NeuroImage: Clinical 33 (2022) 102933

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The heartbeat evoked potential is a questionable biomarker in nightmare disorder: A replication study

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ARTICLE INFO

Keywords:
Nightmare
Heartbeat evoked potential
Sleep
REM
Replication

ABSTRACT

Frequent nightmares are highly prevalent and constitute a risk factor for a wide range of psychopathological conditions. Despite its prevalence and clinical relevance however, the pathophysiological mechanisms of nightmares are poorly understood. A recent study (Perogamvros et, al 2019) examined the heart beat evoked potential (HEP) in a small group of nightmare sufferers (N = 11) and matched healthy controls (N = 11) and observed markedly different (Hedges' g = 1.42 [0.62–2.22]) HEP response across the groups during Rapid Eye Movement (REM) sleep. Moreover, the HEP correlated with depression scores in the nightmare group only. The authors concluded that the HEP in REM sleep could be used as a trait-like biomarker reflecting pathological emotional-and sleep regulation in nightmare disorder. To replicate the above study, we performed the same analyses of HEPs in two separate, and larger databases comprising the polysomnographic recordings of nightmare sufferers and matched controls ($N_{Study\ 1} = 39$; $N_{Study\ 2} = 41$). In contrast to the original findings, we did not observe significant differences in HEP across the two groups in either of the two databases. Moreover, we found no associations between depression scores and HEP amplitudes in the relevant spatiotemporal cluster. Our data cast doubts on the utility of HEP as a biomarker in the diagnostic and treatment procedures of nightmare disorder and suggests that the interpretation of HEP as a marker of impaired arousal and emotional processing during REM sleep is premature and requires further validation.

1. Introduction

Frequent nightmares, the weekly (or more frequent) experience of intense and emotionally distressing dreams, is a prevalent sleep complaint affecting about 5 % of the adult population (Nielsen and Carr, 2017; Sandman et al., 2013). Frequent nightmares are associated with a wide range of psychopathological conditions (Gieselmann et al., 2019; Rek et al., 2017; Swart et al., 2013), often precede the onset of mental complaints (Li et al., 2016; Liempt et al., 2013; Soffer-Dudek, 2016), and their targeted treatment can also ameliorate daytime symptoms (Seeman, 2018; Sheaves et al., 2019; Yücel et al., 2020). In spite of their clinical relevance however, nightmares are rarely assessed in clinical settings (Schredl, 2010), and are usually considered as epiphenomenal symptoms of an underlying mental disorder (Spoormaker and Montgomery, 2008). In addition, the severity of nightmare complaints and the success of therapy is exclusively evaluated on the basis of subjective reports limiting our understanding of the pathophysiology of nightmare disorder, as well as the development of new therapeutic approaches.

Frequent nightmares are also associated with poor sleep quality (Li et al., 2010; Sandman et al., 2015; Schredl, 2009). Accordingly, a growing number of studies indicate that nightmare sufferers compared to matched controls exhibit altered sleep physiology, such as increased microarousals (Blaskovich et al., 2019; Simor et al., 2013a), altered sleep spindle activity (Picard-Deland et al., 2018), and increased high-frequency power in non-rapid-eye-movement (NREM) sleep (Blaskovich et al., 2020; Marquis et al., 2017), abnormal motor activity (Germain and Nielsen, 2003), and indices of impaired parasympathetic

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https://doi.org/10.1016/j.nicl.2021.102933
Received 23 August 2021; Received in revised form 12 December 2021; Accepted 30 December 2021
Available online 31 December 2021

regulation during different sleep stages (Nielsen et al., 2010; Simor et al., 2014). Interestingly, these alterations were observed regardless of the occurrence of nightmares, suggesting that altered physiological activity during sleep might be an integral part of nightmare disorder, albeit the specificity of these markers as well as their contribution to unpleasant dream experiences is still unclear (Simor and Blaskovich, 2019)

In a recent study, Perogamvros and colleagues (2019) examined the heartbeat-evoked potential (HEP) in a group of nightmare sufferers and healthy controls, and observed different HEP in the nightmare group, specifically during the REM stage. The authors concluded that their findings corroborate the "notion that nightmares are essentially a REM pathology and suggest that increased emotional arousal during REM sleep, as measured by HEP, is a physiological condition responsible for frequent nightmares" (Perogamvros et al., 2019, p.1).

The HEP is an evoked electroencephalographic (EEG) potential that is time-locked to the R-peak of the heartbeat(although in some studies the T-peak was used for ECG-EEG synchronisation), and is considered to be a marker of interoception reflecting the cortical processing of afferent cardiac signals (Park and Blanke, 2019). The timing of individual heartbeats are transmitted the cortex mainly through vagal afferents (Salamone et al., 2020), although somatosensory neural pathways may also contribute to neurovisceral processing (Park and Blanke, 2019). A growing number of studies indicate that the HEP is modulated by arousal (Coll et al., 2021; Luft and Bhattacharya, 2015; Wei et al., 2016), self-relevant emotional processing (Coll et al., 2021; Couto et al., 2015; MacKinnon et al., 2013; Marshall et al., 2018), and is altered in pathological conditions of emotional dysregulation (Pang et al., 2019; Schmitz et al., 2020).

Emotional dysregulation and increased sensitivity to sensory experiences (including interoception) was assumed to contribute to emotional arousal in nightmare sufferers (Carr and Nielsen, 2017; Levin and Nielsen, 2007), particularly during the emotionally more intense state of REM sleep (Perogamvros and Schwartz, 2012). Since the HEP can also be observed during sleep (Immanuel et al., 2014; Lechinger et al., 2015) it was expected to emerge as a reliable biological marker of pathological sleep-and emotional regulation in nightmare disorder (Perogamvros et al., 2019). In line with this hypothesis, the amplitude of the HEP clearly differentiated a group of nightmare sufferers and matched healthy controls: in a time window extending from 449 to 504 ms after the ECG R-peak, the HEP response of the control group showed a negative peak over right frontal electrodes, while no deviation from the baseline was observed in the group of nightmare sufferers. Nevertheless, the study included a small sample (11 patients and 11 controls), and the effect size (Hedges' $g = 1.42$ [0.62–2.22]) of the REM-specific difference in HEP largely exceeded the effects observed in other clinical samples (Coll et al., 2021). Since small samples are susceptible to inflated effect sizes, it is crucial to verify the replicability of this finding (Button et al., 2013). In addition, In addition, the HEP amplitudes differentiating the nightmare from the control group showed a strong ($\tau = -0.5$, $p = 0.03$) correlation with depressive symptom scores within the nightmare group only; however, higher scores were linked to more negative HEP values, producing a counterintuitive pattern: patients with more severe depressive symptoms showed HEPs that resembled the HEPs of control participants.

In order to replicate the above study, we performed the same analyses of HEPs in two separate, and larger databases comprising the polysomnographic recordings of nightmare sufferers and matched controls ($N_{Study\ 1} = 39$; $N_{Study\ 2} = 41$).

2. Methods

2.1. Participants

We present a novel analyses of a database that was collected by our laboratory in the previous years and was reported in past publications (Blaskovich et al., 2020; Simor et al., 2014). One participant from Study 1 and three participants from Study 2 were excluded due to noise in the ECG signal. The final database included the polysomnographic data of 80 participants in total: 19 nightmare sufferers (NMs) and 20 healthy controls (CTLs) in Study 1, and 21 NMs and 20 CTLs in Study 2. Eligible participants were selected from the respondents of a large-scale online survey including questionnaire-based data on sleep habits, affect, and personality (more details on the included questionnaires were reported previously: (Blaskovich et al., 2020; Simor et al., 2013b)). NMs and CTLs were selected based on their responses to questionnaires on nightmare and bad dream frequency, and were invited to a personal interview before the sleep laboratory assessments. Participants enrolled in the nightmare group reported at least one nightmare or bad dream per week, whereas control participants reported less than two or three nightmares per year. Those participants who reported the onset of negative dream experiences in relation to a traumatic event or indicated that the content of their dreams were related to a prior trauma were excluded from the study. To control for comorbidity, participants showing clinically relevant signs of depression or anxiety in the screening questionnaires according to Hungarian norms (Rózsa et al., 2001; Sipos et al., 1994) were included in the study. In Study 2 (but not in Study 1) NM participants and controls were matched for dream recall frequency. Participants reported no prior or current psychiatric, neurological or chronic somatic disorders, did not regularly take medications, and none of them reported higher than moderate (1 or less drink/week) alcohol consumption. Selected participants were invited to spend two nights monitored by polysomnography in the sleep laboratory of the Semmelweis University and of the Budapest University of Technology and Economics, in Study 1 and Study 2, respectively. In Study 2, participants were shown a set of negative and neutral IAPS (Lang et al., 1997) pictures before they went to bed on the second night. Participants were asked to provide subjective evaluations (valence and arousal), while physiological data (skin conductance response and heart rate) were collected during the presentation of the images. The procedure and the results of these measurements will be reported elsewhere (Tomacsek et al. in preparation). Sample characteristics are detailed in Table 1. The protocols of the studies were approved by local Ethical Review Committees for Research in Psychology, in line with the Declaration of Helsinki and written informed consents were obtained.

2.2. Polysomnography

In Study 1, participants were fitted with gold-coated (Ag/AgCl) scalp EEG electrodes fixed with EC2 Grass Electrode Cream (Grass Technologies, Warwick, Rhode Island, USA). Nineteen scalp derivations (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2 referenced to the mathematically linked mastoids) were placed according to the standard 10–20 system (Jasper, 1958). In addition, bipolar polygraphic signals were recorded as follows: EOG with electrodes placed above and below the left and the right canthi, respectively, submental EMG and bipolar ECG with electrodes placed on the left and the right chest. Impedances were kept below 8 kΩ. Signals were collected, prefiltered (0.33–1500 Hz), amplified, and digitized with 4096 Hz/channel sampling rate (synchronous) with 12-bit resolution by using the 32-channel EEG/polysystem (Brain-Quick BQ 132S; Micromed, Mogliano Veneto, Italy). A further 40 dB/decade anti-aliasing digital filter was performed by firmware, which low pass filtered the data at 450 Hz and downsampled it at 1024 Hz. In Study 2, we followed the same recording protocol, but we used only seventeen scalp EEG locations (frontopolar electrodes were not used), and signals were recorded with Micromed SD LTM 32 Bs (Micromed S.p.A., Mogliano Veneto, Italy) and SystemPLUS 1.02.1098 software (Micromed Srl, Roma, Italy). Signals were high-pass filtered at 0.15 Hz and low-pass filtered at 250 Hz by 40 dB/decade anti-aliasing hardware input filters. Data were collected with 22 bit resolution and with an analogue to digital conversion rate of 4096 Hz/channel (synchronous). The firmware applied a further 40 dB/decade anti-aliasing digital filter

Table 1
Sample characteristics of Study 1 and Study 2.

	Sample size (Num. of females)	AGE (mean ± SD)	BDI (mean ± SD)	NMF (mean ± SD)	BDF (mean ± SD)
STUDY1 NIGHTMARE	N = 19 (F = 10)	20.95 ± 1.58	15.2 ± 3.9	5.0 ± 1.3	4.6 ± 1.6
STUDY1 CONTROL	N = 20 (F = 10)	21.6 ± 1.5	10.7 ± 1.5	0.5 ± 0.6	0.6 ± 0.8
STUDY2 NIGHTMARE	N = 21 (F = 14)	23 ± 3.3	6.6 ± 6.1	6.2 ± 1.1	6.7 ± 0.8
STUDY 2 CONTROL	N = 20 (F = 15)	21.4 ± 1.5	3.6 ± 2.5	2.1 ± 1.0	2.4 ± 1.2

BDI - Beck Depression Inventory, NMF - Nightmare Frequency and BDF - Bad Dream Frequency.

which low-pass filtered the data at 463.3 Hz. The digitized and filtered EEG was subsequently undersampled at 512 Hz. Sleep was scored according to the AASM Manual for the Scoring of Sleep and Associated Events (Berry et al., 2012) by a trained scorer blind to the group membership of the participants

2.3. Assessment of negative affect

Comparably to Perogamvros and colleagues (2019) we assessed the Hungarian version of the Beck Depression Inventory (BDI, (Rózsa et al., 2001) to estimate negative affect in our participants and to correlate BDI scores with the specific cluster of HEP amplitudes obtained from REM sleep periods.

2.4. HEP analyses

We performed the same steps of the HEP analysis pipeline reported by Perogamvros and colleagues (2019) using the Fieldtrip toolbox (Oostenveld et al., 2011). In brief, continuous EEG and ECG signals were band-pass filtered between 1 and 40 Hz, and downsampled to 256 Hz, and re-referenced to a common average before the processing of independent component analysis (ICA). (Downsampling to 256 Hz was only used for the ICA similarly to the pipeline of the original study). Independent components reflecting eye movements were detected semi-automatically and were identified by visually inspecting their waveforms and topographical distribution (Delorme and Makeig, 2004). Vigilance states identified as at least five minutes spent in WAKE, NREM, or REM were selected and concatenated in order to detect the R-peaks, separately for each state. The HEPLAB toolbox (Perakakis, 2019) was used for the semi-automatic detection of the R-peaks of the ECG signal within the previously selected and concatenated vigilance states. R-peaks detected within a period including the border of two concatenated segments were discarded and were not used for the selection of HEP epochs. The EEG and the ECG signals were segmented to epochs of 1000 ms, extending between –300 ms and + 700 ms time-locked to the R peaks, yielding to an average number of 471 (±646) and 158 (±208) WAKE, 15,320 (±2391) and 15,416 (±3446) NREM, and 6893 (±1627) and 5696 (±1721) REM trials in Study 1, and 566 (±653) and 657 (±982) WAKE, 18,104 (±3138) and 16,632 (±3505) NREM, and 6651 (±1813) and 5517 (±1663) REM trials in Study 2, for the NMs and CTLs, respectively. In order to control for the confounding effects of ECG artifacts on HEP waveforms, we examined the differences in ECG amplitudes between −300 ms and + 700 ms aligned to the R-peaks, and similarly to the original study we did not apply ICA to attenuate the cardiac artifact. The average interbeat intervals and heart rate variability (the standard deviation of normal-to-normal interbeat intervals) were also assessed separately for each vigilance state, using the same procedure described by the original study. Given that several participants spent very low amount of time in wakefulness (<5 min) during the recording night leading to smaller sample sizes in both studies, in the case of wakefulness we pooled together the available data of Study 1 and Study 2 and contrasted the HEP in the wake condition across NMs (N = 29) and CTLs (N = 23) in this aggregated dataset.

2.5. Statistical analyses

Group differences in HEPs were examined by cluster-based permutation t-tests (Maris and Oostenveld, 2007) using the Fieldtrip toolbox (Oostenveld et al., 2011). In brief, two-tailed paired sample *t*-tests were performed for all pairs of data points in time and space. Due to the differences in sampling rate between the studies (1024 vs. 512 Hz), the time ranges considered by the original study (extending between 200 and 600 ms after the R-peaks) consisted of steps of approximately 1 and 2 ms, in Study 1 and Study 2, respectively. Clusters were defined if adjacent time points or electrode locations (at least two neighboring electrodes) showed significant differences at a two-tailed α level below 0.05. These observed clusters were selected to compute the observed cluster statistic defined by the sum of all the *t*-values that formed a given cluster. In order to control for Type 1 error, the same process was repeated 1,000 times on randomly formed samples (by randomly shuffling the values of the grouping variable (NMs vs CTLs) using Monte-Carlo simulations). These simulations served to create 1000 clusters under the null hypothesis (no significant differences across the compared groups). From these simulations the largest clusters were extracted in order to create the distribution of the maximal clusters produced simply by chance. Finally, the observed cluster statistics were tested (with an alpha value of 0.05) against the probability distribution of the largest simulated clusters. The same procedure was applied for the averaged HEP trials in WAKE, NREM, and REM sleep. Moreover, to focus on the cluster that differentiated NMs from CTLs in the original study (449–504 ms), we compared the averaged HEP amplitudes within the specific cluster across the NM and CTL groups, and examined if ECG amplitudes over the specific time range could be confounded with the HEPs. ECG amplitudes over the specific time range were first statistically compared by t-tests, and then used as covariates in ANCOVA models testing HEP differences across NMs and CTLs within the specific cluster. Within-group associations between HEP in the frontal sites and BDI scores were also assessed by Kendall τ correlation coefficients. Statistical analyses were performed in Matlab (version 8.3.0.532, R2014a, The MathWorks, Inc., Natick, MA) and in Jasp (Team, 2018).

3. Results

3.1. Sleep architecture

The proportion of sleep stages and conventional measures of sleep architecture of the NM and CTL groups are presented in Table 2 for Study 1 and Study 2, respectively. As reported in previous analyses of partially overlapping databases (Blaskovich et al., 2020; Simor et al., 2012), in Study 1 NMs showed slightly lower sleep efficiency and spent more time in REM sleep than CTLs, whereas in Study 2, only the proportion of slow wave sleep differed significantly, showing lower amounts in NMs versus CTLs.

3.2. HEP during REM in nightmare and control participants: Study 1

Following the procedure of the original study, first we compared the HEP in REM sleep across NMs and CTLs in both databases, separately. In Study 1, no significant differences emerged in HEP during REM sleep within the 200–600 ms time window (Fig. 1/**A**). Since the authors of the

Table 2
Sleep architecture in Nightmare sufferers (NMs) and control participants (CTLs). Sleep efficiency reflects the ratio spent asleep respective to the time spent in bed. The proportion of Stage 1, Stage 2, SWS, and REM is given in relation to the total time spent asleep (Total sleep time). SWS – Slow wave sleep, REM – Rapid Eye Movement sleep. + - Mann-Whitney *U* test. (The Mann-Whitney *U* test was used if the assumption of normal distribution was not met).

	Study 1 NMsMean (SD)	CTLsMean (SD)	Mann-Whitney *U* test (p value)	Study 2 NMsMean (SD)	CTLsMean (SD)	Test statisticT–test (p value)
Total time in bed (min)	515.3 (26.2)	498.8 (34.1)	137 (0.08)	474.7 (43.2)	468.48 (40.1)	0.47 (0.6)
Total sleep time (min)	465.0 (45.4)	472.7 (36.8)	209 (0.8)	439.9 (39.0)	438.9 (41.8)	0.08 (0.9)
Sleep Efficiency (%)	90.3 (8.3)	94.8 (4.9)	284 (0.02)	92.8 (4.5)	93.8 (5.9)	0.6 (0.5)
Sleep latency (min)	16.8 (23.5)	7.7 (7.2)	147 (0.15)	12.5 (13.5)	11.9 (10.5)	0.2 (0.8)
REM latency (min)	87.5 (37.3)	89.9 (41.7)	191 (0.8)	101.2 (47.1)	94.8 (37.9)	0.47 (0.6)
Stage 1 (%)	3.9 (2.9)	2.6 (1.6)	142 (0.12)	3.9 (3.5)	2.2 (1.7)	144 (0.08) +
Stage 2 (%)	51.8 (4.7)	54.3 (6.0)	240 (0.28)	48.8 (4.9)	46.9 (4.2)	1.3 (0.19)
SWS (%)	15.9 (4.5)	18.3 (4.6)	255 (0.13)	21.5 (4.3)	24.8 (3.6)	−3.7 (0.0006)
REM (%)	28.3 (4.4)	25.0 (4.6)	110 (0.01)	25.9 (4.4)	24.8 (3.6)	0.85 (0.4)

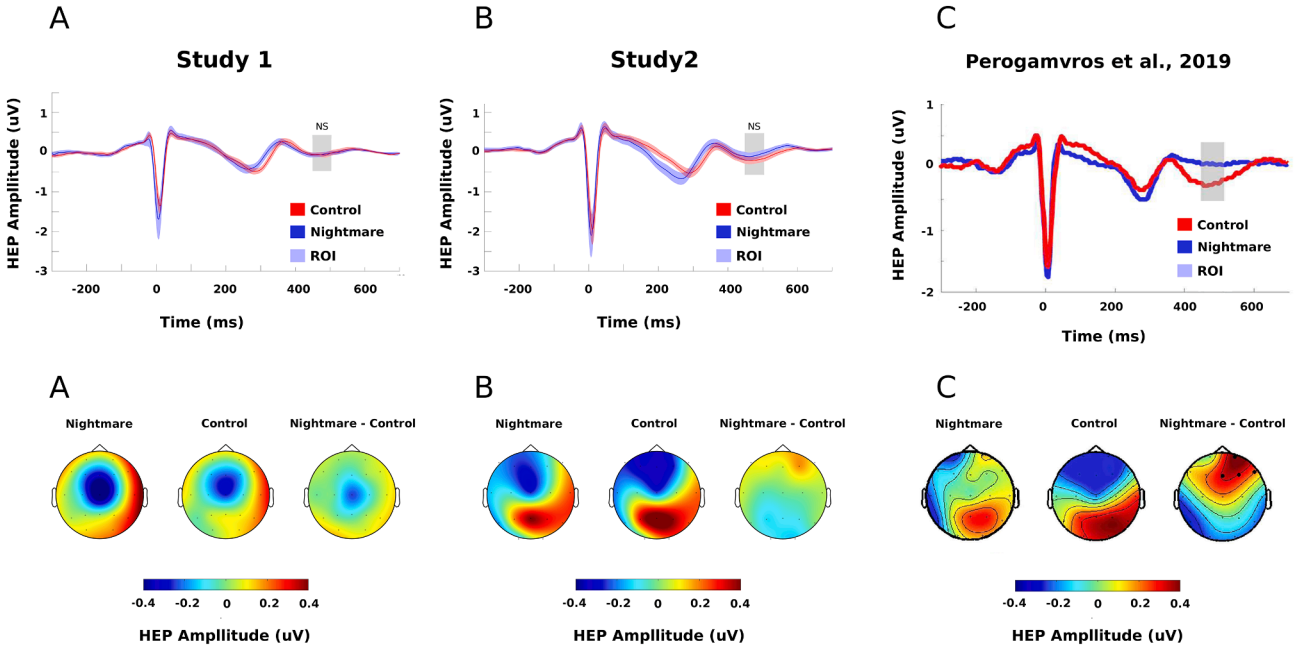

Fig. 1. Heartbeat evoked potential (HEP) in REM sleep in the nightmare and control group. In contrast to the original study, no significant differences between the two groups (nightmare sufferers and control group) were observed in Study 1 (A), and Study 2 (B). In order to compare our findings with the original study (upper panel), the HEP amplitudes of right frontolateral electrodes comprising the observed cluster in the original study are visualized. The lower panel indicates the topographical distribution of HEP between 449 and 504 ms, the time range of interest (ROI) showing significant differences in the original study.

original study observed a significant difference (cluster level $p = 0.032$) over 449 and 504 ms, we performed an additional HEP analysis limited to that time range. No significant differences emerged within this time range after cluster-based correction of multiple comparisons either. To examine whether group differences on a nominal level resembled or not the pattern observed in the original study, we ran an additional statistical comparison (between 449 and 504 ms) without correction for multiple comparisons. Nominally significant differences (uncorrected $p < 0.05$) were observed at Cz, T4, and O2 electrodes in a narrow time range between 449 and 487 ms; however, we observed more positive values in CTLs, compared to NMS, whereas the opposite pattern was observed in the original study (Fig. 1/**C**).

3.3. HEP during REM in nightmare and control participants: Study 2

The comparison of HEP during REM sleep did not yield significant differences across NMs and CTLs in Study 2 (Fig. 1/**B**). Comparably to the findings of Study 1, no significant differences in HEP emerged either when we restricted our analyses to the time range (449 – 504 ms) reported in the original study. HEP differences between NMs and CTLs were not significant on a nominal level with respect to the uncorrected statistical threshold ($p < 0.05$). In sum, the original finding indicating different HEP during REM sleep across NMs and CTLs did not replicate in our databases of Study 1 and Study 2 (see Fig. 1).

3.4. HEP analyses in NREM and WAKE

In line with the analyses of the original study, we examined whether the HEP differed across NMs and CTLs during NREM sleep. First, we contrasted the NREM HEP amplitudes of the two groups between 200 and 600 ms using cluster-based permutation statistics. In study 1, no significant differences were observed between the two groups between 200 and 600 ms. Focusing on the cluster observed in the original study, we examined the averaged HEP amplitudes between 449 and 504 ms over frontal (Fp1, Fp2, F7, F8, F3, F4, Fz), central (C3, C4, Cz, T3, T4), and parietal electrodes (T5, T6, P3, P4, Pz, O1, O2). The mean HEP amplitude was not significantly different over the frontal and parietal electrodes (frontal: $t(37) = 0.19$, $p = -0.84$, Cohen's $d = 0.06$; parietal: $t(37) = 1.37$, $p = 0.18$, Cohen's $d = 0.44$), but CTLs showed significantly greater average HEP amplitudes over the central electrodes $t(37) = -2.9$, $p = 0.006$, Cohen's $d = -0.93$). To examine whether this difference was related to ECG activity, we contrasted the averaged ECG amplitudes over

this specific time range across the two groups. The averaged ECG amplitudes between 449 and 504 ms were also significantly different across NMs and CTLs (t(37)= − 2.09, p = 0.04, Cohen's d = − 0.66) indicating that HEP amplitudes might be confounded by cardiac activity and related artifacts.

In study 2, NMs and CTLs did not show significantly different NREM HEP amplitudes in time (between 200 and 600 ms) and space (over 17 electrodes). No significant differences emerged either when we compared the HEP amplitudes over the time range of interest (449–504 ms) in frontal (F7, F8, F3, F4, Fz), central (C3, C4, Cz, T3, T4), and parietal (T5, T6, P3, P4, Pz, O1, O2) electrode sites (frontal: (t(39)= − 1.46, p = 0.15, Cohen's d = − 0.45; central: (t(39)= − 0.66, p = 0.51, Cohen's d = − 0.20; parietal: t(39) = 1.6, p = 0.11, Cohen's d = 0.50). Contrary to Study 1, the averaged ECG amplitude between 449 and 504 ms was not significantly different between the two groups (t(39) = -0.22, p = 0.82, Cohen's d = − 0.06).

No significant differences emerged in HEP during wakefulness across NMs and CTLs in the pooled dataset containing the HEP trials of 29 NMs and 23 CTLs.

3.5. Cardiac activity in REM sleep: Potential confounders

In addition, we examined three parameters extracted from REM sleep: the a) mean ECG amplitudes at 449–504 ms after the R-peak, b) inter-beat intervals, and c) heart rate variability using the standard deviation of normal-to-normal interbeat intervals (SDNN). In study 1 (see Fig. 2/**A**), the mean ECG amplitudes were different across NMs and CTLs, showing higher amplitudes in CTLs (NMs: 15.45 ± 21.11, CTLs: 28.62 ± 18.67, t(37) = -2.16, p = 0.037, Cohen's d = − 0.69). Interbeat intervals (t(37) = − 1.01, p = 0.32, Cohen's d = − 0.32), and the SDNN (t(37) = − 1.11, p = 0.27, Cohen's d = − 0.35) value did not yield significant differences across the groups. In study 2 (Fig. 2/**B**), ECG amplitudes did not (t(39) = − 0.73, p = 0.46, Cohen's d = − 0.23), but interbeat intervals and heart rate variability did exhibit significant differences across the two groups (t(39) = − 3.71, p = 0.0006, Cohen's d = − 1.15; t(39)= − 2.05, p = 0.04, Cohen's d = − 0.64, respectively).

Given that compared to the original study (Fig. 2/**C**) we observed group differences in some of the cardiac measures reflecting differences in ECG activity across the groups (Fig. 3), we aimed to verify if these parameters might have masked group differences in HEP during REM sleep. Therefore, we performed ANCOVA models with the averaged HEP amplitude of the spatiotemporal cluster observed by the original study (449 – 504 ms over right frontal electrodes) as the outcome variable, group as the predictor, and ECG amplitudes, interbeat intervals, and heart rate variability as separate covariates in three successive models. As shown in Table 3, with the inclusion of the cardiac parameters as covariates in the models the main effect of Group on HEP amplitudes was not significant, indicating that differences in cardiac activity did not suppress group differences in HEP amplitudes.

3.6. Associations between depression scores and HEP amplitude in the frontal cluster

Pearsons's r correlation coefficients (and Kendall Tau B values if the assumption of normality was not met) were extracted between HEPs in the original cluster and BDI scores within the NM and CTL groups. In contrast to the original finding that reported a significant negative correlation between HEP and depression scores within the NM group only, we found no significant associations in Study 1 (NMs: Pearson's r = -0.25, p = 0.29; CTLs: r = − 0.38, p = 0.09) and Study 2 (NMs: Kendall's Tau B = -0.04, p = 0.79; CTLs: r = 0.26, p = 0.11).

4. Discussion

Our aim was to replicate the findings of Perogamvros and colleagues (Perogamvros et al., 2019) who observed significantly different HEP amplitudes in a group of NMs versus CTLs, specifically during REM sleep. According to the interpretation of the authors, larger HEP in REM sleep may reflect increased interoception related to enhanced emotional arousal and sensory processing that characterizes the REM state of idiopathic nightmare sufferers. In addition, the authors proposed that the HEP in REM sleep could be used as a trait-like biomarker reflecting pathological emotional-and sleep regulation in nightmare disorder (Perogamvros et al., 2019). The present study however, analyzing two separate and relatively larger databases of NMs and CTLs, did not replicate the original findings.

Nightmares by definition occur during sleep and interfere with sleep maintenance due to abrupt awakenings and hyperarousal. Accordingly, having frequent nightmares were associated with alterations in different sleep-specific physiological parameters such as microarousals (Simor et al., 2013a), changes in spectral power (Marquis et al., 2017; Blaskovich et al., 2020), or sleep spindles (Picard-Deland et al., 2018). Nevertheless, the diagnosis and treatment of frequent nightmares is still based on self-reports, as the specificity and robustness of these pathophysiological indices is not yet confirmed. Whereas the subjective aspects of frequent nightmares are undoubtedly relevant, uncovering core components of the pathophysiology of the disorder would contribute to improve diagnostic procedures and objective evaluations of clinical outcomes. Hence, the field is ripe for robust and reliable biomarkers that could index the severity of impaired emotional processing and disrupted sleep regulation in patients suffering from frequent nightmares.

The use of the HEP as a potential biomarker of intensified emotional and sensory processing during (REM) sleep is particularly appealing since the cortical response time-locked to the heartbeats was shown to be modulated by enhanced processing of bodily signals (interoception), arousal, and clinical conditions involving emotional dysregulation (Coll et al., 2021; Park and Blanke, 2019; Perogamvros et al., 2019). Moreover, the assessment of HEP is relatively easy and requires only routine assessment of EEG and ECG that applied during nocturnal sleep provides a large number of trials.

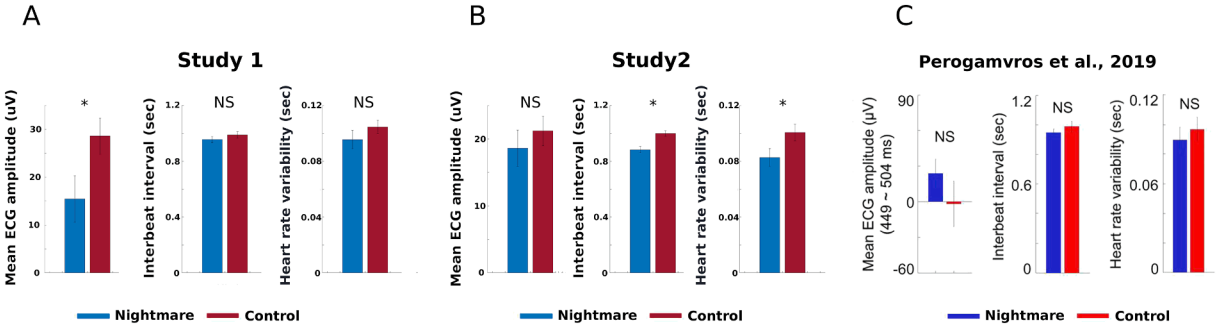

Fig. 2. Cardiac parameters in the nightmare and control groups. Mean ECG amplitudes were significantly different in Study 1 ($p < 0.05$), whereas in Study 2, nightmare sufferers showed significantly lower interbeat intervals and variability of heart rate ($p < 0.05$) than controls.

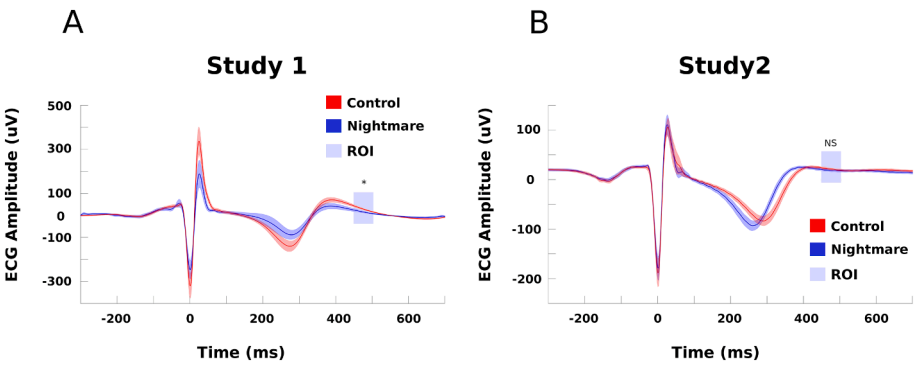

Fig. 3. Averaged ECG amplitudes in the nightmare and control groups in REM sleep. ECG amplitudes differed in Study 1 within the time range of interest (ROI, 449–504 ms). In Study 2 we observed faster heart rate and lower heart rate variability in the nightmare group that is also apparent in the averaged ECG amplitude showing a shorter time course in the QRST complex.

Table 3
Analyses of covariance between right frontal HEP amplitudes over 449–504 ms as the outcome, group membership (NMs and CTLs) as the predictor, and cardiac parameters as covariates in separate models. IBI – interbeat intervals, SDNN – standard deviation of normal to normal heartbeats.

	Study 1		Study 2	
Covariates	Group effectF (p value)	CovariateF (p value)	GroupF (p value)	CovariateF (p value)
None	0.01 (0.9)	–	1.3 (0.26)	–
ECG amplitude	1.5 (0.22)	15.1 (0.0004)	2.71 (0.11)	10.72 (0.002)
IBI	0.001 (0.97)	0.04 (0.84)	2.27 (0.13)	1.07 (0.3)
SDNN	0.19 (0.65)	4.3 (0.04)	2.5 (0.11)	2.47 (0.12)

Perogamvros and colleagues were the first to examine HEP in nightmare disorder, and in a small group of nightmare sufferers (N = 11) and matched controls (N = 11) observed statistically different HEP responses between the two groups that appeared only in REM sleep. More specifically, a right frontal cluster of electrodes between 449 and 504 ms after the R-peak exhibited more positive amplitude in NMs compared to CTLs. In our study, we followed the same procedure described in the original study but used two larger databases (19 NMs and 20 CTLs, and 21 NMs and 20 CTLs in Study 1 and Study 2, respectively). Our results do not corroborate the findings of the original study: no significant differences were observed in HEP during REM sleep in either of the two studies. In study 1, the HEP within the time range of interest (449–504 ms) during NREM sleep showed significant differences over central sites across the two groups; however, the analysis of ECG amplitudes suggested that this difference was confounded with cardiac artifacts. In addition, Perogamvros and colleagues (Perogamvros et al., 2019) observed a negative correlation between HEP amplitudes and depression scores within the nightmare group, but not in controls. Although the authors were careful to interpret this correlation based on only eleven data points they nevertheless suggest that the association between HEPs and depression scores might reflect the role of REM sleep in emotional information processing, and its dysfunction in nightmare disorder (Levin and Nielsen, 2007). Our study however, did not replicate the associations between HEPs and depression scores in either of the two databases. We may also note that Perogamvros and colleagues interpret their findings as signs of stronger HEP response reflecting increased emotional and sensory processing in nightmare sufferers compared to healthy controls. Nevertheless, the interpretation of the positive or negative deflection of the HEP is not that straightforward as the (positive or negative) direction of the HEP might vary according to the reference electrodes, the time range of interest, as well as the locations where the HEP is identified. Therefore, framing the HEP as larger or smaller seems to be premature at the current state of HEP studies (Coll et al., 2021). We suggest that the notion of larger or smaller HEP (indicating increased or decreased interoceptive processing) requires further validation by evaluating (optimally within the same study) the observed HEP response in REM against other conditions in which interoception, arousal, or emotional processing is clearly increased naturally or by experimental manipulation.

Although the notion of a biomarker implies that the measure is robust, stable and "immune" to minor differences across studies, we should mention the differences across our replication studies and the original one. First, the original study recruited patients who were seeking treatment, whereas the nightmare groups in the replication studies were selected by standardized questionnaires on nightmares. Therefore, we may speculate that the NM group of the original study consisted of patients with more severe symptomatology. Nevertheless, the NM groups involved in our studies also showed significantly higher scores in scales assessing psychopathological symptoms compared to controls, and no associations were observed between the severity of comorbid psychopathology (as measured by depressive symptoms) and the HEP. In addition, the original study used only one night of sleep to analyse HEP, whereas we examined the sleep recordings of the second night (after the first, habituation night) that participants spent in our lab. Hence, differences in HEP might be attributed to the first-night effect leading to relatively more disrupted sleep in nightmare sufferers (Agnew et al., 1966; Kis et al., 2014), albeit such an effect is expected to influence both NREM and REM sleep, and not just the latter. All in all, we may not exclude that such differences across the original and the replication studies contributed to the discrepant observations, indicating that the HEP might be sensitive to more variable state-like factors. Interoceptive processing during sleep might also vary as a function of different state fluctuations that is an inherent property of the heterogeneous state of sleep (Halasz and Bodizs, 2013; Lecci et al., 2017). Accordingly, HEP seems to be modulated by different sleep stages (Lechinger et al., 2015) as well as different microstates in REM sleep (Simor et al., 2021). Since disrupted sleep in nightmare disorder is not limited to REM sleep, but also showed alterations in NREM sleep, especially NREM to REM transitions (Blaskovich et al., 2020; Blaskovich et al., 2019), future studies may investigate the HEP in more detail focusing on the more transient, microstructural dimensions of sleep periods. Moreover, future studies should examine and exclude the confounding effect of cardiac parameters on HEP with more refined techniques (Buot et al., 2021). We should note that with respect to cardiac parameters our two studies showed some differences. Whereas the relatively increased ECG amplitude of the control participants in Study 1 may merely be attributed to non-specific factors among which the most likely is the position of ECG electrodes, lower interbeat intervals and HRV in the NM group indicates physiological differences across the NM and the CTL group in Study 2. Although interbeat intervals and HRV were not related to HEPs when entered as covariates in

our ANCOVA models, they nonetheless reflect increased sympathetic activity in NM participants in our second database. We may speculate that apart from the minor differences between Study 1 and Study 2 in the selection of our participants, the procedure involving the viewing of arousing pictures before falling asleep might have specifically increased sympathetic activity in the NM group in Study 2. Nevertheless, such state-like factors did not influence our main findings showing the lack of HEP differences in both studies.

In sum, our data cast doubts on the utility of HEP as a biomarker in the diagnostic and treatment procedures of nightmare disorder. Identifying reliable neurophysiological correlates of nightmare disorder might promote the understanding of the pathophysiology of disturbed dreaming; however, while several studies detected neurophysiological alterations in nightmare sufferers during sleep (Nielsen and Carr, 2017; Simor and Blaskovich, 2019) and wakefulness (Marquis et al., 2021; 2019), current findings are still somewhat mosaic and should be replicated in larger databases. Since frequent nightmares are comorbid with a large variety of psychopathological states (Levin and Nielsen, 2007; Spoormaker and Montgomery, 2008), the nightmare groups examined to date are probably quite heterogeneous. Hence, it is still not clear how the previously identified group differences across nightmare sufferers and controls are confounded by comorbid conditions such as insomnia, depression or PTSD. Moreover, the trait-like and state-like aspects of these biomarkers are also a question of further inquiry. A recent study examining multiple nights per participants suggests that the state-like neurophysiological correlates of disturbed dreaming are different from other alterations that may characterize the sleep patterns of nightmare sufferers regardless of the occurrence of nightmares (Paul et al., 2019). Future studies, applying multiple sleep EEG assessments in larger samples should disentangle the trait-and state-like neurophysiological alterations that might be later used as biomarkers of nightmare disorder. The measurement of multiple nights with sleep EEG and additional physiological measures (e.g. ECG, skin conductance) along with the assessment of dispositional and state-like subjective reports may shed more light on the pathophysiology of sleep regulation and on the role of comorbid symptoms in nightmare disorder.

Funding

Research supported by the Higher Education Institutional Excellence Program of the Ministry of Human Capacities in Hungary, within the framework of the Neurology thematic program of the Semmelweis University. PP was supported by a project from the Spanish Ministry of Science, Innovation and Universities (PGC2018-096655-A-I00). PS was supported by the by the (Hungarian) National Research, Development and Innovation Office (NKFI FK 128100).

Data availability

Study data and analyses scripts will be made available upon request.

CRediT authorship contribution statement

Tamás Bogdány: Conceptualization, Investigation, Formal analysis, Data curation, Writing – original draft. **Pandelis Perakakis:** Methodology, Software, Writing – review & editing. **Róbert Bódizs:** Methodology, Investigation, Writing – review & editing. **Péter Simor:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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