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Published in:
Sleep

Sleep
13(5):430–440, Raven Press, Ltd., New York

Electroencephalogram Power Density and Slow Wave Sleep as a Function of Prior Waking and Circadian Phase

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Summary: Human sleep electroencephalograms, recorded in four experiments, were subjected to spectral analysis. Waking prior to sleep varied from 12 to 36 h and sleep was initiated at different circadian phases. Power density of delta and theta frequencies in rapid-eye-movement (REM) sleep and non-REM (NREM) sleep increased monotonically as a function of prior waking. The increase of power density in the theta frequencies contrasts with the reported decrease of theta activity as detected by period–amplitude analysis. Slow wave activity (power density, 0.25–4.0 Hz) in NREM sleep during the first 3 h of sleep did not deviate significantly from the homeostatic process *S* of the two-process model of sleep regulation. In contrast, visually scored slow wave sleep, stages 3 and 4, deviated from this prediction at some circadian phases. It is concluded that, in accordance with the two-process model of sleep regulation, slow wave activity in NREM sleep depends on prior waking and is not significantly influenced by circadian phase. **Key Words:** Circadian rhythms—Electroencephalogram—Homeostasis—Slow wave sleep—Spectral analysis—Two-process model.

Visual scoring of human sleep electroencephalogram (EEG) has revealed that stage 4 (1) and slow wave sleep (SWS, stages 3 and 4) (2,3) are primarily determined by the duration of prior wakefulness, although some authors have reported that circadian phase may exert a small influence (4). Spectral analysis using fast Fourier algorithms (5–11) and period–amplitude analysis (12–17) have also been applied to describe the relationship between the prior history of sleeping and waking and the subsequent sleep EEG. Both methods have led to the conclusion that slow-wave, or delta, activity is enhanced after extended waking. There is, however, some discrepancy in the changes observed in higher frequency components of the EEG. Feinberg and collaborators (16), using period–amplitude analysis, reported that the incidence of theta frequencies de-

Accepted for publication March 1990.
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creased after 40 h of waking, whereas Borbély and colleagues (5) found an increase in power density in theta frequencies.

One aim of this article was to further document the relation between prior waking and EEG power density over a broad frequency range during both rapid-eye-movement (REM) and non-REM (NREM) sleep. Prior waking was varied by initiating experimental sleep episodes at different circadian phases. By this protocol, prior waking and circadian phase are varied simultaneously. Therefore, the data are suitable to test the prediction of the two-process model (18,19) that slow wave activity (SWA) increases as a monotonic function of prior waking, even when sleep is initiated at different circadian phases. In the two-process model, a regulating variable increases in a saturating way during waking and decreases during sleep. The increase of S is independent of circadian phase. Since it is assumed that S is reflected in SWA (power density in the delta frequencies) during sleep, the model allows a quantitative prediction of the value of SWA in virtually all sleep–wake schedules. A second aim of this article was to quantitatively compare the prediction of the model with data on SWA, which were obtained in four experiments (exps).

Although an increasing number of laboratories are applying spectral or period–amplitude analysis, visual scoring according to established criteria (20) is still often the only method used for quantification of the sleep EEG. Data based on visual scoring have been interpreted as being in accordance (2) or at variance (21–24) with the two-process model of sleep regulation. Although in general changes in stages 3 and 4 (SWS) correlate well with changes in EEG power density in the low-frequency range (8), a dissociation between these two variables has been reported in healthy subjects (25,26) and depressed patients (27). However, a detailed analysis of the correlations between visual scoring and spectral analysis is not available. Therefore, a third aim of this article was to describe the interrelations between SWA as detected by spectral analysis and visually scored stages 3 and 4 and SWS.

METHODS

Data were compiled from experiments carried out in Zurich (exp 1, 2, and 4) and Groningen (exp 3) (Table 1). Details on experimental protocols and procedures used for EEG recording and analysis of the EEG are described elsewhere (9,11,28,29). In short, subjects were healthy men in their 20s, without sleep complaints. In all experiments, subjects had slept in the laboratory during at least 1 night before sleep EEGs were

TABLE 1. *Protocols of the four experiments and slow wave sleep (SWS) and rapid eye movement (REM) sleep in the first 3 h of sleep*

	Baseline sleep			Displaced sleep			
Experiment (no. subjects)	Sleep period, clock time	SWS, min (SEM)	REM, min (SEM)	Sleep period, clock time	Prior waking	SWS, min (SEM)	REM, min (SEM)
1 (9)	23–07	71.2 (6.4)	22.9 (4.5)	19–07	12 h	58.9 (7.2)	23.1 (4.4)
2 (8)	23–07	80.8 (4.6)	17.6 (2.6)	07–SA	24 h	70.1 (5.2)	32.6 (5.6)
3 (8)	00–08	70.6 (4.0)	17.9 (2.6)	11–SA	27 h	75.8 (2.9)	23.9 (3.7)
4 (9)	23–07	70.0 (3.4)	28.0 (1.7)	19–SA	36 h	109.3 (2.8)	18.4 (3.3)

Waking before baseline sleep was 16 h in all experiments.
SA, spontaneous awakening.

recorded. The EEGs were derived from C3–A2 and C4–A1. For the analysis, the C3–A2 lead was used unless the quality of the signal was unsatisfactory. After low-pass filtering (25 Hz, 24 dB/octave), EEG signals were digitized with a sampling rate of 128 Hz (exps 1, 2, and 4) or 64 Hz (exp 3). Subsequently, the EEG was subjected to spectral analysis by fast Fourier transformation (FFT). Spectra were calculated per 4-s epochs between 0.25–25.0 Hz (exps 1, 2, and 4) or between 0.25–15.0 Hz (exp 3). In all exps, a rectangular window was applied. Data were reduced to 0.5 or 1.0 Hz bins. The EEG recordings were scored according to the criteria of Rechtschaffen and Kales (20) per 20-s epochs (exps 1, 2, and 4) or 30-s epochs (exp 3). All records were scored only once and the scorers were not blind to the condition in all experiments. All EEGs of a subject were always scored by the same scorer. Despite the fact that EEGs were scored by different scorers in two laboratories, SWS in the first 3 h of baseline sleep was similar across experiments ($F_{3,30} = 1.10$, $p = 0.37$, Table 1).

After matching the time sequence of power spectra with the visual scores, power spectra were calculated for NREM sleep (stages 2, 3, and 4) and REM sleep separately. Thus, epochs of movement time, stage 0 (waking, W), and stage 1 were excluded from the analysis. The timing of baseline sleep, experimental sleep, and the hours of waking preceding experimental sleep in the four experiments are listed in Table 1. All baseline nights were preceded by 16 h of waking. In three experiments, the subjects could decide when they wanted to rise after the experimental nights (spontaneous awakening), but all slept at least 3 h. Therefore, this analysis was based on the first 3 h of sleep.

RESULTS

Power spectra during the first 3 h of sleep are depicted in Fig. 1. In each subject and frequency bin, data were expressed relative to spectral values in the first 3 h of baseline sleep. Since ratios are not normally distributed, the data were log transformed. Next they were averaged over subjects. In NREM sleep, power density from 0.25 to 11.0 Hz varied significantly across the four conditions (one-way analysis of variance, ANOVA, on log transformed values). The largest changes were present between 1–2 Hz. For those frequencies for which the ANOVA yielded a significant effect of condition, spectral values during experimental sleep episodes were compared with baseline values. After 12 h of waking (exp 1, clock time (ct) 19 h), power density in the 0.25–0.5-Hz bin was significantly lower than in the baseline (with 16 h prior waking, pw). After extending wakefulness to 24 (exp 2; ct, 7 h), 27 (exp 3; ct, 11 h), and 36 h (exp 4; ct, 19 h), spectral values in the delta and theta frequencies were significantly elevated in the range of 1.75–9.0 Hz. After 24 (exp 2; ct, 7 h) and 27 h (exp 3; ct, 11 h) of pw, no significant elevations of power density were observed in the lowest bins (0.25–1.5 and 0.25–1.0 Hz for 24 and 27 h, respectively), but after 36 h (exp 4; ct, 19 h) of pw significant enhancements were present between 0.25–9.0 Hz. In REM sleep, significant nonrandom variations in spectral values were present in some of the bins in the range of 0.75–7.0 Hz (Fig. 1). Deviations from baseline were significant only after 27 (exp 3; ct, 11 h) and 36 h (exp 4; ct, 19 h) of wakefulness.

To visualize SWA in NREM sleep during the first 3 h after sleep onset as a function of pw, the spectral power between 0.25–4.0 Hz was summated and expressed as a percentage of SWA in the corresponding interval of baseline sleep (Fig. 2). The SWA varied significantly over the four exps ($F_{3,30} = 13.94$, $p < 0.0001$) and was a monotonic function of pw. Pairwise comparisons revealed that SWA in exps 3 (pw, 27 h; ct, 11 h)

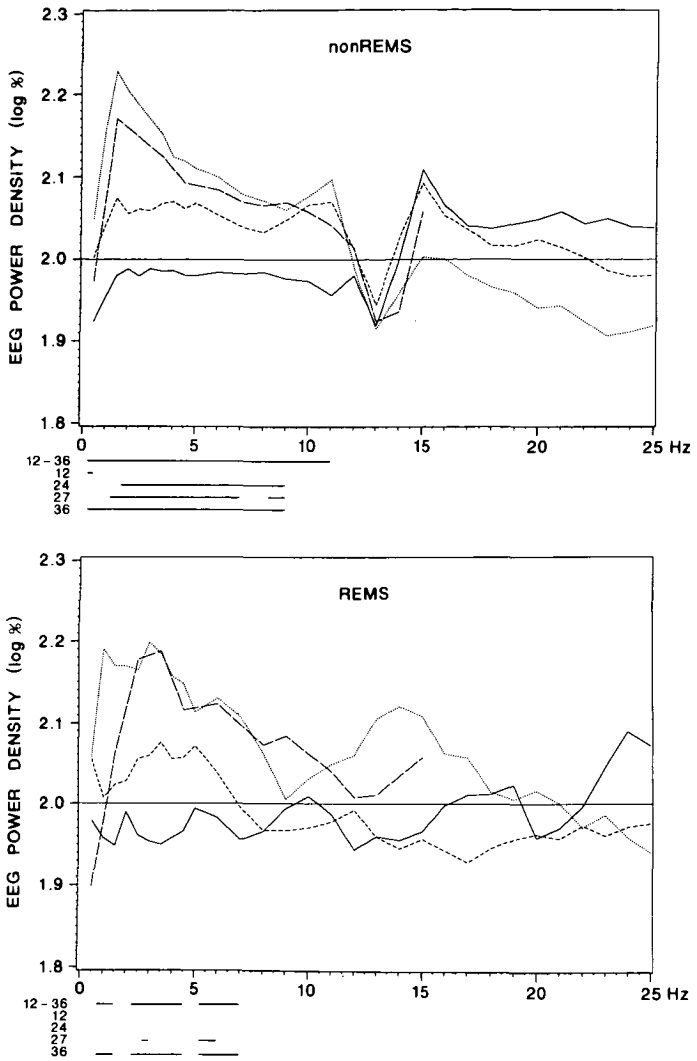

FIG. 1. EEG power density in NREM sleep (**top**) and REM sleep (**bottom**) during the first 3 h after sleep onset in four experiments. In each subject and frequency bin, data were expressed relative to power density in the corresponding frequency bin in NREM sleep or REM sleep during the first 3 h of baseline sleep and log transformed. Lines under the abscissa indicate significant ($p < 0.05$) variation of power density over the four experiments (label 12–36) as assessed with a one-way ANOVA, or significant deviation from baseline levels ($p < 0.05$, two tailed *t*-test). Significance of the deviation from baseline was tested only for those frequency bins that had yielded significant variation of power density by ANOVA. Exp 1 (_____): prior waking, 12 h; lights off, 1900 h (label 12); exp 2 (– – –): prior waking, 24 h; lights off, 700 h (label 24); exp 3 (— —): prior waking, 27 h; lights off, 1100 h (label 27); and exp 4 (· · · · ·): prior waking, 36 h; lights off, 1900 h (label 36).

and 4 (pw, 36 h; ct, 19 h) was significantly higher than in exp 1 (pw, 12 h; ct, 19 h) ($p < 0.05$ in all cases). In exp 4 (pw, 36 h; ct, 19 h), SWA was also significantly higher than in baseline and exp 2 (pw, 24 h, ct, 7 h). No other significant differences were observed. The time course of process *S* was calculated according to the saturating exponential function $S_t = 1 - ((1 - S_0)*e^{-t/\tau})$. The time constant τ was set to 18.18 h (19). When subjects are on a 16-h waking – 8 h sleep schedule, S_0 (i.e., *S* on awakening) attains a

value of 0.093. The values of S at the beginning of the experimental sleep episodes were calculated and expressed as a percentage of the value of S at the beginning of baseline sleep (Fig. 2). It should be kept in mind that due to the exponential decline of S during sleep, the ratio of S at sleep onset in baseline and experimental conditions is identical to the ratio calculated for the mean value of S over the first 3 h. The deviation of SWA from the S curve was calculated for all individual data points. The mean deviation of $-4.14 \pm 12.84\%$ (SEM) did not differ significantly from 0 (t-test, $p > 0.05$). To investigate whether the deviation from the prediction varied as a function of condition, the residuals were subjected to ANOVA. No significant effect of condition on the residuals was obtained ($F_{3,30} = 2.26$; $p > 0.1$).

To compare spectral analysis with visual scoring, time in stages 3 and 4 and SWS (stages 3–4) during the first 3 h of experimental sleep episodes was also expressed relative to baseline values (Fig. 2). All three variables varied significantly across conditions ($p < 0.01$ in all cases). However, their time courses differed. Stage 3 rose

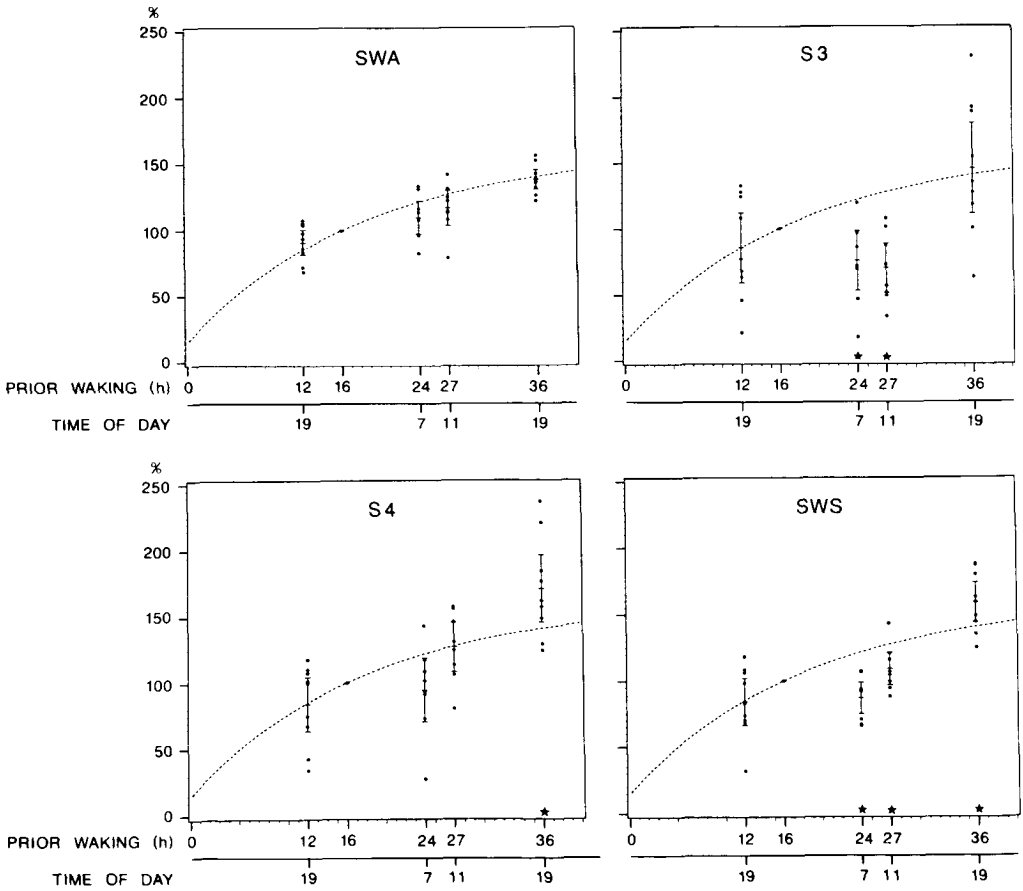

FIG. 2. SWA **(top left)**, stages 3 (S3) **(top right)** and 4 (S4) **(bottom left)**, and SWS **(bottom right)** calculated for the first 3 h of sleep, as a function of prior waking. The time course of process S is indicated by the dashed line. All variables are expressed as a percentage of the corresponding variable in the first 3 h of baseline sleep. Dots represent individual data points; vertical bars indicate mean ± 1 SEM. The baseline reference values (= 100%) are indicated with a dot at prior waking = 16 h. Data are plotted at time of lights off. Significant deviations ($p < 0.05$) from the prediction are indicated by stars.

significantly only after 36 h of waking (exp 4; ct, 19 h), whereas stage 4 was already significantly enhanced after 27 h of waking (exp 3; ct, 11 h). Not surprisingly, the time course of SWS was intermediate between those of stages 3 and 4. Characteristic for all three variables was the marked increase after 36 h of waking, when sleep was initiated at 1900 h (exp 4). The sleep stages were also compared to the theoretical S curve. The deviations averaged over all four experiments were -23.17 ± 8.00 ($p < 0.01$), 1.18 ± 6.44 (NS), and $-7.81 \pm 4.92\%$ (NS) for stages 3 and 4 and SWS, respectively. The deviations from the theoretical S curve varied significantly over the four conditions for all three variables (stage 3, $F_{3,30} = 5.55$, $p < 0.005$; stage 4, $F_{3,30} = 4.43$, $p < 0.01$; SWS, $F_{3,30} = 9.52$, $p < 0.001$). When sleep was initiated at 700 h (exp 2; pw, 24 h), SWS and stage 3 were significantly lower than predicted. But significant deviations between the prediction and the data derived from the visual scoring were also present in other experiments (Fig. 2).

The correlations between changes in SWA and sleep stages are summarized in Table 2. Calculated over all experiments, stage 3 did not correlate significantly with SWA, whereas stage 4 and SWS were significantly positively correlated with SWA. These correlations were, however, not present in all data sets. Stage 4 was significantly correlated with SWA in exps 1 (pw, 12 h; ct, 19 h) and 2 (pw, 24 h; ct, 7 h) but not in exps 3 (pw, 27 h; ct, 11 h) and 4 (pw, 36 h; ct, 19 h). A significant negative correlation between stage 3 and SWA was observed in exp 2 (pw, 24 h; ct, 7 h).

DISCUSSION

Spectral analysis of the EEG in NREM sleep demonstrated that variations in the duration of waking prior to sleep result in variations in spectral components of the sleep EEG in the range of 0.25–11.0 Hz. Power density in the range of 1.25–7.0 Hz increased monotonically with increasing duration of prior wakefulness. These results are in accordance with previous exps in which FFT was applied (5,7). It could be argued that the increase in theta power is due to leakage that may occur when a rectangular window is used. Therefore the data of one experiment (exp 4; pw, 36 h; ct, 19.00 h) were reanalyzed with a Kaiser–Bessel window ($\alpha = 3$. For a description of the characteristics of this window see reference 30). No major differences between the data obtained with the two windows were observed. Thus sleep deprivation also resulted in significant enhancements of power density in the delta and theta frequencies (0.25–8.0 Hz, $p < 0.05$ in all frequency bins) when spectra were calculated with a Kaiser–Bessel window.

Although an enhancement of the number and the amplitude of delta waves has also

TABLE 2. *Correlation between slow wave activity and sleep stages in four experiments*

		Stage 3		Stage 4		SWS	
Experiment	(no.[a])	r	$p <$	r	$p <$	r	$p <$
1	(9)	0.113	(NS)	0.811	(0.01)	0.529	(NS)
2	(8)	−0.739	(0.05)	0.868	(0.01)	0.401	(NS)
3	(8)	−0.399	(NS)	0.327	(NS)	−0.484	(NS)
4	(9)	−0.529	(NS)	0.450	(NS)	0.014	(NS)
All	(34)	0.089	(NS)	0.807	(0.01)	0.638	(0.01)

For the calculation of the Pearson product moment correlation data were expressed as percentage of baseline and log transformed.

[a] Number of sleep episodes.

been detected by period–amplitude analysis, application of this technique has resulted in the conclusion that after extended waking theta activity decreases (16). These discrepancies between the results of FFT and period–amplitude analysis are not limited to human sleep but are also present in rodent sleep. Sleep deprivation induces a rise of power density in delta and theta frequencies in the rat (31), hamster (32), and the diurnal chipmunk *Eutamias sibiricus* (33), whereas period–amplitude analysis suggested that in the rat theta activity is reduced after extended waking and exercise (34). These discrepancies are probably related to the filtering of the EEG prior to the period–amplitude analysis: if the filtering of the EEG is not exactly adjusted and exclusively restricted to the frequency of interest, there is a considerable risk of misinterpretation. For instance, in the absence of adequate filtering, theta waves superimposed on lower frequencies are not detected by period–amplitude analysis (35). Only those theta waves that cross the zero-voltage level are detected by period–amplitude analysis. Any increase in the number and/or amplitude of delta waves will therefore result in a reduction in the theta activity detected. These limitations do not apply to FFT, where all frequency bands are analyzed independently of each other. With this technique we have noted consistently in various experimental situations (our data, 5,7,36) and age groups (37) that power values of delta and theta frequencies change in the same direction. Therefore, it does not seem necessary to postulate two separate generators for these EEG frequencies in NREM sleep, as was suggested on the basis of period–amplitude analysis of rat sleep (38).

Although spectral analysis is a powerful method of EEG analysis, it has certain limitations. For instance, if the EEG is adequately filtered, the average amplitude and number of waves within a certain period can be estimated by period amplitude analysis, information that is not obtained by spectral analysis.

In accordance with a previous experiment (5), not only the power spectrum of NREM sleep but also the power spectrum in REM sleep changed after varying pw, but significant changes were only present when sleep pressure was high. Reduction of sleep pressure (i.e., only 12 h of pw; ct, 1900 h; exp 1) did not result in a significant reduction of power values in REM sleep. Qualitatively, the changes in the power spectrum are comparable in REM and NREM sleep. However, in NREM sleep, the major changes occur in the low delta band, whereas in REM sleep they are seen in the high delta band. It has been reported previously that extending prior wakefulness increases EEG power density in delta, theta, and alpha frequencies during wakefulness (39). This may suggest that the effect of pw on the EEG-generating mechanisms is independent of the vigilance state, although the manifestation of the effect may show state-specific features.

Within the delta and theta range, power densities were not equally affected. In NREM sleep, power density between 1.25–2.0 changed most when pw was varied from 16 to 36 h. However, when sleep pressure was reduced (exp 1; pw, 12 h; ct, 19 h) only the lowest frequency bin was significantly affected. This suggests that power density in the lowest delta range is at a near-maximal level already after a normal waking episode. A further increase of "sleep pressure" affects mainly the higher delta frequencies. A similar differential effect within the delta band was found when pw was varied from 2 to 20 h (7).

From this analysis, it seems justified to conclude that power densities of the delta and theta frequencies in NREM sleep are a monotonic function of pw. Close inspection of Fig. 1 may suggest that when sleep is initiated at 700 h (exp 2; pw, 24 h) the spectral distribution is somewhat atypical. Power density is at a uniformly increased level

between 1–5 Hz, whereas after a further extension of waking by only 3 h (sleep initiation at 1100 h; exp 3; pw, 27 h), a peak appears at 2 Hz. Thus, we cannot exclude the possibility of a circadian influence on the distribution of power over the different frequencies in NREM sleep. This circadian effect may be mediated by an effect of REM sleep or REM sleep pressure on the NREM power spectrum, since in experiments in which REM sleep pressure was experimentally enhanced a similar phenomenon was observed (10,40). Alternatively, the altered spectral distribution may be related to the fact that sleep pressure was only moderately increased. A small reduction of sleep pressure (exp 1; pw, 12 h; ct, 19 h) also induced a pattern of changes in the power spectrum that did not mirror the pattern observed after extension of waking to 27 h (exp 3; ct, 1100 h), 36 h (exp 4; ct, 1900 h), or 40 h (ct, 2300 h; data from reference 5). The detection of a circadian influence on the relative power spectra as presented in Fig. 1 is complicated by the nonlinear nature of the function describing the relation between power and pw. Since the time constants of these functions are different for adjacent frequencies in the delta band (7) and probably depend on the time interval considered, the ratios of power values in adjacent frequencies are not constant. Therefore a detailed quantitative description of the changes of power in separate frequencies over a wide range of pw is needed before a circadian influence on the power spectrum can be unambiguously established.

From these data it is, however, clear that when power is summated over the 0.25–4.0-Hz range, the resulting variable, SWA, increases monotonically. Its time course corresponded closely to the time course of the theoretical process *S*, which increases according to a saturating exponential function (compare 41), and no significant difference between the data and the prediction was present at any circadian phase.

So even in the morning when REM pressure is high (42), SWA in NREM sleep is at the level that is predicted by the homeostatic process that is independent of circadian phase. Some caution is needed, though, since this analysis was based on the first 3 h of sleep. An analysis on a finer time basis may still detect a circadian influence on SWA.

However, in two exps (2 and 4) in which the analysis was restricted to the first NREM episode, SWA did not deviate significantly from the predicted level (11,28).

In our experiments we used clock time as a phase marker of the circadian system. Interindividual differences in phase position relative to clock time may exist. Therefore, we cannot exclude the possibility that when subjects would have been synchronized according to their circadian phase, a circadian modulation of SWA would have been found.

In contrast to SWA, significant deviations from the time course of process *S* were present for stages 3 and 4 and SWS. In the early morning (7 h) significantly less SWS was present than predicted from process *S*. Lower levels of SWS in the early morning have been reported before (43) and therefore it is unlikely that this result is due to the somewhat higher level of SWS in the baseline night of this experiment (Table 1). One possible explanation for the dissociation between visual scoring and spectral analysis is the circadian variation of REM sleep, with high levels in the early morning (Table 1; 42,43). When REM sleep in the first 3 h of the experimental sleep episodes (Table 1) was expressed as a percentage of REM sleep in the first 3 h of corresponding baseline sleep, a one-way ANOVA on log-transformed values indeed revealed a significant effect of condition ($F_{3,30} = 3.35$, $p < 0.05$). As a consequence of this circadian variation in REM sleep, less time per 3 h is available for NREM sleep in the early morning. Since SWS is usually expressed in minutes per time interval (in this case, 3 h), a circadian influence

on REM sleep may have repercussions on the time in SWS (22). In contrast, SWA, which is basically a density measure, is not necessarily affected by a reduction in NREM time. It is therefore inappropriate to conclude from the circadian influence on time in SWS that there is a circadian influence on NREM sleep intensity.

A dissociation between visual scoring and spectral analysis was also present within experiments. When sleep pressure was high, no significant correlations between SWA on the one hand and stages 3 and 4 and SWS on the other hand were present (Table 2). The obvious explanation for this finding is that visual scoring does not distinguish between epochs containing 50% delta waves and epochs containing 100% delta waves. A similar argument can be advanced with respect to the minimal amplitude criterion (75 μV) of slow waves (20). Calculated over all experiments, the highest correlation was obtained between SWA and stage 4. Therefore, an estimate of the time course of process *S* on the basis of visual scoring should be based on stage 4, and not on stages 3 and 4 combined (SWS).

However, as our results show, changes in sleep stages scored according to standard criteria cannot be extrapolated to changes of SWA. It can be argued that the correlations between SWA and SWS would increase if sleep records would be scored more carefully and by more than one scorer. Although this may be the case to some extent, the fact that the correlation becomes poor when levels of SWS are high, i.e., when few borderline epochs are present, indicates that the quality of scoring is unlikely to be the only cause for the lack of correlation.

Previously it has been reported that within stage 4 a significant variation in delta power density is present in baseline sleep and in recovery sleep after sleep deprivation (5). Taken together, it has to be concluded that data obtained by visual scoring cannot be taken as solid evidence in favor of (2) or against (21–24) the hypothesis that SWA (power density in the delta frequencies) obeys the rules of an hourglass process (18,19,44) that monitors sleep debt.

We conclude that spectral analysis is a sensitive method for analyzing changes in sleep EEGs over a wide frequency range. Quantification of these changes may help to identify the nature of the underlying processes and be useful for the further development of quantitative models of sleep regulation.

Acknowledgment: We thank Drs. Irene Tobler and Peter Achermann for comments on the manuscript and Karin Jaggi for preparing the figures.

This work was supported by the Swiss National Science Foundation, grants 3.234.085 and 31-25634.88, and by the Netherlands Organization for Scientific Research (NWO).

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