRT was correlated with a reduction in some aspects of cortical hyperarousal. This is further backed up by the results of study 3, in which an experimental manipulation led to a partial reduction in cortical hyperarousal instead of a mere correlative finding. Therefore, as discussed in study 3, future studies should further examine the effects of IRT on hyperarousal using experimental manipulation and a randomized-controlled approach. The interplay with impaired fear extinction, as discussed in the integrative model of nightmare etiology (Gieselmann et al., 2019) is of additional interest for future research, because it could help determine whether hyperarousal is just the result of poor fear extinction or whether there are other factors influencing hyperarousal in nightmares that might be still unknown; cf. the model van Someren (2021) proposed for insomnia which states cortical hyperarousal to be an outcome of fragmented REM sleep. Apart from increasing the understanding of the underlying

theoretical framework, this would also enable the development of novel and the improvement of existing treatment approaches for nightmares.

5.2 Implications for the treatment of nightmares

As mentioned in the previous section, a strong link between theoretical and physiological foundations of a disorder and treatment approaches is beneficial to a better understanding of the disorder and the development and tailoring of treatment options. This thesis examined two types of nightmare interventions in varied samples, ranging from otherwise healthy student populations to individuals with BPD in an inpatient setting.

5.2.1 Differences between study interventions

Study 1 and 2 used IRT, a very well-established intervention for nightmares whose proposed mechanisms of action do not include a direct influence on hyperarousal (Morgenthaler et al., 2018; Gieselmann et al., 2019) and could hence be considered a more indirect approach to studying variability in physiological correlates. In contrast, study 3 used the more direct approach of trying to reactivate a relaxation exercise targeted at cortical hyperarousal during sleep. As discussed before, this led to changes in various forms of hyperarousal. However, these changes were not unanimously reflected in changes of nightmare symptoms. Despite the limitations due to lack of control groups or randomization, study 1 and 2 showed a significant reduction in nightmare symptoms in both groups, while the reactivation of a relaxation exercise did not yield similar results. On the one hand, this is not surprising, as IRT is often considered the gold-standard for nightmare therapy (Morgenthaler et al., 2018) and the duration of the intervention was longer than the intervention and reactivation in study 3. On the other hand, there still is a need for more research into the physiological mechanisms that are targeted by IRT and the role of its different components. Whereas psychoeducation and the use of relaxation techniques that often accompany IRT protocols (see study 1 and 2) might promote a slight reduction in arousal, study 3 showed that relaxation is likely not sufficient to influence nightmare symptoms and thus probably not an active component of IRT. Therefore, it is probably more useful to consider the effects of the actual rescripting process, which has previously been described as a potentially effective component of IRT alongside exposition (Kunze, Arntz, Morina, Kindt & Lancee, 2017). This would tie in with the mechanisms of action described in the introduction, since one of them is improved emotion regulation and fear extinction which could, in turn, have an indirect effect on (cortical) hyperarousal.

5.2.2 The utility of directly targeting cortical hyperarousal

Given that the most direct approach to targeting cortical hyperarousal did not yield the desired effects on nightmare symptoms, the question of the utility of that approach is not fully answered yet. The first step to finding an answer would be to successfully experimentally manipulate cortical hyperarousal during sleep. This would allow us to determine if there is a direct connection to nightmare symptoms and therefore, if it actually is a potential target for novel interventions and not only a side effect of a successful treatment. While the relaxation task in study 3 did influence beta and gamma activity during the exercise itself, it did not fully translate to the reactivation at night. By contrast, the IRT from study 1 and 2 was not planned as an experimental manipulation of cortical hyperarousal and therefore did not allow such direct conclusions from cortical hyperarousal to nightmare symptoms. The physiological correlates and changes related to IRT have, however, not been extensively studied yet. A good candidate for this approach could be to try to reactivate an IRT intervention with TMR, as study 1 did show some effects of IRT on gamma activity and Schwartz et al. (2022) could show that it is possible

to reactivate IRT and thus improve its effects on nightmare symptoms. The next steps, depending on the results, could then be to develop and test new interventions targeted at cortical hyperarousal and / or to examine the role of other mechanisms, especially fear extinction (Gieselmann et al., 2019) and biological correlates. Beyond these steps in future research, it is, however, questionable on a more principal level, how useful targeting biological correlates can be for research and development of nightmare interventions.

5.3 Limitations of the biological correlates approach

As hinted at in the last section, a major limitation of the biological correlates approach and therefore also this thesis, is the questionable usefulness of biological correlates in the context of a disconnect between subjective and objective parameters in other sleep disorders. This is best reported for insomnia, where objective and subjective sleep complaints sometimes show no overlap (Xu et al., 2022). Yet, the issue might have further implications. When considering it from a philosophical perspective, the connection between physiological correlates and psychological experiences, such as nightmares, might not be as clear cut. While physiological arousal is measurable, it is not a direct representation of nightmare experiences. The exact neural and physiological correlates of nightmares have, depending on whether a materialistic or an idealistic approach to the philosophy of neuroscience is taken, either not been discovered yet or they can never be physiologically detected due to the mind and therefore the experience of nightmares being a separate entity. Even when assuming a materialistic position, that has dominated the philosophy of neuroscience in recent years (Bickle, Mandik & Landreth, 2019), and therefore the possibility of a direct connection between nightmares and biological correlates, cortical hyperarousal might not be the most suitable outcome measure due to the difficulties with artefacts while recording these high frequency bands (Muthukumaraswamy, 2013). However, when adhering to lower gamma and beta activity this issue could be reduced, and the inclusion of spindle activity (Picard-Deland et al., 2018) could be helpful as well.

5.4 Perspectives for future research

As has been mentioned in the previous sections, the biological correlates and their sensitivity to treatment discussed in this thesis, especially cortical hyperarousal and spindle activity, merit further research both concerning their utility for investigating nightmares and nightmare therapy and the biological correlates themselves. Future research on the biological correlates of nightmares could further explore the role of sleep spindles and what role they actually play in nightmares, especially since it is poorly explained to date, why they would be increased in people with frequent nightmares (Picard-Deland et al., 2018) while they are for example reduced in psychosis (Kammerer, Bott, Strakeljahn & Lincoln, 2024), a disorder sharing some aspects with nightmares, such as the concept of thin boundaries (Nielsen & Levin, 2007). Another concept surrounding EEG activity in nightmares that warrants further research, are slopes of EEG activity. They allow for separation of excitatory and inhibitory components of brain activity (Gao, Petersen & Voytek, 2017) and have been used to investigate both wake and sleep EEG activity so far (Kozhemiako, Mylonas, Pan, Prerau, Redline & Purcell, 2022). Moreover, spectral slopes have already been proposed as another measure of wake-like activity and arousal during sleep (Lendner et al., 2020) but have yet to be investigated in the nightmare context.

Concerning the utility and role of biological correlates in nightmares, further trials to influence cortical hyperarousal and examine their effects on nightmare symptoms should be conducted. As was already mentioned in the discussion of study 3, good candidates for future studies could be either stimulation methods or reactivation of IRT with TMR. This approach is supported by study 1 which did

show some effects of IRT on gamma activity and Schwartz et al. (2022) were able to show that it is possible to reactivate IRT and thus improve its effects on nightmare symptoms. Then there still is the possibility of employing stimulation methods as mentioned in study 3, such as tDCS. They would, however, possibly work to increase cortical hyperarousal and thus potentially cause worsening symptoms. The next steps, depending on the results, could then be to develop and test new interventions derived from experimental manipulation and targeted at cortical hyperarousal. Another important step would be to examine the relationship between hyperarousal and other mechanisms, especially fear extinction (Gieselmann et al., 2019) more closely in order to determine the direction of causality between these factors.

5.5 Conclusion

This thesis assessed the variability in biological correlates, especially increased (cortical) arousal, of nightmares and the potential of different interventions in relation to these correlates in various samples. Increased (cortical) arousal showed sensitivity to treatment in various samples with frequent nightmares. IRT was successful in reducing nightmare symptoms in two different patient groups and influenced different aspects of hyperarousal. An experimental manipulation of a hyperarousal-focused relaxation task, designed to increase knowledge about the causal role of hyperarousal, was only partly successful in that it altered spindle activity but not nightmare symptoms. Future research should therefore focus on further attempts to experimentally manipulate cortical hyperarousal by stimulation methods or by reactivating IRT and should also include other factors of the integrative model of nightmare etiology, especially fear extinction.

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