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Brief communication

Frequent nightmares are associated with blunted cortisol awakening response in women

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HIGHLIGHTS

- Daily cortisol patterns were assessed on a working and leisure day in 188 women.
- The cross-sectional sample included 13 participants with frequent nightmares.
- Cortisol awakening response was smaller in the nightmare subgroup on the working day.
- Findings implicate that nightmares can be associated with HPA functioning.

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ABSTRACT

Nightmares are relatively common sleep complaints that seem to be associated with affective distress. To date, few attempts have been made to link nightmares to the biological markers of the stress response, and the HPA response in particular. The present study examined the relationship between frequent nightmares and the cortisol awakening response (CAR) in a cross-sectional study of working women (N = 188). Analysis revealed that those who reported frequent nightmares (N = 13) showed a blunted CAR on a working day, compared to those who did not report nightmares. This result was independent of psychiatric symptoms, demographic variables, and lifestyle. Our preliminary findings suggest that decreased HPA reactivity might be a trait-like feature of women with frequent nightmares.

1. Introduction

Approximately 5% of the adult population suffers regularly from nightmares — vivid and terrifying dreams that lead to abrupt awakenings [1]. Still, relatively little is known about the pathogenesis of nightmares and its relation to sleep and mental disorders [2]. Within the frames of the "continuity hypothesis", Schredl suggested an association between stressful life experiences and nightmares [3]. Whereas, questionnaire-based studies emphasize the relevance of state-like effects (such as increased emotional pressure) leading to frequent nightmares [3,4], theoretical models [2] as well as longitudinal [5] and twin studies e.g. [6] point to the influence of trait-like vulnerability factors for the development of frequent nightmares. In their multilevel, integrative model Levin and Nielsen [2] proposed that state-like *affect load* as well as trait-like *affect distress* might contribute to the frequent occurrence of terrifying dream experiences. Both factors seem to be related to increased emotional reactivity underlain by impaired fronto-limbic circuitry [2,7], and presumably abnormal stress responses.

Unfortunately, previous studies have mostly relied on reports of subjective stress, and few nightmare studies used biological stress markers. Nonetheless, indirect evidence suggests an association between the HPA axis activity and nightmares. For instance, some of the brain regions implicated in nightmare formation [8] – the hippocampus, the amygdala and the medial prefrontal cortex in particular – abundantly express glucocorticoid receptors, influence HPA axis activity and regulate stress responses [9]. Additionally, the cortisol awakening response (CAR) – which refers to the sharp increase in cortisol following awakening and indicates the reactivity of the HPA system – has been negatively correlated with impaired sleep quality [10]. On the other hand, frequent

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nightmares have also been associated with impaired sleep quality [1], reduced sleep efficiency, increased nocturnal awakenings, relatively decreased slow wave sleep (SWS) and increased REM pressure [see [1]]. Moreover, several studies have shown that PTSD – a severe psychiatric condition in which affected individuals often experience vivid nightmares – is related to a blunted CAR [2,12–14].

The above findings led us to the assumption that the altered functioning of the HPA system might contribute to the pathogenesis of frequent nightmares. In particular, in light of the previously reported associations between sleep disturbances, PTSD symptoms and reduced CAR we expected that frequent nightmares would be associated with a blunted CAR. This hypothesis was examined within a non-clinical sample of women who provided seven cortisol samples through a working and a leisure day.

2. Methods

This article reports on analyses performed on the Hungarian subset of the Daytracker Study, an investigation of the relationship between well-being and health in working women. Only women were included in this study, as there are very few studies that address the population of working women [15]. The study was approved by the Research Ethics Committees of Semmelweis University and University College London, and all participants signed an informed consent form. Participants received a small honorarium at the end of the study.

2.1. Participants

Participants were recruited from full-time female employees of Semmelweis University in Budapest via emails and flyers. The inclusion criteria were explicitly declared during recruitment, thus volunteers applied only if not 1) pregnant; 2) suffering from acute or chronic illness such as cardiovascular disease, diabetes, cancer, and endocrine disorder; 3) diagnosed with mental disorder (e.g. major depression, PTSD, and bipolar disorder); 4) taking steroid, hypertensive or anti-inflammatory medication or beta-blockers. From the initial 202 included participants, we excluded those with missing data on nightmares (N = 6), and morning cortisol level (N = 8). Thus, the final size of the study sample was 188.

2.2. Procedure and assessment

After a briefing about the study protocol, participants completed two 24 h assessments on a working day and on a leisure day. The 24-hour periods started at 17 h and ended next day. To avoid any sequence effects, assessment randomly started on a working or a leisure day. During the assessments, participants provided seven saliva samples each day — using Salivettes (Sarstedt, Leicester, UK). Participants were instructed not to eat, drink or brush their teeth until after the 30 min post-waking sample, and 15 min before later saliva samplings. Saliva samples were timed immediately at waking, 30 min after awakening, at 10 h, 12 h, 15 h, 17 h, and at bedtime. Saliva samples were stored in a cold place or refrigerator until they were transported to the university lab within 1–2 days. Subsequently, the samples were kept frozen at −20 °C until analysis. Analysis was carried out using a high sensitivity chemiluminescence assay at the Technical University in Dresden (Germany). Inter- and intra-assay coefficients of variance (CVs) were <8%. CAR was calculated using the area-under-the-curve with respect to ground (AUC_G), using the waking and the 30 min post-awakening cortisol values [16]. We chose this method as it is relatively robust and after natural log transformation it followed normal distribution (Shapiro–Wilk normality tests: W = 0.99, $p = .520$, and W = 0.99, $p = .423$ for working and leisure day CAR, respectively).

Standardized survey questions and questionnaires were used to assess demographic data, mental and somatic health, lifestyle, and sleep quality [see 17]. These factors were used as covariates to exclude known confounders of the CAR [16]. Tests relevant to the current study included depressive symptoms (CES-D, Cronbach's $\alpha = .88$), trait anxiety (STAI-T, $\alpha = .92$), perceived health (PHQ-15, $\alpha = .80$), Jenkins sleep problem questionnaire ($\alpha = .75$), and morningness–eveningness scale ($\alpha = .89$). The items of these questionnaires were rated on four- or five-point Likert scales.

Participants also answered single questions – that were dichotomized later – about alcohol consumption (non-drinker/drinker), smoking status (non-smoker/smoker), and number of children. Stress was assessed using ecological momentary assessment (EMA) [18], whereby participants answered the question "*On a scale of 1 to 5, please rate how stressed you are at this moment*" seven times over one workday and leisure day at the same time when saliva samples were taken (see below). Mean stress scores were calculated for each day. Participants were asked if they had nightmares frequently using a single binary question: "*Do you frequently have nightmares that wake you up?*". This measure has been used commonly in nightmare studies [2]. Moreover, participants reported the emotional quality of dreams on days of the measurement using single choice questions ("*How would you describe the emotional quality of your dreams?*"; options: very unpleasant, unpleasant, neutral, pleasant, very pleasant, do not remember).

2.3. Statistical analysis

Welch's t-tests and chi-square tests were used to compare the characteristics of the nightmare and non-nightmare groups. To investigate the effect of frequent nightmares on CAR, we carried out separate ANCOVAs on working and leisure days controlling for age, BMI, morningness, education, depression, anxiety, physical symptoms, sleep quality, alcohol consumption, smoking, physical exercise, and sleeping time. Data analysis was performed with R 3.1.2 [19].

3. Results

Preliminary analysis showed that participants with frequent nightmares had a significantly lower BMI, were more depressed and anxious, reported more sleep problems and somatic symptoms, and showed a lower morningness score. The frequent nightmare group also reported more stress than participants without frequent nightmares on both days, although this difference was on the threshold of statistical significance. Differences were not significant for sleep duration, demographic, and lifestyle related variables (see Table 1).

Fig. 1 shows the profiles of cortisol output over the work and leisure days. We found typical diurnal profiles, with relatively high cortisol on waking, an increase over the first 30 min of the day, and progressive decreases in output across the day. Those participants who experienced nightmares frequently showed a significantly smaller CAR than those who did not experience nightmares frequently $F(1,186) = 6.98$, $p = .009$, $\eta_p^2 = .04$ (values without covariates). The relationship remained significant after controlling for all covariates ($F(1,153) = 4.72$, $p = .030$, $\eta_p^2 = .026$), however due to the list-wise deletion of missing values, the sample size changed to 155 (nightmare group = 11, non-nightmare group = 144). Moreover, given that the inclusion of covariates only controls for linear relationships between the outcome and the predictors, we conducted an additional analysis on a subsample of non-nightmare sufferers matched to the subgroup of nightmare sufferers by age, BMI, sleep quality (Jenkins score), and morningness scores. The difference in CAR between the nightmare group and the matched control was significant on the working day $F(1,24) = 4.30$, $p = .049$, $\eta_p^2 = .15$ (for details of the matched sample, please refer to the online supplement).

The difference in CAR between the nightmare and non-nightmare groups was not significant on the leisure day $F(1,183) = 0.78$, $p = .379$, $\eta_p^2 = .004$. There were no significant differences between the two groups at the other time points of either day ($ts < 1.53$, $ps > .15$). Moreover, the working day CAR and the leisure day CAR of