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REM sleep deprivation during 5 hours leads to an immediate REM sleep rebound and to suppression of non-REM sleep intensity

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Summary Nine healthy male subjects were deprived of REM sleep during the first 5 h after sleep onset. Afterwards recovery sleep was undisturbed. During the deprivation period the non-REM EEG power spectrum was reduced when compared to baseline for the frequencies up to 7 Hz, despite the fact that non-REM sleep was not experimentally disturbed. During the recovery interval a significant rebound of REM sleep was observed, which was only accompanied by a very slight increase of power in the lower non-REM EEG frequencies.

In order to control for intermittent wakefulness, the same subjects were subjected to non-REM sleep interruption during the first 5 h after sleep onset 2 weeks later. Again subsequent recovery sleep was undisturbed. The interventions resulted in a similar amount of wakefulness in both conditions. During the intervention period, the non-REM EEG power spectrum was only marginally reduced in the delta frequency range. REM sleep duration was only slightly reduced. During the recovery interval, however, a substantial increase in EEG power in the delta frequency range was noted, without notable changes in REM time.

It is concluded that an increased pressure for REM sleep results in longer REM episodes and a reduced intensity of non-REM sleep.

Key words: REM sleep; Non-REM sleep; Sleep deprivation; EEG power spectrum

The episodic occurrence of bursts of rapid eye movements during sleep in man (Aserinski and Kleitman 1955) is one of the signs showing the alternation of 2 very distinct states of sleep: rapid eye movement (REM) sleep and non-REM sleep. For non-REM sleep, recent studies have quantified an intensity dimension which can be monitored by means of the sleep EEG signal (Borbély 1982; Daan et al. 1984; Beersma et al. 1987; Dijk et al. 1987b). Experimental manipulations of non-REM sleep lead to compensatory reactions in non-REM sleep intensity rather than in non-REM sleep duration. It is hypothesized that a homeostatic process underlies such changes observed in the sleep EEG. This process is called process S. The level of S increases during waking and decreases during sleep. It is assumed that the momentary level of S (i.e., the momentary need for non-REM sleep) determines the subsequent intensity of non-REM sleep. The duration of non-REM sleep, however, does not depend strongly on the need for non-REM sleep.

Similar statements cannot be made for REM sleep. An intensity dimension of REM sleep has not been found so far. The frequency of rapid eye movements cannot be considered a measure of REM intensity because experimental manipulations of the need for REM sleep do not show consistent changes in rapid eye movement densities (Aserinski 1969; Zimmerman et al. 1980; Antonioli et al. 1981). It seems that the density of

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rapid eye movements during REM sleep is primarily linked to non-REM sleep intensity (Borbély and Wirz-Justice 1982).

So, while the need for non-REM sleep is predominantly satisfied by adjusting the intensity of non-REM sleep, the need for REM sleep is mainly satisfied by allotting sufficient time to it. Nevertheless, the two states of sleep both have their temporal requirements. Reciprocal interaction models have been proposed in order to understand the temporal alternation of REM and non-REM sleep (McCarley and Hobson 1975; Beersma et al. 1984; McCarley and Massaquoi 1986). These models are, however, very qualitative. Many experiments have to be designed before they can be quantified in sufficient detail to describe the changes in the sleep EEG which can be induced by experimental interventions. One of the first questions to raise concerns the influence of the pressure for REM sleep on non-REM sleep intensity. The present study tries to quantify this influence by manipulating REM pressure through REM sleep deprivation. The result may be useful to model the mutual interaction between the two sleep states and provides some insight into the processes underlying their alternation.

Methods

Nine healthy male subjects, mean age 23 years (range 21–25) gave informed written consent to participate in a study including 2 series of 3 consecutive nights in the laboratory. The 2 series of nights were at least 2 weeks apart and are called condition 1 and condition 2. The first night in both conditions was an adaptation night. Time in bed was 8 h starting between 11.45 p.m. and 0.30 a.m. depending on the subject's customary bed time. The second night in both conditions was a baseline night, scheduled at the same time interval and recorded according to standard procedures. The electroencephalogram (EEG), electromyogram (EMG), and electro-oculogram (EOG) were recorded. The EEG was derived from C3-A2 and C4-A1. Records were made at 10 mm/sec.

During the third night of condition 1, the subjects were deprived of REM sleep by awakening at the first sign of its occurrence. Subjects were asked to sit upright and to fill out rating scales in order to be wide awake. After 3 min they were instructed to turn off the light and to continue sleeping. By this procedure the subjects did not immediately return to REM sleep. The REM sleep deprivation was continued during the first 5 h from sleep onset. Thereafter the subjects were no longer disturbed. They were instructed to sleep as long as they were able.

Subjects were told that condition 1 and condition 2 were identical and that 2 series of experiments were needed for statistical reasons. Condition 2, however, served as a control. Now the subjects were woken from non-REM sleep, and REM sleep was left undisturbed. An attempt was made to balance the number of awakenings, the total time awake, and the distribution of awakenings over the 5 h deprivation interval in both conditions. For that purpose subjects were woken up in the first non-REM episode. They were subsequently left undisturbed until a REM sleep episode occurred, after which the procedure was repeated. In some subjects more than one interruption of single non-REM episodes was needed in order to balance the number of awakenings. In condition 2 subjects also had to fill out rating scales for 3 min and sleep interruptions were restricted to the first 5 h after sleep onset.

Baseline nights and experimental nights were scored in 30 sec epochs according to established criteria (Rechtschaffen and Kales 1968). Sleep onset was defined on the basis of the first occurrence of stage 2 which was followed by 10 min including at most 2 min of wakefulness, stage 1, or movement time. Apart from classical scoring, the EEG signals were low-pass filtered at 25 Hz (24 dB/oct). The preamplifier time constant was 1 sec. The EEG signals were subsequently subjected to A/D conversion with a sampling rate of 64 Hz. The digitized data were processed by a Fast Fourier Transformation routine. Power spectra were calculated over 4 sec intervals in 0.25 Hz bins. Finally these were condensed into 1 Hz wide frequency bins. The visual scores of the records were also fed into the computer. This was needed for the calculation of power spectra per sleep stage and for the removal of movement time epochs.

Brief disruptions of EEG signals were removed automatically on the basis of the rectified EMG.

Results

The two sets of baseline nights were very similar in all respects. Statistical testing did not yield P values below 0.2 (Wilcoxon's matched pairs signed ranks test, two-sided) for sleep latency, stages 0, 1, movement time, REM and non-REM. As a consequence we have taken the average of the 2 nights as the best estimate of a subject's baseline value. Results are listed in Table I and accumulation curves of sleep stages from sleep onset are presented in Fig. 1. Sleep latency values and times of sleep onset in the 3 groups of nights were very similar. As a consequence of the experimental sleep interruptions in the first 5 h of sleep, there was much more wakefulness in the experimental nights when compared to baseline. The

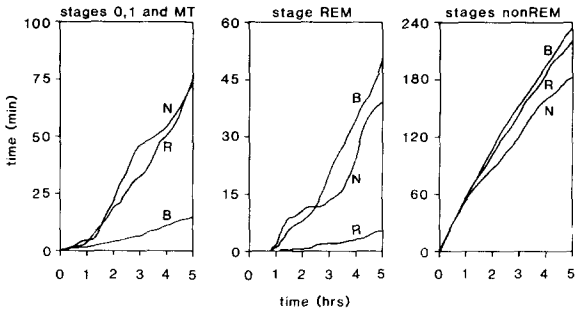

Fig. 1. Accumulation of sleep stages during the first 5 h after sleep onset in minutes, in 9 subjects. B = baseline sleep, R = REM deprivation condition, N = non-REM interruption condition.

two sets of experimental nights, however, did not significantly differ from each other with respect to this measure. The same holds for the accumulation of stage 1 sleep. During the experimental manipulation interval, there was more stage 1 than in baseline but differences between experimental

TABLE I

Means and standard deviations (min) of sleep parameters in baseline nights and in experimental conditions. Intermittent waking includes epochs scored as movement time. S1 indicates stage 1. Friedman's non-parametric analysis of variance with repeated measures was applied for comparing the 3 conditions. When values were significantly different, comparisons between conditions have been made by means of Wilcoxon's matched pairs signed ranks test (2-sided).

	Baseline	REM dep.	Non-REM intrpt.	ANOVA
Sleep latency	13.1 ± 8.7	15.6 ± 7.8	19.1 ± 15.4	n.s.
Sleep onset time	00:19 ± 12	00:20 ± 10	00:24 ± 16	n.s.
The first 5 h after sleep onset				
Intermittent waking	6.8 ± 2.9	51.8 ± 14.2	53.9 ± 15.1	$P = 0.0011$
	$P = 0.009$ *	n.s. **	$P = 0.002$ ***	
Intervention frequency	—	5.5 ± 1.9	4.9 ± 1.8	$P = 0.0455$
		n.s. **		
Accumulated time in S1	8.5 ± 2.5	22.6 ± 9.6	19.1 ± 12.1	$P = 0.0067$
	$P = 0.009$ *	n.s. **	$P = 0.002$ ***	
Accumulated REM time	49.9 ± 16.8	5.4 ± 4.0	39.7 ± 14.9	$P = 0.0006$
	$P = 0.009$ *	$P = 0.009$ **	$P = 0.044$ ***	
Accumulated non-REM time	235.2 ± 14.4	220.3 ± 20.8	184.1 ± 21.6	$P = 0.0003$
	$P = 0.013$ *	$P = 0.009$ **	$P = 0.009$ ***	
The 2 h and 15 min recovery interval				
Intermittent waking	4.9 ± 3.9	5.1 ± 5.0	4.4 ± 3.9	n.s.
Accumulated time in S1	6.8 ± 3.8	5.3 ± 3.9	5.9 ± 4.9	n.s.
Accumulated REM time	48.3 ± 11.8	61.3 ± 13.8	44.8 ± 11.5	$P = 0.0319$
	$P = 0.050$ *	$P = 0.024$ **	n.s. ***	
Accumulated non-REM time	74.8 ± 11.9	63.2 ± 12.4	79.8 ± 11.7	$P = 0.0183$
	n.s. *	$P = 0.013$ **	n.s. ***	

* Compares REM deprivation and baseline nights.
** Compares non-REM interruption and REM deprivation nights.
*** Compares non-REM interruption and baseline nights.

conditions again were non-significant. A slight difference resulted in the number of forced awakenings between the two conditions. Four out of 9 subjects were woken one time more in the REM deprivation condition than in the non-REM interruption condition. This difference was non-significant when tested by means of Wilcoxon's matched pairs signed ranks test (two-sided). As a result the 2 experimental conditions were reasonably similar with respect to the total duration of intermittent wakefulness, the total number of awakenings and the temporal distribution of forced waking.

The REM deprivation procedure yielded a 90% reduction in REM sleep time. The non-REM interruption procedure resulted in a slight reduction of REM sleep duration when compared to baseline. Differences between experimental conditions were highly significant. The experimental protocol thus succeeded in obtaining very distinct amounts of REM sleep over the first 5 h of sleep in the 2 experimental conditions.

For the accumulation of non-REM sleep time similar results were obtained. The REM deprivation condition yielded a small but significant reduction of non-REM sleep time over the first 5 h from sleep onset. The non-REM interruption condition yielded a substantial reduction of non-REM sleep time. This difference was significant when compared to baseline as well as when compared to the REM deprivation condition.

After 5 h of interrupted sleep, the subjects were left undisturbed and slept as long as they were able. The longest common sleep period amounted to 7 h and 15 min, so the accumulation of sleep stages is plotted only for the residual 2 h and 15 min (Fig. 2). The data in the last section of Table I also refer to this interval. It appeared that very small amounts of time were spent in wakefulness, stage 1 sleep and movement time in all conditions. Differences were not significant.

For the accumulation of REM sleep a different picture emerged (Fig. 2b). The total amount of REM sleep during the period after REM sleep deprivation was significantly longer than in the same time interval of baseline sleep. The accumulation of REM time after non-REM interruptions was not significantly different from baseline. Al-

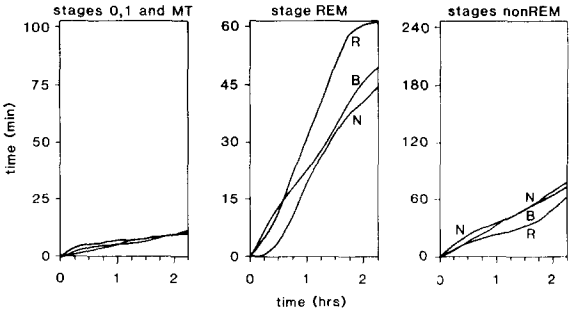

Fig. 2. Accumulation of sleep stages during the 2 h and 15 min recovery interval in minutes, in 9 subjects. B = baseline sleep, R = REM deprivation condition, N = non-REM interruption condition.

though the increase of REM sleep during the rebound period was only 30%, it must be noted that the effect was quite impressive. In 6 out of 9 subjects, the duration of the first rebound REM episode was longer than any other REM episode in the 4 recorded nights (containing an average of 16.1 ± 2.5 REM episodes with a duration over 5 min/subject). In 1 subject this REM episode was the second longest and in the other 2 subjects it was the third longest episode.

The loss of non-REM sleep time which accumulated during REM deprivation was not compensated in the rebound period. Instead a significant further *reduction* of non-REM sleep time was observed. In the non-REM interruption condition a non-significant increase of non-REM sleep time was observed in the rebound period.

In view of the supposed intensity dimension of non-REM sleep, which is postulated to be proportional to the power density of the sleep EEG signal (Borbély et al. 1981), we have studied the changes in the EEG power spectrum. In Fig. 3 the average power spectra during non-REM sleep and their standard deviations are presented. In Fig. 3a and b (and also in Fig. 4a and b) only 8 subjects contribute to the results, due to breathing artefacts in the EEG records of the REM deprivation night of 1 subject. Fig. 3a shows the 5 h interval of REM deprivation and Fig. 3c of non-REM interruption. The respective recovery intervals are presented in Fig. 3b and d. All values are presented relative to the values obtained in the corresponding time intervals of the corresponding baseline

night. During REM deprivation a significant reduction of the non-REM EEG power spectrum is observed in the frequency range up to 7 Hz. In the recovery period a slight rebound occurred in the delta frequency range, but this is not significant. During non-REM interruption, significant differences from baseline sleep are only observed at higher frequencies. Up to 13 Hz a slight suppression of powers is noted, while there is an increase of power in the 14 and 15 Hz bands. In spite of the small suppression of power in the interruption period, a substantial rebound is found in the recovery period. The effects are most pronounced in the delta frequency range. A direct comparison of the 2 recovery intervals (Fig. 3b and d) revealed significantly more power in the 2 Hz band after non-REM interruption than after REM deprivation. Non-significant trends in the same direction were observed for all frequencies up to 7 Hz (Wilcoxon, 2-sided, n = 8).

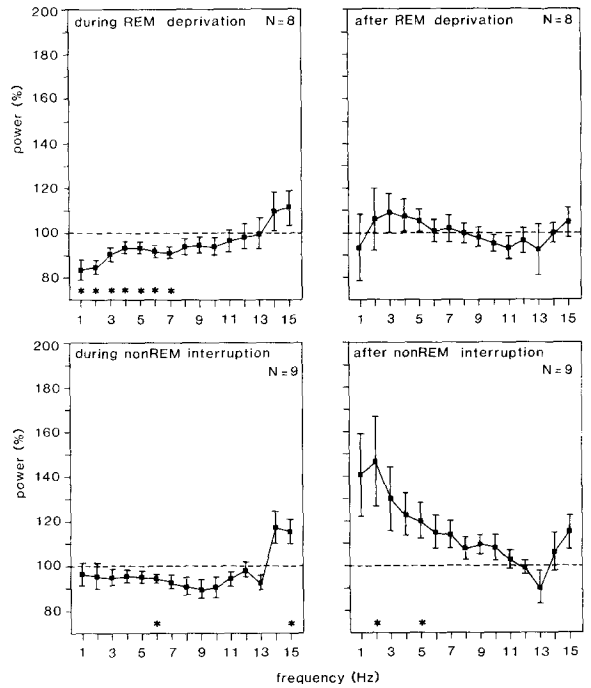

Fig. 3. EEG power spectra during non-REM sleep, relative to the power spectra obtained in the same time intervals of baseline non-REM sleep. a shows the results regarding the 5 h REM deprivation period; b the corresponding 2 h and 15 min recovery interval; c the 5 h non-REM interruption period; and d the corresponding 2 h and 15 min recovery interval. Asterisks denote significant differences ($P < 0.05$) from baseline (Wilcoxon's matched pairs signed ranks test, 2-sided).

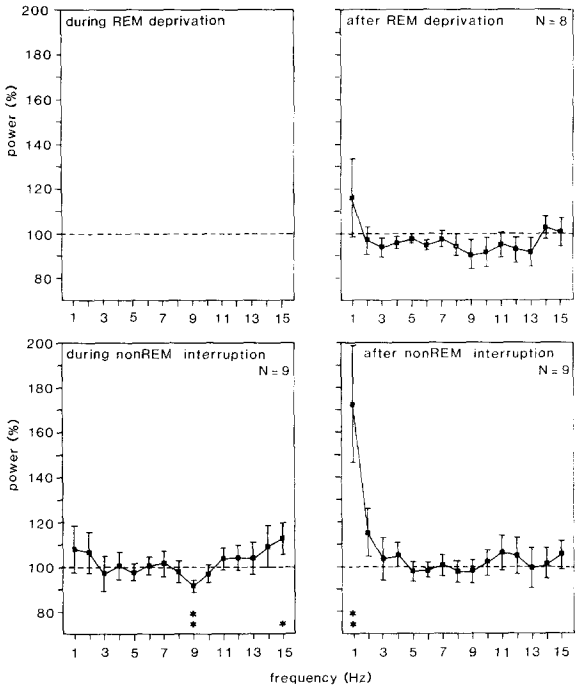

Fig. 4. EEG power spectra during REM sleep, relative to the power spectra obtained in the same time intervals of baseline REM sleep. a shows no data because REM sleep hardly occurred during the 5 h REM deprivation period; b shows the corresponding 2 h and 15 min recovery interval; c the 5 h non-REM interruption period; and d the corresponding 2 h and 15 min recovery interval. Asterisks denote significant differences ($P < 0.05$ for a single asterisk; $P < 0.01$ for a double asterisk) from baseline (Wilcoxon's matched pairs signed ranks test, 2-sided).

Power spectra during REM sleep are presented in Fig. 4. During REM deprivation very little REM sleep accumulated and the corresponding power spectrum could not be reliably calculated. In the other curves incidentally significant differences were noted: during non-REM deprivation a suppression in the alpha range is observed whereas an increase in the 15 Hz band is noted. During recovery from non-REM deprivation a substantial increase of low frequency activity (up to 1 Hz) may indicate the intrusion of slow waves in REM sleep.

Sleep EEG power density is proposed to be an

expression of the need for non-REM sleep. In fact, EEG power density is shown to be proportional to the rate of recovery of process S (Dijk et al. 1987b; Dijk 1988). Consequently, a measure of the total recovery of S is obtained by integrating sleep intensity over time. This integration of power over time yields the energy content of the sleep EEG signal. As a result we thus calculated the EEG energy accumulation curves for both experimental conditions (Fig. 5), relative to the energy accumulated by each subject over 435 min in baseline, which latter values are taken as 100%. The similarity of the courses of EEG energy accumulation in the 2 sets of baseline nights is very remarkable. In spite of the fact that they were at least 2 weeks apart and electrodes were placed twice, the average amount of EEG energy in 7 h and 15 min of the second set of baselines was 99.9% of the average for the first set ($\pm 6.54\%$, S.E.M.). At the end of the 5 h interval, the 3 conditions show different amounts of accumulated EEG energy ($P = 0.022$, Friedman 2-way non-parametric ANOVA). The experimental conditions both show reduced amounts of sleep EEG energy when compared to baseline ($P < 0.02$, Wilcoxon matched pairs signed ranks test, 2-sided).

During the first 1.5 h of recovery (Fig. 5b) the accumulation of EEG energy is similar for all conditions. Thereafter an increase in EEG energy is observed during recovery from non-REM interruption. At the end of the recovery interval a significant difference between recovery from REM deprivation and from non-REM interruption is noted (Wilcoxon matched pairs signed ranks test, 2-sided, $P = 0.033$).

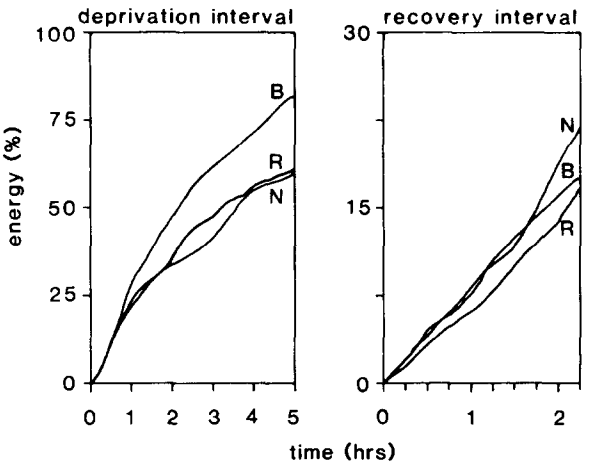

Fig. 5. The accumulation of energy in the sleep EEG signal integrated from 0.25 to 15 Hz, relative to the total amount of energy that accumulated in 7 h and 15 min of baseline (= 100%) for the first 5 h after sleep onset (a) and for the subsequent 2 h and 15 min (b). B = baseline; R = REM deprivation condition; N = non-REM interruption condition. Number of subjects is 9, except for condition R, with 8 subjects.

Discussion

In search for the effects of REM pressure on non-REM sleep intensity, a REM sleep deprivation study has been designed. REM sleep was deprived by awakening subjects at the first signs of REM sleep. By this procedure an increased amount of wakefulness was introduced in the experimental night. A control experiment in which a similar amount of wakefulness resulted from awakening out of non-REM sleep was therefore carried out. However, an unwanted methodological consequence resulted. Since we had to know the number of awakenings from REM sleep before an equal frequency of awakenings from non-REM sleep could be achieved, the REM deprivation experiment had to be done first. Automatically, subjects were more acquainted with the situation when starting the non-REM interruption condition than when starting the REM deprivation condition. Possibly, the corresponding adaptation phenomena could explain part of the results. There are two arguments against this reasoning. One is that the experimental nights were each the third in a series of 3 nights in the laboratory; it is likely that adaptation was almost complete at that time. The other argument stems from comparison between the 2 sets of baseline data. No systematic differences were observed, in spite of the fact that the first baseline night was the second and the second baseline night was the fifth in the laboratory.

The deprivation of REM sleep during the first 5 h of sleep in combination with a control study in

which subjects were woken up from non-REM sleep strongly emphasizes the existence of regulatory mechanisms for the timing of sleep states. Evidence in favour of such control stems from 2 different types of observation. One of these concerns the regulation of the duration of REM episodes. Within a single night, an impressive rebound in REM sleep was found in response to REM sleep deprivation. The duration of REM episodes was considerably increased, which led to a more rapid accumulation of REM sleep in the recovery part of the night. The power spectrum of the EEG signal during REM sleep was not systematically changed by the deprivation procedure. The significant changes of EEG power in the 9 Hz and the 15 Hz bands, observed during the non-REM interruption condition, did not lead to changes in these bands during recovery. Therefore it seems justified, as a first order approach, to neglect the power spectrum during REM sleep as being a part of the control system. Instead, the duration of REM sleep is an important parameter.

The other observation concerns the variation in non-REM sleep intensity as shown by changes in the non-REM EEG power spectrum. The power spectrum during non-REM sleep varied in response to the experimental manipulations. The values obtained after non-REM interruption exceeded baseline values considerably in the delta frequency range. After REM sleep deprivation, however, the spectrum in the delta range was only slightly elevated over baseline values. This difference was observed in spite of the fact that the total amount of energy which accumulated during the first 5 h of sleep was not significantly different between the 2 experimental conditions. This provides a strong suggestion, therefore, that a high pressure for REM sleep suppresses the intensity of non-REM sleep. This notion is further supported by the fact that the non-REM power spectrum during the REM deprivation period was significantly lower than baseline for the frequencies between 0.25 and 7 Hz. In this 5 h period the non-REM episodes were undisturbed. The intervals of wakefulness induced at the onset of REM episodes are expected to increase the pressure for non-REM sleep. As a consequence an increase of EEG powers in these lower frequencies was expected. The actually observed decrease might thus be caused by the increasing pressure for REM sleep during this interval.

The precise temporal course of EEG power over a single non-REM episode deserves some further attention in this respect. On average the power in the EEG signal during non-REM sleep episodes shows a gradual increase until it suddenly drops shortly before the onset of a REM period (Achermann and Borbély 1987). If the influence of a high pressure for REM sleep were simply to reduce the *duration* of non-REM sleep episodes, such an effect would at least qualitatively explain the observed reduction of the lower EEG frequencies in the power spectrum. To test this idea we calculated the duration of the first non-REM episode during the recovery periods in both conditions. After REM deprivation we found 61 ± 13 min and after non-REM interruption the first non-REM episode lasted for only 54 ± 12 min. Although the difference was not significant, it must be noted that the trend was opposite to the predicted direction. In conclusion it seems that high pressures for REM sleep do not suppress non-REM intensity by shortening the non-REM period but by suppressing non-REM sleep intensity continuously.

Apart from the effects of REM sleep deprivation, the data show the impact of the manipulation of non-REM sleep intensity on subsequent undisturbed sleep. Interruptions in non-REM sleep lead to a rebound in the lower EEG frequency region during non-REM sleep. This phenomenon has been studied with other deprivation techniques, yielding similar results (Dijk et al. 1987b; Dijk and Beersma 1989). In all cases changes in the power spectra in response to manipulations of non-REM intensity occurred in the 1–7 Hz range. Furthermore, it appeared that the magnitude of the rebound EEG energy could be predicted from the amount of EEG energy reduction during the interruption interval (Dijk et al. 1987b). Also in the present study the amount of EEG energy during recovery from non-REM interruption can be predicted from the data obtained during the interruption interval, according to the following reasoning. At the end of the 5 h non-REM interruption period an amount of 59.7% of total base-

line energy had accumulated (see Fig. 5a). During baseline this amount of EEG energy had already occurred at 2 h and 48 min after sleep onset. In the subsequent 2 h and 15 min of baseline, EEG energy increased further by 22.9%. This amount was also expected for the recovery interval after non-REM interruption. The actual value was 21.6% which is very close to the predicted value. The rebound in EEG energy accumulation was, however, not immediate but occurred only after 1.5 h (Fig. 5b). It remains to be resolved whether this is due to chance or whether it is a specific consequence of the deprivation method applied in this study. In any case, however, it can be concluded that at the end of the night the intensity of non-REM sleep is also under strict homeostatic control. The accumulation of REM sleep time is of considerable importance, though, since the accumulation of EEG energy after REM sleep deprivation is significantly reduced.

For the impact of non-REM intensity on the accumulation of REM sleep time the data are less clear. As in a study by Dijk et al. (personal communication), in this study there is a suggestion of a shift towards REM sleep when non-REM sleep is experimentally disturbed. A (non-significant) trend for REM sleep to accumulate earlier during non-REM deprivation as compared to baseline was observed when the accumulation of REM sleep was plotted as a function of time asleep (data not shown). Similar interactions have been noted in response to total sleep deprivation. During the first recovery night an increase in sleep intensity is observed without much change in REM sleep duration. The second recovery night, however, shows an increased duration of REM sleep (Williams et al. 1964). It has been suggested that the high pressure for non-REM sleep postpones the REM sleep rebound to the second recovery night.

The influence of increased REM pressure on non-REM sleep intensity is not accounted for in the 2-process model of sleep regulation (Daan et al. 1984). Modulation of REM pressure may, according to the present experiment, modulate non-REM sleep intensity and, therefore, alter the course of process S. It remains to be established, however, whether the circadian variation of REM pressure is of sufficient strength to modulate non-REM intensity detectably. The data available up to now do not show such circadian variation in non-REM sleep intensity (Dijk et al. 1987a).

Obviously, the alternation between REM and non-REM sleep is not just a sequence of REM and non-REM episodes. Compensatory reactions correct for variations in REM sleep duration or non-REM sleep intensity within single nights. Reactions are not restricted to the sleep state which has been manipulated, although both REM sleep and non-REM sleep are obviously controlled by homeostatic mechanisms. The present experiment may provide some of the data needed for further attempts to model the interactions between the homeostatically regulated needs for REM and non-REM sleep.

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