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Increased EEG sigma and beta power during NREM sleep in primary insomnia

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ABSTRACT

The hyperarousal model of primary insomnia suggests that a deficit of attenuating arousal during sleep might cause the experience of non-restorative sleep. In the current study, we examined EEG spectral power values for standard frequency bands as indices of cortical arousal and sleep protecting mechanisms during sleep in 25 patients with primary insomnia and 29 good sleeper controls. Patients with primary insomnia demonstrated significantly elevated spectral power values in the EEG beta and sigma frequency band during NREM stage 2 sleep. No differences were observed in other frequency bands or during REM sleep. Based on prior studies suggesting that EEG beta activity represents a marker of cortical arousal and EEG sleep spindle (sigma) activity is an index of sleep protective mechanisms, our findings may provide further evidence for the concept that a simultaneous activation of wake-promoting and sleep-protecting neural activity patterns contributes to the experience of non-restorative sleep in primary insomnia.

1. Introduction

Chronic insomnia is defined by persistent difficulties initiating or maintaining sleep or non-restorative sleep accompanied by significant daytime impairments (Edinger et al., 2004). It affects about 10% of the general population and commonly occurs as a co-morbid condition in other medical or mental disorders. Primary insomnia (PI), an exclusionary diagnosis of poor sleep, ruling out psychiatric, medical, substance and additional sleep-related pathology, is estimated to affect up to 3% of the general population (Ohayon, 2002).

Despite considerable advances in knowledge, the pathophysiology of PI remains to be further elucidated. According to current etiological models, cortical hyperarousal represents a final common pathway in the development and maintenance of the disorder (Riemann et al., 2010; Perlis et al., 1997), and EEG spectral power in the beta range has been suggested to be an index of cortical arousal. Indeed, current evidence indicates that EEG beta power is increased in PI patients compared to good sleeper controls (Buysse et al., 2008; Marzano et al., 2008; Staner et al., 2003; Krystal et al., 2002; Perlis et al., 2001a, 2001b, 2001c; Merica et al., 1998; Lamarche and Ogilvie, 1997; Merica and Gaillaird, 1992; Freedman, 1986; for a conflicting result see Bastien et al., 2003). Furthermore, there is preliminary evidence that cognitive-behavioral therapy for insomnia, the first-line treatment for PI, reduces beta activity in insomnia patients (Cervena et al., 2004; Jacobs et al., 1993).

However, several aspects of increased high frequency power in PI patients remain to be further elucidated. First, while most studies found increased beta power in NREM sleep, findings in REM sleep are inconsistent. Perlis et al. (2001b) as well as Merica et al. (1998) reported that PI patients' beta activity is also increased during REM sleep. However, Krystal et al. (2002) did not find any REM-related differences to controls. Second, there is evidence that beta activity is associated with sleep misperception in PI, i.e. increased beta power is associated with an underestimation of total sleep time and an overestimation of sleep onset latency (Krystal et al., 2002; Perlis et al., 2001a). However, in the largest study to date, this association has not been observed (Buysse et al., 2008). Third, it is not clear whether beta activity in PI patients is primarily increased in early (Buysse et al., 2008) or late NREM sleep periods (Perlis et al., 2001b). And last, Buysse et al. (2008) reported a significant sex difference with beta power being exclusively increased in female PI patients, a finding that has not been reported in the other investigations.

Because of these inconsistent findings, the current study aimed at further investigating: (a) the differences in sleep-related arousal processes in PI patients and healthy controls by investigating NREM and REM sleep spectral power values; (b) their association with sleep perception; (c) the temporal pattern of high frequency activity over the course of the night; and (d) potential sex differences.

2. Methods

2.1. Participants

Twenty-five patients with PI according to DSM-IV-TR criteria (APA, 2000) and 29 sex- and age-matched good sleeper comparison subjects were included in the

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present analysis. The data for the analysis were taken from a study designed to investigate sleep-related memory consolidation in patients with PI and good sleeper controls (Nissen et al., 2011). Insomnia patients were referred to the sleep lab by their primary care provider or by a medical specialist. Healthy controls were recruited through local advertisements. An experienced physician examined all participants to rule out any psychiatric or relevant somatic disorders. All participants underwent a standard physical examination, including electrocardiogram (ECG), electroencephalogram (EEG) and routine laboratory investigation to exclude those with serious medical conditions. All participants were free of any psychoactive medication for at least 2 weeks prior to the sleep laboratory examination. During the sleep laboratory visit, participants had to refrain from alcohol and caffeine. Female participants were studied during their follicular phase. Participants with a periodic leg movements during sleep (PLMS) arousal index per total sleep time greater than 5.0 h^{-1} or a sleep apnea index per total sleep time of more than 5.0 h^{-1} were excluded from the current analysis. All participants were informed in detail about the purpose of the investigation and provided their written informed consent prior to the onset of the study. The study had been approved by the local ethics committee and has been carried out in accordance with the Declaration of Helsinki.

2.2. Polysomnography

A standard laboratory procedure was conducted in all participants for one experimental night. Sleep was recorded on 24-channel Sagura EEG-polysomnographs for 8 h from 'lights out' (10–11 pm) until 'lights on' (6–7 am). All recordings included EEG (C3-A2; C4-A1), EOG (horizontal and vertical) and EMG (submental), and were scored visually by experienced raters in 30-s periods according to the criteria of Rechtschaffen and Kales (1968). All participants were screened for apneas and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oxymetry, and bilateral tibialis anterior EMG. Sleep recordings were evaluated for the following parameters of sleep continuity: total sleep time (TST); sleep efficiency (ratio of TST to time in bed × 100%); sleep onset latency defined as time from lights out until sleep onset (defined as first epoch of stage 2); number of awakenings; arousal index (number of arousals per hour); and wake after sleep onset (WASO) defined as difference between sleep period time (SPT; time from sleep onset until final awakening) and TST. Sleep architecture parameters included the amounts of stages 1, 2, slow wave sleep (SWS) and rapid eye movement (REM) sleep as percentage of SPT.

2.3. Spectral analysis

During the night, continuous EEG (C3 referenced to the right ear) was amplified with a time constant of 0.3 s and a low pass at 70 Hz (12 dB/octave), digitized at 200 Hz and stored for off-line analysis. An all-night spectral analysis was performed on the same 30-s epochs for which sleep stages had been determined. Within each epoch, spectral power was calculated using the fast Fourier transform (FFT) algorithm from 22 windows (512-points each) overlapping by half, resulting in a spectral resolution of 0.39 Hz. Within each FFT window, the EEG was demeaned and detrended by subtracting the linear least-squares regression line before applying a Welch window and calculating the FFT. The 22 spectral power estimates were averaged to increase the stability of the estimate. The goal of the further analysis was to minimize the effects of confounding variables on the spectra averaged across epochs, such as the number of movements or arousals and other sleep parameters that can be analyzed separately. This was done by two techniques: (a) arousals and myoclonias were visually marked during staging and epochs including any such events were excluded from the analysis; (b) a fully automatic exclusion of 'deviant' epochs from the average was performed. Deviant epochs were those containing movements or arousals as determined during staging; furthermore, the total (0.8–48 Hz) and γ-band (32–48 Hz) log power of each epoch was related to the corresponding median-filtered value (the median of values in the 5 min preceding and 5 min following the epoch) and an epoch was excluded if the deviation was larger than the difference between the median and the first quartile of all median-filtered values across the night. In this way, artifacts mainly restricted to low frequencies (such as EOG events) as well as those occurring mainly in higher frequencies (such as EMG contamination) were eliminated in a data-driven way. All-night spectral power averages were obtained across all artifact-free epochs of sleep stage 2 and REM sleep separately.

2.4. Questionnaires

Subjective estimates of TST, sleep onset latency and WASO were assessed with the 'Schlaffragebogen A' (SF-A; Görtelmeyer, 1981). This questionnaire was administered in the morning after the PSG night and captures subjective aspects of sleep in the preceding night. Additionally, participants were asked to fill in the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and Beck Depression Inventory (BDI; Beck and Steer, 1987).

2.5. Statistical analysis

Descriptive presentation of the data includes mean values and standard deviations. The logarithmic (base e) spectra for artifact-free sleep epochs were averaged across each night separately for NREM stage 2 and REM sleep. The analysis of NREM sleep was restricted to stage 2 sleep in order to eliminate the influence of different NREM sleep stage distributions across subjects. Logarithmic spectral band power was calculated after adding the spectral power values of FFT bins with center frequency within the following frequency bands: delta-1 (0.1–1.0 Hz), delta-2 (1.0–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta-1 (16–24 Hz), beta-2 (24–32 Hz), and gamma (32–48 Hz). Group differences for absolute power in these spectral bands were analyzed using independent *t*-tests. Following the criteria of Krystal et al. (2002) we performed exploratory group comparisons between 'subjective insomnia' patients and 'objective insomnia' patients. For 'subjective insomnia', one of the following 3 criteria had to be met: (1) TST ≥ 6.5 h, (2) age < 60 years: TST 6.0–6.5 h and sleep efficiency > 85%, and (3) age ≥ 60 years: TST 6.0–6.5 h and sleep efficiency > 80%. The level of significance was set at $p < 0.05$ (two-tailed) for all analyses.

3. Results

3.1. Sample characteristics

The group of PI patients consisted of 16 women and 9 men (age: 47.8 ± 7.2 years). They had a mean score of 11.3 ± 3.6 on the PSQI, and 9.6 ± 4.5 on the BDI. Mean BMI was 23.3 ± 2.6 kg/m^2. The average duration of PI was 12.9 ± 10.3 years. The control group consisted of 18 women and 11 men (age: 46.5 ± 5.0 years). The mean PSQI score was 3.6 ± 1.5, the mean BDI score was 3.0 ± 3.1, and the mean BMI was 23.8 ± 3.0 kg/m^2. There were no significant group differences for age [$t(52) = 0.74$, $p = 0.46$], sex distribution [$\chi^2(1,52) = 0.02$, $p = 0.89$], and BMI [$t(52) = -0.61$, $p = 0.54$]. Consistent with other PI samples, the patient group had significantly higher PSQI values [$t(52) = 10.03$, $p < 0.001$] and BDI values [$t(52) = 6.12$, $p < 0.001$].

3.2. Polysomnography

Polysomnographic data are presented in Table 1. PI patients had a significantly lower total sleep time, sleep efficiency, stage 2% and REM % compared to healthy controls. Additionally, WASO was significantly increased in the patient group.

3.3. Spectral analysis for NREM stage 2 and REM sleep

The two groups did not differ in the percentage of epochs excluded (stage 2: 39.8 ± 16.3% (PI) vs. 33.3 ± 13.2% (controls), $p = 0.11$; REM: 38.6 ± 20.0 (PI) vs. 35.4 ± 17.1 (controls), $p = 0.72$). Spectral parameters for both NREM stage 2 and REM sleep are summarized in Table 2. PI patients showed significantly increased sigma (Cohen's $d = 0.89$), beta-1 (Cohen's $d = 0.74$), and beta-2 (Cohen's $d = 0.70$) power during NREM stage 2 sleep compared to healthy controls. No group differences were observed for REM sleep parameters.

3.4. Association between high frequency activity and sleep perception

Both for the entire sample and for the patients group, NREM stage 2 sigma, beta-1 and beta-2 power did not correlate with the difference between subjective and objective measures of total sleep time, sleep onset latency, or WASO ($p > 0.1$ for all analyses). Furthermore, the group of 'subjective insomnia' patients ($n = 7$) did not demonstrate any significant differences in NREM stage 2 sigma (1.76 ± 0.46), beta-1 (0.33 ± 0.44) or beta-2 (−0.75 ± 0.55) values in comparison with the group of 'objective insomnia' patients ($n = 18$; sigma: 1.94 ± 0.46, beta-1: 0.58 ± 0.52, beta-2: −0.59 ± 0.41; $p > 0.1$ for all group comparisons). Polysomnographic data of the two insomnia subgroups are presented in Table 1.