

Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure

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The impact of sleep deprivation (high sleep pressure) vs sleep satiation (low sleep pressure) on waking EEG dynamics, subjective sleepiness and core body temperature (CBT) was investigated in 10 young volunteers in a 40 h controlled constant posture protocol. The differential sleep pressure induced frequency-specific changes in the waking EEG from 1–7 Hz and 21–25 Hz. Frontal low EEG activity (FLA, 1–7 Hz) during sleep deprivation exhibited a prominent increase as time awake progressed, which could be significantly attenuated by sleep satiation attained with intermittent naps. Subjective

sleepiness exhibited a prominent circadian regulation during sleep satiation, with virtually no homeostatic modulation. These extremely different sleep pressure conditions were not reflected in significant changes of the CBT rhythm. The data demonstrate that changes in FLA during wakefulness are to a large extent determined by the sleep-wake dependent process with little circadian modulation, and reflect differential levels of sleep pressure in the awake subject. *NeuroReport* 12:2277–2281 © 2001 Lippincott Williams & Wilkins.

Key words: Circadian; Nap; Sleep deprivation; Sleep homeostasis; Spectral analysis; Subjective alertness; Waking electroencephalogram

INTRODUCTION

The electroencephalogram (EEG) is a reliable indicator of the process and regulation of sleep. Computerized analyses of the EEG during sleep in humans have demonstrated that the power of low frequency (0.75–7 Hz) components declines across the sleep episode and increases with the duration of wakefulness preceding sleep [1,2], almost independently of circadian phase [3]. There is now compelling evidence that low frequency EEG components, in particular slow-wave activity (SWA; EEG power density in the 0.75–4.5 Hz band), are largely controlled by mechanisms involved in sleep homeostasis (i.e. response to sleep loss). Dose–response studies have demonstrated an intimate relationship between SWA in the sleep EEG and prior wake duration across a range of 2–40 h of wakefulness (for review see [4]).

All of the aforementioned studies in humans have been based on EEG changes during sleep. More recent data provide evidence that sleep compensatory mechanisms can already be detected while subjects are awake. Quantitative EEG analyses during extended wakefulness have revealed frequency-specific circadian and homeostatic influences [5–7]. In particular, frontal low-frequency activity (1–7 Hz) exhibits a prominent increase with time awake and little circadian modulation [7]. This, together with the observed frontal dominance of sleep regulatory processes during sleep [8], indicates that frontal areas of the brain may be

more susceptible to sleep loss than other areas of the brain, a hypothesis first proposed by Horne [9].

To further elucidate the association between frontal EEG activity during wakefulness and the sleep/wake homeostat, subjects underwent a protocol in which the duration of wakefulness preceding sleep was systematically manipulated. The amount of prior wakefulness in the present study protocol was either extended (40 h) by sleep deprivation or shortened (2.5 h) by scheduling intermittent naps. A dose–response relationship between the amount of wakefulness and its repercussions on EEG dynamics while subjects remain awake has, to our knowledge, not been reported. Such an assessment is needed because duration of time awake together with circadian phase are major modulators of the EEG during sleep and wakefulness. We hypothesized that the level of low EEG power density during wakefulness, in particular in frontal brain areas, is correlated with the amount of prior time awake (i.e. level of sleep pressure).

MATERIALS AND METHODS

Subjects: Six male and four female subjects (age range 24–32 years, mean (\pm s.d.) 27.1 \pm 2.3) were studied. All subjects were non-smokers, free from medical, psychiatric, and sleep disorders as assessed by history, a physical examination, questionnaires and an adaptation night in the sleep laboratory. Subjects were instructed to abstain from

caffeine and alcohol for one week before the study; their compliance was verified on the day of admission to the laboratory with urinary toxicologic analysis. They were asked to keep a regular sleep-wake schedule (bedtimes and waketimes within ± 30 min of self-selected target time) prior to their admission to the laboratory. Adherence to this regular schedule was verified with a wrist actigraph (Cambridge Neurotechnologies, UK) and sleep diaries. Female subjects were studied during their follicular phase. All subjects gave written informed consent. The protocol, screening questionnaires and consent form were approved by the Ethical Committee, Medical Faculty of the University of Basel.

Protocol: The entire study comprised two protocol blocks (4 days each) with an off-protocol episode of 2–4 weeks in between (Fig. 1). Following two scheduled days in the laboratory (sleep at habitual times), subjects underwent a 40 h sleep deprivation (SD) under constant routine conditions (for details of methods see [7]) or a 40 h constant posture nap protocol (Nap) in a balanced crossover design (intra-subject comparison). The SD and the Nap protocol started at habitual waketime (lights on, Fig. 1) after an 8 h baseline night. The 8 h sleep episodes were timed in such a way that they were centered at the midpoint of the subject's habitual sleep episode as assessed by actigraphy and sleep logs taken 1 week prior to the study. During the Nap protocol, subjects were scheduled to an alternating

cycle of 150 min of wakefulness and 75 min of sleep. During both protocols posture remained constant throughout. An 8 h recovery night followed the 40 h Nap or SD protocol.

Assessment of subjective and objective sleepiness: Subjective sleepiness was assessed every 30 min on the Karolinska Sleepiness Scale (KSS) [10]. The Karolinska Drowsiness Test (KDT) [10,11] was performed every hour during scheduled wakefulness after habitual waketime. During the KDT the subjects were instructed to relax and fixate for 3 min on a 5 cm black dot, attached to the wall at 1.5 m distance.

EEG recording and analyses: Bipolar EEGs were calculated off-line from a continuous 12-referential EEG recording. All signals were on-line digitized (12 bit AD converter, 610 μ V/bit; storage sampling rate at 128 Hz for the EEG) and digitally filtered at 30 Hz (4th order Bessel type anti-aliasing filters, total 24 dB/Oct.) using a time constant of 1.0 s (Vitaport-3 digital recorder, TEMEC Instruments BV, Kerkrade, The Netherlands). The raw signals were stored on-line on a Flash RAM Card (Viking, USA) and downloaded off-line to a PC hard drive. EEG data collected during the 3 min KDT were scored for artifacts and subjected to a fast Fourier transform routine (Vitaport paperless sleep scoring software). Two-second epochs were off-line subjected to spectral analysis using a fast Fourier transform (FFT, 10% cosine window) resulting in a 0.5 Hz bin resolution. For data reduction, artifact free 2 s epochs were averaged over 20 s epochs. Next, the 20 s epochs were further reduced by averaging them over each 3 min KDT. EEG power spectra during each 3 min KDT were calculated for the derivation Fz-Cz in the range 0.5–25 Hz. Analyses were based on absolute EEG power density (μ V²/0.5 Hz) and on relative EEG power density (%). Relative EEG power density was calculated in such a way that EEG power spectra were log-transformed for each frequency bin and subject in order to obtain a normal data distribution. After log-transformation, the difference between EEG power density obtained after 39 h into the SD (high sleep pressure) and the Nap protocol (low sleep pressure), and EEG power spectra obtained on day 1 during the same circadian phase (baseline), was calculated for each frequency bin and subject. Next, data were averaged across subjects. Averaged values over subjects were re-transformed and expressed as percentage of the baseline value before plotting the data.

Thermometry: Core body temperature (CBT) and eight surface skin temperatures were recorded continuously throughout the study using a rectal thermistor and skin temperature sensors with data stored in 20 s epochs. Here, we only report data on CBT.

Statistics: The statistical package SAS (SAS Institute Inc., Cary, NC, Version 6.12) was used. Two-way ANOVA for repeated measures (rANOVA) with the factors sleep pressure and time intervals were performed for each power value in each frequency bin separately. Subjective sleepiness ratings and the time course of CBT were analyzed with two-way rANOVAs with factors sleep pressure and

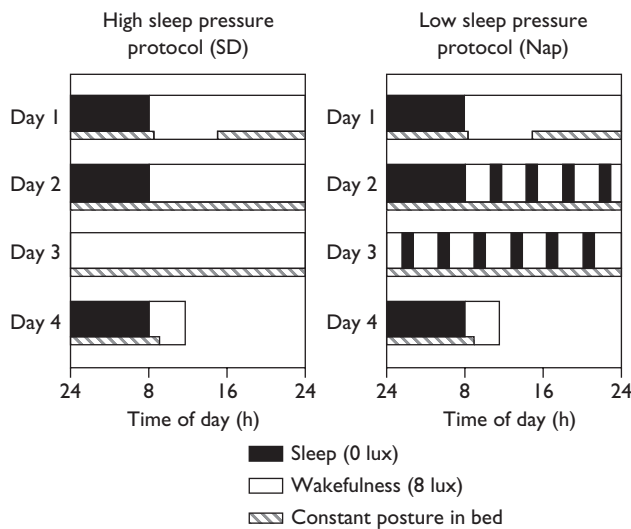


Fig. 1. Overview of the high and low sleep pressure protocol design. Subjects were scheduled to 8 h sleep episodes and 16 h of scheduled wakefulness according to their habitual bedtimes (24.00–08.00 h in the present subject, black bars). Except for the initial 8 h episode on day 1, subjects remained in a constant near-recumbent posture (20°) during scheduled wakefulness and supine during scheduled sleep (hatched bars). The light levels during scheduled wakefulness were < 8 lux, typically between 3 and 5 lux. During scheduled sleep/nap episodes subjects were in complete darkness (0 lux). Left: High sleep pressure protocol (SD): 40 h of extended wakefulness starting at habitual waketime on day 2. Right: Low sleep pressure protocol (Nap): 40 h of an alternating regimen of 150 min scheduled wakefulness and 75 min scheduled sleep, starting at habitual waketime on day 2.

time interval. Before entering the two-way rANOVA, subjective sleepiness ratings (KSS) and EEG power density were binned into 3.75h intervals per subject. This corresponded to a total of 11 time points across both the SD and Nap protocol. CBT was binned into 1.25h intervals which corresponded to 32 time points across the protocols. All p values derived from rANOVAs were based on Huynh-Feldt's (H-F) corrected degrees of freedom, but the original degrees of freedom are reported. For *post-hoc* comparisons Duncan's multiple range test was used.

RESULTS

EEG power density and different levels of sleep pressure: Absolute EEG power spectra under high sleep pressure (i.e. after 39h into the SD protocol) and under low sleep

pressure (i.e. after 39h into the Nap protocol) are illustrated in Fig. 2 (upper panels) together with EEG spectra during baseline conditions recorded the day before at a similar circadian phase. A rANOVA with the factors sleep pressure and time (baseline *vs* 39h into the SD/Nap protocol) showed a significant interaction for these two factors in the following frequency bins: 0.5–7 Hz, 9–11 Hz and 20.5–25 Hz ($p < 0.05$, for each frequency bin). *Post hoc* comparisons on relative EEG power density (see Materials and Methods) revealed a significant increase in EEG power density in the range 0.5–7 Hz in the high sleep pressure condition as well as in the range 20.5–25 Hz (Fig. 2, left bottom panel, $p < 0.05$, for each frequency bin). The same analysis applied to the low sleep pressure condition revealed a significant increase in the frequency bins 5–5.5,

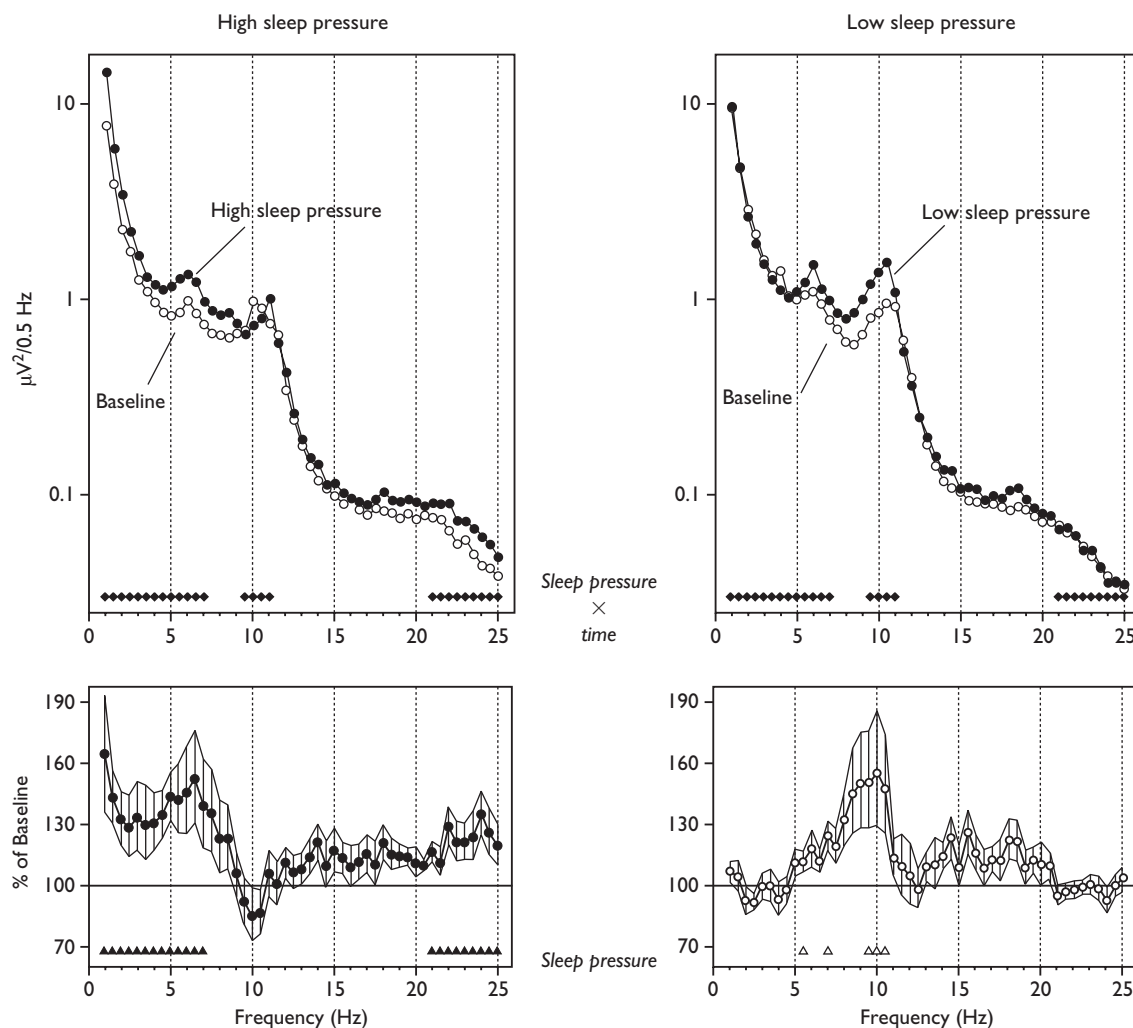


Fig. 2. Frontal EEG power spectra (Fz-Cz) during wakefulness after high sleep pressure (SD protocol), low sleep pressure (Nap protocol) and baseline. Top panel. Absolute power spectra are plotted in the frequency bins from 0.5 to 25 Hz during baseline and after 39h into the SD (left) and the Nap protocol (right), respectively (mean values; $n = 10$). The circadian phase of the baseline EEG recording on day 1 corresponded to that after 39h into the SD- or Nap protocol. Symbols near the abscissa (diamonds) indicate frequency bins for which a significant interaction between sleep pressure (high vs low) and time point (baseline vs treatment) was found ($p < 0.05$). Bottom panel: Effects of high and low sleep pressure on the power spectrum during wakefulness. Data after 39h into the SD or Nap protocol were expressed as percentage (mean values \pm s.e.m., $n = 10$) of the corresponding value during baseline conditions. Horizontal symbols (triangles) indicate frequency bins for which the value in the high or low sleep pressure condition was significantly different from the baseline value (Duncan's multiple range test on log-transformed ratios $p < 0.05$).

6.5–7 and 9.0–10.5 Hz (Fig. 2, right bottom panel, $p < 0.05$). Power density in none of the frequency bins differed significantly between the two baseline recordings ($p > 0.1$, for each frequency bin).

Time course of frontal low EEG activity, subjective sleepiness and CBT: Subjective sleepiness exhibited a circadian modulation during both the Nap- and the SD protocol. The overall buildup of subjective sleepiness was not present in the Nap protocol (Fig. 3, 2-way rANOVA; sleep pressure \times time: $F(10,90) = 13.0$; $p < 0.0001$). *Post hoc* comparisons indicated that subjective sleepiness was significantly lower in the Nap protocol from around midnight until the end of the protocol ($p < 0.05$). Low EEG activity (%) in the frontal derivation increased across the SD protocol, whereas in the Nap protocol only small changes in the time course were observed (sleep pressure \times time: $F(10,90) = 4.1$; $p < 0.05$). The first significant change in frontal low EEG activity between conditions was at around the CBT minimum, with higher values in the high sleep pressure condition. This increase remained significant for the remainder of the protocol ($p < 0.05$). Frontal EEG beta activity in the range 21–25 Hz increased across the SD protocol and, to a lesser extent, across the Nap protocol (data not shown). However, the interaction sleep pressure \times time did not yield significance ($F(10,90) = 1.5$; $p = 0.2$). The time course of CBT did not show any significant difference between the two conditions (Fig. 3, bottom panel; sleep pressure \times time: $F(31,279) = 0.6$; $p = 0.8$).

DISCUSSION

The present data reveal and confirm that naps, scheduled over the entire circadian cycle, attenuate the homeostatic drive for sleepiness, whereas its circadian modulation remains unaffected. The observed changes in frontal low EEG activity during wakefulness seem to represent the levels of sleep pressure attained by each protocol. This confirms our hypothesis that frontal low EEG activity can be used to monitor different levels of sleep pressure in the awake subject. Thus, the present data provide further evidence that changes in frontal low EEG activity during wakefulness may be determined to a large extent by the homeostatic sleep–wake dependent process. The decrease in FLA during the second day of the SD protocol indicates the presence of a circadian modulation of FLA. In contrast, the different levels of sleep pressure did not affect CBT, and no significant reduction in CBT occurred during episodes when the subjects were allowed to sleep.

The increased frontal low EEG activity in the high sleep pressure protocol are in good accordance with previous studies in which the effect of sleep deprivation on waking EEG power spectra has been quantified [5,6,11,12] and showed a frontal dominance of the effect [7,13]. Our current data demonstrate for the first time that this increase in waking low EEG activity is intimately related to the sleep–wake dependent homeostat. This waking EEG parameter may be useful in monitoring the homeostatic regulation of sleep need, recently found to be under strong genetic control [14]. The rather prominent circadian drive for subjective sleepiness could not be circumvented by multiple naps. Thus, the modulation of alertness levels is strongly circadian even under very low homeostatic

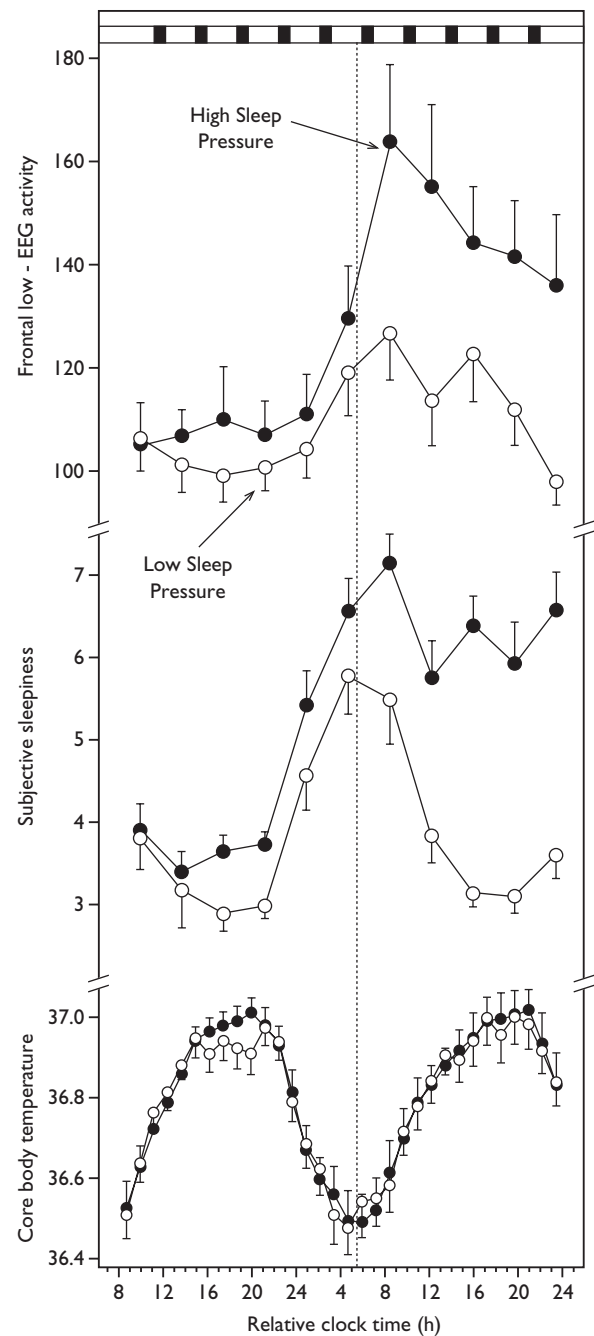


Fig. 3. Dynamics of frontal low EEG activity (EEG power density in the 1–7 Hz band) during wakefulness, subjective sleepiness on the Karolinska Sleepiness Scale and core body temperature (CBT) across the 40h SD (high sleep pressure) and Nap protocol (low sleep pressure). The upper two panels indicate the timing of the naps (black bars) and scheduled episodes of wakefulness (white bars) respectively for the SD and Nap protocol. Data were binned into 3.75 h time intervals for low-EEG activity and subjective sleepiness and into 1.25 h time intervals for CBT (mean values \pm s.e.m., $n = 10$). Data are plotted against the midpoint of the time intervals. Relative clock time represents the average clock time at which the time intervals occurred. For statistics see text.

pressure (i.e. short duration of prior wakefulness). It confirms findings gathered in a forced desynchrony protocol in humans living under a 20 hour day, where a significant effect of circadian phase on subjective sleepiness was already present after 0–3.3 h of elapsed time awake [15]. This is of practical importance, since shift workers and transmeridian travelers often try to overcome their sleepiness with multiple naps. Although napping can be an effective countermeasure against neurobehavioral decrements, working at night, in particular at times around the circadian trough, remains a critical working hazard zone in spite of being sleep satiated.

Even though the circadian rhythm of subjective sleepiness closely followed that of core body temperature (CBT) in the high and low sleep pressure protocol, CBT itself was not significantly changed, which confirms findings from other constant routine protocols [16,17]. This result corroborates the finding by Kräuchi *et al.* [18], that at lights-off without any postural change, a general pre-capillary skin vasodilation takes places concomitant with a small decrease in CBT which is not related to sleep *per se*, but rather to a general relaxation of the subjects.

CONCLUSION

These data demonstrate that activation of sleep regulatory processes by extreme manipulation of the duration of prior wakefulness (i.e. sleep deprivation and sleep satiation) results in frequency-specific EEG changes during wakefulness. In particular, the increase in frontal low EEG activity

(FLA) with duration of time awake was closely related to the level of sleep pressure. Time course analysis of FLA revealed a minor circadian and a major homeostatic modulation, which was positively related to subjective sleepiness. FLA may be useful to monitor the homeostatic accumulation of sleep pressure in the awake subject.

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