

## Waking EEG in primary insomnia

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Quantitative analysis of the waking EEG has been proposed as an objective method for measuring neurobehavioral impairment in primary insomnia. Thirty six patients with DSM-IV primary insomnia diagnosis (mean age 36 years) and 29 controls, matched for age and education, participated in the study. Waking EEG from 21 scalp electrodes was subjected to spectral analyses using a fast Fourier transform algorithm. Significantly lower values of power in the theta range and higher values of beta power were found in insomniacs as compared to control subjects. This theta power decrease in patients suffering from insomnia was not uniform throughout the brain, but it was pronounced in prefrontal derivations. Lower values of theta power correlated negatively and higher values of beta power correlated positively with Hyperarousal Scale score. Results of the research presented here support the notion of twenty-four hour hyperarousal in primary insomnia. Attenuated theta and enhanced beta power can be electrophysiological correlates of dysfunctional arousal in insomnia. Less waking theta power in insomniacs suggests a decrease in homeostatic sleep propensity.

Key words: hyperarousal, primary insomnia, waking EEG

Primary insomnia is a common disorder, with a prevalence about 6% (Ohayon 2002). Because of a negative impact on subjective well-being and objective health status, it has been increasingly recognized as a matter of public concern. Specifically, insomniacs are at higher risk of coronary heart disease (Schwartz et al. 1999) and major depressive disorder (Ford and Kamerow 1989). Available data indicate that insomnia is related to innate predisposition and environmental factors (Drake et al. 2004). Sleep EEG spectral analysis provided further objective information on the pathogenesis of the disorder. For instance, Besset and coworkers (1998) found in sleep-maintenance insomnia lower delta percent and decreased sleep spindle index during baseline night and on recovery night after partial sleep deprivation. This led them to the proposal that inability to maintain sleep might result from insufficient homeostatic sleep pressure. Merica and coauthors (1998) demonstrated that NREM power, for all frequencies below the beta range, had slower rise rates and reached lower levels. With the deepening of sleep, from prevalent spindles to prevalent delta, thal-

amocortical cells become progressively hyperpolarized (Steriade et al. 1993), thalamocortical neurons in patients with insomnia appear to be hyperpolarized at a slower rate (Merica et al. 1998). There is also well-documented evidence for enhanced power in the beta range (Merica et al. 1998), suggesting excessive arousal. Not only slow wave sleep is deficient, but also initiating sleep is disturbed. Freedman (1986) revealed in patients with sleep onset insomnia less power at 9 Hz and more beta power prior to sleep at usual bedtime and increased beta power during sleep stage 1. Additional evidence has been provided by Merica and Gaillard (1992) who found in patients with insomnia higher beta activity and lower delta activity during sleep onset. According to Lamarche and Ogilvie (1997), sleep onset process is dampened in psychophysiological insomnia, with more aroused EEG patterns around entry into sleep (reduced increase in delta power and less decrease in beta power).

The aforementioned studies on EEG spectra in chronic insomnia focused solely on the temporal sequence of distinct frequency bands during sleep, sleep onset or in period directly preceding falling asleep. Daytime waking EEG patterns in insomnia, either spatial or temporal, were not investigated, although a number of psychophysiological correlates

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of daytime hyperarousal have been identified: no difference in mean daytime sleep latency despite poor nocturnal sleep (Lichstein et al. 1994, Niemcewicz et al. 2001), chronic activation of both limbs of stress system (the hypothalamic-pituitary-adrenal axis and the sympathetic system) with hypersecretion of adrenocorticotrophic hormone (ACTH) and cortisol (Vgontzas et al. 1998, 2001), elevated metabolic rates (Bonnet and Arand 1995), and greater global cerebral glucose metabolism not only during sleep but also during wakefulness (Nofzinger et al. 2004).

Daytime consequences are diagnostic for insomnia (American Psychiatric Association 1994). This begs the question which electrophysiological variables parallel behavioral findings. Therefore, the aim of the study was to investigate electrophysiological correlates of insomnia in the waking EEG.

The study was performed in thirty six patients with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association 1994) primary insomnia (21 females and 15 males) recruited from Sleep Disorders Clinic, Psychiatry Department of the Medical University of Warsaw, and 29 healthy subjects (13 females and 16 males), matched for age and education. All subjects gave their informed written consent before participating. The study was approved by the University Bioethics Committee.

Both healthy volunteers and patients were required to be free of any prescription or nonprescription drugs for at least 2 weeks prior to the study. Benzodiazepines abuse was checked by urinary screening after the second night of polygraphic sleep recording. Sleep habits were confirmed by wrist actigraphy and sleep diaries.

Each subject underwent psychometric assessment including the Minnesota Multiphasic Personality Inventory (MMPI-2), the Hyperarousal Scale (Regestein et al. 1993), the Beck Depression Inventory (BDI, Beck et al. 1961) and the Hamilton Depression Rating Scale (HDRS, 17-items, Hamilton 1967). Severity of insomnia was quantified by means of 8-item version of the Athens Insomnia Scale (AIS, Soldatos et al. 2003).

All participants were studied on two consecutive nights with laboratory-based polysomnography (PSG). The first night allowed for adaptation and to rule out other sleep disorder. On the second night, EEG signal was recorded from 21 derivations (EADS 220 BrainScope) following an extended version of the international 10-20 system (with additional electrodes at Fpz and Oz) versus reference electrode positioned

between Fz and Cz. The impedance of the electrodes was kept below 10 k $\Omega$ . EEG signals were high-pass filtered at 0.15 Hz and low-pass at 30 Hz. Sleep stages were visually scored according to the criteria of Rechtschaffen and Kales (1968).

Directly after second night of PSG, waking EEG from 21 scalp electrodes was obtained during consecutive four sessions of routine diagnostic Multiple Sleep Latency Test (MSLT, Carskadon 1994, Littner et al. 2005). Sleep latencies were compared between insomniacs and healthy controls, and then the first two minutes of the artifact-free waking EEG were selected. All EEG data was recalculated to average reference and subjected to spectral analyses using a fast Fourier transform algorithm (FFT). FFT was counted in 2-s epochs at a sampling rate 128 Hz. EEG power spectra were calculated across the following bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta-1 (12–15 Hz), beta-2 (15–18 Hz), beta-3 (18–25 Hz), and beta-4 (25–30 Hz). Both the detection of artifacts as well as the spectral analysis were conducted with NeuroGuide 2.4 ([www.appliedneuroscience.com](http://www.appliedneuroscience.com)).

For statistical analysis, Glimmix procedure (SAS 9.1, SAS Institute Inc., 1996) was used. Prior to statistical analysis, relative power (the percentage of power in any band compared with the total power in the whole spectrum) was log-transformed in order to obtain a normal distribution. Statistical model included EEG power as dependent variable and following independent variables: derivation, group (healthy subjects, insomniacs), MSLT session (time awake), age, hyperarousal (Hyperarousal Scale score), and interactions: group by derivation, group by session and group by hyperarousal. The relationships between EEG power and hyperarousal score were calculated using Spearman rank correlation test. The *P* value for all tests was set at 0.05.

There were no significant group differences in mean age between insomniacs and controls (36 SD  $\pm$  12.3 vs. 38 SD  $\pm$  11.5;  $t=1.59$ ,  $P=0.11$ ).

Insomniacs presented with higher scores on AIS (12.68  $\pm$  3.09 vs. 2.63  $\pm$  1.49,  $t=-13.74$ ,  $p<0.0001$ ), elevated level of arousal on Hyperarousal Scale (64.3  $\pm$  8.25 vs. 43.3  $\pm$  15.41,  $t=-5.92$ ,  $P<0.0001$ ) and higher scores on depression scales BDI (6.9  $\pm$  4.79 vs. 1.6  $\pm$  2.57,  $t=-4.97$ ,  $P<0.0001$ ) and HDRS (5.2  $\pm$  2.13 vs. 0.2  $\pm$  0.66,  $t=-10.97$ ,  $P<0.0001$ ). Significant differences in MMPI personality profile were found. When compared with controls, subjects with insomnia had higher values on depression ( $t=-3.81$ ,  $P=0.0004$ ), hypochon-

dria ( $t=-3.29$ ,  $P=0.0019$ ), hysteria ( $t=-2.63$ ,  $P=0.0116$ ), psychastenia ( $t=-2.38$ ,  $P=0.0212$ ) and social introversion ( $t=-2.05$ ,  $P=0.0458$ ) MMPI scales.

On polysomnographic measures, insomniacs compared to controls showed longer wake time after sleep onset ( $27.48 \pm 24.59$  vs.  $12.77 \pm 13.05$  min, respectively,  $t=49.26$ ,  $P<0.0001$ ). Mean sleep latencies in MSLT sessions did not differ significantly in healthy individuals and insomniacs.

Since exploratory brain mapping revealed group differences in theta power on prefrontal locations and no interactions group by derivation were found, average power of prefrontal derivations for 3 sites (Fp1, Fp2, and Fpz) was used as factor derivation. There was a significant site effect for theta power (6 Hz:  $F_{20,4619}=43.53$ ,  $P<0.0001$ , 7 Hz:  $F_{20,4640}=11.2$ ,  $P<0.0001$ , 8 Hz:  $F_{20,4155}=19.24$ ,  $P<0.0001$  with factor derivation) which was higher over prefrontal regions. No interactions group by derivation nor group by session were found, i.e., in all sessions of MSLT, both in insomniacs as well as in controls, the topographic distribution of theta power was similar. Being insomniac or healthy control (factor group) affects the average prefrontal power of 6 Hz ( $F_{1,145}=15.56$ ,  $P<0.0001$ ), 7 Hz ( $F_{1,183}=27.29$ ,  $P<0.0001$ ) and 8 Hz ( $F_{1,183}=13.61$ ,  $P<0.0003$ ). As shown in Figure 1A, in all the consecutive sessions of MSLT, power within 6, 7 and 8 Hz frequencies was higher in controls than in insomniacs.

To investigate the temporal changes of the prefrontal theta power, the time course of the fluctuations in the theta band was analyzed across 4 consecutive MSLT sessions. There were no significant effects of session nor a significant group by session interactions.

Because of internal correlations between the psychometric scales for further analysis of the interactions between power in the theta and beta band and the results of psychometric scales, only Hyperarousal Scale was included into the model.

Average theta power at prefrontal sites showed a significant effect of hyperarousal in 6 Hz ( $F_{1,145}=3.54$ ,  $P<0.0001$ ) and 8 Hz bands ( $F_{1,183}=5.79$ ,  $P<0.0001$ ) and significant interaction group by hyperarousal effect within 6 Hz ( $F_{1,145}=10.87$ ,  $P=0.0012$ ), 7 Hz ( $F_{1,183}=20.21$ ,  $P<0.0001$ ) and 8 Hz ( $F_{1,183}=11.08$ ;  $P=0.011$ ). Additional analysis using the Spearman correlation (rho coefficient correlation) revealed negative correlation between score on Hyperarousal Scale and values of theta (6–8 Hz) power in prefrontal derivations, averaged for all sessions ( $\rho=-0.29$ ,  $P<0.024$ , Fig. 1B).

There was a significant group effect for beta-3 ( $F_{1,4664}=91.5$ ,  $P<0.0001$ ) and beta-4 ( $F_{1,4646}=3.9$ ;  $P=0.048$ ) power, with insomniacs having higher values. Significant effect of hyperarousal on power in beta-3 ( $F_{1,4664}=167.7$ ;  $P<0.0001$ ) and beta-4 ( $F_{3,4646}=79.55$ ;  $P<0.0001$ ) range was found. Additionally, as can be seen from the Figure 1C, Spearman rank correlation test revealed positive correlation between hyperarousal score and values of power in beta frequency range 18–30 Hz, averaged for all sessions ( $\rho=0.3$ ;  $P<0.018$ ). Beta-3 ( $F_{20,4664}=28.61$ ;  $P<0.0001$ ) and beta-4 ( $F_{20,4646}=28.61$ ;  $P<0.00001$ ) bands showed significant derivation effect with highest values of power at central sites. Significant session effect was demonstrated for beta-4 frequency ( $F_{3,4646}=7.31$ ;  $P<0.0001$ ): as time progressed, the beta-4 power pro-

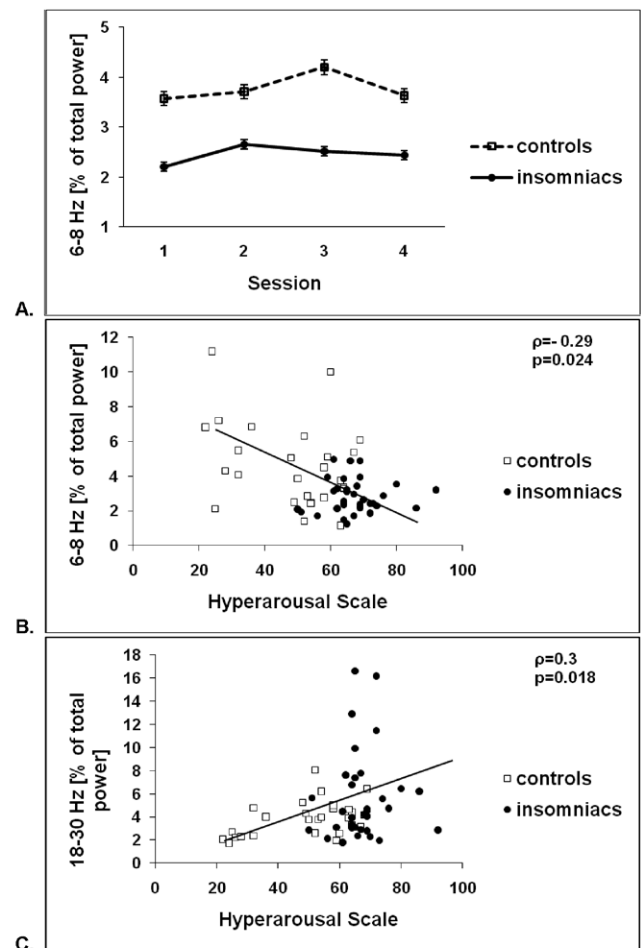


Fig. 1. (A) Least square means of theta power in successive MSLT sessions in prefrontal derivations. Vertical bars show standard errors. (B) Correlation between averaged values for all sessions of prefrontal theta power and hyperarousal score. (C) Correlation between averaged values for all sessions of beta 3 and beta 4 power and hyperarousal score.

gressively increased. There was also significant group by session interaction ( $F_{3,4664}=4.0$ ;  $P=0.0075$ ), with the wake-dependent increase in the beta-4 range more pronounced in patients. Moreover, age-related increase in power was seen for beta-3 ( $F_{31,4664}=78.91$ ,  $P<0.0001$ ) and beta-4 frequencies ( $F_{31,4664}=17.43$ ,  $P<0.0001$ ). Age was found to be positively correlated with beta power in frequency range 18–30 Hz ( $\rho=0.33$ ;  $P<0.0001$ ).

No significant between groups differences for delta, alpha higher than 8 Hz, beta-1 and beta-2 power were observed.

In this paper we explore whether waking EEG differs in insomniacs from healthy subjects and seek to identify possible determinants. Overall, our sample showed typical symptomatology. When compared with controls, group of patients presented with greater insomnia severity, as measured using AIS, heightened level of arousal on Hyperarousal Scale and higher scores on depression scales. These results are consistent with the available data. Previous findings suggest that AIS diagnostic cut-off score for patients with insomnia is six points (Soldatos et al. 2003) or 8 points (Fornal-Pawłowska et al. 2011). In Regestein and others (1993) study average rating for patients was 48.9 and for controls 30.8, whereas our patients and controls averaged 64.3 and 43.3, respectively. Elevated scores on depression scales may indicate worse mood secondary to sleep disorders (Vandeputte and de Weerd 2003) or common pathophysiology of both primary insomnia and depressive disorder. Nevertheless, mean BDI and HDRS scores in our study, although significantly different, were out of clinical range.

Extensive research on personality patterns in insomnia revealed mainly neurotic-depressive MMPI profiles (Kales and Kales 1984). Patients in the current study showed the so-called neurotic triad, i.e. higher values on hysteria, depression and hypochondria MMPI scales (3-2-1 code), consistently with the previous paper by Niemcewicz and coworkers (2001).

As indicated above, many symptoms of sleep disorders are not limited to disturbed sleep in the night, but the main problem is worse daytime functioning. Therefore, the key concept in the pathogenesis of insomnia is twenty-four hour hyperarousal. Classical polysomnography did not explain worse functioning in patients, because both our groups slept nearly the same. The patients presented with wake after sleep onset only 15 minutes longer than controls. The difference seems too little to justify all daytime symptoms

of primary insomnia. Similar minor unspecific differences in variables related to sleep continuity were obtained by other authors (Kales and Kales 1984, Niemcewicz et al. 2001).

Despite all the daytime complaints MSLT showed that insomniacs were not sleepier than healthy volunteers. These results are consistent with the previous papers (Lichstein et al. 1994, Niemcewicz et al. 2001) reporting no greater daytime sleep latency in patients with insomnia. Emerging data indicate that waking is a multidimensional state. Readiness to fall asleep should be distinguished from alertness, the ability to adequate and overall perception, interactions and communication. MSLT does not provide noticeable results in insomnia, because independent dimensions of waking may be differentially affected by different disorders. For instance, patients with insomnia are less sleepy on Epworth Sleepiness Scale than narcoleptics and patients with sleep apnea, however, they do not differ from subjects with narcolepsy and sleep apnea on recently developed Toronto Hospital Alertness Scale (THAT) and ZOGIM Alertness Scale (Moller et al. 2006).

It is well established that sleep propensity is determined by interaction of homeostatic and circadian process (Borbély 1982). Converging evidence demonstrates that both the homeostatic and circadian process have also an effect on waking EEG (Aeschbach et al. 1997, 1999, Cajochen et al. 1995, 2002, Finelli et al. 2000). Differential effects for each EEG frequency, and each vigilance state, were identified. For instance, variations within delta band are a measure of sleep intensity (Borbély 1982), but increase in theta power is a function of sleep pressure in waking (Aeschbach et al. 1997, 1999, Cajochen et al. 1995, 2002, Finelli et al. 2000, Tinguely et al. 2006).

Quantitative analysis of the waking EEG can be utilized as an objective measure of neurobehavioural functioning. Available information comes from normative studies (Aeschbach et al. 1997, 1999, Cajochen et al. 1995, 2002, Finelli et al. 2000, Tinguely et al. 2006) and research conducted on patients presenting with seasonal affective disorder (Cajochen et al. 2000) and obstructive sleep apnea syndrome (Grenèche et al. 2008). These papers provide new insights into the mechanisms behind sleep disorders. For instance, waking EEG measures confirm high sleepiness in obstructive sleep apnea syndrome (Grenèche et al. 2008), but in patients with seasonal affective disorder suggest higher arousal, in spite of subjective sleepiness (Cajochen et al. 2000).

Prolonged wakefulness results in increased theta power (Cajochen et al. 1995, 2002, Aeschbach et al. 1997, 1999, Finelli et al. 2000, Tinguely et al. 2006). Thus, theta power can be used as an indicator of central dysfunction in insomnia. In our study quantitative analysis of the waking EEG revealed lower theta (6–8 Hz) power in patients. Moreover, theta power attenuation appears to be accompanied by higher scores on the Hyperarousal Scale. Less theta power in insomniacs suggests a decrease in homeostatic sleep propensity (Cajochen et al. 1995, 2000).

Another finding of our investigation was that the significant differences in the theta power were observed only in the prefrontal derivations. This is in line with studies showing that most pronounced changes in lower frequency bands occur over anterior cortical areas. The frontal predominance of theta power is constant and independent of the vigilance fluctuations, the same in waking as in major sleep states, and indicates location of the theta activity generator (Tinguely et al. 2006).

It has been already proposed that the enhanced power in beta frequency range may reflect the activity of brain structures participating in attentive behavior (Wróbel et al. 2007) and in arousal (Chapotot et al. 2000). Consistently with these observations, we found higher mean beta-3 and beta-4 power and greater progressive wake-dependent increase in the beta-4 power in patients with insomnia. The wake-dependent increase in beta activity has been previously reported by Aeschbach and coauthors (1999). Age-related increase in beta power shown in our study is not unexpected result taking in account that aging appears to be associated with activation of the hypothalamic-pituitary-adrenal axis (Van Cauter et al. 2000).

There are several limitations to this study. We did not demonstrate neither circadian nor homeostatic EEG fluctuations in theta/alpha band (Cajochen et al. 1995, 2000), probably due to methodological differences. Data was not collected under constant routine conditions which allow to exclude the distorting influence of physical activity, body position, changes in lighting and different meals.

In conclusion, our findings support the notion of twenty-four hour hyperarousal in primary insomnia. This is confirmed by higher scores on Hyperarousal Scale, which increased parallelly to the severity of insomnia, no difference in mean daytime sleep latencies on MSLT, higher wake after sleep onset in PSG, decrease in theta power during waking, and increase in beta

power, positively correlated with hyperarousal. Attenuation of theta and enhancement of beta power can be electrophysiological correlates of impaired behavioral functioning in insomnia. Less theta power in insomniacs suggests a decrease in homeostatic sleep propensity.

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