Regional Differences of the Human Sleep Electroencephalogram in Response to Selective Slow-wave Sleep Deprivation

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The purpose of this study was to assess the topographic changes in sleep recuperative processes in response to selective slow-wave sleep (SWS) deprivation. SWS was suppressed on two consecutive nights by means of acoustic stimulation. The electroencephalogram (EEG) power of baseline, deprivation and recovery nights was analysed in 1 Hz bins. During the SWS deprivation nights, large decreases of EEG power were found at frontopolar, central and parietal derivations encompassing the delta, theta and alpha range, while only slow delta (0.5–2 Hz) was affected at the frontal derivation. Recovery sleep was characterized by a generalized increase of power during non-REM sleep encompassing the delta, theta and alpha bands, with a clear antero-posterior gradient. The coherent behaviour of different EEG bands with traditionally different electrophysiological meanings during non-REM sleep suggests that, in light of the recent advances in sleep neurophysiology, a re-examination of the functional role of EEG rhythms during sleep is needed. The 'resistance' to selective SWS deprivation of the frontal area, together with its larger increase of EEG power during recovery, may be interpreted as a sign of a greater sleep need of the frontal cortical areas, confirming that some aspects of the regulatory processes of human sleep are local in nature and may show use-dependent characteristics.

Introduction

According to the two-process model of sleep regulation (Borbely, 1982), sleep structure, timing and duration are regulated by a circadian and a homeostatic component. The latter, represented by Process S, is dependent on prior sleep and waking history. Process S increases during wakefulness in an exponentially saturating way and then declines exponentially during sleep.

The EEG slow-wave activity (SWA: EEG power in the 0.75–4 Hz band), as assessed by spectral analysis of the EEG signal, has been traditionally considered to be the electrophysiological correlate of Process S. SWA reflects sleep intensity and shows a monotonic decay over the first three non-REM–REM sleep cycles (Borbely *et al.*, 1981). Daytime naps reverse the build-up of SWA, causing a reduction of SWA in subsequent nocturnal sleep (Feinberg *et al.*, 1985). Conversely, partial or total sleep deprivation results in an enhancement of this quantitative EEG parameter during recovery sleep, the extent of the increase being a function of prior waking duration (Borbely *et al.*, 1981; Brunner *et al.*, 1990; Dijk *et al.*, 1991).

It has also been demonstrated that SWA is not only determined by the length of previous wakefulness and by the time since sleep onset, but even depends on the events within non-REM sleep. In fact, the experimental suppression of slow waves during the first 3–5 h of sleep by means of acoustic stimulation leads to a considerable enhancement of slow-wave sleep (SWS) and EEG power density in the following hours of undisturbed sleep (Dijk *et al.*, 1987; Dijk and Beersma, 1989). An elaborate version of the two-process model, formalized by Achermann and Borbely, took these results into account by specifically addressing the time course of SWA within non-REM–REM sleep episodes (Achermann and Borbely, 1990).

These homeostatic dynamics of EEG power also affect the cortical topography of the sleep EEG along the antero-posterior axis. Werth and co-workers (Werth *et al.*, 1996, 1997) showed that human sleep is characterized by a fronto-occipital power gradient, the frontal areas being specifically involved in sleep homeostasis. A frontal predominance of EEG power in the delta band has been confirmed in a recent study on sleep EEG topography based on the analysis of 27 derivations (Finelli *et al.*, 2001). This anterior predominance is even greater in the recovery sleep that follows total sleep deprivation (Cajochen *et al.*, 1999; Finelli *et al.*, 2001).

In a previous study we applied an acoustic stimulation technique to selectively suppress SWS during two consecutive nights (Ferrara *et al.*, 1999a). The large compensatory SWS rebound found in the recovery night supported the idea that the amount of delta sleep is more linked to SWS in the previous sleep periods than to total sleep duration. The main aim of the present study is to assess, for the first time, the homeostatic changes of Hz-by-Hz EEG power during sleep in response to two nights of SWS deprivation. Previous selective SWS deprivation studies, in which SWS amount was reduced but never completely suppressed for a few hours during either diurnal or nocturnal sleep, indicated that this experimental manipulation of sleep structure increased the amount of SWS in the subsequent sleep period, but an enhancement of the SWA was not always found (Dijk *et al.*, 1987; Dijk and Beersma, 1989; Gillberg *et al.*, 1991; Gillberg and Akerstedt, 1994). We hypothesize that our longer and more complete curtailment of the amount of SWS will lead to a significant increase of EEG power in the low-frequency range during recovery sleep, in response to the decrease in the same frequency range induced by the acoustic stimulation. Any change in sleep EEG power would be exclusively attributable to the loss of SWS accumulated during two consecutive nights. In fact, our SWS deprivation procedure did not modify the indices of sleep continuity (stage 1 percentage, movement time, number of movement arousals and of full awakenings) and kept both total sleep duration and length of prior wakefulness constant (Ferrara *et al.*, 1999a). Moreover, at variance with previous studies which recorded EEG only from central derivations, topographic changes in sleep recuperative processes will also be assessed, by analysing the EEG power from different scalp locations along the antero-posterior axis. According to recent findings (Finelli *et al.*, 2001), which evaluated the effects of a different deprivation procedure (40 h of total sleep deprivation) on recovery sleep by using another analytic method (EEG power maps topography), a frontal predominance of the compensatory increase in EEG power, particularly in the low-frequency range, can be expected. Finally, we will provide the first Hz-by-Hz topographic study of EEG power changes during two entire nights of selective SWS

deprivation; in fact, previous works only reported on intra-night dynamics of SWA after a partial, short-term suppression of delta waves.

Materials and Methods

Subjects

Ten normal right-handed male subjects (age range 20–30 years, mean age = 23 years) were selected as paid volunteers from a university student population. All subjects gave informed consent before participating in the study. They reported drinking less than three caffeinated beverages per day. They usually slept 7–8 h per night, went to bed between 23:00 and 00:00, and did not take naps during the day. Other requirements for inclusion were: no excessive daytime sleepiness and no other sleep, medical or psychiatric disorders. These characteristics were assessed by a 1 week sleep log and by a clinical interview.

Procedure

The study protocol was approved by the local Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. Participants slept for six consecutive nights in a sound-proof, temperature-controlled room: (1) adaptation; (2) undisturbed baseline (BSL); (3) baseline with awakenings (BLA); (4) SWS deprivation-1 (DEP1); (5) SWS deprivation-2 (DEP2); and (6) recovery (REC). Every night, subjects arrived in the laboratory at ~9.00 p.m. for electrode hook-up. Polygraphic sleep recordings always started at 11.30 p.m. (±30 min), and ended after 7.5 h of accumulated sleep. Upon final awakening, after electrode removal, the subjects were free to leave the laboratory to attend their normal life schedule. During the daytime, they attended their university courses and/or studied in their own homes or in the faculty's library. Participants were required to avoid napping and strenuous physical exercise throughout the experiment; their compliance was confirmed by wrist actigraphic recordings (AMI motion logger 16 K).

During nights 3–6, participants were awakened twice and a psychophysiological test battery was administered. All the subjects were trained to asymptotic performance levels during the days preceding the study. The battery lasted ~13 min. Results on performance upon awakening have been reported elsewhere (Ferrara *et al.*, 1999b, 2000). The first night-time awakening was scheduled after 2 h and the second after 5 h of accrued sleep. Performance was assessed with subjects lying down in bed in the dark. At the end of testing, subjects were asked to go back to sleep.

Slow-wave Sleep Deprivation Procedure

During nights 4 and 5, two experimenters continuously monitored the EEG chart and delivered a tone (frequency, 1000 Hz; intensity, 40–110 dB) by pressing a button whenever at least two delta waves (≤4 Hz, >75 μV), determined by visual inspection, appeared in a 15 s recording interval. Acoustic stimuli were administered through a loudspeaker placed ~40 cm above the subjects' heads. Beginning from the lowest intensity, it was increased in steps of 5 dB if no response occurred (sleep stage shift, K complex, EEG desynchronization, alpha burst, muscle tone increase, slow eye movements). In this manner, we prevented the subjects from fully entering stage 3 by lightening their sleep. Full awakenings were carefully avoided.

Polygraphic Recordings

An Esaote Biomedica VEGA 24 polygraph set at a paper speed of 10 mm/s was used for polygraphic recordings. EEG signals were high-pass filtered with a time constant of 0.3 s and low-pass filtered at 30 Hz (30 dB/octave); seven unipolar EEG channels (C3-A2, C4-A1, Fpz-A1, Fz-A1, Cz-A1, Pz-A1, Oz-A1) were applied using the international 10–20 system. Only data concerning the five derivations along the antero-posterior axis will be reported.

The submental electromyogram (EMG) was recorded with a time constant of 0.03 s. Bipolar horizontal and vertical eye movements were recorded with a time constant of 1 s. The bipolar horizontal electro-oculogram (EOG) was recorded from electrodes placed ~1 cm from the medial and lateral canthi of the dominant eye, and bipolar vertical EOG from electrodes located ~3 cm above and below the right eye pupil. Electrode impedance was maintained at <5 kΩ. Left central EEG (C3-A2), EMG, and horizontal and vertical EOG were used visually to score sleep stages in 20 s epochs, according to the standard criteria (Rechtschaffen and Kales, 1968). With regard to delta sleep scoring, the amplitude criterion (>75 μV) expressed by Rechtschaffen and Kales was strictly followed.

Quantitative Analysis of Signals

The polygraphic signals (seven EEG channels, 2 EOG and EMG) were analog-to-digital converted on-line with a sampling rate of 128 Hz and stored on the disk of a personal computer. Artefacts were excluded off-line on a 4 s basis by visual inspection; as regards REM sleep, only tonic periods were included in the analyses, to avoid artefactual influences of rapid eye movements on EEG power. Power spectra of five derivations along the antero-posterior axis (Fpz-A1, Fz-A1, Cz-A1, Pz-A1, Oz-A1) were computed by a fast Fourier transform routine for consecutive 4 s epochs, resulting in a frequency resolution of 0.25 Hz. Values >25 Hz were not used in the analysis. By collapsing four adjacent 0.25 Hz bins (1–25 Hz), the data were reduced to a 1 Hz bin width. The two lowest bins (0.5–0.75 Hz) were also collapsed and tentatively included in the analysis of the effects of SWS deprivation on these low-frequency oscillations (Achermann and Borbely, 1997). A further data reduction of power spectra was achieved by averaging 15 consecutive 4 s epochs to yield a 60 s spectrum. As a result, this spectrum comprised three consecutive 20 s visually scored epochs. Power spectra were calculated separately for non-REM (stages 2 + 3 + 4) and REM sleep.

Bins are referred to and plotted in this study by the lowest frequency included (e.g. the 2 Hz bin refers to the averaged values of the bins centred at 2.00, 2.25, 2.50 and 2.75 Hz).

Statistics

As regards visually scored sleep parameters, one-way repeated measure analyses of variance (ANOVA) with 'night' as a four-level factor (BLA, DEP1, DEP2, REC) were carried out on the duration and latency of each sleep stage (except for stages 3 and 4 — S3, S4), intra-sleep wakefulness (ISW); movement time (MT); number of awakenings (NA); number of movement arousals (MA); total sleep time (TST); total bed time (TBT); and sleep efficiency index (SE). We only considered BLA, DEP1, DEP2 and REC because two nocturnal experimental awakenings were scheduled in these four nights (see Procedure), at variance with BSL, during which sleep was uninterrupted.

With regard to S3, S4 and SWS duration and latencies, the ANOVA only included BLA and REC as levels of the 'night' factor, in order to assess the presence of a rebound effect during recovery sleep. In this case, too, BSL was not considered because it was an uninterrupted night. However, S3, S4 and SWS duration during BSL and BLA nights were statistically equivalent. Both SWS deprivation nights were not considered in this analysis, since S3 and S4 were virtually absent during DEP1 and DEP2 (see Results).

Statistical significance was set at a probability level of ≤0.05. The Scheffé *F*-test was used for *post hoc* comparisons of the means.

As regards sleep EEG power, absolute power values were log-transformed before the statistical tests in order to approximate a normal distribution. Since preliminary ANOVAs, carried out separately for each derivation, showed that DEP1 and DEP2 did not significantly differ in any 1 Hz bin, EEG power values of the two SWS deprivation nights were averaged and will always be referred to as DEP.

The differences between scalp locations in Hz-by-Hz EEG power during non-REM and REM baseline sleep were assessed by means of one-way ANOVAs with 'derivation' (Fpz, Fz, Cz, Pz, Oz). To correct for multiple comparisons, the Bonferroni correction was applied. Considering the mean correlation between the variables ($r = 0.69$), the alpha level was then adjusted to ≤0.02.

The effects of SWS deprivation on sleep EEG power were investigated separately for non-REM (stages 2 + 3 + 4) and REM sleep by calculating, for the 0.5 Hz bin and for each other 1 Hz bin, the ratio of power between DEP or REC and the baseline night (BLA) and then comparing the relative values (i.e. the DEP/BLA and REC/BLA ratios) by means of repeated measure ANOVAs. Also in this case, after the Bonferroni correction the alpha level was set to ≤0.02.

Table 1
Means (SE) of the visually scored EEG parameters during each experimental night

Variable	Night					*F*	*P*	Mean differences
	1: BSL	2: BLA	3: DEP1	4: DEP2	5: REC			
Stage 1	32 (4.7)	43 (4.7)	36 (2.7)	34 (2.89)	34 (5.1)	2.01[a]	n.s.	
Stage 2	264 (10.7)	250 (10.3)	301 (11.1)	316 (7.5)	240 (11.4)	23.29[a]	0.0001	3, 4 > 2, 5
Stage 3	29 (11.4)	26 (3.4)	1.4 (1.3)	2.7 (1.0)	27 (3.7)	0.06[b]	n.s.	
Stage 4	29 (6.7)	27 (7.2)	0.1 (0.1)	0.2 (0.2)	52 (11.8)	19.30[b]	0.002	
SWS	58 (8.6)	53 (8.4)	1.5 (0.4)	2.9 (1.1)	79 (12.9)	23.37[b]	0.001	
REM	103 (4.6)	116 (5.7)	112 (9.2)	125 (12.7)	114 (4.4)	0.77[a]	n.s.	
ISW	23 (8.1)	13 (2.6)	40 (18.3)	16 (4.7)	6 (1.8)	2.81[a]	n.s.	
MT	5 (0.6)	5 (0.6)	8 (0.9)	6 (1.0)	6 (0.9)	2.47[a]	n.s.	
MA	65 (10.8)	61 (8.7)	65 (8.3)	67 (7.6)	60 (10.8)	0.55[a]	n.s.	
NA	10 (1.7)	12 (2.6)	20 (7.5)	12 (2.9)	8 (1.5)	2.07[a]	n.s.	
TBT	499 (10.6)	494 (7.1)	520 (10.9)	512 (9.3)	492 (8.0)	2.31[a]	n.s.	
TST	457 (12.1)	462 (7.0)	451 (13.3)	478 (11.1)	468 (7.8)	2.00[a]	n.s.	
SE (%)	91.7 (2.1)	89.6 (2.2)	85.0 (3.8)	91.2 (1.8)	93.7 (0.9)	5.65[a]	0.004	5 > 3
S1 Lat.	16 (5.9)	14 (4.1)	18 (5.5)	11 (2.9)	12 (3.3)	1.66[a]	n.s.	
S2 Lat.	20 (6.1)	18 (4.5)	21 (5.5)	14 (3.2)	17 (3.3)	1.35[a]	n.s.	
S3 Lat.	39 (6.9)	35 (5.0)	–	–	28 (3.7)	7.70[b]	0.02	
S4 Lat.	44 (9.1)	42 (5.2)	–	–	34 (3.9)	13.75[b]	0.005	
REM Lat.	92 (8.7)	102 (12.7)	141 (34.2)	120 (20.1)	98 (10.6)	1.17[a]	n.s.	

ANOVA results and *post hoc* comparisons (Scheffé *F*-test) are also reported. BLA = baseline with awakenings; BSL = undisturbed baseline; DEP1 = first night of SWS deprivation; DEP2 = second night of SWS deprivation; ISW = intra-sleep wake; MA = number of movement arousals; MT = movement time; NA = number of awakenings; REC = recovery; REM = rapid eye movement sleep; REM Lat. = stage REM latency; S1 Lat. = stage 1 latency; S2 Lat. = stage 2 latency; S3 Lat. = stage 3 latency; S4 Lat. = stage 4 latency; SE = sleep efficiency index (percentage of efficiency); SWS = slow-wave sleep (stages 3 + 4); TBT = total bed time; TST = total sleep time. All variables, except SE, are expressed in min.

[a]Degrees of freedom = 3, 27.

[b]Degrees of freedom = 1, 9.

Results

Sleep Measures Derived from Visual Scoring

Table 1 summarizes measures derived from visual scoring. Results on sleep measures visually scored in 30 s epochs and expressed as percentages were published elsewhere (Ferrara *et al*., 1999a). The acoustic stimulation technique allowed us to achieve an almost complete selective SWS suppression in both deprivation nights; in fact, the mean SWS durations were 1.5 and 2.9 min in DEP1 and DEP2, respectively. During the DEP1, a mean of 328 (SE = 53.0) acoustic stimuli were delivered, with a mean intensity of 56 dB (SE = 4.5). During the DEP2, as a result of an increase in arousal thresholds, probably due to greater SWS pressure, 740 (SE = 99.5) acoustic stimuli were delivered, with a mean intensity of 72 dB (SE = 3.6). The number of acoustic stimuli delivered was significantly increased in DEP2 as compared to DEP1 (Wilcoxon signed-rank test, $Z = -2.8$; $P = 0.005$) as well as their mean intensity [one-way ANOVA, $F(1,9) = 33.87$, $P = 0.0003$].

The SWS deprivation procedure caused a significant increase of stage 2 duration in both deprivation nights, followed by a stage 4 and SWS rebound during recovery sleep. The increased SWS pressure also caused a significant shortening of stage 3 and 4 latencies during the recovery night. Sleep efficiency was also increased during REC, but only as compared to DEP1, during which (non-significant) increases of intra-sleep wake and of the number of awakenings were found.

Sleep EEG Power during Non-REM Sleep

All night EEG power was calculated for each midline derivation (Fpz, Fz, Cz, Pz, Oz) during BLA, DEP and REC sleep episodes (Fig. 1). There was a clear antero-posterior EEG power gradient during sleep, although the frontopolar (Fpz) derivation did not strictly follow this gradient, being closer to the central (Cz) than to the frontal (Fz) lead across the whole frequency range. The sharp decline in power with increasing frequency was a common feature for each derivation. Visual inspection of Figure 1 showed a peak of EEG power in the sigma range (12–14 Hz) at Cz and Pz. The centro-parietal predominance in the 12–14 Hz range was statistically confirmed (see Table 2). On the other hand, an Fz predominance of EEG power in the very slow frequency range (1–2 Hz), in the alpha range (9–11 Hz) and in the 15–20 Hz range was evident. The 3–8 Hz range was characterized by the dominance of the fronto-central locations.

Sleep EEG Power during REM Sleep

All night mean EEG power during REM sleep was calculated for each derivation (Fpz, Fz, Cz, Pz, Oz) during BLA, DEP and REC sleep, and is reported in Figure 2. As during non-REM sleep, an inverse relation between EEG frequency and power is also evident during REM sleep at each scalp location. There was a clear antero-posterior EEG power gradient with a fronto-central predominance in the delta/theta frequency range (Fig. 2*A*,*B*). This pattern was supported by the statistical analyses (see Table 3). Although spectral analysis of REM sleep EEG was performed only on those epochs not contaminated by rapid eye movements, the possibility that this result could be partially due to the uncontrolled influence of slow eye movements on the EEG power cannot be completely excluded. However, any ocular artefact should have mostly influenced the frontopolar derivation, which is closer to the eyes: this was not the case (see Table 3). A shift toward a more posterior dominance (Pz–Oz) is also clear in the 8–10 Hz bins. Finally, a slight occipital predominance in the beta range was visually detectable, although it was not statistically confirmed.

Effects of SWS Deprivation on EEG Power during Non-REM Sleep

In order to evaluate the effects of SWS deprivation on EEG power during non-REM sleep, for the 0.5 Hz bin and for each other 1 Hz

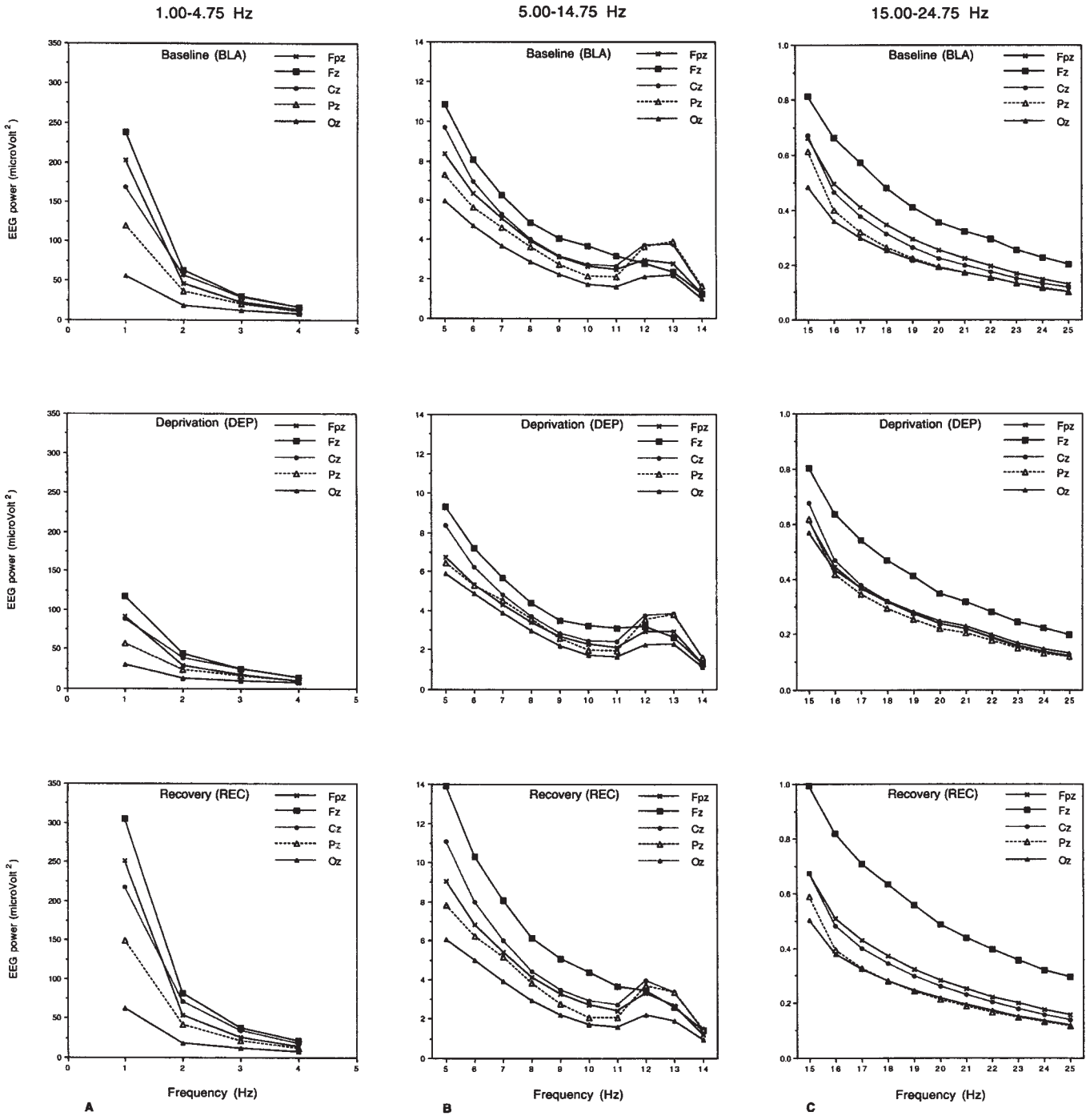

Figure 1. All-night absolute EEG power (μV^2) for non-REM sleep (NREM, stages 2, 3 and 4) in the frontopolar (Fpz), frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz) derivations during baseline (BLA), SWS deprivation (DEP — averaged EEG power values of the two SWS deprivation nights) and recovery (REC) sleep. Single-Hz bins have been plotted referring to the traditional delta (*A*), theta-alpha-sigma (*B*) and beta (*C*), in order to group together bins with equivalent power. Consequently, each panel has different *y*-axis scales.

bin, power values during DEP and REC nights were expressed relative to the corresponding values during baseline (BLA) sleep (Fig. 3). The deprivation procedure caused a generalized decrease of EEG power in the 0.5–11 Hz on fronto-centro-parietal derivations. This decrease was limited to 0.5–4 Hz on the occipital derivation, where a larger increase of the higher frequencies (≥15 Hz) was evident as compared to the other derivations, except Pz. On the other hand, recovery sleep was characterized by an increase in the low-frequency bins (0.5–7 Hz) which was larger at Fz, also encompassing a broader frequency range. The increase of EEG power during REC seems indeed to follow an antero-posterior gradient, being prominent at Fz and practically absent at Oz.

ANOVAs showed that the frontopolar midline derivation (Fpz) was characterized by the largest decreases of EEG power during SWS deprivation, encompassing the 0.5–11 Hz range (Fig. 3*A*, bottom). On the other hand, at Fz (Fig. 3*B*, bottom) we obtained a significant decrease of EEG power only in the slow-delta range

Table 2
Results of one-way ANOVAs with 'derivation' (Fpz, Fz, Cz, Pz, Oz) assessing the differences between scalp locations in Hz-by-Hz EEG power during non-REM sleep of the baseline (BLA) night

Frequency (Hz)	*F*(4,36)	*P*	Mean differences
1	70.92	0.0001	Fpz > Pz, Oz; Fz > Cz, Pz, Oz; Cz > Pz, Oz; Pz > Oz
2	55.72	0.0001	Fpz > Oz; Fz > Fpz, Pz, Oz; Cz > Pz, Oz; Pz > Oz
3	32.56	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz >Pz, Oz; Pz >Oz
4	16.96	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz >Pz, Oz; Pz >Oz
5	9.68	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz > Oz
6	7.42	0.0002	Fz > Oz; Cz > Oz
7	7.98	0.0001	Fpz > Oz; Fz > Oz; Cz > Oz
8	9.31	0.0001	Fpz > Oz; Fz > Oz; Cz > Oz
9	13.24	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz > Oz
10	17.99	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz > Oz
11	12.24	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz > Oz
12	6.94	0.0003	Cz > Oz; Pz > Oz
13	14.05	0.0001	Cz > Oz; Pz > Oz
14	5.50	0.0015	Cz > Oz; Pz > Oz
15	3.39	0.0188	Fz > Oz
16	4.62	0.0041	Fz > Oz
17	4.75	0.0035	Fz > Oz
18	4.59	0.0042	Fz > Oz
19	4.14	0.0074	Fz > Oz
20	3.60	0.0144	Fz > Oz

To correct for multiple comparisons, the Bonferroni correction was applied. Considering the mean correlation between the variables ($r = 0.69$), the alpha level was adjusted to ≤0.02. Only significant ANOVAs and results of *post hoc* comparisons of the means (Scheffé *F*-test) are reported.

(0.5–2 Hz). Cz was also particularly affected by SWS deprivation; in fact, at this scalp location there was a significant decrease of EEG power in the 0.5–5 and the 9–11 Hz ranges during DEP compared to BLA (Fig. 3*C*, bottom). Similarly, Pz showed significant decreases in the 0.5–5 Hz range (Fig. 3*D*, bottom). Finally, a significant decrease of EEG power only in the slow-delta range (0.5–2 Hz) at Oz was found (Fig. 3*E*, bottom).

As regards recovery sleep, at Fpz we found a significant increase of EEG power only in the slow-delta range (0.5–2 Hz), while Fz was characterized by the largest increases, which encompassed the 0.5–8 Hz range. The central derivation showed a significant EEG power enhancement in the 0.5–4 Hz range, while the parietal derivation showed significant increases in the 0.5–1 Hz range. No significant increases of EEG power during recovery sleep were found at Oz.

Effects of SWS Deprivation on EEG Power during REM Sleep

Also for REM sleep, EEG power values during DEP and REC nights were expressed, for the 0.5 Hz bin and for each other 1 Hz bin, relative to the corresponding values during baseline (BLA) sleep (Fig. 4).

The SWS deprivation procedure caused an increase of EEG power in the whole frequency range that seemed particularly evident centrally (Cz, Fig. 4*C*). Nonetheless, after the Bonferroni correction, ANOVAs showed that these effects were never significant. Even the clear EEG power increase including the faster frequencies at the more posterior derivations (Pz and Oz, Fig. 4*D*,*E*) was, in fact, far from being statistically significant.

On the other hand, recovery sleep was characterized by a general increase of EEG power in the lower frequency range (0.5–8 Hz) at the fronto-central derivations; this increase was limited to the 6–8 Hz range at the parieto-occipital areas. According to the ANOVAs, these increases were statistically significant only in the 4–7 Hz range at Fz and in the 4–9 Hz range at Cz (Fig. 4*B*,*C*, bottom).

Topographic Differences of Delta EEG Power across the Three Parts of the Night

As reported in the Procedure section, during nights 3–6 participants were awakened twice and administered a psychophysiological test battery. Consequently, these nights were divided into three parts, lasting 2, 3 and 2.5 h, respectively. According to the two-process model of sleep regulation (Borbely, 1982), progressively lower levels of Process S (indexed by delta activity) should be found in the three parts of each night. Moreover, the level of Process S should be higher in the recovery night, at least in the first part.

For each part of the night, we calculated the mean delta EEG power by averaging four adjacent 1 Hz bins (1–4.75 Hz). Data from the two SWS deprivation nights were again collapsed (see Fig. 5*B*). Log-transformed data from the three parts of BLA and REC nights were then submitted to two-way ANOVAs 'night' (BLA, REC) by 'derivation' (Fpz, Fz, Cz, Pz, Oz). A significant rebound of delta activity was evident only in the first part of the recovery night [$F(1,9) = 14.93$, $P = 0.004$] indicating that, after two consecutive nights of selective SWS deprivation, the recovery process is fulfilled after the first 2 h of sleep. There was a significant fronto-occipital gradient of delta EEG power in each of the three parts of the night (all $P < 0.0000001$), although the frontal predominance present during the first 2 h of sleep became progressively less clear in the second and third parts of the night. Finally, the increase of delta power during the first part of the recovery night was particularly prominent at the frontal derivation ($P = 0.02$), but it was significant also at Cz ($P = 0.03$) and Oz ($P = 0.04$).

Dynamics of Delta Activity in the First 40 min of Baseline and Recovery Sleep

The development of delta activity (1.00–4.75 Hz) was analysed for the first 40 min of the first non-REM sleep episode with a time resolution of 1 min, as a further index of sleep pressure. The curves obtained for each midline derivation during BLA, DEP and REC sleep are plotted in Figure 6.

During both BLA and REC sleep, a clear growth pattern of delta activity is evident at each derivation, while the SWS deprivation procedure caused a flattening of the curves. An exponential growth model (estimation method: Quasi-Newton; Statistica 4.1, Statsoft Inc.) applied to the BLA and REC data explained percentages of variance ranging between 46.1 and 54.5%.

To compare the curves obtained for each derivation during BLA and REC nights, the following variables were derived from the individual log-transformed data: (i) the slope of the linear regression curves [An exponential regression model can be converted into a linear one by simply log-transforming the data. Consequently, the linear trend of the log-transformed delta activity indicates that the original data showed an exponential growth.]; (ii) the intercept of the same curves; and (iii) the peak time, i.e. the time from stage 2 onset to the first maximum level of delta activity. These variables were submitted to repeated measure ANOVAs 'night' (BLA, REC) by 'derivation' (Fpz, Fz, Cz, Pz, Oz). Neither the slope or peak time of delta activity showed any significant main effect or interaction. On the other hand, the intercept showed a significant main effect for 'night' [$F(1,9) = 7.49$, $P = 0.02$], indicating that during REC the curve fitting delta activity started from a higher level (mean = 1.52, SE = 0.56) compared to BLA (mean = 1.42, SE = 0.52), presumably due to an

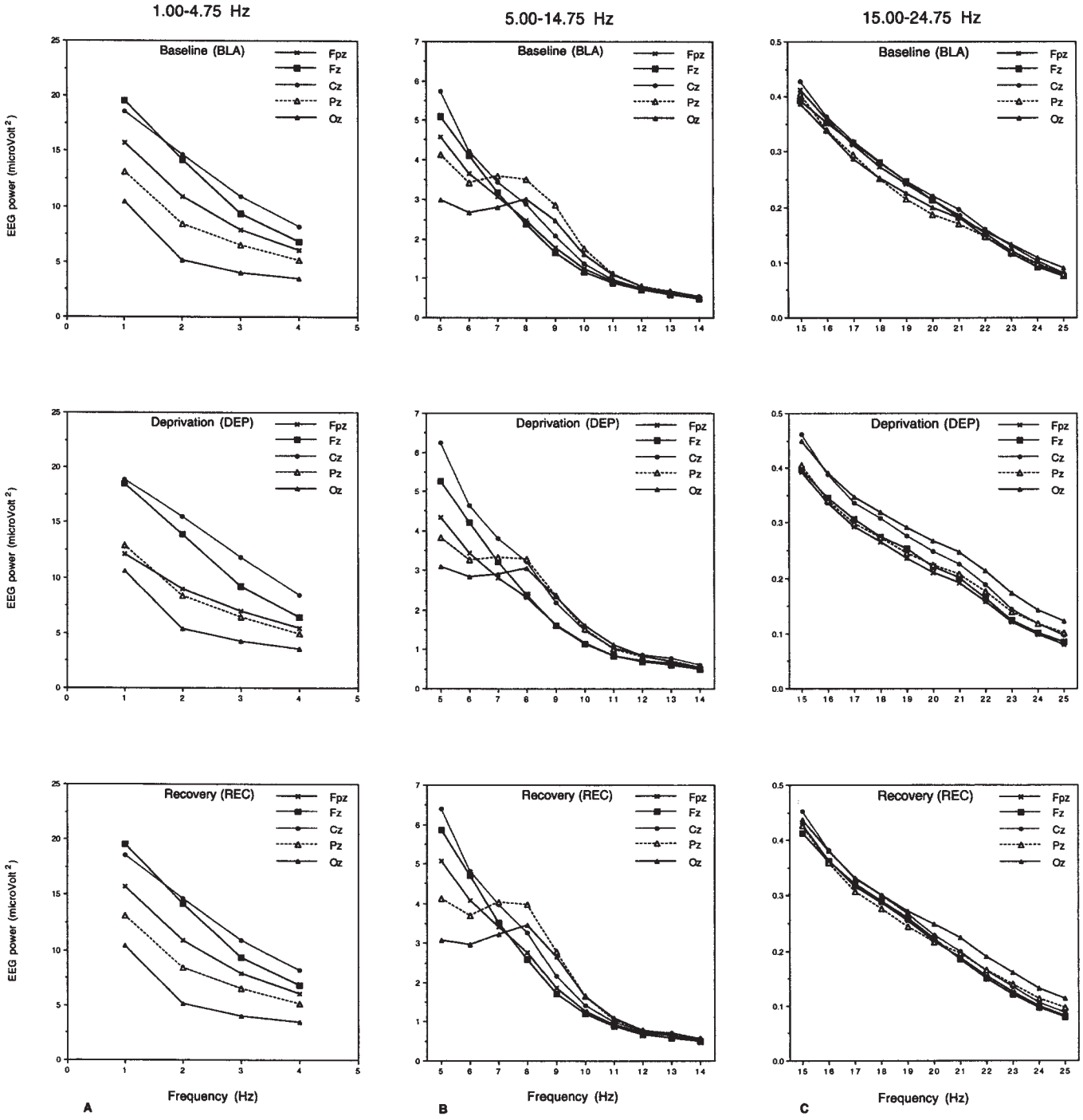

Figure 2. All-night absolute EEG power (μV^2) for REM sleep in the frontopolar (Fpz), frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz) derivations during baseline (BLA), SWS deprivation (DEP — averaged EEG power values of the two SWS deprivation nights) and recovery (REC) sleep. Single-Hz bins have been plotted referring to the traditional delta (*A*), theta-alpha-sigma (*B*) and beta (*C*), in order to group together bins with equivalent power. Consequently, each panel has different *y*-axis scales.

increased slow-wave sleep pressure, i.e. to an enhancement of the level of S (Dijk *et al.*, 1990). Coherently, the SWS deprivation procedure caused an increase of SWS pressure even in the DEP nights, as indicated by the higher starting level of the delta curves compared to BLA (Fig. 6*B*).

A significant main effect for 'derivation' was also found [$F(4,36) = 13.42$, $P = 0.0000009$]. *Post hoc* comparisons showed that the intercept of the curve fitting delta activity at the occipital derivation is lower than those at the other considered derivations (all $P < 0.01$).

Discussion

This is the first study to report large regional differences in response to selective SWS deprivation. During selective SWS deprivation nights, we obtained significant reductions of sleep EEG power in the delta–theta–alpha frequency range at

Table 3
Results of one-way ANOVAs with 'derivation' (Fpz, Fz, Cz, Pz, Oz) assessing the differences between scalp locations in Hz-by-Hz EEG power during REM sleep of the baseline (BLA) night

Frequency (Hz)	*F*(4,36)	*P*	Mean differences
1	11.85	0.0001	Fz > Fpz, Pz, Oz; Cz > Oz
2	41.20	0.0001	Fpz > Oz; Fz > Fpz, Pz, Oz; Cz > Fpz, Pz, Oz; Pz > Oz
3	34.74	0.0001	Fpz > Oz; Fz > Pz, Oz; Cz > Fpz, Pz, Oz; Pz >Oz
4	21.78	0.0001	Fpz > Oz; Fz > Oz; Cz > Fpz, Pz, Oz; Pz >Oz
5	19.76	0.0001	Fpz > Oz; Fz > Oz; Cz > Pz, Oz; Pz >Oz
6	8.91	0.0001	Fpz > Oz; Fz > Oz; Cz > Oz
8	5.14	0.002	Pz > Fpz, Fz
9	10.05	0.0001	Pz > Fpz, Fz; Oz > Fpz, Fz
10	5.60	0.0013	Pz > Fz; Oz > Fz

To correct for multiple comparisons, the Bonferroni correction was applied. Considering the mean correlation between the variables ($r = 0.69$), the alpha level was adjusted to ≤0.02. Only significant ANOVAs and results of *post hoc* comparisons of the means (Scheffé *F*-test) are reported.

frontopolar, central and parietal derivations. On the other hand, the frontal derivation showed a higher 'resistance' to the deprivation procedure, with significant reductions of EEG power limited to the slow-delta range (0.5–2 Hz). Notwithstanding this, a clear antero-posterior gradient of EEG power increases during recovery sleep was found. The frontal derivation indeed showed the largest rebound effect, encompassing the 0.5–8 Hz range. This generalized increase of power can be seen as the electroencephalographic counterpart of the coalescence of different rhythms recently shown by Steriade's group as a typical feature of some cortico-thalamic networks generating the EEG synchronization at a cellular level (Steriade, 1999, 2000, 2001).

These topographic differences in sleep homeostatic processes further confirm that some aspects of the regulatory processes of human non-REM sleep are local in nature. Similar homeostatic EEG dynamics are also present during REM sleep. As a matter of fact, the REM periods of the SWS deprivation nights were characterized by a generalized increase of EEG power, which was even clearer during the recovery night.

Significant increases of non-REM sleep EEG power after SWS deprivation were previously reported only as regards central derivations and in largely different experimental paradigms. Djik and co-workers (Dijk *et al.*, 1987; Dijk and Beersma, 1989) found an intra-night enhancement of EEG power in the delta and theta bands, during the first hour of undisturbed sleep after 3–5 h of selective SWS deprivation. Others (Gillberg and Akerstedt, 1994) have reported an increase of delta activity in the recovery night following a 4 h sleep during which SWS deprivation was accomplished. Taken together, these results point out that 'the slow-wave content of sleep seems more important for sleep-to-sleep homeostasis than sleep duration' (Gillberg and Akerstedt, 1994).

Although there is evidence of experience- or use-dependent processes during sleep, involving both REM sleep and SWS sleep (Maquet, 2001), we do believe that not even part of the EEG power changes reported in the recovery night may be attributed to the repeated testing administered during the preceding nights (see Procedure). To avoid a progressive improvement of performance during the experiment due to a practice effect, all our subjects were trained to asymptotic performance levels during the days preceding the study (Ferrara *et al.*, 2000). Consequently, any experience-dependent effect on SWS (due to the exposure to new tasks or to the expansion of the behavioural repertoire) would have appeared during the sleep periods that preceded the experimental nights. Moreover, the behavioural testing lasted only ~13 min, instead of the several hours of stimulation known to affect the SWS (Horne and Minard, 1985) or SWA sleep content (Kattler *et al.*, 1994). Two out of three tasks used were very simple, requiring only a motor response (a simple reaction time and a finger tapping task) and the only task requiring 'higher' cognitive performance (a subtraction task) lasted just 3 min. The effects on sleep structure of such a brief stimulation must still be proved.

Regional Differences in EEG Power during Non-REM Sleep

Several regional differences in non-REM sleep EEG are present during baseline sleep episodes. Simplifying, we observed three clusters of regional differences during non-REM sleep (see Table 2): (i) a fronto-central predominance in the 1–11 Hz range; (ii) a centro-parietal dominance in the 12–14 Hz range (the sigma range); and (iii) a frontal dominance in the 15–20 Hz range.

In particular, a specific frontal predominance in the very slow frequency range (1–2 Hz) and in the alpha range (9–11 Hz) was also present. The former, also reported by Werth and co-workers in the initial part of sleep (Werth *et al.*, 1996, 1997), again suggests that the frontal association area shows the higher sleep need and intensity, as a consequence of its intensive use during wakefulness. In fact, the prefrontal cortex is the most active brain area during wakefulness (Gusnard *et al.*, 2001). Conversely, a frontal predominance of delta activity, a marker of non-REM sleep intensity, has been described during sleep (Werth *et al.*, 1996, 1997; Cajochen *et al.*, 1999; Finelli *et al.*, 2001). It is accompanied by a larger reduction of regional cerebral blood flow (rCBF) as compared to other cortical areas (Maquet, 2000). This frontal deactivation may be due to an increased local use-dependent sleep intensity, reflected in more intense recovery processes.

The frontal maximum of alpha power, also recently shown by Finelli and co-workers (Finelli *et al.*, 2001), may be interpreted in the light of a re-examination of the psychophysiological literature (Pivik and Harman, 1995), suggesting the existence of a different alpha activity associated with sleep-maintaining processes. The increase of frontal alpha activity during recovery sleep (discussed below) seems to confirm this interpretation.

The centro-parietal peak in the 12–14 Hz range has been previously described (Jobert *et al.*, 1992; Werth *et al.*, 1997; Zeitlhofer *et al.*, 1997) and can be related to the anatomical characteristics of thalamo-cortical systems generating sleep spindles (Steriade *et al.*, 1993). Similarly, the frontal predominance of the low-beta activity (15–20 Hz) may itself be a consequence of the underlying generating mechanisms, which are not fully understood. In recent years, neurophysiological studies have shown that fast rhythms are not necessarily indicators of alertness, since they are cyclically generated by the slow sleep oscillation of cortical cells (Steriade, 2001). In light of these neuro- and electrophysiological observations, a re-examination of the functional role of traditional EEG bands during sleep is needed in the near future.

Regional Differences in Response to SWS Deprivation during Non-REM Sleep

The decreases of EEG power during the two nights of SWS suppression were particularly large at frontopolar, central and parietal derivations, where they included a broad range of frequency bins encompassing delta, theta and alpha bands. On the other hand, obtaining a significant decrease of EEG power at

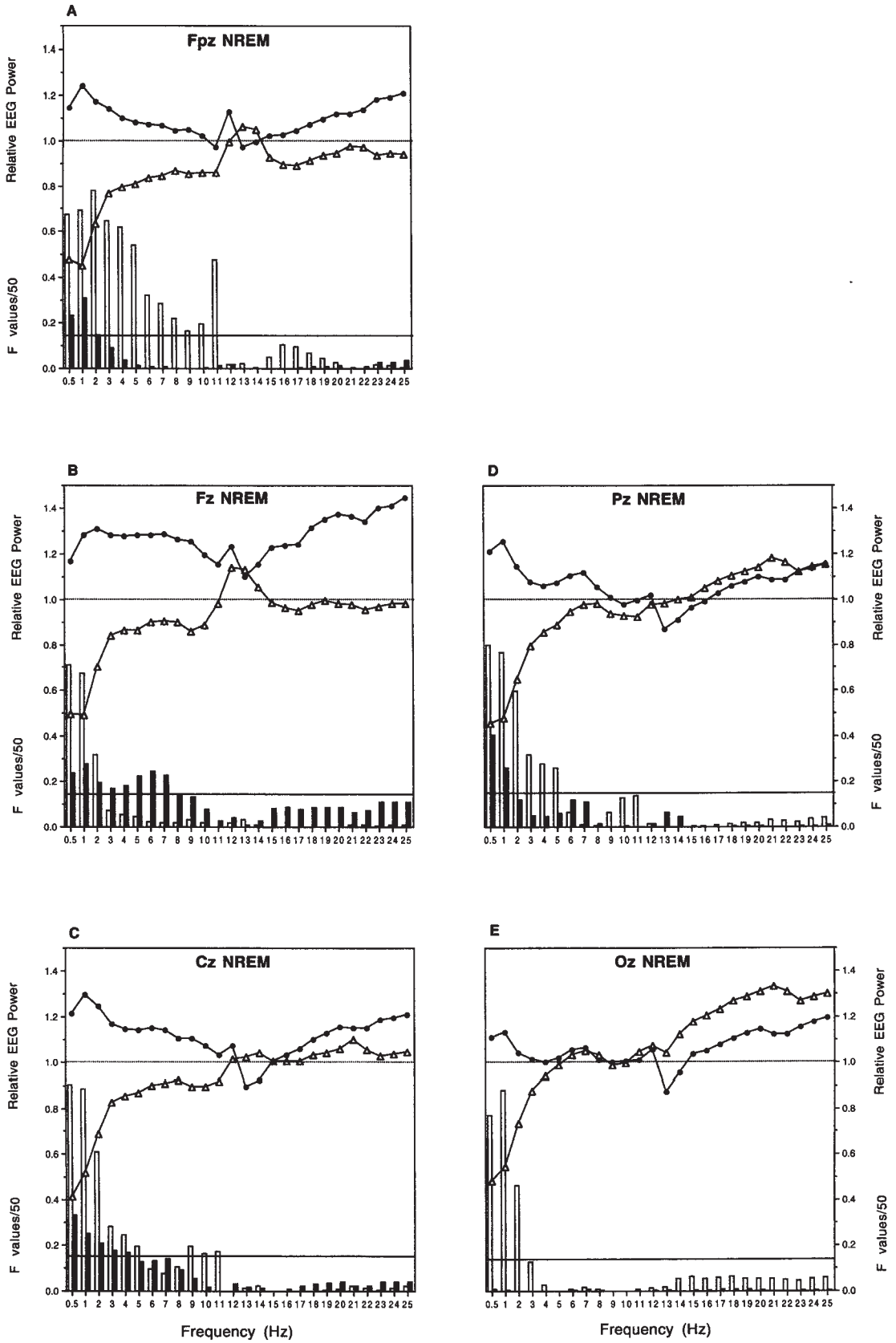

Figure 3. EEG power for non-REM sleep (NREM) during SWS deprivation (DEP — averaged EEG power values of the two SWS deprivation nights, open triangles) and recovery sleep (REC, filled circles), expressed as ratios of each bin to the corresponding baseline (BLA) power. The horizontal dotted line represents the baseline level of EEG power (value = 1). The ANOVA results (*F*-values) are also reported for each bin, in the bottom of each panel. The white bars indicate the DEP versus BLA comparisons, while the black bars show the REC versus BLA comparisons. The *F*-values have been divided by 50 to optimize bar scaling. The continuous line indicates the level of statistical significance after the Bonferroni correction ($P \leq 0.02$).

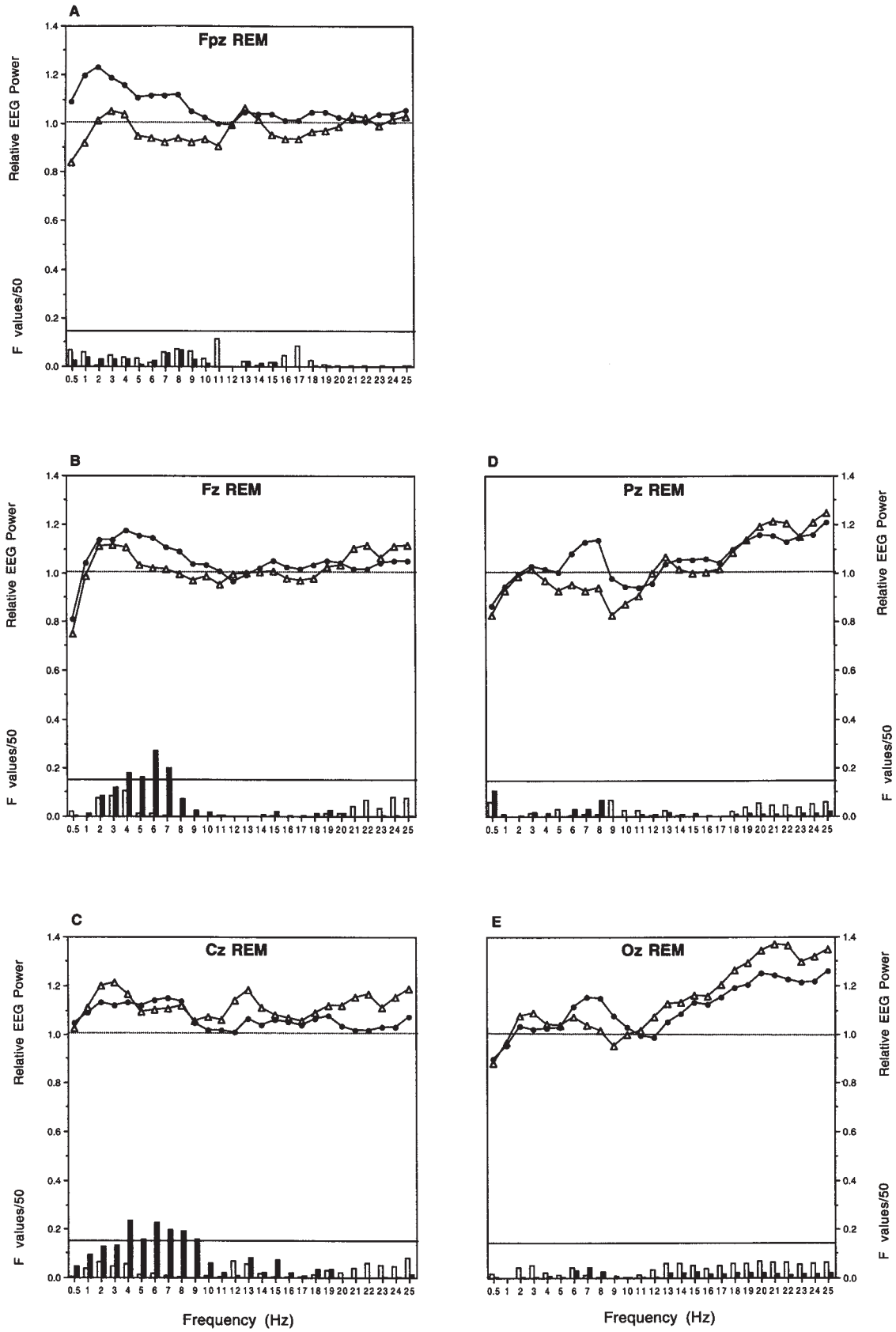

Figure 4. EEG power for REM sleep during SWS deprivation (DEP — averaged EEG power values of the two SWS deprivation nights, open triangles) and recovery sleep (REC, filled circles), expressed as ratios of each bin to the corresponding baseline (BLA) power. The horizontal dotted line represents the baseline level of EEG power (value = 1). The ANOVA results (*F*-values) are also reported for each bin, in the bottom of each panel. The white bars indicate the DEP versus BLA comparisons, while the black bars show the REC versus BLA comparisons. The *F*-values have been divided by 50 to optimize bar scaling. The continuous line indicates the level of statistical significance after the Bonferroni correction ($P \leq 0.02$).

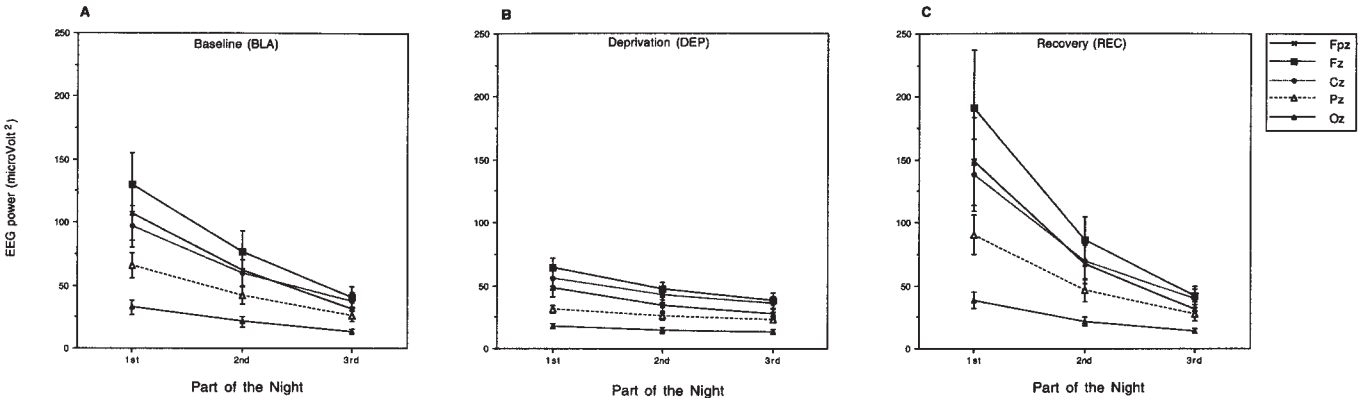

Figure 5. Time course of mean delta activity (absolute EEG power in the 1.00–4.75 Hz range, ±SE) at each midline derivation (Fpz, Fz, Cz, Pz, Oz) during the three parts of baseline (BLA, *A*), SWS deprivation (DEP — averaged EEG power values of the two SWS deprivation nights, *B*) and recovery (REC, *C*) nights. Each night was divided into three parts lasting, 2, 3 and 2.5 h, by two experimental awakenings (see Procedure for more details).

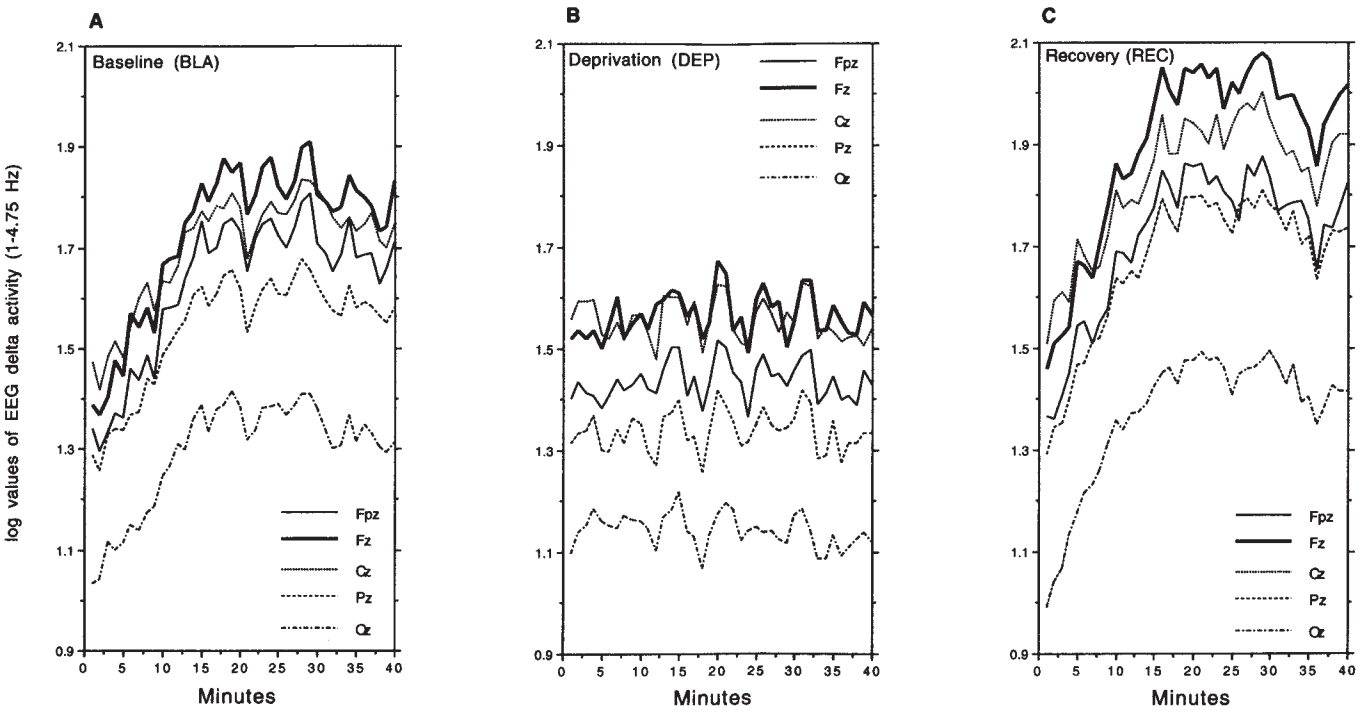

Figure 6. Dynamics of delta activity (log-transformed EEG power in the 1.00–4.75 Hz range) during the first 40 min of non-REM sleep for each midline derivation (Fpz, Fz, Cz, Pz, Oz) during baseline (BLA), slow-wave sleep deprivation (DEP — averaged EEG power values of the two SWS deprivation nights) and recovery (REC) nights.

the frontal derivation turned out to be very difficult. Only the slow-delta range (0.5–2 Hz) was indeed significantly affected by the SWS deprivation procedure. [However, results concerning the 0.5 Hz bin are to be considered with some caution, since the possibility of low-frequency artefacts can not be completely ruled out.] The distinct behaviour of slow- (0.5–2 Hz) and fast-delta (3–4 Hz) during both deprivation and recovery nights has to be underlined. More specifically, the 0.5–2 Hz bins showed a coherent and uniform behaviour over different scalp locations (see Fig. 3*A*,*B*,*D*,*E*, bottom parts of panels). Other authors (Benoit *et al.*, 2000) found that these two delta bands show little correlation with each other, also differing in their relationships with theta and alpha frequencies. Similarly, a detailed analysis (Achermann and Borbely, 1997) of the EEG power evolution across sleep episodes, found that the decrease in power from the first to the second episode was significant only beyond 1.9 Hz. It can be hypothesized that these differences may, at least in part, reflect the different origins (cortical or thalamocortical) of the slow and fast delta waves (Benoit *et al.*, 2000). The frontal predominance just in the 1–2 Hz range observed in the present study and elsewhere (Werth *et al.*, 1996, 1997) could support a frontally centred origin of the slow-delta rhythm.

The 'resistance' of the frontal cortical areas to SWS deprivation can be interpreted as a sign of a higher sleep need. The frontal predominance of delta activity – as a marker of non-REM sleep

intensity — during baseline sleep (Werth *et al.*, 1996, 1997; Cajochen *et al.*, 1999; Finelli *et al.*, 2001) becomes even more pronounced after total sleep deprivation (Cajochen *et al.*, 1999; Finelli *et al.*, 2001). In the present study, too, the frontal derivation showed the largest rebound effect during recovery sleep (see Fig. 3*B*), despite the fact that, at the same recording site, the SWS deprivation procedure caused significant changes only in a narrow EEG frequency range. More specifically, increases were found in the 0.5–8 Hz range, encompassing the delta, theta and alpha bands. Similarly, Finelli and co-workers recently reported specific frontal increases of EEG power in the 1–10 Hz range after total sleep deprivation (Finelli *et al.*, 2001). While an increase of delta and theta EEG power is largely expected, the significant increase in the alpha range may appear counter-intuitive. Nevertheless, this result supports the above-mentioned re-conceptualization of alpha activity during sleep (Pivik and Harman, 1995); in fact, an EEG rhythm associated with sleep-maintaining processes should be expectedly enhanced during recovery sleep. Accordingly, a recent micro-structural analysis of the changes of EEG power during sleep onset showed that alpha activity decreases up to the end of stage 1, but starts to increase again after stage 2 onset, when the EEG synchronization process is characterized by a uniformly increasing trend of EEG power across the 1–16 Hz frequency range (De Gennaro *et al.*, 2001b).

We believe that, rather than being trivial, this generalized increase of power indicates that different EEG bands with traditionally different electrophysiological meanings may exhibit a homogeneous behaviour during sleep. The need for an electroencephalographic 'simplification' is supported by robust neurophysiological evidence which has reduced the multiplicity of EEG rhythms to a few basic cellular operations (Steriade, 1999, 2000). According to Steriade, the classification of the oscillations of brain electrical activity during sleep within frequency bands only has a didactic purpose (Steriade, 2000). In fact, several oscillations, generated in the thalamus and cortex, are grouped within complex wave sequences by a cortically generated slow (<1 Hz) oscillation (Steriade, 2000, 2001). Moreover, fast rhythms (20–50 Hz) are also generated during the depolarizing phase of slow sleep oscillation, in contrast with the idea that these rhythms are reliable and exclusive indicators of alertness (Steriade, 2001). Interestingly, in the present study an increase of EEG power in the beta range during recovery sleep was found, further suggesting that a re-examination of the functional role of EEG rhythms during sleep is needed.

A pattern of EEG power reductions restricted to a narrow frequency range was found during the SWS deprivation nights also at the occipital derivation. In this case, however, the absence of any significant rebound in the recovery night indicates a lower need for recuperative processes over the posterior brain sites. In fact, we found a clear antero-posterior gradient of EEG power increases during recovery sleep, characterized by a frontal prevalence.

Taken together, these data further confirm that some aspects of the regulatory processes of human sleep are local in nature, as previously demonstrated during sleep onset by single-cell recordings in monkeys (Pigarev *et al.*, 1997) and by EEG spectral analysis in humans (De Gennaro *et al.*, 2001a). Our results are also in accordance with the topographic differences in the EEG power changes reported by others after partial and total sleep deprivation (Werth *et al.*, 1998; Cajochen *et al.*, 1999; Finelli *et al.*, 2001) and may imply that the human sleep EEG shows use-dependent characteristics (Kruger and Obal, 1993).

Regional Differences in Response to SWS Deprivation during REM Sleep

The SWS deprivation procedure caused changes in EEG power also during REM sleep. During the selective SWS deprivation nights, a general increase of EEG power in the entire 0.5–25 Hz frequency range was found, which seemed particularly evident at the vertex. The redistribution of the low-frequency EEG power in the REM sleep episodes may have partly compensated for the reduction of non-REM sleep intensity during the selective SWS deprivation. Moreover, recovery sleep was characterized by an increase of EEG power in the delta–theta frequency range at the fronto-central derivations. Similarly, an increase of EEG power in the delta–theta range during REM sleep has been reported after total and partial sleep deprivation (Borbely *et al.*, 1981; Brunner *et al.*, 1990, 1993). Taken together, these results seem to indicate that the strong modifications of the EEG power homeostasis (in the low frequencies in particular), induced during non-REM sleep by acoustic stimulation, are able to induce recovery processes also during REM sleep. These homeostatic EEG dynamics are to some extent evident during the REM sleep of the SWS deprivation nights and more clearly during the REM periods of the following recovery night. These observations, together with previous results (Borbely *et al.*, 1981; Brunner *et al.*, 1990, 1993), indicate that the EEG power in the delta–theta frequency range is modulated by a common homeostatic process in non-REM and REM sleep, and should be taken into account in the current models of sleep regulation.

In conclusion, this study demonstrates that the obliteration of visually scored slow-waves in sleep EEG by means of acoustic stimulations strongly attenuates the EEG power of non-REM sleep in a frequency range whose width depends on the scalp recording site. The 'resistance' to selective SWS deprivation of the frontal area, together with its larger increase of EEG power during recovery, strongly supports the idea that the homeostatic non-REM sleep regulating process exhibits regional differences in the brain. The specific involvement of the frontal cortex in the sleep process is in line with the hypothesis that the human sleep EEG shows use-dependent characteristics (Kruger and Obal, 1993). A coherent behaviour of the slow-delta frequency (0.5–2 Hz) during different nights and over different scalp locations was also found, supporting the hypothesis that slow and fast (3–4 Hz) delta waves may have different origins (cortical or thalamocortical). The homeostatic EEG dynamics during REM sleep (both in the deprivation and recovery nights) and the homogeneous behaviour of different traditional EEG bands during non-REM sleep of the recovery night suggest that, in view of recent advances in sleep neurophysiology (Steriade, 1999, 2000, 2001), a re-examination of the functional role of EEG rhythms during sleep is needed.

Notes

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