



SHORT PAPER

Hyperarousal captured in increased number of arousal events during pre-REM periods in individuals with frequent nightmares

Borbála Blaskovich^{1,2}  | Vivien Reicher³ | Ferenc Gombos^{4,5} | Victor I. Spoormaker^{1,6} | Péter Simor^{7,8} 

¹Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

²Department of Cognitive Science, Budapest University of Technology and Economics, Budapest, Hungary

³Department of Ethology, Eötvös Loránd University, Budapest, Hungary

⁴Department of General Psychology, Pázmány Péter Catholic University, Budapest, Hungary

⁵MTA-PPKE Adolescent Development Research Group, Budapest, Hungary

⁶IUBH University of Applied Sciences, Erfurt, Germany

⁷Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

⁸Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary

Correspondence

Péter Simor, Institute of Psychology, ELTE Eötvös Loránd University, 1064 Budapest, Izabella utca 46 Budapest, Hungary.
Email: simor.peter@ppk.elte.hu

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Summary

The aim of this study was to investigate hyperarousal in individuals with frequent nightmares (NM participants) by calculating arousal events during nocturnal sleep. We hypothesized an increased number of arousals in NM participants compared with controls, especially during those periods where the probability of spontaneous arousal occurrence is already high, such as non-rapid eye movement to rapid eye movement transitions (pre-rapid eye movement periods). Twenty-two NM participants and 23 control participants spent two consecutive nights in our sleep laboratory, monitored by polysomnography. Arousal number and arousal length were calculated only for the second night, for 10 min before rapid eye movement (pre-rapid eye movement) and 10 min after rapid eye movement (post-rapid eye movement) periods, as well as non-rapid eye movement and rapid eye movement phases separately. Repeated-measures ANOVA model testing revealed significant Group (NM participants, controls) × Phase (pre-rapid eye movement, post-rapid eye movement) interaction in case of the number of arousals. Furthermore, post hoc analysis showed a significantly increased number of arousals during pre-rapid eye movement periods in NM participants, compared with controls, a difference that disappeared in post-rapid eye movement periods. We propose that focusing the analyses of arousals specifically on state transitory periods offers a unique perspective into the fragile balance between the sleep-promoting and arousal systems. This outlook revealed an increased number of arousals in NM participants, reflecting hyperarousal during pre-rapid eye movement periods.

KEYWORDS

arousal, arousal length, electroencephalogram, hyperarousal, nightmare, sleep

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1 | INTRODUCTION

Nightmares are highly unpleasant mental experiences that occur mainly – but not exclusively – during rapid eye movement (REM) sleep, and often provoke abrupt awakenings. The awakenings are followed by a quick orientation and vivid recall of the dream experience (Spoormaker, Schredl, & van den Bout, 2006). Frequent nightmares have a surprisingly high prevalence – approximately 2–5% – in the general population (Sandman et al., 2013), and a very high prevalence rate (above 30%) within psychiatric samples (Swart, van Schagen, Lancee, & van den Bout, 2013). Frequent nightmares are one of the core symptoms of post-traumatic stress disorder (PTSD), and are hypothesized to be the product of an imbalanced arousal system resulting in abnormal cortical hyperarousal during sleep (Germain, 2013).

In the context of sleep, arousals are periodically appearing, transient episodes of wakefulness or increased levels of vigilance that interrupt the continuity of sleep (Halász, Terzano, Parrino, & Bódizs, 2004). Frequent arousals are usually considered as signs of disrupted sleep related to a specific pathology such as periodic limb movement (PLM) or sleep-disordered breathing (Miglis, 2016). However, arousals also have a vital role of keeping sleep reversible, monitoring the surrounding environment and helping the organism to adapt to potential threats. Nevertheless, an imbalance between the arousal and sleep-promoting system can result in an increased number of arousals causing fragmented, impaired sleep continuity, even in the case of preserved sleep efficiency. Using electroencephalography (EEG) and sleep microstructural analysis, such deviations in cortical activation can be well detected (Halász et al., 2004), yielding scored arousals a robust marker for the arousal system.

To our knowledge, the literature on arousals in sleep of individuals with frequent nightmares is surprisingly scarce. A previous study focusing on the cyclically alternating pattern analyses reported reduced A1 and increased A2 and A3 subtypes in participants suffering with frequent nightmares (NM) compared with controls, indicating abnormal arousal processes (Simor, Bódizs, Horváth, & Ferri, 2013). However, other studies using the AASM scoring method (Berry et al., 2017) for calculating arousals during non-(N)REM and REM periods (Germain & Nielsen, 2003; Paul, Schredl, & Alpers, 2015) found no difference between individuals with frequent nightmares and control participants. On the other hand, a recent study that analysed the last 5 min of REM periods before awakening (in order to relate it to dream reports) did show a significantly higher amount of arousals in participants with frequent nightmares compared with healthy controls (Paul, Alpers, Reinhard, & Schredl, 2019).

Additionally, previous studies found several neurophysiological alterations in participants with frequent nightmares that provide indirect evidence for abnormal arousal processes in this sleep disorder. Such markers were reduced slow-wave sleep (SWS) and increased awakenings (Simor, Horváth, Gombos, Takács, & Bódizs, 2012), increased alpha power during NREM and REM sleep (Simor,

Horváth, Ujma, Gombos, & Bódizs, 2013), or impaired, reduced parasympathetic regulation of heart rate variability (Nielsen, Paquette, Solomonova, Lara-Carrasco, Colombo et al., 2010; Simor et al., 2014).

Here, we hypothesize that the sleep of individuals with frequent nightmares (NM participants) is characterized by a hyperactive arousal system, which manifests in an increased number of arousal events. On the basis of our previous work (Simor et al., 2014), we also hypothesize that the differences are best captured in periods of sleep where the probability of spontaneous arousals is already high. Because arousals occur most commonly during the ascending slope of sleep (from NREM to REM; Halász et al., 2004), we expect an increased number of arousals before – but not necessarily after – REM sleep.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were recruited at the Budapest University of Technology and Economics and the Eötvös Loránd University as well as through social media. Participants first completed an online screening questionnaire on sleeping and dreaming habits, including items about dream recall frequency, nightmare frequency (highly disturbing dream ending with abrupt awakening) and bad dream frequency (highly disturbing dream without immediate awakening), as well as standardized questionnaires and items regarding psychological well-being, alcohol and drug consumption, and prior or current psychiatric or neurological disease. Inclusion criteria were: (a) frequent dream recall in both groups (remember their dreams more than 2–3 times per month); (b) regarding nightmares either 2–3 nightmares per month (NM participants) or less than 2–3 nightmares per year (controls); (c) regarding bad dream frequency at least one bad dream per week (NM participants) or not more than 1 bad dream per month (controls); (d) no prior history of neurological, psychiatric or chronic somatic disorder; (e) moderate alcohol intake (not more than once per week); (f) no drug consumption or regular medication (except contraceptives). Potential subjects were invited to take part in an interview with a psychologist, in which they were questioned about recent traumatic experiences (in the last 5 years) as well as their nightmares to exclude individuals with recent adversities (0 excluded) and with trauma- or acute stress-related nightmares (4 excluded). In the current analysis, 22 NM participants ($M_{age} = 22.91$, $Std_{age} = 3.1$, 8 male) and 23 control participants ($M_{age} = 21.83$, $Std_{age} = 1.85$, 6 male) were included. Participation was rewarded by either partial course credits (for university students) or monetary compensation (approximately 45€ in Hungarian forints for participants outside of the university system). Written informed consents were obtained and 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.

2.2 | Procedure

Each participant spent two consecutive nights – monitored by polysomnography (PSG) – in our sleep laboratory. Arrivals and bed times were adjusted to the preferences of the participants (between 09:00 hours and 23:30 hours), whereas awakenings were scheduled after at least 7 hr of sleep, between 07:00 hours and 08:00 hours. The first night was used as a habituation night, and only data from the second night were analysed.

2.3 | Sleep macrostructure and arousal scoring

In this experiment, 17 scalp electrodes were used, referred to the mathematically linked mastoid electrodes, combined with bipolar electrooculography, electrocardiography and electromyography (EMG) placed on the chin. Sleep stages were scored manually by trained experts, according to the standardized criteria (Berry et al., 2017). Muscle- and technical-related artefacts were discarded based on visual inspection of 4-s segments of the recording. Arousals were scored according to standardized criteria (Berry et al., 2017). EEG spectral analyses and questionnaire-related data are described elsewhere (Blaskovich, Reichardt, Gombos, Spoomaker, & Simor, 2019). Arousal number and length were calculated throughout the entire second night sleep recording for REM and NREM periods, separately. Furthermore, to investigate arousal index and arousal length during the ascending and descending slopes of sleep, pre-REM (10-min-long NREM epochs directly before REM phase) and post-REM (10 min of NREM intervals directly after REM phase) periods were defined, and arousal number and length was calculated for these NREM periods as well.

2.4 | Statistical analysis

Statistical analyses were carried out with MATLAB (version 9.4.0.813654 [R2018a]; The MathWorks, Natick, MA, USA) and JASP (Version 0.9. 0.1, Team JASP, 2018, Amsterdam). Skewness

and kurtosis of data distribution, and the Shapiro–Wilk tests were used to assess the normality of each variable. Differences in arousal index and length across pre-REM and post-REM periods between the NM and control groups were examined by repeated-measures analyses of variance (rmANOVA) model. We tested a 2×2 model including Phase (pre-REM, post-REM) as a within-subject factor and Group (NM participants, controls) as a between-subject factor. Uncorrected degrees of freedom, p -values and partial eta-squared (η_p^2) as a measure of effect size are reported. Post hoc group differences between the NM and control participants were evaluated by Welch-test (in case of unequal variance) or Mann–Whitney U -test (if normal distribution was not fulfilled). Effect sizes are reported in Cohen's d or rank biserial correlation r values.

3 | RESULTS

We observed a significant effect of phase and a significant phase (pre-REM, post-REM) \times group (NM participants, controls) interaction for the number of arousals (Figure 1a; Table 1), but no overall effect of group. For arousal length, we only observed a significant effect of phase; the effect of group and the group \times phase interaction were not significant (Figure 1b; Table 1). As a control analysis, the same model was tested for the entire NREM and REM sleep periods as well – where arousal number was normalized by the NREM and REM duration, respectively – resulting in only significant main effect for phase.

To better understand the significant interaction, post hoc analyses were conducted. As Table 2 shows, NM participants had significantly higher arousal events during the pre-REM period – when compared with controls – a difference that was not present in the post-REM period. In sum, NM participants experienced a higher number of arousals during NREM to REM sleep-state transitions, but the duration of arousals was not different across the groups.

In response to a reviewer question, we examined to what extent this increased number of arousals was associated with the pattern of

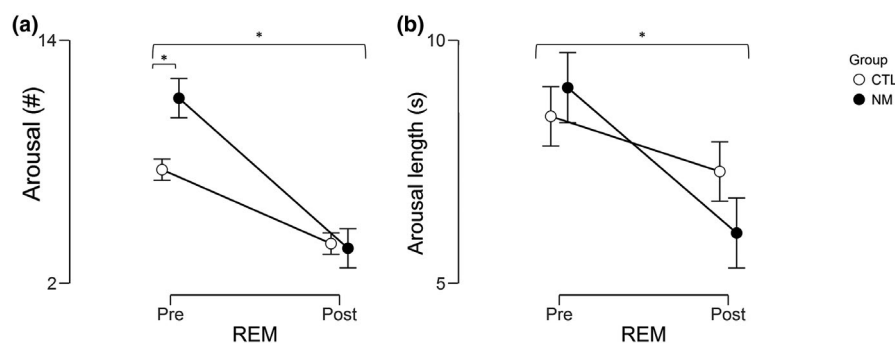


FIGURE 1 Difference in number of arousals and arousal length during pre- to post-rapid eye movement (REM) states between the nightmare (NM) and control (CTL) participants. (a) Mean arousal number in the NM and CTL participants 10 min before (Pre) and 10 min after (Post) REM periods. (b) Mean arousal length in NM and CTL participants during pre- and post-REM periods. Error bars represent standard error of the mean (SEM). Asterisks denote significant interaction and differences

	Group	Phase	Group × Phase
Arousal length	$F_{1,43} = 0.174$, $p = .679$, $\eta_p^2 = 0.004$	$F_{1,43} = 9.615$, $p = .003$, $\eta_p^2 = 0.183$	$F_{1,43} = 1.944$, $p = .17$, $\eta_p^2 = 0.043$
Arousal number	$F_{1,43} = 3.602$, $p = .064$, $\eta_p^2 = 0.077$	$F_{1,43} = 51.597$, $p < .001$, $\eta_p^2 = 0.545$	$F_{1,43} = 5.952$, $p = .019$, $\eta_p^2 = 0.122$

Note: The table shows the test statistics (F -values), p -values and partial eta-squared values of univariate ANOVAs.

TABLE 1 The effects of Group (NM participants, controls), Phase (pre-REM, post-REM), and Group × Phase interaction on arousal length and number of arousals

TABLE 2 Differences in number of arousals between the NM and control participants during pre-REM and post-REM periods

	NM (N = 22)		CTL (N = 23)		Welch t-test ($t_{26,28}$)/Mann – Whitney U-test		Effect size (Cohen's d /rank biserial correlation)
	Mean	SD	Mean	SD	t or U value	p-value	d or rb value
Pre-REM arousal (#)	11.136	6.549	7.609	2.388	2.38	.012*	0.716
Post-REM arousal (#)	3.727	2.676	3.957	2.402	241	.613	-0.047

Note: One-tailed tests with the assumption that the NM group is greater than the CTL group. p -values corresponding to Welch t-tests and Mann-Whitney U-tests.

Abbreviations: CTL, control participants; NM, nightmare participants; REM, rapid eye movement.

*Represents statistical significance.

reduced low-frequency activity and increased high-frequency EEG activity during the pre-REM phase that we have observed previously in this sample (Blaskovich et al., 2019). Neither beta ($\tau_{NM} = 0.115$, $p_{NM} = .461$; $\tau_{CTL} = -0.235$, $p_{CTL} = .133$) nor gamma ($\tau_{NM} = 0.089$, $p_{NM} = .571$; $\tau_{CTL} = -0.235$, $p_{CTL} = .133$) or delta ($\tau_{NM} = 0$, $p_{NM} = 1$; $\tau_{CTL} = -0.244$, $p_{CTL} = .119$) EEG power during these states correlated significantly with the number of arousals.

4 | DISCUSSION

In this study, we aimed to investigate whether individuals with frequent nightmares showed signs of a hyperactive arousal system during sleep, by looking at the number and length of arousal events occurring during nocturnal sleep, with a special focus on the most vulnerable transitory states. We found that NM participants experienced an elevated number of arousals specifically in pre-REM periods.

Arousals are considered to be one of the most robust indicators of cortical activation during sleep (Halász et al., 2004). In the course of the descending slope (post-REM) of the sleep cycle, the sleep-promoting system is highly activated. This activation inhibits the activation of the arousal system, resulting in few arousals in response to external or internal sensory stimuli (Halász, Bódizs, Parrino, & Terzano, 2014). In contrast, during the ascending slope of sleep (pre-REM), the tonic inhibition of the sleep-promoting system is reduced and the wake-promoting system becomes more active, resulting in an elevated number of arousals (Halász et al., 2014, 2004). As such, pre-REM periods offer a unique window into the fragile balance between the sleep-promoting and wake-promoting systems. We propose that the increased number of arousals during pre-REM periods

in the NM participants reflect the hyperactivity of the arousal system. This hyperarousal is probably not limited to these pre-REM periods, rather it is a continuously occurring phenomena in individuals with frequent nightmares, just like it has been hypothesized in individuals with primary insomnia (Riemann et al., 2010). Both frequent nightmares and insomnia were primarily diagnosed at the phenomenological level; however, recent studies applying EEG analyses during sleep indicate an imbalance between the sleep-promoting and arousal-promoting systems in both sleep disorders (Riemann et al., 2010; Simor & Blaskovich, 2019).

Previous studies focusing on the sleep architecture of individuals with frequent nightmares yielded somewhat inconsistent results. Some studies showed REM-specific (e.g. increased REM latency, more REM periods; Nielsen, Paquette, Solomonova, Lara-Carrasco, Popova et al., 2010), or NREM-specific abnormalities (e.g. reduced SWS; Simor et al., 2012), whereas others found no differences in objective sleep parameters between the NM and control groups (Paul et al., 2015). We propose that a more dynamic analysis of sleep state transitions might provide more reliable data compared with this traditional approach of averaging activity in NREM and REM periods separately. To the best of our knowledge, this is the first study investigating differences in arousal events during pre-REM and post-REM periods. So far there have been two other studies concentrating on pre- to post-REM cortical arousal changes as indicated by spectral power. These studies showed state-specific elevation in alpha activity (Simor et al., 2014), reduced SWS sleep during the whole night and reduced low-frequency activity accompanied by increased high-frequency activity during pre-REM compared with post-REM periods (in same sample: Blaskovich et al., 2019) in individuals with frequent nightmares. These changes in oscillatory activity are neither visible in the sleep EEG for the human eye nor should these be

considered equivalent to arousal events, as segments with arousals – due to muscle artefacts – are mainly excluded from the EEG for fine-grained spectral analyses. In comparison, the arousal number is the most conservative, well accepted and commonly used measure in sleep research and medicine, and its fundamentals are much better understood (Halász et al., 2004). It is thus a much more straightforward marker of arousal and, as a consequence, a robust validation of the previous indirect lines of evidence.

These findings support the notion of a hyperactive arousal system that can be detected by spectral power and microstructural analyses of sleep. Furthermore, these results suggest that focusing on the most vulnerable state transition periods will benefit our understanding of sleep and have potential relevance for clinical research, as nightmares have been reported to predict the development of PTSD in deployed military personnel (van Liempt, Van Zuiden, Westenberg, Super, & Vermetten, 2013). Because PLMs are highly prevalent in PTSD and have been related to hyperarousal during sleep (Spoormaker & Montgomery, 2008), the lack of tibial EMG and information about PLMs could be considered a limitation of this study. One study has shown increased PLM in idiopathic nightmare sufferers (Germain & Nielsen, 2003), although this has not been reported in other studies (Nielsen, Paquette, Solomonova, Lara-Carrasco, Colombo et al., 2010; Nielsen, Paquette, Solomonova, Lara-Carrasco, Popova et al., 2010; Paul et al., 2015; Simor et al., 2012). In our own work (Simor et al., 2012), we did not observe clinically significant PLMs in any of the NM subjects, which might be due to their comparatively young age similar to the age-range in the present study. However, to further investigate the role of increased arousal events in individuals with frequent nightmares, future studies should also include measurements regarding PLM and sleep apnea in order to gain more information about their prevalence in idiopathic nightmare disorder as well as their putative influence on arousals.

In summary, in consonance with our results, a growing number of studies support the hypothesis that individuals with frequent nightmares exhibit trait-like hyperarousal during sleep (for a short review, see Simor & Blaskovich, 2019). For future studies investigating hyperarousal during sleep, we would highly recommend “zooming in” on the data, by focusing the attention of the analysis on state transitions and on vulnerable periods that may provoke arousals. Adopting this view could be especially important in sleep disorders (such as frequent nightmares), which do not have such robust and well-defined sleep macro- and microstructural characteristics as with other highly investigated sleep disorders (e.g. narcolepsy, obstructive sleep apnea).

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CONFLICT OF INTEREST

The authors do not report any conflict of interest.

AUTHOR CONTRIBUTIONS

B.B. contributed to conceptualize the design of the study, contributed to data collection, data analyses and wrote the first version of the manuscript. V.R. and F.G. contributed to data analyses. V.I.S. and P.S. contributed to conceptualize the design of the study and supervised data analyses. B.B., V.R., F.G., V.I.S. and P.S. contributed to the writing of the manuscript.

ORCID

Borbála Blaskovich  <https://orcid.org/0000-0003-1951-2420>

Péter Simor  <https://orcid.org/0000-0003-0695-166X>

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