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Power Density in Theta/Alpha Frequencies of the Waking EEG Progressively Increases During Sustained Wakefulness

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Summary: Electroencephalogram (EEG) power density and self-rated fatigue were assessed in nine healthy women during a 40-hour period of sustained wakefulness under constant behavioral and environmental conditions (constant routine protocol). Waking EEG recordings were performed for 4 minutes after 3, 10, 27 and 34 hours of prior wakefulness. EEG power density in the 6.25- to 9.0-Hz frequency range progressively increased across the four recordings, suggesting an endogenous homeostatic component in the regulation of the theta/alpha frequencies under constant conditions. Subjective fatigue also exhibited an increasing component in the course of the constant routine protocol, with a clear circadian modulation. Fatigue ratings and the theta/alpha power density of the waking EEG recorded at the same four time points during the constant routine protocol correlated significantly. Our data demonstrate the presence of a homeostatic component in the control of EEG power density in the 6.25- to 9.0-Hz range. **Key words:** Constant routine—Spectral analysis—Waking EEG—Subjective fatigue.

Changes in the electroencephalogram (EEG) power spectrum of non-rapid eye movement sleep (NREMS) as a function of prior wakefulness are well documented (1–3). In particular, NREMS power density in frequencies between 0.25 and 7.0 Hz has been shown to increase monotonically with increasing duration of wakefulness (2–40 hours) prior to sleep. Several lines of evidence suggest that the duration of waking also modifies spectral components in the waking EEG. Faster frequency components of the waking EEG (7–17 Hz) were found to be more pronounced after sleep deprivation, whereas activity in the slower components (<7 Hz) was increased following a sleep episode (4). Prolonged wakefulness in train drivers resulted in an increase of power density in the alpha and theta range (5). According to these results and other studies on subjects in real-life conditions, EEG alpha (8–12 Hz) and theta activity (4–8 Hz) might represent an objective measure of fatigue (5) and/or reduced performance (6).

Thus, qualitative analyses of the constituent frequency components of the waking EEG may provide some useful EEG parameters for objective assessment of fatigue and other consequences of sleep loss. If such measures can be validated to reflect sleepiness and to predict imminent sleep during vehicular operation, shift work and in sleep disorders with hypersomnia, they may become new tools in the diagnosis of sleep disorders and preventing sleep-related accidents.

The constant routine (CR) protocol is a an experimental setting in which subjects are kept awake under controlled constant conditions in order to expose rhythmic and homeostatic influences on physiological parameters. By minimizing masking effects of the sleep–wake cycle, of physical activity, food intake and sensory stimulation, the CR protocol allows an accurate assessment of homeostatic and circadian effects on the EEG signal and on fatigue. It was hypothesized that under these conditions the increase in subjective fatigue during sustained wakefulness would be paralleled by a rise in EEG power density in alpha and theta frequencies.

METHODS

Nine healthy women (24–66 years old, mean 52.7 ± 4.3) participated in four identical CR protocols: two

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during summer and two during winter. In both seasons, the two CR protocols were separated by 1 week of bright light treatment. All subjects were paid volunteers, and they were free of drugs and medication, including hormone preparations, for at least 3 months. At the time of the experiment, they refrained from drinking alcohol and caffeine-containing beverages. Premenopausal women were studied during the follicular phase of the cycle. Subjects were instructed to keep regular sleep schedules and a sleep diary during the week prior to the experiment. A baseline sleep episode spent in the laboratory with bedtimes individually adjusted to the habitual sleep times preceded each CR protocol, which started immediately upon awakening and lasted for the next 40 hours. Throughout this protocol, subjects were sitting in bed in a propped-up body position (45° angle) and were kept awake by a technician who was constantly with the subject and enforced adherence to the stringently timed procedures of the CR protocol. The protocol and its procedures were adapted from Czeisler et al. (7). Sustained wakefulness under such constant behavioral and environmental conditions (temperature 22°C, humidity 67%) represents a very standardized total sleep deprivation. The illumination during the entire CR protocol was <80 lux. During these 40 hours of wakefulness spent under time isolation and in a sound-attenuated chronobiology bedroom, isocaloric meals (sandwiches) and isotonic drinks (Isostar, Wander AG, Switzerland) were given every 2 hours in order to meet the individually determined energy requirements and to supply minerals. In order to ensure wakefulness, the subjects were not allowed to close their eyes at any time during the CR protocol.

Throughout the CR, half-hourly self-ratings of fatigue were obtained on 100-mm visual analogue scales. During each of the four CR protocols, the waking EEG signal was recorded after 3 hours (day 1 at 1000 hours), 10 hours (day 1 at 1700 hours), 27 hours (day 2 at 1000 hours), 34 hours (day 2 at 1700 hours) and after 40 hours (day 2 at 2230 hours) of wakefulness. The last recording took place immediately before the start of recovery sleep. Because subjects were aroused by the ongoing preparations for the sleep recording and by the approaching end of sleep deprivation, the conditions during the last waking EEG recording clearly differed from the four recordings on the CR protocol. This last recording was therefore excluded from the analysis. Each recording lasted for 4 minutes, during which the subjects were instructed to relax, to watch a small picture on the wall, to keep their eyes open and to avoid movement. These instructions were intended to maximize signal quality. During the entire 4-minute period of an EEG recording, an experimenter was in the bedroom with the subject in order to enforce wakefulness and proper execution of the task. At incipient behavioral signs of sleep (lowering of eyelids, drowsiness, gazing or rolling eyes) during the task, the instructions were repeated or the subject was verbally entertained. During these 4-minute periods, two EEG signals (C3-A2, C4-A1), two electrooculogram (EOG) signals and one electromyogram (EMG) and electrocardiogram (ECG) signal were recorded on polygraph paper (10 mm/second paper speed; Nihon Kohden, Japan). The EEG signals were high-pass filtered with a time constant of 1.0 seconds and low-pass filtered at 35 Hz (12 dB/octave), on-line digitized at a sampling rate of 128 Hz and subjected to spectral analysis by a fast Fourier routine. Power spectra were computed for consecutive 4-second epochs and 0.25-Hz frequency bins by applying a Kaiser–Bessel window. By computing the mean values over adjacent frequencies, the data were reduced to 0.5-Hz bin width for frequencies between 0.25 and 5.0 Hz and to 1-Hz bin width for frequencies between 5.25 and 25.0 Hz. Bins are referred to and plotted in this paper by the highest frequency included (e.g. the 2.5-Hz bin refers to the averaged values of 2.25 and 2.5 Hz; the 6-Hz bin refers to the averaged values of 5.25, 5.5, 5.75 and 6.0 Hz). In connection with the on-line calculation of the 4-second spectra, a time mark was written on the polygraph paper in 4-second intervals in order to allow synchronization of EEG spectra and paper recording. All records of waking EEG (C3-A2) were visually inspected on a 4-second basis. Four-second epochs with eye blinks or artifacts due to body movements, slow eye movements and sweating were excluded from subsequent analyses.

RESULTS

Because no significant effect of season, light treatment or interaction between these two factors was found for any frequency bin of the EEG power spectrum [three-factor analysis of variance (ANOVA) for repeated measures], the data from each of the four CR protocols were averaged for each subject to obtain a single power spectrum for each of the selected time points across the CR protocol; they were then averaged across subjects.

Figure 1 illustrates power spectra of the waking EEG recorded after 3, 10, 27 and 34 hours of prior wakefulness. Repeated measures ANOVA with the factor "prior waking duration" revealed a significant effect ($p < 0.05$) on power density values in the frequency bins between 6.25 and 9.00 Hz. The effect of "prior waking duration" was highly significant for power density averaged within the 6.25- to 9.0-Hz band ($F_{3,24} = 9.68$; $p < 0.008$). Power density in this frequency band is plotted in Fig. 2 for the first four time points across

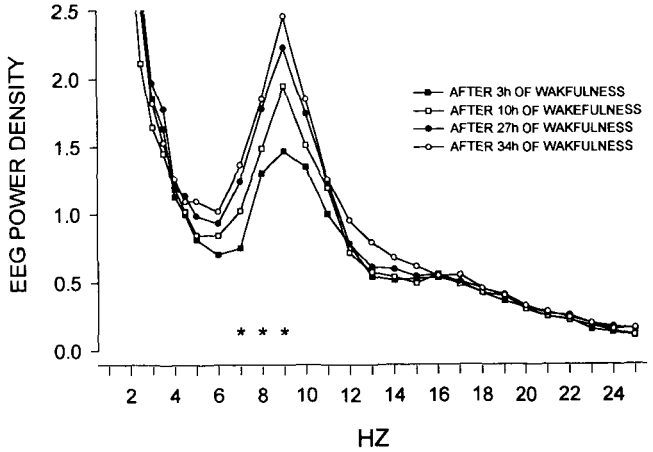

FIG. 1. EEG power density (μV^2/Hz) in single frequency bins (0.25–25 Hz). Asterisks above the abscissa indicate frequency bins for which significant changes over time were present (n = 9).

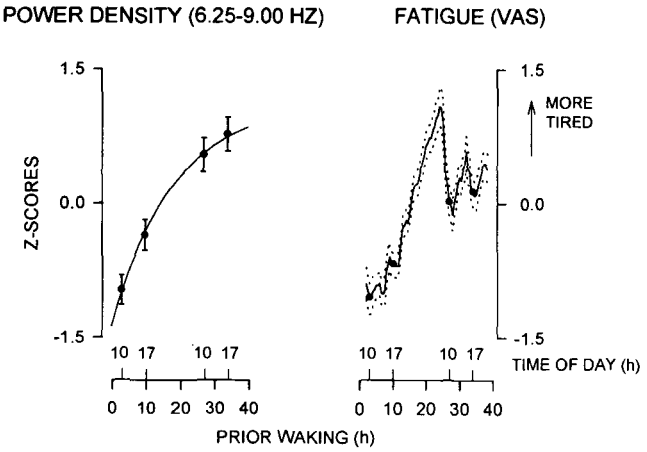

FIG. 2. EEG Power density (6.25–9.00 Hz) and subjective fatigue [visual analogue scale (VAS)] as a function of prior waking. The time course of the simulated data is indicated by the solid line (left panel). Both variables were z-transformed in respect to time for each subject separately. Dots (left panel) and the solid line (right panel) represent mean data (n = 9); vertical bars (left panel) and the dotted lines (right panel) indicate ± SEM.

the CR protocol. Post hoc comparisons revealed that power density after 27 and after 34 hours of wakefulness was significantly higher than after only 3 hours of wakefulness (paired t test, $p < 0.03$). The difference between the values obtained after 34 and after 10 hours also reached significance.

The time course of half-hourly self-ratings of fatigue across the CR protocol is presented in the right panel of Fig. 2. A strong circadian modulation as well as temporarily higher values of fatigue in the afternoon of the second day of sleep deprivation are superimposed on a global trend of increasing fatigue [for details see Brunner et al. (8)]. In order to obtain an estimate of subjective fatigue at each time point in which the EEG was recorded, three consecutive half-hourly values around the times of an EEG recording were averaged. These values, representing self-rated fatigue around 1000 and 1700 hours of the first and second day of sleep deprivation, varied significantly over the four time points (ANOVA; $F_{3,24} = 12.8$; $p < 0.002$). Fatigue was significantly higher after 27 and 34 hours of wakefulness than after 3 and 10 hours of prior waking (paired t test; $p < 0.001$ for all four comparisons). EEG power density in the 6.25- to 9.0-Hz band and the estimates of fatigue around the times of EEG recording showed a significant correlation ($r = 0.61$; $p = 0.024$; $n = 36$).

The increase of EEG power density in the 6.25- to 9.0-Hz band across the four time points was simulated iteratively for each subject according to a saturating exponential function given by $A_{sim,t} = S_{max} - (S_{max} - A_{sim,0})*e^{-t/\tau}$. $A_{sim,t}$ is the simulated value of EEG power density at time t, $A_{sim,0}$ the initial value at time 0 and S_{max} represents the asymptote of the exponential function. For the above equation it was assumed that the build-up of theta/alpha power in the waking EEG across wakefulness follows an exponential function analogous to that of sleep propensity, which is conceptualized in the two-process model of sleep regulation as Process S (9). The time constant τ of the exponential increase of sleep propensity was found to be 18.18 (10). Assuming the same value of τ (18.18), the parameters $A_{sim,0}$ and S_{max} were determined by the following procedure: EEG power density in the range of 6.25–9.0 Hz was z-transformed and repeatedly simulated using the above equation by systematically varying $A_{sim,0}$ and S_{max}. In each subject, the minimum mean square difference between simulated and actual data determined the best choices of $A_{sim,0}$ and S_{max}. When averaged over the nine subjects, the mean values for $A_{sim,0}$ and S_{max} were −1.37 and 1.13, respectively. The deviations of the simulated from the actual data did not vary significantly across the four time points [(Fig. 2, left panel); Friedman ANOVA χ^2 (df = 3) = 0.73; p = 0.9].

DISCUSSION

The present analysis of the EEG signal during wakefulness demonstrates that power density in the frequency range of 6.25–9.0 Hz increases monotonically in the course of sustained wakefulness. This finding corroborates earlier reports of increased EEG power density in the theta/alpha frequency range across prolonged periods of wakefulness (4,5,11,12). Because the present experiment was carried out under the constant conditions of a CR protocol, the data further suggest that these EEG changes in the course of wakefulness are not due to masking effects and behavioral changes brought about by coping with sleep deprivation. In contrast to the experiment of Torsvall and Åkerstedt

(5), in which subjects were studied while being on the job, we did not find an increase of power density in the delta frequencies. The close behavioral control of our subjects during the recording of the EEG signal virtually prevented episodes of "microsleep" and may explain why no increase in delta activity was found in the present study.

Enhanced power density in the theta/alpha range in more recent studies contrasts with opposite findings of older experiments conducted across several days of sleep loss (13). However, the decreases in alpha activity in these older studies were reported to reflect the decreased ability of the subjects to maintain an alpha EEG pattern with closed eyes. Therefore, these results do not contradict our findings because earlier experiments rather quantified the presence of "microsleep", whereas more recent studies focused on EEG changes during wakefulness while striving to prevent episodes of "microsleep".

The increase of power density in the 6.25- to 9.0-Hz band in the course of sustained wakefulness could be closely approximated by a saturating exponential function. The duration of prior wakefulness has been shown to affect the EEG signal during sleep. In particular, power density of slow frequency components (0.75–4.5 Hz) of the sleep EEG has been described to be a function of prior wakefulness and sleep (9,10). Whereas the changes in the EEG signal of NREMS are most pronounced in the low delta frequencies, the changes of the waking EEG are present in the theta/alpha frequency range. However, the dynamics of these EEG changes in the two different vigilance states are similar and are adequately described by an exponential saturating function. This time course suggests an underlying homeostatic regulation depending on the duration of prior wakefulness and sleep. Whereas delta power density, which manifests this homeostasis in the sleep EEG, depends rather exclusively on the duration (quantity) of prior wakefulness and sleep, the alpha/theta frequencies of the waking EEG are known to depend also on the quality of wakefulness. Attention, sensory stimulation and increased arousal are strong influences that attenuate or "block" the alpha rhythm (14–16). An activation of our subjects occurred in the present study during the last hour of the CR protocol, when preparations for the sleep recording took place. Because of this change in conditions, the last EEG recording was excluded from the simulation of theta/alpha power density. However, our data from the last EEG recording are in agreement with the effects of sensory stimulation on the EEG signal. Power density in the 6.25- to 9.0-Hz band was considerably below the value expected from the simulation based on the first four measurements. Because external factors that interfere with the subjects' attention and activation are minimized during the CR protocol, our data provide strong evidence for the existence of an endogenous homeostatic component in the regulation of the waking EEG.

Self-rated fatigue increased in the course of 40 hours of wakefulness and showed a pronounced circadian modulation, with some signs of an ultradian 12-hour rhythm (8). Subjective fatigue and EEG power density in the theta/alpha range obtained at the four selected time points along the CR protocol correlated significantly. This small number of EEG recordings is not sufficient for a comparison of the time course of both these parameters, particularly because the times selected miss the strong circadian trough in subjective alertness. A more detailed analysis of the time course of fatigue and power density in the theta/alpha frequencies is necessary to reveal the extent of a putative circadian component in the waking EEG.

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