The frontal predominance in human EEG delta activity after sleep loss decreases with age

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Abstract

Sleep loss has marked and selective effects on brain wave activity during subsequent recovery sleep. The electroencephalogram (EEG) responds to sleep deprivation with a relative increase in power density in the delta and theta range during non-rapid eye movement sleep. We investigated age-related changes of the EEG response to sleep deprivation along the antero-posterior axis (Fz, Cz, Pz, Oz) under constant routine conditions. Both healthy young (20–31 years) and older (57–74 years) participants manifested a significant relative increase in EEG power density in the delta and theta range after 40 h of sleep deprivation, indicating a sustained capacity of the sleep homeostat to respond to sleep loss in ageing. However, the increase in relative EEG delta activity (1.25–3.75 Hz) following sleep deprivation was significantly more pronounced in frontal than parietal brain regions in the young, whereas such a frontal predominance was diminished in the older volunteers. This age-related decrease of frontal delta predominance was most distinct at the beginning of the recovery sleep episode. Furthermore, the dissipation of homeostatic sleep pressure during the recovery night, as indexed by EEG delta activity, exhibited a significantly shallower decline in the older group. Activation of sleep regulatory processes in frontal brain areas by an extension of wakefulness from 16 to 40 h appears to be age-dependent. These findings provide quantitative evidence for the hypothesis that frontal brain regions are particularly vulnerable to the effects of elevated sleep pressure ('prefrontal tiredness') and ageing ('frontal ageing').

Introduction

According to the two-process model of sleep regulation, sleep pressure accumulates during wakefulness and dissipates in the course of the following sleep episode (Borbély, 1982). Electroencephalogram (EEG) activity in low-frequency components (0.75–7.0 Hz) is the key electrophysiological marker of this homeostatic process (Borbély *et al*., 1981) – most apparent in frontal brain areas during sustained wakefulness (Cajochen *et al*., 1999a, 2001; Finelli *et al*., 2001) and during the following sleep episode (Werth *et al*., 1997; Cajochen *et al*., 1999b; Finelli *et al*., 2000). Positron emission tomography studies have demonstrated that the decline of regional cerebral blood flow (rCBF) during slow-wave activity (SWA) is most prominent in frontal cortical areas (Maquet *et al*., 1990, 1997; Braun *et al*., 1997; Hofle *et al*., 1997; Kajimura *et al*., 1999; Nofzinger *et al*., 2002). Thus, frontal brain areas, especially the prefrontal cortex (PFC), may represent a brain region particularly vulnerable to the effects of sleep loss (Horne, 1992, 1993; Harrison *et al*., 2000; Thomas *et al*., 2000; Jones & Harrison, 2001; Muzur *et al*., 2002).

Besides sleep regulatory processes, there is mounting evidence that the PFC is also susceptible to age-related changes (Moscovitch & Winocur, 1995; Gunning-Dixon & Raz, 2003; Tisserand & Jolles, 2003). Neurobehavioural functions highly dependent on PFC regions decline with age, whereas those less dependent on the PFC remain better conserved (e.g. Dempster, 1992; for a critical review, see Greenwood, 2000).

Both the general enhancement of recuperative SWA response to sleep loss in the young and age-related changes in neurobehavioural functions are associated with the PFC. How these two processes modify the sleep EEG along the antero-posterior axis has, to our knowledge, not yet been investigated. Older volunteers exhibit lower absolute levels of SWA (0.75–4.5 Hz) during sleep episodes, as a result of a progressive decline starting already in their second decade of life (Smith *et al*., 1977; Ehlers & Kupfer, 1989; Landolt *et al*., 1996; Carrier *et al*., 2001; Landolt & Borbély, 2001). There is also evidence that middle-aged volunteers exhibit a longer time constant in the dissipation of SWA during baseline nights (Dijk *et al*., 1989). However, these data are largely based on a single derivation from central brain regions. Therefore, we aimed at quantifying the homeostatic response to sleep deprivation in the spectral composition of the sleep EEG along the antero-posterior brain axis, comparing healthy young with older participants. If functions subserved by the PFC are impaired in non-pathological ageing, and if age modifies homeostatic sleep regulation after sleep deprivation, two compensatory reactions of the PFC are possible: an increase of PFC activity (the PFC needs to be more active to sustain high neurobehavioural performance) or a decrease (the PFC cannot adequately compensate for the augmented duration of wakefulness). Based on the aforementioned literature we predicted the latter, and hypothesised that sleep deprivation will lead to a less pronounced increase in frontal low EEG components during the recovery night. Furthermore, we predicted a shallower SWA decline during the recovery sleep episode in older compared with young volunteers. To test these hypotheses, we examined both age groups during a 40-h sleep deprivation protocol under stringently controlled constant routine conditions.

Materials and methods

Study participants

Study volunteers were recruited via advertisements at different universities and in newspapers in Switzerland. Sixteen young (eight women and eight men, age range 20–31 years, mean: 25 ± 0.9 SEM) and 16 older volunteers (eight women and eight men, age range 57–74 years, mean: 64.9 ± 1.4) were included following initial screening of more than 500 potential applicants. All study participants were non-smokers, did not take any drugs (urinary drug screening before study began) or medication, and were free from medical, psychiatric and sleep disorders. Four young female volunteers used oral contraceptives. All young women were studied during the follicular phase of their menstrual cycle. The health of all volunteers was assessed by questionnaires, physical examination, interviews and a polysomnographically recorded screening night. During the baseline week preceding the study, volunteers were instructed to keep their individual bed- and wake-time within a self-selected range of ± 30 min, and to attempt to sleep for 8 h. This was assessed by a wrist activity monitor (Cambridge Neurotechnologies®, Cambridge, UK) and sleep logs. Study participants were asked to abstain from excessive caffeine and alcohol consumption. The study protocol, the screening questionnaires and the consent form were approved by the Ethical Committee of Basel, Switzerland, and were in agreement with the Declaration of Helsinki. After a thorough personal discussion of all protocol details with an investigator, the study participants gave their written informed consent.

Protocol

The protocol consisted of two baseline nights in the sleep laboratory followed by a 40-h episode of sleep deprivation and an 8-h recovery sleep episode. The entire protocol was carried out under constant routine (CR) conditions (< 8 lux, temperature 21 °C, semi-recumbent posture in bed, regular small isocaloric snacks and water, and no time cues (Czeisler *et al.*, 1985; for details, see Cajochen *et al.*, 2001). The timing of the 8-h sleep episodes during the laboratory study was scheduled by centring the midpoint of the study participants' habitual sleep episodes at home during the baseline week (as assessed by actigraphy). Continuous polysomnographic recording started after the first baseline night. The older study participants received a daily low-dose heparin injection (Fragmin®, 0.2 mL, 2500 IE/UI, Pharmacia AG, Dübendorf, Switzerland) while recumbent in the CR.

Sleep EEG recordings and analysis

The sleep EEG was recorded from 12 derivations (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, Oz) referenced against linked mastoids (A1, A2), together with two electrooculograms, one electrocardiogram and one submental electromyogram using a digital ambulatory sleep recording system (Vitaport-3 digital recorder, TEMEC Instruments BV, Kerkrade, the Netherlands). All signals were filtered at 30 Hz (fourth order Bessel type anti-aliasing low-pass filter, total 24 dB/Oct). A time constant of 1.0 s was used prior to on-line digitisation (range 610 µV, 12-bit AD converter, 0.15 µV/bit, sampling rate at 128 Hz for the EEG). The raw signals were stored on a Flash RAM card (Viking, USA) and downloaded off-line to a local computer hard drive. Sleep stages were visually scored per 20-s epoch according to standard criteria (Rechtschaffen & Kales, 1968). Artefact-free sleep EEGs (automated artefact detection algorithm: CASA, 2000 PhyVision BV, Gemert, the Netherlands) were subjected to spectral analysis using a Fast Fourier Transformation (FFT, 10% cosine 4-s window) resulting in a 0.25-Hz bin resolution. For data reduction, artefact free 4-s epochs were averaged over 20-s epochs. Sleep EEG power spectra were calculated during non-rapid eye movement (NREM) sleep (stages: two, three and four) in the frequency range from 0.5 to 32 Hz. Here, we report EEG power density derived from the midline (Fz, Cz, Pz and Oz) during NREM sleep in the range from 0.75 to 25 Hz.

Statistics

The statistical packages SAS® (SAS Institute, Cary, NC, USA; Version 6.12) and Statistica® (Stat Soft, 2000. STATISTICA for Windows, Tulsa, OK, USA) were used. Two-, three- and four-way analyses of variance for repeated measures (rANOVA) with the factors 'age' (young vs. older), 'derivation' (Fz, Cz, Pz and Oz) and 'night' (baseline, recovery) or 'time interval' (2-h intervals) were performed for each EEG power value in each frequency bin separately. Analyses were based on log-transformed EEG power density ($\mu V^2/0.25$ Hz) and on relative EEG power density (log ratios, %). Prior to plotting, the data were averaged across subjects, then re-transformed and expressed as a percentage of the baseline night values. All *P*-values derived from rANOVAs were based on Huynh–Feld's (H–F) corrected degrees of freedom, but the original degrees of freedom are reported. *Post-hoc* comparisons were performed by using Duncan's multiple range test (corrected for multiple comparisons; $P < 0.05$ was considered significant). For two *post-hoc* comparisons in Fig. 3, non-parametric tests (Mann–Witney *U*-test and Wilcoxon test) were applied, as the values in the older group did not fulfil criteria for normal distribution.

Results

Sleep measures derived from visual scoring during the baseline and the recovery night

Table 1 summarizes sleep measures during the baseline and the recovery night (% of total sleep time). Two-way rANOVAs with the factors 'age' and 'night' were performed for each variable separately. A main effect of age was found for the variables: total sleep time, sleep efficiency, wakefulness after sleep onset, stage two, stage four, SWS, NREM sleep, REM sleep (for all measures: $F_{1,30} > 5.5$; $P < 0.05$) and a tendency for movement time and stage one ($P = < 0.7$). The main factor 'night' yielded significance in all variables (for all measures: $F_{1,1} > 6$; $P < 0.05$), except for movement time and NREM sleep, REM sleep and REM latency. The interaction between the factors 'age' × 'night' yielded significance for stage four SWS as well as sleep latencies to stage one and two ($F_{1,30} > 4$; $P < 0.05$). *Post-hoc* comparisons revealed that the older volunteers had significantly less SWS during both the baseline and the recovery night (Duncan's multiple range test; $P < 0.05$). *Post-hoc* comparisons performed for sleep latency one and two indicated significant shorter sleep latencies during the recovery night for the young group (Duncan's multiple range test; $P < 0.05$; sleep latencies were calculated on log-transformed values).

Age-related changes in EEG power density (0.75–25 Hz) during the baseline and the recovery night after sleep loss

To examine EEG power density in the range of 0.75–25 Hz during NREM sleep for both age groups, all-night power density during the

TABLE 1. Relative values (percent of total sleep time) are shown for sleep stages

| | Baseline night | | Recovery night | | | | |
	Young group	Older group	Young group	Older group	Age	Night	Age × night
TST(min)	438.1 ± 7.2	407.0 ± 8.4	449.9 ± 9.8	429.1 ± 7.2	*	*	–
SE (%)	91.3 ± 1.5	84.8 ± 1.7	93.9 ± 2.1	89.5 ± 1.5	*	*	–
% MT	0.6 ± 0.5	0.2 ± 0.3	1.6 ± 0.4	0.8 ± 0.6	°	–	–
% Wakefulness	4.5 ± 1.5	14.5 ± 2.4	1.3 ± 0.5	8.1 ± 1.6	**	*	–
% Stage 1	12.6 ± 1.4	14.6 ± 1.6	6.5 ± 0.8	9.7 ± 0.8	°	**	–
% Stage 2	50.3 ± 1.3	59.6 ± 2.7	46.5 ± 1.2	57.6 ± 3.1	*	*	–
% Stage 3	10.3 ± 0.7	8.0 ± 1.4	13.7 ± 1.2	12.7 ± 1.2	–	**	–
% Stage 4	6.9 ± 1.5	1.7 ± 0.5	14.3 ± 2.0	4.6 ± 1.1	**	**	*
% SWS	17.2 ± 1.7	9.7 ± 1.9	27.9 ± 1.6	17.3 ± 2.3	*	**	*
% NREM	80.0 ± 1.0	83.9 ± 1.2	80.9 ± 1.2	84.5 ± 1.4	*	–	–
% REM	20.0 ± 1.0	16.1 ± 1.3	19.1 ± 1.2	15.5 ± 1.4	*	–	–
SL1 (min)	10.2 ± 2.3	8.0 ± 0.8	3.9 ± 0.6	8.2 ± 1.8	–	**	*
SL2 (min)	15.2 ± 2.3	11.0 ± 0.9	6.3 ± 0.8	10.4 ± 1.8	–	**	**
RL (min)	78.9 ± 5.9	92.5 ± 21.4	73.6 ± 8.7	71.1 ± 7.0	–	–	–

TST = (min; stages 1–4 + REM sleep); SE = [(TST/time after lights off) × (100)]; % MT = (after sleep onset) × 100; % wakefulness (after sleep onset) × 100; % SWS = (stage 3 + stage 4) × 100; % NREM sleep = (SWS + stage 1 + stage 2) × 100; SL1 = sleep latency to stage 1 (min); SL2 = sleep latency to stage 2 (min); RL = rem latency to REM sleep (min); $*P < 0.05$, $**P < 0.001$, $°P < 0.1$. Values are indicated ± SEM ($n = 16$ in each age group). MT, movement time; NREM, non-rapid eye movement; REM, rapid eye movement; SE, sleep efficiency; SWS, slow wave sleep; TST, total sleep time.

recovery and the baseline night were calculated for the midline derivations (Fz, Cz, Pz and Oz) in each frequency bin (Fig. 1). A three-way rANOVA (on log-transformed values) with the factors 'age', 'derivation' and 'night' yielded a main effect for the factor 'night' in all frequency bins ($P < 0.05$), except within the higher spindle frequency range from 14.5 to 15.75 Hz. A main effect of 'age' was found in the frequency bins 0.75–5.25 Hz and 6.75–7.75 Hz (delta and theta range) and 11.75–14.75 Hz (spindle range). Figure 1 shows higher absolute EEG power in those frequency bins for the young than for the older age group. The interaction of the factors 'age' × 'night' and 'age' × 'derivation', respectively, was significant for some frequency bins in the delta as well as in the spindle frequency range ($P < 0.05$ for each frequency bin, bottom panel in Fig. 1). The interaction for these three factors was significant in the frequency bins between 1.25 and 3.75 Hz.

For analysing the overall response to elevated sleep pressure during the recovery night in the young and older study participants, the absolute EEG power spectra were calculated for each derivation and frequency bin and expressed as percentage of the baseline values (Fig. 2). A two-way rANOVA (log-ratios) with the factors 'age' × 'derivation' yielded a significant interaction in the frequency bins between 1.25 and 3.75 Hz ($P < 0.05$ for each frequency bin; vertical dotted lines in Fig. 2 emphasise the significant frequency range). Further analyses with both age groups were based on a collapsed EEG delta band in the range of 1.25–3.75 Hz, because these frequency bins exhibited a significant three-way interaction.

Age-related differences in regional EEG delta power after sleep loss

A two-way rANOVA 'age' × 'derivation' exhibited significant interaction ($F_{3,90} = 11.3$, $P < 0.0001$ on log-ratios) for the relative EEG delta power density to sleep deprivation, indicating a different regional response to elevated homeostatic sleep pressure with age. The main effect of 'age' was not significant ($P > 0.1$), whereas the factor 'derivation' yielded significance ($F_{3,90} = 24.3$; $P < 0.0001$). *Post-hoc* comparisons (Mann–Whitney *U*-test) indicated a significant

difference in the frontal derivation ($P = 0.0014$) and a tendency ($P = 0.055$) in the central derivation between the older and the young group (Fig. 3). Within the age groups there was a significant fronto-occipital gradient in the young between Fz and Cz, Cz and Pz, Pz and Oz (*post-hoc*: Wilcoxon, $P < 0.05$) and a lack of such a significant gradient in the older group except for Pz and Oz ($P < 0.05$).

Age-related changes in the time course of relative EEG delta power density during the baseline and recovery night

In order to assess age-related modifications in the temporal distribution of EEG delta power along the antero-posterior axis, relative EEG power density in this frequency range was calculated for 2-h intervals throughout the baseline and the recovery night for each age group separately (Fig. 4). During both nights, EEG delta power declined over consecutive NREM sleep episodes in young and older subjects. A four-way rANOVA, performed on EEG delta power density (log ratios; Table 2) yielded a number of significant results, and an almost significant interaction between the factors: 'age' × 'night' × 'derivation' × 'time interval' ($P = 0.061$; uncorrected P-value: $P = 0.028$). A three-way rANOVA with the factors 'age' × 'derivation' × 'night' performed for each time interval separately resulted in a significant interaction during the first and third quarter of the night ($F_{3,90} = 4.2$ and $F_{3,90} = 5.8$; $P < 0.05$). *Post-hoc* comparisons revealed that the differences between young and older subjects occurred mainly during the first quarter of the night (Duncan's multiple range test $P < 0.05$ for Fz and Pz). No significant *post-hoc* comparisons resulted during the third time interval ($P > 0.1$ for all derivations). When a separate rANOVA (three-way rANOVA with the factors 'age' × 'night' × 'time interval') for each derivation was performed, a tendency ($P < 0.1$) for the interaction of these factors emerged for the frontal, central as well as the parietal derivation, and a significant interaction for the occipital derivation ($P < 0.05$).

To quantify the 'steepness' of EEG delta activity decrease during the baseline and the recovery night, the difference in relative EEG delta power density between the first and fourth 2-h interval was
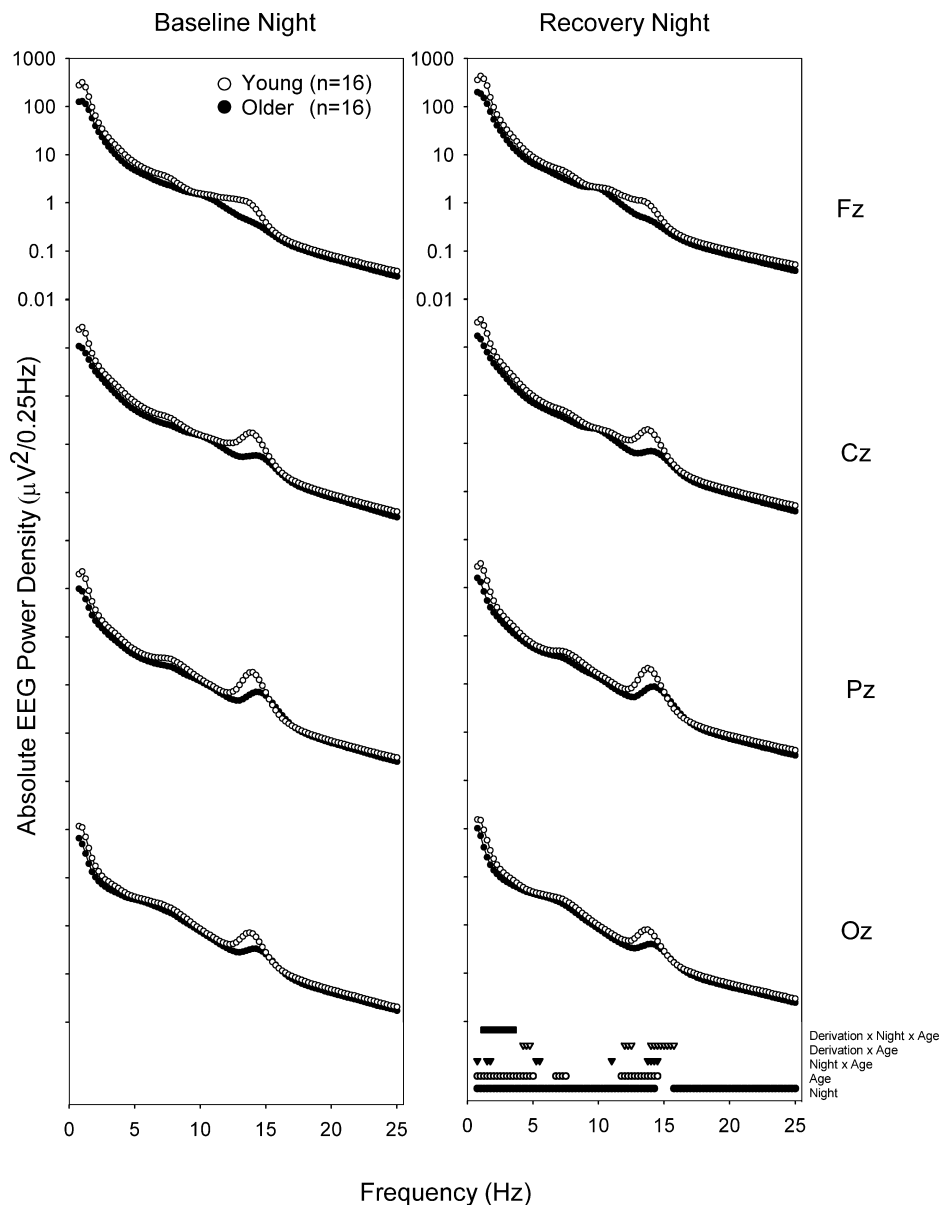
FIG. 1. Absolute electroencephalogram (EEG) power spectra during NREM sleep in the midline derivations (Fz, Cz, Pz and Oz) during the baseline (left panel) and the recovery night (right panel) for the young (open circles) and older age group (filled circles). Mean values are shown for each 0.25-Hz frequency bin in the range of 0.75–25 Hz ($n = 16$ in both age groups). Horizontal circles near the abscissa at the bottom indicate frequency bins for which the factor 'night' (filled circles) and the factor 'age' (open circles) were significant. Filled black triangles show frequency bins for which the interaction 'age' × 'night' turned out to be significant, and white triangles represent the significant values of the interaction for the factors 'age' × 'derivation'. Black squares at the bottom indicate frequency bins for which the interaction 'age' × 'night' × 'derivation' yielded significant values.

calculated for each derivation and age group separately (Fig. 5). A three-way rANOVA with the factors: 'age' × 'derivation' × 'night' yielded a significant interaction between these factors ($F_{3,90} = 8.0$; $P < 0.05$). *Post-hoc* comparisons revealed no significant differences in the steepness of the temporal EEG delta power gradient during the baseline night between both age groups. However, a significantly higher steepness in EEG delta between intervals 1 and 4 was found during the recovery night in young participants in the frontal derivation (Duncan's multiple range test: $P < 0.05$) and a tendency ($P < 0.1$) for the central and the parietal derivation.

A two-way rANOVA ('age' × 'derivation') calculated for the baseline night separately did not reveal a significant interaction between these factors. However, significant effects were found for the

main factors 'age' and 'derivation' ($F_{1,30} = 12.1$ and $F_{3,90} = 25.4$; $P < 0.05$ for both factors). The same analysis performed for the recovery night yielded a significant interaction for the factors 'age' × 'derivation' ($F_{3,90} = 5.1$; $P < 0.05$). This indicates that the age-related dissipation of EEG delta activity during the recovery night depends on brain location (i.e. EEG derivation).

Based on our initial hypothesis, we predicted an age-related reduction in frontal predominance of low EEG components along the antero-posterior axis and a shallower decline of EEG delta power between the beginning and the end of the night. Therefore, we calculated the overall differences in EEG delta activity between time intervals 1 and 4, and between the derivation Fz and Oz, and between the baseline and the recovery night, resulting in a single measure for
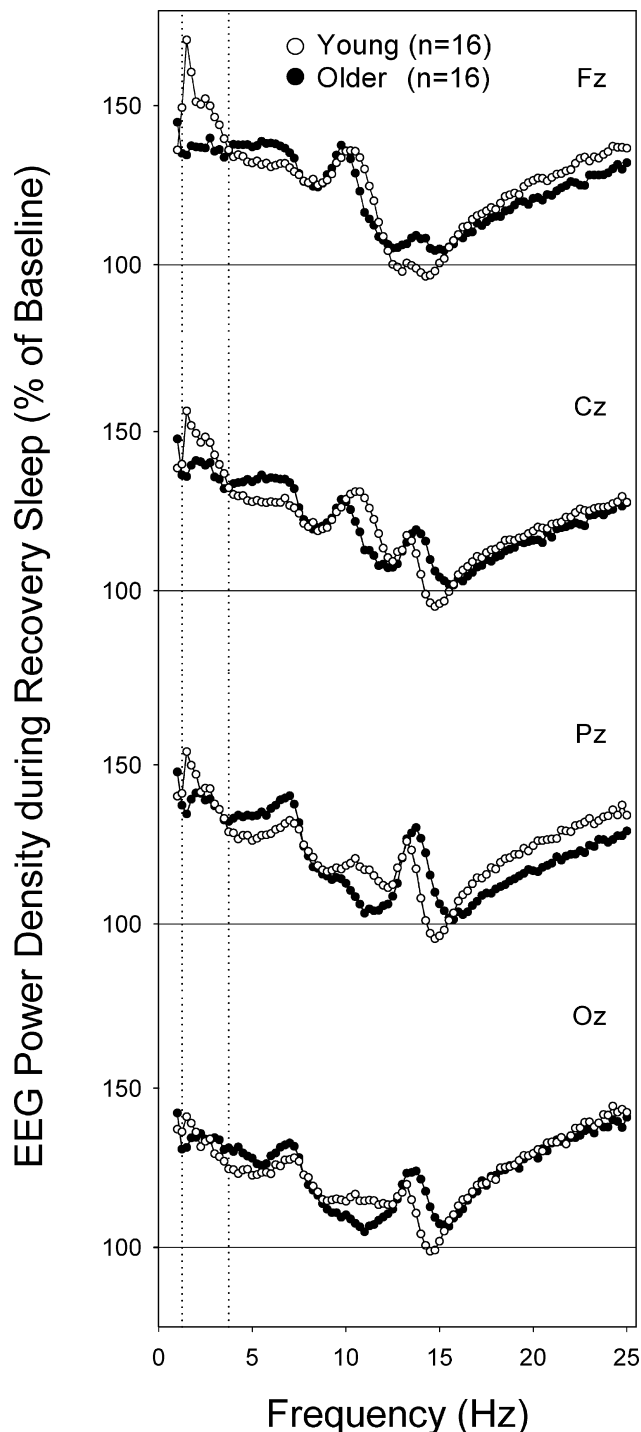
FIG. 2. Relative sleep electroencephalogram (EEG) spectra during NREM sleep expressed as percentage of the baseline night (100%) for the young (open circles) and older group (filled circles) along the antero-posterior axis (Fz, Cz, Pz and Oz) and the frequency range of 1.00–25 Hz. The vertical dotted lines delineate the frequency bins within the delta range (1.25–3.75 Hz), which yielded a significant two-way interaction in rANOVA with the factors 'age' × 'derivation'.

the older and young group. This contrast [mean value: 0.61 ± 0.12 (SEM) for the young and 0.19 ± 0.05 for the older group] was significantly higher in the young (*t*-test for independent samples; $P = 0.003$).
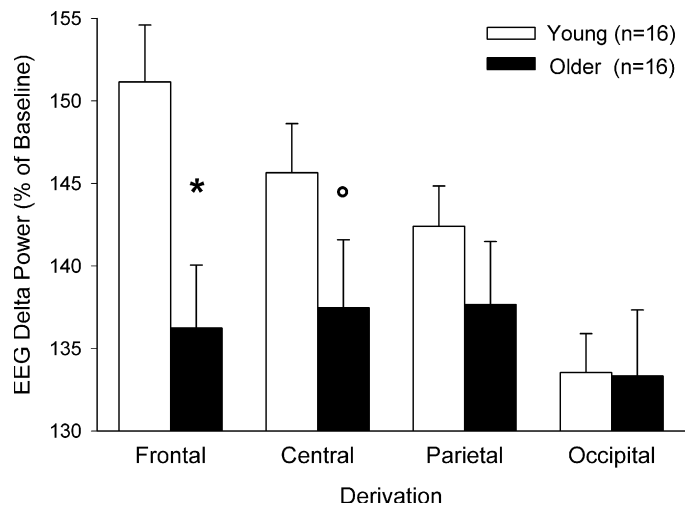

FIG. 3. Relative electroencephalogram (EEG) delta power density (1.25–3.75 Hz) during NREM sleep along the antero-posterior axis (Fz, Cz, Pz and Oz) in the young (white bars) and older (black bars) group (mean values +1 SEM; $n = 16$ for both age groups) after 40 h of sleep deprivation. Values are expressed as percentage of the baseline night. (*$P < 0.05$; °$P < 0.1$).

Discussion

We could confirm the hypothesis that the response to elevated sleep pressure during a subsequent sleep episode is attenuated in frontal brain areas with age. The relative increase in EEG delta power density after sleep deprivation declined significantly along the antero-posterior axis in the young, and this decline was no longer present in the older group. Furthermore, dissipation of homeostatic sleep pressure during the recovery night, as indexed by EEG delta activity, revealed a significantly less profound decrease in the older age group when compared with the young.

Age-related homeostatic response to sleep loss

Our data confirmed previous findings of a relative increase of EEG power in the delta, theta, low alpha and the lower spindle range as well as a decrease in the higher spindle range in response to extended wakefulness in the young age group (Borbély *et al.*, 1981; Dijk *et al.*, 1987, 1993; Feinberg *et al.*, 1987; Finelli *et al.*, 2000; Knoblauch *et al.*, 2002). An increase of SWS during the recovery night after sleep deprivation in healthy middle-aged and older subjects had been reported in earlier studies (Webb, 1981; Carskadon & Dement, 1985; Reynolds *et al.*, 1986; Brendel *et al.*, 1990), but the absence of sleep EEG spectral analysis and the heterogeneity of these study designs does not allow for a direct comparison with our data. More recent studies in older and middle-aged volunteers also reported results derived from EEG spectral analysis (Dijk *et al.*, 1999a, 2000) as well as after 25 h of sleep deprivation (Gaudreau *et al.*, 2001; Drapeau & Carrier, 2004). Our results corroborate those findings, in that older participants exhibited significant lower absolute SWA levels during both the baseline and the recovery night when compared with the young. Furthermore, both age groups in our study responded with a significant increase in SWA during the recovery night after sleep deprivation, which has also been reported previously for an older (Dijk *et al.*, 1999a, 2000) and a middle-aged group of study participants (Gaudreau *et al.*, 2001; Drapeau & Carrier, 2004). However, none of the previously cited studies reported age-related changes after sleep deprivation over a broad frequency range (0.75–25 Hz). We have
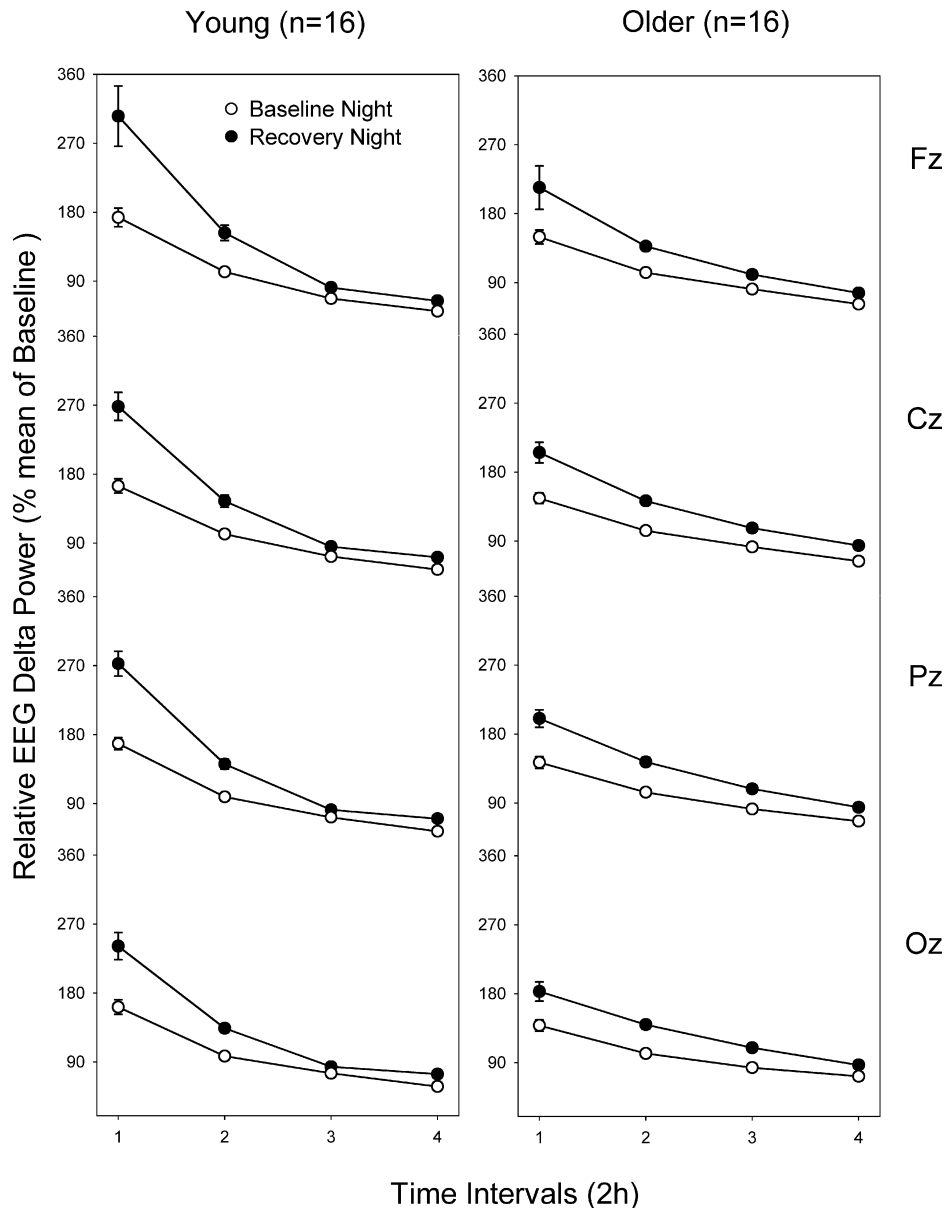
Young (n=16)   Older (n=16)

FIG. 4. Time course of relative electroencephalogram (EEG) delta power density plotted as percentage of corresponding baseline means during NREM sleep in the baseline (open circles) and recovery night (filled circles) for the young (left-hand panel) and older subjects (right-hand panels, mean values per 2-intervals ± 1 SEM, $n = 16$ for both age groups).

evidence that both the young and older age group responded to sleep deprivation with a significant increase in EEG power density in a broad frequency range during the recovery night – in fact, with the exception of the high spindle range, all frequency bins between 0.75 and 25 Hz were affected. Targeting the focus more on the markers of sleep homeostasis, the rebound of EEG activity during recovery sleep was further analysed in the EEG delta range. The relative increase of EEG power density in this frequency range derived from a central derivation (Cz) did not significantly differ between age groups when averaged over the entire night. This is in good accordance with a previous study, where the EEG was recorded from central derivations (C3 and C4; Dijk et al., 1999a, 2000). This supports the interpretation that the responsiveness of the sleep homeostat is still operational in healthy ageing, but at lower absolute EEG delta activity levels. In contrast, another study has reported a less intense homeostatic

response of SWA after a 25-h sleep deprivation in middle-aged healthy subjects (Gaudreau et al., 2001; Drapeau & Carrier, 2004). This divergence to our and other findings may be due to the fact that first, the sleep deprivation episode was shorter and, second, recovery sleep started at a different circadian phase (i.e. in the morning). Taken together, at first glance, the relative homeostatic response in SWA to high sleep pressure seems not to be altered by age. However, it remains to be elucidated if the build-up of homeostatic pressure during the preceding episode of wakefulness is likewise similar in these age groups.

Age-related regional differences of EEG delta activity

The assessment of the regional distribution of EEG power density in the delta range of young participants exhibits an antero-posterior

TABLE 2. A four-way rANOVA performed on relative EEG delta activity values during the baseline and recovery night for the young and older group with the factors: 'age', 'night', 'derivation', 'time interval'

Effect	F-values	d.f.	P-values (H–F)
Night	287.3	1.30	< 0.001
Night × Age	0.7	1.30	= 0.406
Derivation	3.3	3.90	= 0.058
Derivation × Age	3.6	3.90	< 0.05
Time interval	216.9	3.90	< 0.001
Time interval × Age	10.2	3.90	< 0.001
Night × Derivation	8.3	3.90	< 0.001
Night × Derivation × Age	6.7	3.90	< 0.05
Night × Time interval	7.8	3.90	< 0.001
Night × Time interval × Age	2.6	3.90	= 0.061
Derivation × Time interval	28.0	9.27	< 0.001
Derivation × Time interval × Age	2.1	9.27	= 0.091
Night × Derivation × Time interval	3.9	9.27	< 0.05
Night × Derivation × Time interval × Age	3.9	9.27	= 0.065

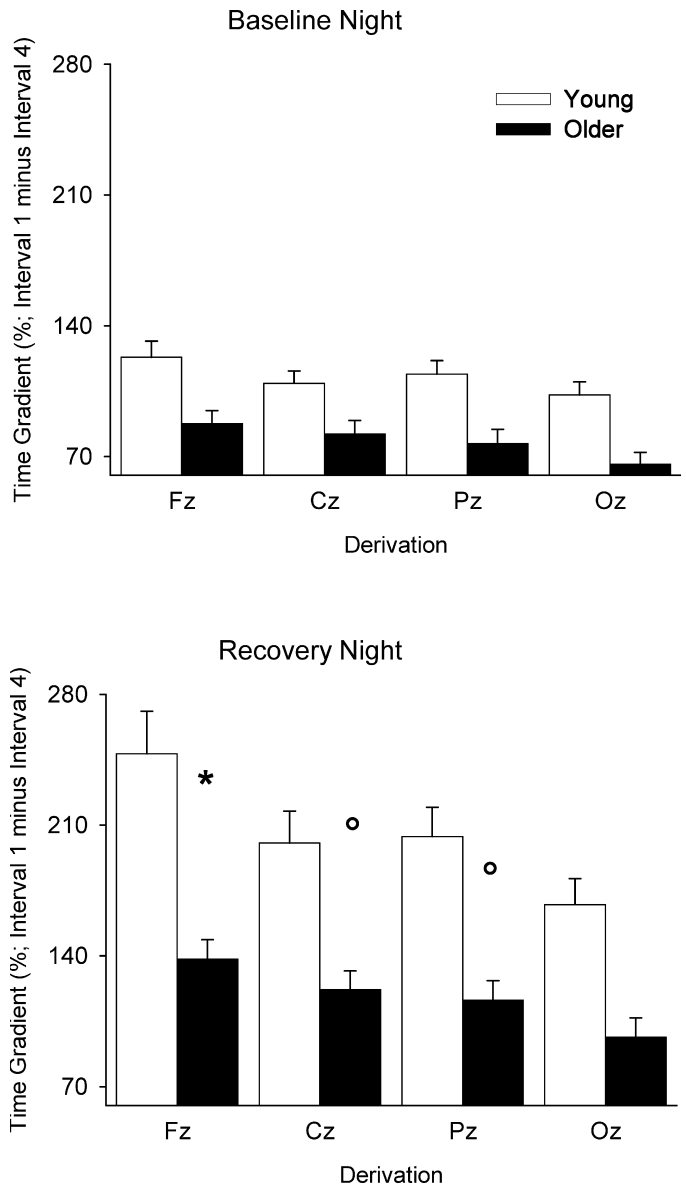d.f., degrees of freedom; H–F, Huynh–Feld corrected.

FIG. 5. The difference in EEG delta activity (1.25–3.75 Hz) between the first and the fourth 2-h interval of the corresponding night (i.e. each value is expressed as mean of the corresponding baseline) along the antero-posterior axis (Fz, Cz, Pz and Oz). The upper panel shows the values for the baseline and the lower panel those for the recovery night. Black bars = older, white bars = young subjects (+ 1 SEM; $n = 16$ in both age groups). (*$P < 0.05$; °$P < 0.1$).

gradient with highest values in frontal brain regions during baseline sleep episodes (Werth *et al.*, 1997; Knoblauch *et al.*, 2002). An age-related attenuation of this gradient has been reported, with a parietal EEG delta dominance in aged healthy volunteers during baseline sleep episodes (Landolt & Borbély, 2001). To our knowledge, the present study is the first looking at age-related changes in the antero-posterior EEG delta gradient after sleep loss. We found a clear frontal diminution of relative EEG delta power density in the older participants, which was in sharp contrast to the young cohort, who responded to sleep loss with enhanced frontal activity in this frequency range. The function of enhanced EEG delta activity after an extended duration of prior wakefulness is not fully understood, but several explanations have been pursued. It has been suggested that enhanced EEG delta activity after sleep loss represents a recuperative effect of SWA in cerebral brain areas intensively stimulated during daytime (i.e. 'frontal tiredness', Horne, 1993; Harrison & Horne, 1998). In terms of mechanisms, enhanced EEG delta activity after sleep deprivation could reflect more hyperpolarized thalamocortical and cortical neurons, which serve to protect the brain from incoming sensory stimuli and therefore allow more 'deep' sleep (Steriade *et al.*, 1993; McCormick & Bal, 1997). Along these lines and based on animal data (Cirelli *et al.*, 1996; Cirelli & Tononi, 2000), Tononi and Cirelli hypothesised that enhanced synaptic potentiation (i.e. structural changes in synaptic strength) in cortical circuits occurring during wakefulness is positively correlated with the enhancement of SWA during the following sleep episode (Tononi & Cirelli, 2003). Our data may indirectly suggest that the synaptic potentiation rate in frontal brain areas during wakefulness decreases with age, resulting in a concomitant diminution of SWA increase in the respective brain areas during sleep.

In brain imaging studies, a negative covariation of rCBF and EEG delta activity has been observed in frontal regions of the cortex (Hofle *et al.*, 1997; Maquet *et al.*, 1997). Decrease of rCBF in frontal brain areas, particularly the anterior cingulate cortex (Paus *et al.*, 1997; Paus, 2000), may be associated with attenuation of the cortical arousal system during sleep (Hofle *et al.*, 1997). The diminished frontal predominance of EEG delta activity in the older group after extended wakefulness can thus be interpreted as a selective age-related 'alleviated dampening' of cortical arousal during sleep. Such a lower arousal threshold during sleep could underlie the typical age-related increase in sleep fragmentation (Miles & Dement, 1980; Bliwise, 1993; Dijk *et al.*, 1999b, 2001).

Whether the regional amount of SWA during sleep is determined in each brain region not only by the duration but also by the intensity of activity during prior wakefulness has not yet been unambiguously clarified. Recently, it has been reported that the total amount of SWA was not affected by the level of mental workload preceding the sleep episode in humans; however, EEG recordings were only taken from a single central derivation (De Bruin *et al.*, 2002). Another study in humans demonstrated a relatively small local augmentation of EEG delta power density (0.75–4.5 Hz) during subsequent NREM sleep after unilateral activation of the left somatosensory cortex during

wakefulness (Kattler *et al.*, 1994). Investigation of continuous auditory stimulation during wakefulness yielded both an increase in power density in the alpha and spindle frequency range, and changes in fronto-temporal coherence over a broad frequency range during subsequent SWA (Cantero *et al.*, 2002). In animal studies, experience-dependent SWA generation has been found in light-deprived cats (Miyamoto *et al.*, 2003). In rats whose whiskers were cut on one side in order to reduce the sensory inputs in the contralateral cortex, a shift of the interhemispheric asymmetry of EEG power (0.75–6 Hz) during NREM sleep was reported (Vyazovskiy *et al.*, 2000). Hence, there is mounting evidence of a 'use' or 'experience'-dependent process that occurs during sleep and affects EEG synchronization. This has led to the hypothesis that the sleep EEG shows use-dependent characteristics and reveals presumably not global but local processes (Krueger & Obal, 1993; Borbély, 2001). A very recent study has brilliantly demonstrated selectively localized SWA induction triggered by a learning task (Huber *et al.*, 2004), providing further evidence for a link between sleep and learning. The significance of the here reported altered pattern of frontal EEG delta activity during recovery sleep in the elderly in association with the use-dependent activity of frontal areas needs further clarification. As all of the aforementioned studies on use- or experience-dependent aspects on sleep regulation reported small and short-lasting effects (i.e. at the beginning of the sleep episode), we were interested in the temporal characteristics of the observed age-related disappearance of frontal predominance after sleep loss.

EEG delta activity dissipation during the baseline and recovery night

Our data confirm and extend a previous result in older volunteers showing that the decline in relative EEG delta activity after sleep deprivation is shallower than in young study participants (Dijk *et al.*, 1999a, 2000). The reduced decay rate of EEG delta activity has been postulated to reflect an age-related alteration of the dynamics of the homeostatic regulatory process (Dijk *et al.*, 1999a). Another study in older volunteers (age range: 57–64 years) reported that the decline of relative SWA over the course of the night flattened even during baseline (Landolt *et al.*, 1996, Landolt & Borbély, 2001), as we also found. However, in the young volunteers, this time gradient of SWA dissipation during the recovery night increased significantly more steeply in frontal areas compared with the older participants, whereas no significant changes were present in more parietal regions. Taken together, the regional dissimilarity between young and older subjects in the rebound of EEG delta power was most pronounced in the first part of the recovery night. However, the reduced steepness of the time course of EEG delta activity in the older group represents a more long-lasting effect, already measurable during the baseline night. This further supports the interpretation of intact sleep homeostatic regulation with age albeit on a lower EEG amplitude level.

Conclusion

The activation of sleep regulatory processes by an extension of wakefulness from 16 to 40 h revealed a smaller increase of relative EEG delta power density in frontal brain areas in older study participants, particularly during the first part of the recovery night. This is in accordance with the assumption that frontal brain areas are subjected to a double vulnerability – the ageing process *per se* and the short-term response to sleep loss.

Abbreviations

CR, constant routine; EEG, electroencephalogram; NREM, non-rapid eye movement; PFC, prefrontal cortex; rCBF, regional cerebral blood flow; REM, rapid eye movement; SWA, slow-wave activity (EEG power density during NREM sleep between 0.75 and 4.5 Hz).

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