

Cortical hyperarousal in NREM sleep normalizes from pre- to post- REM periods in individuals with frequent nightmares

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Abstract

Study Objectives: Frequent nightmares have a high prevalence and constitute a risk factor for psychiatric conditions, but their pathophysiology is poorly understood. Our aim was to examine sleep architecture and electroencephalographic markers – with a specific focus on state transitions – related to sleep regulation and hyperarousal in participants with frequent nightmares (NM participants) versus healthy controls.

Methods: Healthy controls and NM participants spent two consecutive nights in the sleep laboratory. Second night spectral power during NREM to REM (pre-REM) and REM to NREM (post-REM) transitions as well as during NREM and REM periods were evaluated for 22 NM participants compared to 22 healthy controls with a similar distribution of age, gender and dream recall frequency.

Results: We found significant differences between the groups in the pre-REM to post-REM changes in low and high frequency domains. NM participants experienced a lower amount of slow-wave sleep and showed increased beta and gamma power during NREM and pre-REM periods. No difference was present during REM and post-REM phases. Furthermore, while increased pre-REM high frequency power seems to be mainly driven by PTSD symptom intensity, decreased low frequency activity occurred regardless of PTSD symptom severity.

Conclusion: Our findings indicate that NM participants had increased high frequency spectral power during NREM and pre-REM periods, as well as relatively reduced slow frequency and increased fast frequency spectral power across pre-and post- REM periods. This combination of reduced sleep-protective activity and increased hyperarousal suggests an imbalance between sleep regulatory and wake promoting systems in NM participants.

Keywords: Nightmare, PTSD, sleep, pathophysiology, EEG

Statement of significance

The prevalence of frequent nightmares is high in the general population and in psychiatric samples, but their pathophysiology remains poorly understood. Our results show reduced low frequency and increased high frequency EEG activity in pre-REM periods that normalizes to post-REM periods. Increased power in the higher frequencies during pre-REM sleep correlated to subjective posttraumatic stress disorder (PTSD) symptom severity, whereas reduced low frequency activity occurred regardless of PTSD severity. Understanding the pathophysiology of frequent nightmares is highly relevant for the identification of treatment targets for nightmares, and could lead to a better understanding of the sleep pathophysiology of PTSD. Finally, our analyses show that it is methodologically beneficial to focus sleep analyses on sleep state transitions, such as the highly active pre-REM and the more quiescent post-REM sleep stages.

Introduction

Nightmares are highly unpleasant mental experiences during sleep that typically end in abrupt awakenings. At awakening, the individual is quickly alert and able to recall a vivid and emotionally negative dream experience^{1,2}. The prevalence of having frequent nightmares is surprisingly high, reaching approximately five percent in the general population³⁻⁶. Frequent nightmares are associated with disturbed sleep⁷⁻¹¹, fear for sleep¹², impaired daily functioning¹³, and correlate with a wide variety of pathological conditions such as depressive and anxiety symptoms¹⁴ and psychotic-like symptoms¹⁵. Furthermore, sleep complaints and nightmares constitute as one of the main symptom of post-traumatic stress disorder (PTSD), which are hypothesized to derive from impaired regulation of sleep and arousal that leads to hyperarousal and interferes with the restorative capacity of sleep¹⁶⁻¹⁹. Nightmare disorder is categorized as a separate sleep-wake disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*¹, although it is generally not a main focus of attention among health professionals^{10,20}. This is unfortunate as nightmares are extremely common (around 30%) among psychiatric patients¹¹ and related to more severe psychopathological profiles²¹.

Notwithstanding this high prevalence and impact, the pathophysiology of nightmares remains elusive due to a lack of experimental data. Nightmares tend to occur less frequently in the sleep laboratory setting²² or even when measured with polysomnography in the clinic¹³. Yet some previous work has revealed that nightmares are associated with increased REM density²³ and seem to predominantly – but not exclusively – occur during REM sleep^{24,25}. Polysomnographic studies focusing on the macro- and micro-structure of sleep in individuals with frequent nightmares have been rather inconsistent. Some reported irregularities during REM phase, such as increased spectral power in high alpha activity²⁶ or larger heartbeat evoked potentials²⁷, others show more pronounced abnormalities during NREM sleep, for instance reduced amount of slow-wave sleep (SWS)²⁸ or increased electroencephalogram (EEG) desynchrony and predominantly rapid low-voltage activity²⁹ (measured by increased cyclic alternating pattern (CAP) A2 and A3 subtypes). Additionally, other studies are reporting changes in a more global sense, for example generally fragmented sleep architecture²⁸ or increased slow theta power during sleep³⁰. In a previous study on individuals with frequent nightmares, particular interest has been given to NREM to REM transitions, a highly instable

state that appears to be particularly vulnerable for intrusions of ‘wake-like activity’ during sleep^{31,32}.

In the present study, we examined the sleep architecture, as well as the EEG markers of sleep regulation and arousal-related cortical activity in a group of participants with frequent idiopathic nightmares (NM participants) compared to a group of healthy controls. To better quantify sleep fragmentation we addressed NREM to REM (pre-REM) transitions – when there is already a predisposed vulnerability for higher vigilance states disrupting sleep continuity³³ – and compared these with REM to NREM (post-REM) transitions. We also analyzed REM and NREM periods separately. Based on previous studies investigating sleep characteristics of individuals with frequent idiopathic nightmares^{28,30} a globally distributed reduction in slow frequency power (delta) was hypothesized during NREM phase in the NM participants compared to the control participants. Furthermore, this difference was expected to be present mainly during the fragile state transition periods (especially during pre-REM periods).

Methods and Materials

Participants

Participants were recruited from a pool of students of the Budapest University of Technology and Economics and the Eötvös Loránd University, and through advertisements in social media. NM participants and controls were selected after completing an online screening questionnaire that included items concerning sleep quality^{34–36}, dream recall frequency³⁷ (DRF), nightmare and bad dream frequency²⁶ to assess sleep disturbances. Alcohol intake, mind-wandering experiences³⁸, along with standardized questionnaires and items focusing on psychological well-being^{39,40}, previous and current neurological, psychiatric and chronic somatic diseases and regular medication consumption were measured. Inclusion criteria for the NM participants were based on the frequency of both typical nightmares leading to awakenings as well as so called bad dreams that do not lead to abrupt awakening, in line with the ongoing debate questioning the awakening criterion for nightmares^{14,41} (see Supplementary Table **S1** for the cross table of the detailed group split). Individuals reporting: 1) to remember their dreams more than 2-3 times/months; 2) 2-3 nightmares/months (NM participants) or less than 2-3 nightmares/year (controls); 3) at least one bad dream/week (NM participants) or not more than 1 bad dream/months (controls); 4) no prior history of neurological, psychiatric, or chronic somatic disorder; 5) moderate alcohol intake (not more

than once/week); 6) no regular medication (except contraceptives) were invited to take part in a first interview with a psychologist. During this interview, participants were questioned about recent potential traumatic experiences (in the last five years) as well as the frequency and quality of their nightmares to exclude individuals with recent traumatic experiences and with trauma-or acute stress related nightmares.

After the screening, fifty participants (26 controls, 24 NM participants) were invited to take part in the experiment. One participant left the experiment after the first night, and the data of five additional participants were not included in the final data analyses (three of the recordings were too noisy for spectral analysis, in one participant we identified comorbid night terrors, and one control participant had insufficient amount of sleep (sleep efficiency < 60%) on the experimental night). Finally, 22 NM participants and 22 controls (see **Table 1**) were included in the present study. University students participated for partial course credits and participants not enrolled in the universities received monetary compensation (approximately 45€ in Hungarian forints). The study protocol was approved by the United Ethical Review Committee for Research in Psychology, Hungary (EBKEB 2016/077), in line with the Declaration of Helsinki and written informed consents were obtained.

Questionnaires

Selected participants completed the *PTSD Checklist for DSM-5 (PCL-5)* to assess PTSD-like symptoms⁴². This 20-item self-report measure that assesses DSM-5 symptoms of PTSD is suitable to screen individuals for PTSD, but from a dimensional point of view, also to quantify the severity of PTSD-like symptoms in clinical and subclinical populations⁴³. For additional information about lifetime traumatic experiences, participants filled out the Life Event Checklist for DSM-5 (LEC-5)⁴⁴. This is a 17-item based self-report measure aiming to assess exposure to extraordinarily stressful events. In addition, participants completed the Hungarian version of the *Spielberger Trait Anxiety Inventory (STAI-T)*⁴⁵. To measure the extent of depressive symptoms, we used the short version of the *Beck Depression Inventory (BDI-9)*⁴⁶. Furthermore, subjective sleep quality was assessed before going to bed and after awakening by two 9-point Likert scales concerning the quality of sleep (“How did you sleep last night?”) and sleepiness (“How well rested do you feel now?”).

Procedure

Participants spent two consecutive nights in our sleep laboratory. They were asked to abstain from alcohol 24 hours prior to the study, and to follow regular bedtimes as well as to avoid napping and consuming caffeine in the afternoon of the sleep recordings. Participants arrived to the laboratory between 9:00 PM and 10:30 PM. Bedtimes were scheduled between 10:00 PM and 11:30 PM, adjusted to the preference of each participant. Participants were awakened after at least 7 hours of sleep, between 7:00 AM and 8:00 AM. Upon awakening, participants were asked to answer additional questions of sleep quality and sleepiness (see above). The same procedure was repeated on the second night with the addition of an extra task before the EEG application. In this task, participants were shown a set of negative and neutral IAPS (International Affective Picture System⁴⁷) pictures. Subjective ratings (valence and arousal) as well as physiological data (skin conductance response and heart rate) were collected during the task. The procedure and the results of these measurements will be reported elsewhere (Blaskovich et al. in preparation). The first night was used as an adaptation night, and here we analyzed only the data recorded during the second night.

Polysomnography

All participants were fitted with 17 EEG electrodes (F7, F8, F3, F4, Fz, T3, T4, C3, C4, Cz, T5, T6, P3, P4, Pz, O1, O2) according to the 10-20 electrode placement system⁴⁸, referred to the mathematically linked mastoid (A1 and A2) electrodes. We used bipolar electromyography (EMG) placed on the chin, as well as electrooculography (EOG) and electrocardiography (ECG). Gold-coated Ag/AgCl EEG cup electrodes were fixed with EC2 Grass Electrode Cream (Grass Technologies, Natus Manufacturing Ltd., Galway, Ireland). Data was recorded with Micromed SD LTM 32 Bs (Micromed S.p.A., Mogliano Veneto, Italy) and SystemPLUS 1.02.1098 software (Micromed Srl, Roma, Italy). Impedances were below 8 k Ω . Signals were collected, prefiltered (0.33-1500 Hz; 40 dB/decade anti-aliasing hardware input filter), amplified, and digitized with 4096 Hz/channel sampling rate with 16-bit resolution. Thenceforward, the pre-filtered, amplified and digitized signal was downsampled at 512 Hz.

Sleep macrostructure and spectral power analysis

Sleep stages and conventional parameters of the second night were scored manually according to standardized criteria⁴⁹ by trained experts, blind to the membership of each participant. Recordings were visually inspected on a 4-second basis and segments with muscle- and technical-related artefacts were discarded. Artefact-free, 50% overlapping, 4-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 45 Hz for NREM (including Stage 2 and Stage 3) and REM sleep periods, separately⁵⁰. Pre-REM periods were defined as 10-min intervals of NREM sleep directly before the onset of each REM period (except the last one). Accordingly, post-REM periods included similar 10-min long NREM epochs following the end of each REM period (except the last one that was usually followed by wakefulness). Due to the ultradian rhythm of sleep the amount of stage 2 (N2) and stage 3 (N3) varied between every cycle across participants however, regarding the proportion of these periods there was no difference between the two groups (for more detailed information see Supplementary Tables **S2 A - D**). Band-wise spectral power was extracted by summing up bin-wise values into the traditional frequency ranges of Delta (1.25-4Hz), Theta (4.25-8Hz), Alpha (8.25-13Hz), Sigma (13.25-16Hz), Beta (16.25-31Hz), Gamma (31.25-45Hz) bands and averaged across all channels.

Statistical analyses

Statistical analyses were carried out with R⁵¹, MATLAB (version 7.10.0.499, R2010a, The MathWorks, Inc., Natick, MA) and JASP⁵². Normality of the variables was assessed by the skewness and kurtosis of data distribution, as well as by Shapiro-Wilk tests. Differences in sleep architecture and psychometric measures between NM participants and controls were evaluated by independent samples t-tests, Welch-tests (in case variances in the two groups were statistically different), or Mann – Whitney U tests (if the assumption of normality was violated). The issue of multiple comparisons (except for the bin-wise, single electrode comparisons) was addressed with the Benjamini-Hochberg procedure to estimate false discovery rate (FDR)⁵³. Since the bin-wise, single electrode comparison of pre-to post-REM contrast between the two groups entailed 2992 comparisons a different statistical and correctional approach was applied. In case of the bin-wise spectral power analyses, statistically significant differences across NM and control participants in each frequency bin and electrode site were corrected by cluster-based permutation tests as implemented in the

Fieldtrip toolbox⁵⁴. Cluster-based permutation testing is a frequently used procedure for the analyses of EEG data involving multiple frequencies and electrode sites, and is able to efficiently handle the issue of multiple comparisons⁵⁵. In brief, in case of pre-to post-REM changes we performed two-sided independent samples t-tests for all data points (i.e. in each frequency bin and electrode sites). Clusters were defined if adjacent frequencies or locations showed significant differences at the α level below .05. A cluster statistic was calculated for each identified cluster. The observed cluster statistics were defined by the sum of all the t-values that formed a given cluster. The same process was repeated 1000 times by randomly shuffling the data of NM and control participants using the Monte-Carlo simulation procedure implemented in Fieldtrip⁵⁵. Here again, significant clusters were identified, cluster statistics were extracted, and the largest cluster statistic of each permutation was used to create the probability distribution of clusters. Finally, the observed cluster statistics were tested (with an alpha value of 0.05) against the probability distribution of the largest clusters generated by the Monte-Carlo simulation. Furthermore, significant values apparent only at single channels or single bins were mentioned, but not considered as significant. We used this additional criterion to discard the confounding effects of potential artifacts. In order to compare pre-REM and post-REM periods across NM participants and controls we divided the averaged power spectra of pre-REM periods with that of post-REM ones (Average Spectra of pre-REM / Average Spectra of post-REM) in case of each participant, and compared these contrasts across NM participants and controls with bootstrap tests.

Band-wise spectral power differences across pre-REM and post-REM periods between NM participants and controls were examined by mixed Analyses of Variance (ANOVA) models after averaging band-wise power across all channels. We tested a 2 x 2 x 6 ANOVA model including Phase (pre-REM, post-REM) and Band (Delta, Theta, Alpha, Sigma, Beta, Gamma) as within-subject factors, and Group (NM participants, controls) as a between subject factor. In addition, we ran Phase x Group ANOVAs for each frequency band, separately. Greenhouse-Geisser epsilon (ϵ) corrections were used if the Mauchly's test indicated the violation of the assumption of sphericity. Original (uncorrected) *degrees of freedom* (df values) and corrected p values (if applicable) are reported together with partial eta-squared (η_p^2) as a measure of effect size. Additionally, the associations between psychometric variables and band-wise, average EEG power within the NM subject and control group were examined by hypothesis driven, one tailed Kendall's tau B correlation coefficients.

Results

Psychometric variables and sleep architecture

Group differences (including test statistics and adjusted p-values) regarding psychometric measurements are presented in Supplementary Figure **S3**. NM participants scored higher on PTSD-like symptoms (PCL-5), whereas no significant group differences (only trends) emerged in case of anxiety (STAI-T) scores. Furthermore, group differences in traditional parameters of sleep architecture were calculated and are summarized in **Table 2**. According to these analyses, NM participants spent significantly less amount of time in SWS than controls. NM participants spent apparently more time in Stage 1 (unadjusted $p = .04$); and had more awakenings during NREM sleep than controls (unadjusted $p = .03$); however, these differences were not significant after the correction for multiple comparisons. No other sleep parameters were significantly different across the groups.

Differences in spectral power

In order to examine changes between pre- and post-REM periods we divided the averaged power spectra of pre-REM periods with that of post-REM ones and compared these contrasts across NM participants and controls with bootstrap tests and cluster-based correction. As there was a significant difference between the two groups in SWS and relative spectral power can be highly confounded by delta power differences, we analyzed the absolute spectral power. **Figure 1** illustrates the ratio of this pre-to post-REM contrast between NM participants and controls. That is, the Average Absolute Power Spectra of pre-REM / Average Absolute Power Spectra of post-REM of the NM participants, divided by the Average Absolute Power Spectra of pre-REM / Average Absolute Power Spectra of post-REM of the controls. As **Figure 1** shows, NM participants compared to controls showed reduced pre-to-post-REM spectral power ratio within slow frequencies at all electrode sites between 1.25 - 8 Hz. In addition, NM participants compared to controls, showed significantly increased pre-to-post-REM power ratio in higher frequencies spanning between 15 and 31 Hz. In sum, NM participants exhibited relatively reduced slow frequency power along with relatively increased high frequency power in pre-REM periods, whereas during post-REM periods, spectral power values in NM participants approximated the values of the control group.

To further investigate the dynamics of cortical activity, absolute spectral power of pre- and post-REM NREM segments, as well as NREM and REM periods was analyzed post-hoc by

similar bin-wise cluster-based bootstrap statistics. Regarding pre-REM periods, NM participants compared to controls exhibited an increase in power spectra of the beta and gamma frequency ranges (between 26 and 45 Hz), on mainly temporal and frontal sites (See **Figure 2A**). In post-REM periods, there was no significant difference between NM participants and controls. The contrasts of power spectra across NM participants and controls as well as corresponding statistical tests are presented in **Figure 2B**. In NREM sleep, NM participants compared to controls showed significantly increased power spectra within the beta and gamma bands (between 20-45 Hz) throughout the scalp (see **Figure 3A**). In REM sleep, there was no statistically significant difference across NM participants and controls (see **Figure 3B**). In sum, NM participants exhibited an increase in high frequency power in NREM and pre-REM periods.

Furthermore, band-wise spectral power differences between pre-and-post-REM periods were tested by a Phase x Band x Group mixed ANOVA model. This full model yielded significant main effects for Band ($F_{5,210} = 425.05$, $p < .001$, $\eta_p^2 = .91$), Phase ($F_{1,42} = 332.58$, $p < .001$, $\eta_p^2 = .89$), and Group ($F_{1,42} = 7.37$, $p = .01$, $\eta_p^2 = .15$), as well as significant two-way (Band x Group: $F_{5,210} = 9.72$, $p < .001$, $\eta_p^2 = .19$; Phase x Group: $F_{1,42} = 17.84$, $p < .001$, $\eta_p^2 = .3$) and three-way (Band x Phase x Group: $F_{5,210} = 18.72$, $p < .001$, $\eta_p^2 = .31$) interactions. In order to parse out these interactions, we performed separate ANOVAs for each frequency band. The effects of Group, Phase and of the interaction term are presented in the Supplementary Material **S4** and **S5**. In accordance with the bin-wise analyses, a significant interaction between Group and Phase emerged in case of the delta band, and in case of the theta, beta and gamma frequency bands the interaction showed trends. Delta power was increased during pre-REM periods, in comparison with post-REM ones; however, this increase was less apparent in NM participants as compared to controls (see **S5**). Group differences, that is, lower delta band power in NM participants is attributable to this relative decrease in pre-REM periods: the post-hoc Mann-Whitney U-tests contrasting NM participants vs controls in pre-REM was: $W = 388$, $p < .001$. In contrast, during post-REM periods, delta band power reached the values of the control group ($W = 301$, $p = .17$). In addition, interactions between Phase and Group emerged in case of theta, beta and gamma bands, and remained at a trend level after FDR correction (See **S4** and **S5** for more detail).

Although participants with recent (< 5 years) traumatic experiences and trauma-related nightmares were excluded during the interview, the included participants still reported varying levels of PTSD-symptoms, and there was a significant difference in PCL-5 scores between the NM and control participants (see Table 2). To further investigate this issue, the PCL-5 and LEC-5 questionnaires were analyzed together (for the group allocations see Supplementary Table S6). Fifteen participants scored above the PCL-5 cutoff (33 points)⁵⁶ for increased PTSD probability, yet five of these participants reported no lifetime trauma or adversity. The remaining ten participants did report lifetime adversity, however this traumatic event did not occur in the last five years, suggesting childhood/adolescent adversity ($M_{age} = 22.3$, $SD_{age} = 2.6$). This points to a subgroup of participants with possibly undiagnosed PTSD.

All of these participants were in the NM group and this allowed us to disentangle the effects on spectral power of having frequent nightmares (control versus NM participants without high PTSD probability) and of having high PTSD probability (NM participants with versus NM participants without high PTSD probability). In order to analyze the effect of subgroups on the changes between pre- and post-REM periods, we compared the pre- to post-REM contrasts between NM participants without high PTSD probability and controls. Due to the rather small sample sizes ($N_{NM} = 12$, $N_{CTL} = 22$) Cohens' d effect sizes are reported. Cohens' d values were above 1 on all electrode sites in the delta and theta frequency bands (2.75 – 6 Hz), between $0.6 < d < 1$ on frontal electrodes in the high-sigma, low beta bands (14.75-21 Hz) and below 0.3 in the gamma band (>34 Hz) during pre- to post-REM changes (see Supplementary Figure S7A). When comparing the pre- to post-REM contrast in NM participants with and NM participants without high PTSD probability Cohens' d values spanned between $0.6 < d < 1$ on all electrode sites in the delta and theta band (2.75 – 6 Hz), in the beta band (16.75 – 22.75 Hz), as well as in the gamma band (> 34 Hz) (see Supplementary Figure S7B).

To further investigate subgroup differences a Phase (pre-REM, post-REM) x Group (control, NM participants without and NM participants with high PTSD probability) repeated measures ANOVA was performed for delta, beta and gamma bands separately. Regarding delta, there was a significant main effect for Phase ($F_{1,41} = 237.79$, $p < .001$, $\eta_p^2 = .85$) and for Group ($F_{2,41} = 4.98$, $p = .01$, $\eta_p^2 = .19$) as well as a significant Phase x Group interaction ($F_{2,41} = 9.39$, $p < .001$, $\eta_p^2 = .31$). The post hoc analysis of pre-REM phases showed a significant difference between NM participants without high PTSD probability and controls ($t_{33} = -3.44$, p

= .004, $d = -1.21$) as well as between the NM with high PTSD probability and controls ($t_{31} = -2.61$, $p = .04$, $d = -.95$), but no difference between the two NM subgroups ($t_{21} = -.56$, $p = 1$, $d = -.27$) for the delta band. For the beta band a significant main effect of Phase ($F_{1,41} = 4.54$, $p = .039$, $\eta_p^2 = .1$), no main effect of Group ($F_{2,41} = .23$, $p = .8$, $\eta_p^2 = .01$), but a significant Phase x Group interaction ($F_{2,41} = 3.41$, $p = .04$, $\eta_p^2 = .14$) emerged; however, none of the groups differed significantly according to the post hoc tests. Lastly, regarding gamma there was a significant main effect of Phase ($F_{1,41} = 22.47$, $p < .001$, $\eta_p^2 = .35$), no main effect of Group ($F_{2,41} = 2.23$, $p = .12$, $\eta_p^2 = .1$), and a trend for a significant Phase x Group interaction ($F_{2,41} = 3.11$, $p = .06$, $\eta_p^2 = .13$). The only nominally significant group difference emerged between the NM participants with high PTSD probability and controls ($t_{31} = 2.53$, $p = .05$, $d = 1.05$) in the post hoc analysis of pre-REM periods. For figures for each analysis see Supplementary Figure S8. These results indicate that the reduction of slow activity (delta) during NREM and pre-REM phase is more specific for having frequent nightmares, whereas the increase of high frequency spectral power (gamma) appears to be linked to symptoms of PTSD.

To further explore whether hyperarousal during sleep state transitions was associated with PTSD-like symptoms, Kendall's tau B correlation coefficients were calculated between band-wise spectral power in pre-and-post-REM periods and PCL-5 scores, within each group separately (**Figure 4**). In the NM group PTSD-like symptoms correlated positively with Pre-REM ($\tau = .34$, $p = .01$), but not with post-REM ($\tau = .14$, $p = .18$) gamma power. No such association was found within the controls, neither in pre-REM ($\tau = -.09$, $p = .73$), nor in post-REM periods ($\tau = -.14$, $p = .83$). No additional significant correlations were found between PTSD-like symptoms and other frequency bands.

Discussion

In this sleep laboratory study, we examined a group of NM participants and healthy controls on subjective measures and objective sleep parameters. As regarding the macrostructure of sleep, NM participants spent significantly less amount of time in SWS than controls. Spectral power also clearly differentiated the two groups: in NREM and pre-REM sleep NM participants exhibited increased fast frequency power (within the beta and gamma ranges) compared to the control group. Moreover, delta band power was decreased during pre-REM phases in NM participants compared to controls. In sharp contrast, group differences in spectral power completely disappeared during REM sleep and post-REM periods.

We propose that reduced SWS and increased fast frequency oscillations in NREM sleep may indicate an imbalance between sleep regulatory and wake promoting systems^{31,57} in NM participants. Slow frequency oscillations facilitate the disconnection from the external environment and promote the restorative functions of sleep^{58,59}, whereas increased fast frequency oscillations during NREM sleep are considered to be markers of cortical hyperarousal^{60,61}. In our data, high frequency between-group differences were most pronounced in the beta and gamma bands, around 20 – 45 Hz during stable NREM sleep and 27 – 45 Hz during pre-REM periods. Increased high frequency activity (in the beta band) in NREM sleep of NM participants has been already observed³⁰, although not in all previous work²⁶.

In order to more closely examine the potential imbalance between sleep regulation and wake promotion in NM participants, we specifically focused on spectral power during pre-REM and post-REM periods. Pre-REM periods are particularly sensitive periods with a high occurrence of microarousals⁶², wake-like, elevated alpha power³², and high frequency oscillations⁶³. By contrast, post-REM periods are relatively quiescent states, when the stability of NREM sleep is reinstated and phasic arousals as well as high-frequency activity are less likely to occur^{57,63}. Our results showed a significant Group x Phase interaction from pre- to post-REM in the delta band as well as a nominally significant interaction in the theta, beta and gamma frequency bands. Furthermore, in NM participants compared to controls, pre-REM periods (relative to post-REM ones) were characterized by decreased slow frequency power between 1.25 and 8 Hz, and relatively increased high frequency power between 15 – 31 Hz. The pattern in both groups suggests a normalization of spectral power from pre- to post-REM. Nevertheless, in controls, NREM to REM transitions are marked by increased slow frequency oscillations that may protect the integrity of sleep and compensate for the arousing influences of transitory periods. This simultaneous appearance of sleep-like and wake-like activity, seems to be a crucial feature of sleep having two complementary functions: to maintain the stability of sleep (sleep regulation), and at the same time to monitor the environment in order to detect and (if necessary) to react to potential external threats^{33,57,64,65}. In contrast, NM participants appear to fail to “protect” NREM sleep in the vicinity of REM periods and exhibit reduced low frequency and increased fast frequency activity indicating hyperarousal. We propose that decreased slow frequency and increased fast frequency oscillations indicate an imbalance between sleep regulatory and wake promoting systems^{31,57,65}.

Alternatively, reduced SWS duration and slow frequency activity could be the result of a group difference in circadian rhythms or accumulated sleep debt within the NM participants. Nevertheless, according to the Morningness- Eveningness Questionnaire (MEQ)³⁶ the groups did not differ with respect to circadian preferences (on average between 31-41 points: 'moderate evening type'), and there was no significant difference between the two groups in sleep onset latency (SOL)⁶⁶ neither the first, nor the second night (Supplementary Table S9), arguing against the confounding effects of circadian rhythms and sleep pressure.

It is of note that sleep disruptions in PTSD are also marked by reduced slow frequency and arousal-related activity. According to the meta-analysis of polysomnographic studies by Kobayashi et al.⁶⁷, PTSD patients showed reduced SWS and increased stage 1 and REM density, which fits the notion of increased arousal during sleep. This has been confirmed in another more recent meta-analysis revealing increased 'REM pressure' and nominally reduced sleep depth in PTSD⁶⁸. Furthermore, single studies have shown reduced parasympathetic activity⁶⁹, REM sleep fragmentation⁷⁰, increased motor activity⁷¹, as well as enhanced high frequency electroencephalographic (EEG) power⁷² in the sleep of PTSD patients (for a review see¹⁷). Moreover, trauma associated sleep disorder (TSD)⁷³ has been proposed as a new diagnostic identity that encompasses such hyperarousal-related events in sleep. In line with the notion that there appears to be an overlap between these findings and hyperactivity during sleep in individuals with frequent nightmares (for more detailed information see⁷⁴). Nielsen⁷⁵ proposed that both traumatic and "idiopathic" nightmares are due to the same vulnerability, which has been triggered by different degrees of lifetime adversity. According to this theory, this adversity in individuals with frequent "idiopathic" nightmares happened at an early age and is forgotten or dismissed just because it wouldn't be considered to be above the conventional 'trauma threshold'⁷⁵. To date, there has been only one study focusing precisely on early childhood traumas in individuals with frequent nightmares. The authors⁷⁶ found that self-reported adversity was associated with nightmare severity, even when the adversity happened as early as 0-6 years of age.

To further investigate this proposed parallel between PTSD and frequent nightmares, we examined spectral power changes in NM participants with respect to low and high PTSD probability. These ancillary analysis indicated that the reduction of low frequency spectral power during the vulnerable pre-REM state is associated to the condition of having frequent nightmares. On the other hand, increased high frequency power during this state seems to be

attributed to high PTSD probability. In accordance with this notion we found a correlation between hyperarousal (reflected by gamma power) measured during these transitory pre-REM periods and PTSD-like symptoms (measured by PCL-5⁴²), which was only present in the group of NM participants.

Unfortunately, findings regarding sleep in NM participants are not completely unambiguous across studies^{26,30,31}. Such inconsistencies might be attributed to differences in nightmare severity, the presence of comorbid mental complaints, experimental pre-sleep manipulations, and relatively low sample size limiting the reliability of the reported findings^{26,30,31,71,77}.

We propose that we were able to reveal the EEG marker of hyperarousal (i.e. fast frequency power) by reporting stronger effects than the previous three studies due to our primary focus on sleep state transitions. Furthermore, analyzing our data in a bin-wise manner across all EEG channels provided a more detailed view of the topographical distribution of frequency-specific activity. Another considerable difference with regards to previous studies is the heterogeneity of our NM participants reporting lifelong trauma experiences and high PTSD probability. To the best of our knowledge, this is the first experiment investigating sleep spectral power characteristics in individuals with frequent nightmares that collected information about lifelong traumatic experiences and PTSD symptomatology. We suggest, that due to the intricate link between trauma and frequent nightmares⁷⁸ this heterogeneity is not unusual, but largely unexplored. Future studies focusing on individuals with frequent nightmares, should include scales assessing PTSD symptoms and early childhood adversity to further investigate the relationship between frequent nightmares and PTSD-like symptomatology.

Nevertheless, our findings regarding the NM subgroups are only tentative and should be considered with caution. Future studies focusing on the sleep-related correlates of frequent nightmares and PTSD probability could benefit from increasing the statistical power to better understand the influence of PTSD symptom severity on arousal-related activity. Moreover, studies using forced awakenings protocols may examine the relationship between frequency-specific activity and dream experiences in NM participants as a recent study showed that the combination of reduced low frequency and increased high-frequency EEG power is predictive of dream recall during NREM and REM sleep⁷⁹.

In sum, our findings revealed that reduced SWS and hyperarousal during NREM and pre-REM periods, relatively reduced low frequency and increased fast frequency activity across pre- to post- REM periods are key features of the sleep pathophysiology of NM participants. Whether these neurophysiological parameters constitute a trait-like characteristic enhanced by early lifetime adversity and whether they contribute directly to occurrence of nightmares is a question for future research. The parallel between our results and previous work with PTSD suggests a complex relationship between frequent nightmares, hyperarousal and traumatic experiences. Studying the pathophysiology of frequent idiopathic nightmares could contribute to the understanding of disrupted sleep in PTSD. Moreover, we encourage focusing on specific sleep transition periods (e.g. pre-REM periods) during which the cortex is prone to express arousals and wake-like activity, which provides a unique window to investigate disrupted sleep regulation.

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List of Abbreviations:

PTSD: post-traumatic stress disorder

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

REM: rapid eye movement sleep

NREM: non-rapid eye movement sleep

SWS: slow-wave sleep

EEG: electroencephalogram

CAP: cyclic alternating pattern

NM participants: participants with frequent nightmares

pre-REM: 10-min intervals of NREM sleep directly before the onset of each REM period

post-REM: 10-min long NREM epochs following the end of each REM period

DRF: dream recall frequency

PCL-5: PTSD Checklist for DSM-5

LEC-5: Life Event Checklist for DSM-5

STAI-T: Spielberger Trait Anxiety Inventory

BDI-9: Beck Depression Inventory

IAPS: International Affective Picture System

EMG: electromyography

EOG: electrooculography

ECG: electrocardiography

FFT: fast fourier transformation

FDR: false discovery rate

ANOVA: analyses of variance

MEQ: Morningness- Eveningness Questionnaire

SOL: sleep onset latency

TSD: trauma associated sleep disorder

Ethics Statement

The study protocol was approved by the United Ethical Review Committee for Research in Psychology, Hungary (EBKEB 2016/077), in line with the Declaration of Helsinki and written informed consents were obtained.

Disclosure Statement:

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Figure 1. Bin-wise differences in relative change from pre-REM to post-REM spectral power between nightmare and control participants.

Caption:

Relative change of spectral power from pre-REM to post-REM periods in nightmare (NM) vs. control (CTL) participants. The heatplot indicates the ratio of pre-REM/post-REM values across NMs/CTLs. Black contour indicates significant clusters of bootstrap tests after cluster-based correction for multiple comparisons.

Figure 2. Differences in absolute spectral power between NM participants and controls during pre-REM and post-REM sleep periods

Caption:

A) Absolute spectral power ratios (NM/CTL) in pre-REM periods for each frequency bin and every EEG channel. B) Absolute spectral power ratios (NM/CTL) in post-REM periods for each frequency bin and every EEG channel. Black contour indicates significant clusters of bootstrap tests after cluster-based correction for multiple comparisons.

Figure 3. Differences in absolute spectral power between NM participants and controls during NREM and REM sleep

Caption:

A) Heatplot represents absolute spectral power ratio (NM/CTL) in NREM sleep for each frequency bin and every EEG channel. B) Heatplot represents absolute spectral power ratio (NM/CTL) in REM sleep for each frequency bin and every EEG channel. Black contour indicates significant clusters of bootstrap tests after cluster-based correction for multiple comparisons.

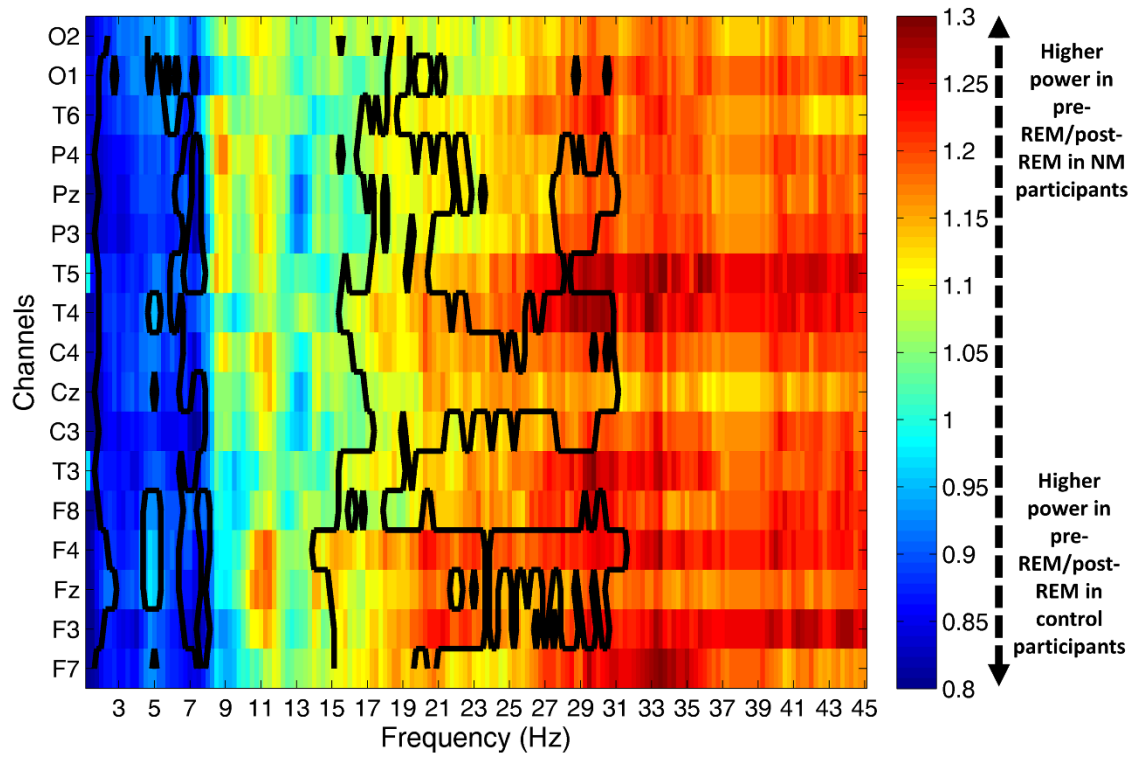
Title: Figure 4. Pre- and post-REM average gamma power correlations with PTSD-like symptoms within nightmare and control participants.

Caption:

Kendall's tau B correlation coefficients (τ) and corresponding p values between gamma spectral power and PCL-5 scores in nightmare (NM) and control (CTL) participants during pre- and post-REM periods.

Figure 1

Relative Change in Spectral Power from Pre-REM to Post-REM periods:
NM vs CTL



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Figure 2

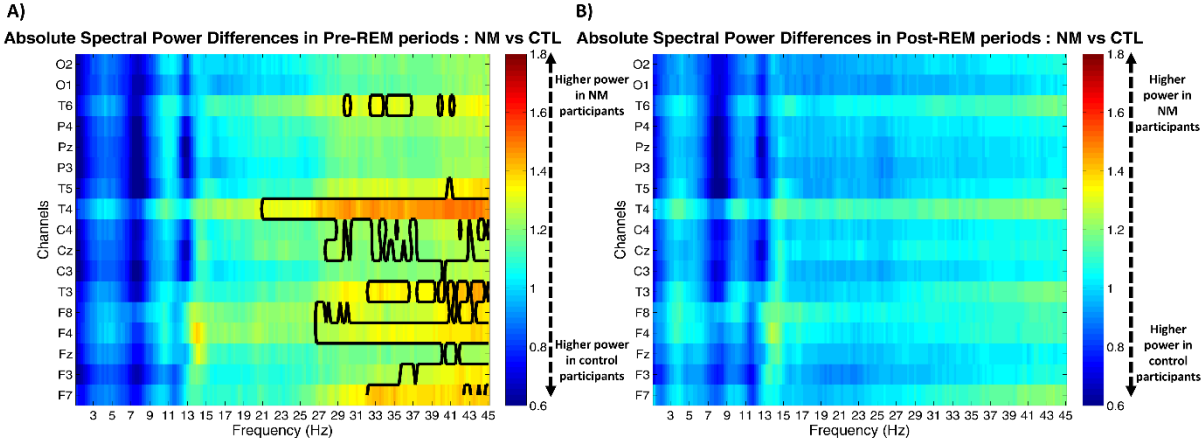


Figure 3

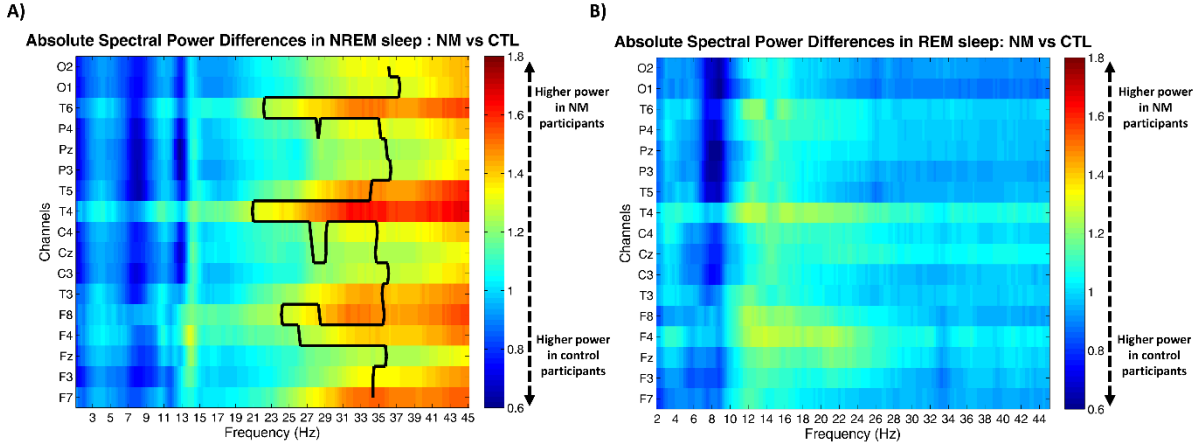
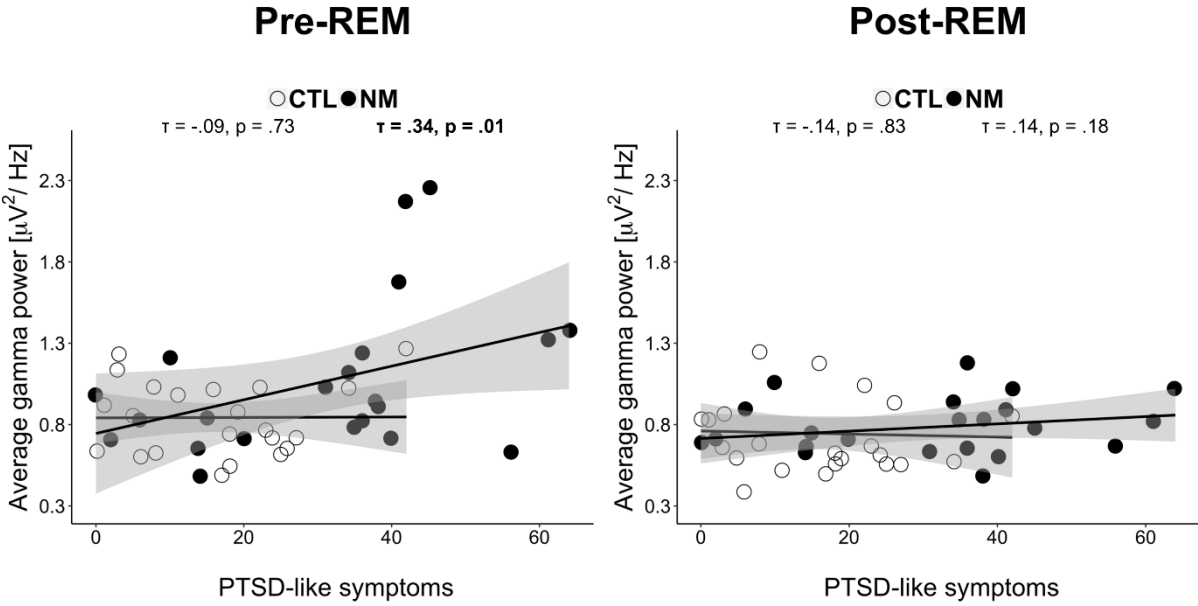


Figure 4



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Table 1. Age and gender of study participants

	NM		CTL	
	M	F	M	F
Gender				
N	8	14	6	16
Mean (Age)	22.25	23.29	22	21.63
Std. Deviation (Age)	1.488	3.795	1.095	2.062

NM = Nightmare participants; CTL = Control participants; M = Male; F = Female; N = Number of participants;

Table 2. Sleep architecture in nightmare and control participants

P-values corresponding to t-tests and Mann-Whitney U tests are corrected for multiple comparisons (Benjamini-Hochberg correction). NM = Nightmare participants; CTL = Control participants; WASO = Wake after sleep onset; NREM = Non-rapid eye movement; S1 = Stage 1; S2 = Stage 2; SWS = Slow-wave sleep; REM = Rapid-eye movement; * - significant after FDR correction, + significant before at $p < 0.05$, but not significant after FDR correction.

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	NM (N = 22)		CTL (N = 22)		Independent samples t-test / Mann – Whitney U test	
	Mean	SD	Mean	SD	t ₄₂ or U value	p value
Sleep duration (min)	439.318	38.195	440.167	41.847	-.07	.944
Sleep efficiency (%)	92.616	4.507	93.935	5.624	176	.344
Relative wake duration (%)	7.384	4.507	6.062	5.624	308	.344
WASO (min)	23.303	22.969	17.515	24.024	299	.351
Sleep latency (min)	12.333	13.186	11.379	10.134	220.5	.761
Relative NREM duration (%)	74.254	4.317	74.851	3.633	-.496	.761
Relative S1 duration (%)	3.881	3.428	2.175	1.623	323	.319+
Relative S2 duration (%)	48.592	4.825	46.797	4.111	1.328	.351
Relative SWS duration (%)	21.781	4.505	25.878	3.561	-3.347	.022*
NREM awakenings (#)	15.136	9.234	9.227	6.582	336.5	.054+
Relative REM duration (%)	25.746	4.317	25.15	3.633	.496	.761
REM latency (min)	101.031	46.004	94.985	37.516	259	.771
REM awakenings (#)	2.818	3.899	2.636	2.517	228	.744