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Original Article

Challenging the sleep homeostat: Sleep in depression is not premature aging

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ABSTRACT

Objectives: The close relationship between major depression and sleep disturbances led to the hypothesis of a deficiency in homeostatic sleep pressure in depression (S-deficiency hypothesis). Many observed changes of sleep characteristics in depression are also present in healthy aging, leading to the premise that sleep in depression resembles premature aging. In this study, we aimed at quantifying the homeostatic sleep–wake regulation in young women with major depression and healthy young and older controls under high sleep pressure conditions.

Methods: After an 8-h baseline night nine depressed women, eight healthy young, and eight healthy older women underwent a 40-h sustained wakefulness protocol followed by a recovery night under constant routine conditions. Polysomnographic recordings were carried out continuously. Sleep parameters as well as the time course of EEG slow-wave activity (SWA) (EEG spectra range: 0.75–4.5 Hz), as a marker of homeostatic sleep pressure, were analyzed during the recovery night.

Results: Young depressed women exhibited higher absolute mean SWA levels and a stronger response to sleep deprivation, particularly in frontal brain regions. In contrast, healthy older women exhibited not only attenuated SWA values compared to the other two groups, but also an absence of the frontal SWA predominance.

Conclusions: Homeostatic sleep regulation and sleep architecture in young depressed women are not equal to premature aging. Moreover, our findings demonstrate that young moderately depressed women exhibit no deficiency in the sleep homeostatic process S as predicted by the S-deficiency hypothesis, but, rather, live on an elevated level of homeostatic sleep pressure.

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1. Introduction

According to the World Health Organization (WHO) depression holds the 2nd rank of diseases causing loss of productive life in the age category between 15 and 59 y worldwide [1]. Despite its high prevalence and socioeconomic impact, as well as considerable research efforts during the past decades, knowledge of the aetiology and pathophysiology of major depression remains quite fragmented [2–4]. However, epidemiological studies have shown that vulnerability to depression is gender and age dependent with a risk that is twice as high risk in women compared to men during the reproductive years [5–7]. Furthermore, environmental factors such as stress, emotional trauma, and viral infections and their interaction with a genetic and epigenetic predisposition have been shown to play a pivotal role in the development of the illness [8–16].

Clinical observations and polysomnographic recordings show that major depression is often associated with sleep disturbances, although sleep disturbances are neither depression-specific nor a

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compulsory symptom for the clinical diagnosis of the illness [17]. The importance of the circadian system and sleep-wake homeostasis in sleep-wake regulation suggests that these two processes may be crucially involved in the pathogenesis of major depression [18]. Reports on sleep disturbances in depression find longer sleep latencies, shortened rapid-eye-movement sleep (REM) latency, increased REM sleep in the beginning of the night, higher wake-up tendency in the latter part of the night, early termination of sleep in the morning, decreased slow-wave sleep (SWS), and electroencephalographic (EEG) slow-wave activity (SWA, EEG power density between 0.75–4.5 Hz) [19]. However, the sleep disturbances are not consistent, as various studies have failed to demonstrate or confirm such changes [20-22]. This inconsistency is mainly due to differences in age, sex, clinical characteristics and subtype of depression, severity of depression, and the heterogeneity of the applied study settings [23-31].

According to the two-process model of sleep regulation, the interaction between a sleep–wake dependent process S (=sleep–wake homeostat) and a circadian process C are responsible for the timing of sleep and wakefulness [32–34]. The findings that manipulation of the sleep–wake cycle (e.g., sleep deprivation, sleep phase



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advance) or circadian phase (e.g., timed light therapy) influences the course of depression gave rise to hypotheses relating the involvement of processes controlled by the circadian pacemaker, the sleep-wake homeostat, or the interaction between both [31,35,36]: the S-deficiency hypothesis [37], the phase-advance hypothesis [38], and the acetylcholine-monoamine imbalance hypothesis [39]. While the latter two mainly deal with changes in the circadian or ultradian timing, the S-deficiency hypothesis refers to alterations in the homeostatic aspect of sleep. It states that sleep disturbances in patients with major depression disorder (MDD) reflect a deficiency in the homeostatic buildup of sleep pressure during wakefulness [37]. Frontal delta EEG activity during NREM sleep is a physiological measure of the dissipation of process S during sleep and of the accumulated need for sleep during wakefulness, respectively [40,41]. Its level is positively correlated with the amount of time spent awake prior to sleep episodes [42]. Thus, within the framework of the S-deficiency hypothesis. MDD would be expected to show a significantly reduced response to a challenge of the sleep-wake homeostat by sleep deprivation, as indexed by EEG delta activity during recovery sleep. So far two studies support the S-deficiency hypothesis in major depression [43-45], whereas one study added refinements such as gender-dependency, with only men exhibiting lower EEG delta activities during sleep [46]. A further study reported no S-deficiency in untreated middle-aged depressive outpatients compared to controls [47].

With age, different alterations of sleep parameters occur, such as increased sleep fragmentation, a reduction of SWS and SWA, and a reduced frontal EEG response to sleep deprivation [48–50]. Although these changes are typical signs of healthy aging, it is striking how similar they are to the sleep abnormalities reported in MDD. Thus, with regard to sleep, it has been argued that depression has similarities to precocious ageing [23]. A refinement of this suggests that depression might bear sleep-related similarities to premature ageing only for restricted sleep characteristics such as sleep efficiency, total sleep time, intermittent time awake during sleep, and REM sleep latency [25].

A dissection of the contributions of circadian and homeostatic processes to sleep-wake regulation can only be assessed by applying specific sleep-wake manipulation schemes such as the forced desynchrony or constant routine protocols [51]. While the forced desynchrony protocol allows for the separating of the influence of the sleep-wake homeostat and the circadian timing system [52], the constant routine protocol is mainly designed to unmask endogenous circadian rhythms by controlling for environmental conditions such as light, food intake, body posture, physical activity, and sleep [51]. Study participants of constant routine protocols usually remain awake from 24 up to 60 h, which leads to a progressive increase in homeostatic sleep drive while at the same time endogenous circadian phase is changing. This setting allows analysis of homeostatic sleep regulation during recovery sleep and the assessment of phase and amplitude of unmasked circadian rhythms not influenced by the homeostat, such as melatonin or core body temperature.

To our knowledge, there are only a few studies in which the homeostatic EEG SWA response to sleep deprivation in depression has been investigated [46,47,53] and there is only one study so far on homeostatic sleep regulation in winter depression under constant routine conditions [54,55]. Here we aimed at investigating sleep architecture and homeostatic sleep regulation during NREM sleep in unmedicated young women with non-seasonal major depressive disorder during a 40-h constant routine protocol (high sleep pressure) compared to age-matched healthy young and older control women. Based on the S-deficiency and the premature aging premise we hypothesized an attenuated homeostatic response to sleep deprivation, as indexed by a reduced EEG delta activity during NREM sleep in young depressed when compared to young healthy women, but not to older healthy women. Second, we expected a decreased frontal predominance of EEG delta activity in young depressed compared to healthy young women.

2. Methods

2.1. Study participants

Eight healthy young (HY, 20–31 y, mean \pm SD = 25.4 \pm 3.8 y), eight healthy older (HO, 57–74 y, mean age = 64.1 \pm 5.5 y), and nine young women with major depression disorder (MDD, 20–32 y, mean age = 26.2 \pm 5.2 y) participated in the study. A two sided *t*-test disclosed no significant age differences between MDD and HY. By definition, the age difference between the young and older cohort was significant (*t*-test; *p* < 0.001).

Study participants were recruited using advertisements at universities in the region of Basel, Switzerland and through selected online portals. All participants underwent a defined screening procedure which included questionnaires referring to physical health, drug consumption, and sleep quality, as well as a medical examination to assess somatic state. The screening for the MDD participants included additional self-reported depression ratings with the Beck Depression Inventory (BDI) [56], whereby only participants with a score >12 were considered for the subsequent clinical interview (mean BDI value = 20.2 ± 9.7). To assess the presence of a major depression disorder a structured clinical interview for DSM-IV Axis I (SCID-I) according to the diagnostic and statistical manual of the American Psychiatric Association (DMS-IV_TR) [17] was carried out with the respective MDD volunteers (mean SCID-I value = 5.1 ± 0.3). The MDD participants had no atypical symptoms, no seasonality, no psychiatric comorbidity according to DSM-IV criteria, and none of them took antidepressants before the study. When participating in the study all women were experiencing an episode of MDD according to DSM-IV criteria.

Among the healthy subjects, only participants with no sleep disturbances as assessed by the Pittsburgh Sleep Quality Index (PSQI) [57] were included in the study (PSQI value <5), whereas for MDD participants a score <8 was allowed (i.e., mild forms of sleep disturbances) (MDD = 6.1 ± 1.7 , HY = 2 ± 1.7 , HO = 3.8 ± 1.7 ; *t*-test: MDD > HY p < 0.001 and MDD > HO p < 0.05). Additionally, sleep disorders were excluded based on recordings during an adaptation night in our laboratory. Applied exclusion criteria included a sleep efficiency of less than 80%, more than 10 periodic leg movements per hour, and an apnea-hypopnoea index >10. Medications other than oral contraceptives were not allowed for all participants. who were drug-free (verified by urinary toxicological analysis), nonsmokers, and had no shift work or flights over more than three time zones during the last three months before the study began. Only intermediate chronotypes as assessed by the diurnal type scale [58] were considered (MDD = 15.9 ± 1.3 , HY = 15.6 ± 3.8 , HO = 18 ± 3.4 ; *t*-test *p* > 0.05). All young women participated in the laboratory part of the study during the follicular phase of their menstrual cycle (days 1-5 after menses onset), and the older women were all post-menopausal. All study participants signed an informed study consent form. The study procedures, as well as all questionnaires and the consent form, were approved by the local Ethics Committee of Basle (EKBB), Switzerland, and all procedures conformed to the Declaration of Helsinki.

2.2. Study protocol

The study comprised an ambulatory part at home (one week) followed by a laboratory part (3.5 days). During the ambulatory part volunteers were asked to restrict caffeine intake to one beverage per day, to drink not more than five alcoholic drinks during the

entire week, and to abstain from heavy physical exercise. Furthermore, they were asked to keep a self-selected regular sleep-wake schedule during the ambulatory part of the study. Compliance was verified by sleep logs and ambulatory activity measurements using a wrist activity monitor (Cambridge Neurotechnology Ltd[®], UK). The timing of the sleep-wake schedule during the protocol was adjusted to individual habitual bedtimes calculated by centering the approximate eight-hour sleep episodes during the baseline week at the individual midpoint of sleep of each participant. Habitual bedtimes between healthy young (11:52 PM ± 69 min) and young depressed (11:53 PM ± 50 min), as well as between healthy young and older, women (11:05 PM ± 31 min) were not significantly different (p > 0.9 and p > 0.1, respectively), but young depressed women differed significantly from healthy older women (p < 0.05; t-test for independent samples). The protocol comprised a habituation night followed by a baseline night in the chronobiology laboratory. The baseline night was followed by 40-h of sustained wakefulness and an eight-h recovery night (Fig. 1).

EEG recordings started in the afternoon after the habituation night. During the laboratory part participants remained under constant conditions: dim-light <eight lux during scheduled wakefulness and zero lux during scheduled sleep episodes, semirecumbent posture position in bed during wakefulness, regular isocaloric meals and water, and constant room temperature (for details of the study protocol see Fig. 1). A daily heparin injection was given to the healthy older women in order to prevent venous thrombosis (Fragmin[®], 0.2 mL, 2500 IU, Pfizer AG, Switzerland). The severity of the depressive episode of young volunteers with major depression was assessed regularly (see Fig. 1) by an independent psychologist on the basis of the Montgomery-Asberg Depression Rating Scale (MADRS) [59] and the Hamilton Rating Scale for Depression (HAMD-17) [60].

2.3. Polysomnography recordings and analysis

Polysomnographic recordings (Vitaport-3 digital recorder TE-MEC Instruments BV, Kerkrade, the Netherlands) during sleep comprised twelve EEG derivations (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, Oz referenced against linked mastoids), two electrooculograms, one submental electromyogram, and one electrocardiogram. All EEG signals were filtered at 30 Hz (fourth-order Besseltype antialiasing low-pass filter, total 24 dB/Oct), and a time constant of 1.0 s was used prior to online digitization (range 610 V, 12 bit AD converter, 0.15 V/bit; storage sampling rate at 128 Hz). Sleep episodes were visually scored on a 20-s epoch basis according to the standard criteria of Rechtschaffen and Kales [61]. EEGs were subjected to spectral analysis using a fast Fourier transform (FFT) with 10% cosine 4-s windows resulting in a 0.25 Hz resolution. Sleep stages (1–4), rapid eye movement (REM) sleep, and movement time (MT) were expressed as percentages of total sleep time (TST) during the respective night for all participants. TST and sleep latencies to stage 1 (SL1), stage 2 (SL2), and REM (RL) were indicated in minutes. Sleep efficiency (SE) was defined as follows: SE = TST/time between lights off and lights on (TIB) x 100. Wake-fulness after lights off (WALO; % of TIB) and wakefulness after sleep onset (WASO; % of TST) were also measured. Non-rapid eye movement (NREM) sleep was defined as stages 2–4 (% of TST).

EEG spectra during the baseline and recovery nights were calculated for the first seven hours of sleep in the frequency range from 0.75 to 25 Hz for all 12 derivations. A mixed-model four-way repeated Analysis of Variance (rANOVA) for the factors group (young depressed women vs healthy voung women vs healthy older women), night (baseline vs recovery), derivation site (frontal vs central vs parietal vs occipital), and hemisphere (left vs right side derivations) disclosed significant lower left hemisphere EEG values for one frequency bin in the delta range (0.75 Hz) and one bin in the theta range (6.5 Hz) (p < 0.05). No further significances of single factors nor of interactions of the factors group*hemisphere, derivation site*hemisphere, night*hemisphere, group*hemisphere*derivation site, and group*hemisphere*derivation site*night were observed (p at least > 0.1, Tukey-Kramer adjusted p values). Hence, spectral values for side and mid-line derivations were collapsed along the anterior-posterior axis resulting in one value for each of the F, C, P, and O sites. Baseline and recovery night spectral values of young depressed and healthy older women were graphically illustrated as a percentage of the respective values of the healthy young group during the baseline and recovery nights whereby the statistical analyses were based on absolute values. Group differences in EEG power density were assessed by mixed-model repeated-measures ANOVA (rANOVA).

NREM/REM sleep cycles were defined according to the criteria of Feinberg and Floyd [62] with the exception that, for the last sleep cycle, no minimum REM-sleep duration was required. Thereafter, each sleep cycle was divided into 10 equal time intervals during NREM sleep and four equal time intervals during REM sleep.

To investigate the decay of SWA (0.75–4.5 Hz) during NREM sleep, being a physiological correlate of the decrease of process S, the following exponential decay function was fitted to the data of each group of participants and all NREM cycles across the base-line and the recovery nights: $SWAt = SWA_{\infty} + SWA_{0} * e(-st)$; with



Fig. 1. Schematic overview of the study protocol. The illustration shows the timing of scheduled sleep and wakefulness, food intake, and psychological assessments in the course of the sustained wakefulness (SW) protocol. Due to 40 h of sustained wakefulness the SW protocol challenges the sleep homeostat leading to high sleep pressure levels. In total, bedrest conditions lasted 56 h (including baseline and recovery nights) whereby the timing of sleep and wakefulness, body posture, light levels, food and water intake, and environmental temperature were controlled for (constant routine conditions). The example shows sleep from 24–8 h, but each individual was assigned their own usual schedule (see Section 2).

SWAt = averaged SWA per sleep cycle, SWA₀ = intercept on the *y* axis, SWA_{∞} = horizontal asymptote for time *t* = ∞ , *s* = slope of the decay, *t* = average timing of the NREM cycle midpoint.

2.4. Salivary melatonin sampling

Saliva collections were scheduled every 30 min throughout the entire 40-h sustained wakefulness protocol. A direct double-antibody radioimmunoassay (RIA) was used for the melatonin assay, which was validated by gas chromatography-mass spectroscopy with an analytical least detectable dose of 0.65 pg/ml (Bühlmann Laboratories, Schönenbuch, Switzerland) [63]. Missing melatonin values were linearly interpolated (mean missing values \pm SD over the entire 40-h sustained wakefulness protocol: MDD 2.44 \pm 3.2; HE 1.9 \pm 2.7; HY 1.6 \pm 1.8). Subsequently, all melatonin values were collapsed into 2.5-h bins per subject before averaging over subjects.

2.5. Subjective mood and sleepiness ratings

Study participants rated their sleepiness and mood at the same time intervals as melatonin samples were taken (every 30 min over the entire 40-h protocol). Mood ratings were measured by the visual analogue scale (VAS) [64] with values from zero mm (depressed mood) to 100 mm (good mood) and sleepiness was assessed by the Karolinska Sleepiness Scale (KSS) with a rating range from one (not sleepy) to nine (very sleepy) [65]. KSS and VAS values were collapsed into 2.5-h bins per subject before averaging over subjects.

2.6. Statistical analysis

The statistical packages SAS[®] (SAS Institute, Inc.; Version 9.1.3) and Statistica[®] (StatSoft Inc., STATISTICA for windows, Version 8.0) were used. Sleep stages were analysed with repeated-measures ANOVA (PROC GLM) and p values were based on Huynh-Feldt corrected degrees of freedom. Post-hoc comparisons on sleep stages were based on Duncan's multiple range test and the levels of significance of these post hoc comparisons were adjusted according to the false discovery rate procedure [66]. Comparisons of EEG spectra, melatonin, subjective sleepiness, and mood between groups were done with mixed-model repeated-measures ANOVA (PROC MIXED) and p values were based on Kenward-Roger's corrected degrees of freedom [67]. Contrasts were assessed with the LSMEANS statement and the respective level of significance was adjusted according to the Tukey-Kramer method [68]. One-, two-, three- and four-way mixed-model rANOVAs were used with the categorical factor group (MDD vs HY vs HO) and the repetitive factors derivation, night, and time interval (e.g., sleep cycle, etc.).

3. Results

3.1. Sleep stages during baseline and recovery nights

Sleep parameters for the baseline and recovery nights based on visual scoring for the young depressed women (MDD), healthy young women (HY), and healthy older women (HO) are summarized in Table 1. A 2-way rANOVA disclosed significant effects of the main factor *group* for total sleep time (TST, p < 0.01), sleep efficiency (SE, p < 0.01), wake after lights off (WALO, p < 0.001), wake after sleep onset (WASO, p < 0.001), and stage 4 sleep (p < 0.05). Post-hoc analysis of significant effects of the factor *group* showed significantly less TST (p < 0.01), lower SE (p < 0.01), and less stage 4 sleep (p < 0.05) of HO compared to MDD and HY. Furthermore, HO had significant longer wake durations after lights off and after sleep onset than MDD and HY (p < 0.01 and p < 0.001, respectively)

and a tendency to less REM sleep compared to HY (p < 0.01). No significant differences between young depressed and healthy young women were observed for any of the sleep parameters (p at least >0.05).

The 40-h of sustained wakefulness resulted in significant alteration in sleep architecture during the recovery night compared to the baseline night for all three groups in the following parameters: higher TST (p < 0.01), increase in SE, decrease in wake times after lights off, lower sleep latency to stage 2 sleep (SL2) (p < 0.05), less stage 1 and stage 2 sleep, and more stage 3 and stage 4 sleep as well as more slow-wave sleep (SWS) and NREM sleep (p < 0.001). For stage 4 sleep, a 2-way rANOVA yielded a significant interaction between *group*night* (p < 0.05) with higher values during the recovery night compared to the baseline night in all three groups (p < 0.001) and significantly higher values of MDD and HY during the recovery night than HO (p < 0.01 and p < 0.05, respectively).

3.2. EEG power density during the baseline and recovery nights

Relative EEG spectra with reference to healthy young women (100%) during NREM sleep for the baseline and recovery nights in the frequency range between 0.75 and 25 Hz are illustrated in Fig. 2. Mixed-model 3-way rANOVA disclosed significant effects of the factor *group* for the delta frequency bins 1–3 Hz (p < 0.05; $F_{2,22} > 3.76$) with significant higher mean EEG power of young depressed women (MDD) than healthy older (HO) women (p < 0.05). Post-hoc comparisons showed no significant differences between MDD and HY or between HY and HO.

EEG power during the recovery night was significantly higher than during the baseline night for all groups for the frequency bins of the delta, theta, and alpha range (0.75-10.5 Hz, p < 0.001;10.75 Hz, p < 0.01; 11 Hz, p < 0.05; $F_{1.21} > 4.73$) as well as in most of the beta frequency bins (16.75–17 Hz, *p* < 0.05; 17.25–25 Hz, p < 0.01; $F_{1,21} > 4.53$). Significant interaction of the factors group*night occurred in the delta frequency bins 1-4 Hz and in some of the theta frequency bins (6.25–6.5 Hz, 7.25–7.75 Hz; $F_{2,21}$ > 3.49) with higher values during the recovery night than the baseline night in MDD for all respective frequency bins (post-hoc comparisons according to LSMEANS statement, Tukey-Kramer adjusted; p < 0.001), in HY in the same range except the frequency bins 7.5–7.75 Hz (p < 0.01), and in HO in some of the delta and theta frequency bins (2-4 Hz, 6-25-6.5 Hz, 7.25 Hz). Post-hoc comparison showed, furthermore, higher values for MDDs than HO in the delta frequency bins 1–3.25 Hz (p < 0.05) and for HY than HO in the delta frequency bins 1.5-1.75 Hz (p < 0.05) during the recovery night.

A mixed-model rANOVA disclosed significant effects of the main factor derivation in all frequency bins, except for some in the theta range (6-7 Hz), and with highest values in the frontal (F) derivations (p < 0.05; $F_{3,66} > 2.81$). Furthermore, the analysis showed significant interaction of the factors group*derivation in all frequency bins of the delta and theta range (0.75-8 Hz, p < 0.001; $F_{6.66} > 2.80$) as well as in some of the frequency bins of the alpha, sigma, and beta range (11.25–14 Hz and 14.75–25 Hz; $F_{6,66} > 2.26$). Post-hoc comparisons showed higher values for MDD than HY and HO for the F derivations in bins of the delta frequency range (1.25–3 Hz, MDD > HO *p* < 0.001, MDD > HY *p* < 0.05) and higher values for MDD than HO in the delta frequency range (3.5-4.25 Hz, p < 0.05) and in the alpha/sigma range (11.5-12.5 Hz, p < 0.05). Finally, mixed-model 3-way rANOVA disclosed significant interactions of the factors group*night*derivation for some of the frequency bins of the delta and theta range (0.75-4.5 Hz, 4.75–5 Hz, and 6.5–7.5 Hz, p < 0.05; $F_{6,63} > 2.26$) with higher values of MDD than HY and HO in the F derivation during the recovery night in the delta frequency bins 1.5-3 Hz (p < 0.05).

Relative EEG spectra per sleep cycle (recovery night cycle spectra in % of baseline values per cycle) during NREM sleep for the Table 1

Sleep parameters of the baseline and recovery nights based on visual scoring for all groups. Sleep parameters are averaged separately across the baseline night and the recovery night (mean \pm SD) for young women with major depression (n = 9), young healthy women (n = 8), and older healthy women (n = 8). TST = total sleep time; SE = sleep efficiency (TST/TIB * 100); WALO = wake after lights off (in % of total time in bed between lights off and lights on); WASO = wake after sleep onset (in % of TST); SL1 = sleep latency to stage 1; SL2 = sleep latency to stage 2; RL = REM latency; MT = movement time after sleep onset (in % of TST); St1–St4 = sleep stages 1–4 (in % of TST); SWS = slow-wave sleep (sum of stages 3 and 4 in % of TST); NREM = non-REM sleep (sum of sleep stages 2–4 in % of TST); REM = REM sleep in % of TST.

| Parameter | Young depressed women | | Healthy young women | | Healthy older women | | 2-Way rANOVA | | | | | |
|-----------|-----------------------|----------------|---------------------|-----------------|---------------------|----------------|--------------|-------------------|-------|-------------------|---------------|-------------------|
| | Baseline | Recovery | Baseline | Recovery | Baseline | Recovery | Group | | Night | | Group x night | |
| | | | | | | | р | F _{2,22} | р | F _{1,22} | р | F _{2,22} |
| TST, min | 444.4 ± 24 | 459.7 ± 15.1 | 446.2 ± 26.9 | 463.6 ± 13.2 | 408.5 ± 42.5 | 434.1 ± 31.2 | ** | 5.86 | ** | 9.43 | - | 0.25 |
| SE, % | 94.4 ± 1.8 | 95.7 ± 3.1 | 93.0 ± 5.6 | 96.7 ± 2.8 | 85.1 ± 8.8 | 90.4 ± 6.5 | ** | 7.8 | * | 7.7 | - | 0.9 |
| WALO, % | 3.9 ± 1.7 | 2.8 ± 3 | 4.1 ± 4.4 | 1.0 ± 0.8 | 12.9 ± 8.3 | 8.1 ± 6.1 | *** | 11.35 | * | 6.44 | - | 0.84 |
| WASO, % | 1.9 ± 1.3 | 1.4 ± 1.8 | 3.0 ± 4.8 | 0.6 ± 0.9 | 14.1 ± 11.7 | 7.5 ± 6.6 | *** | 12.04 | - | 4.08 | - | 1.38 |
| SL1, min | 9.9 ± 7.4 | 6.9 ± 6.7 | 8.6 ± 9 | 2.6 ± 1.3 | 8.5 ± 3.1 | 8.7 ± 9.1 | - | 0.76 | - | 3.51 | - | 1.26 |
| SL2, min | 12.7 ± 7.7 | 9.9 ± 8 | 14.1 ± 9.2 | 5.4 ± 1.8 | 11.1 ± 4.3 | 11.1 ± 8.2 | - | 0.16 | * | 5.93 | - | 2.64 |
| RL, min | 96.1 ± 31 | 85.8 ± 44.3 | 79.6 ± 30.8 | 72.9 ± 40.2 | 120.4 ± 104.8 | 80 ± 34.9 | - | 0.92 | - | 1.42 | - | 0.43 |
| MT, % | 0.6 ± 0.2 | 0.5 ± 0.2 | 0.9 ± 0.5 | 0.8 ± 0.7 | 0.8 ± 0.6 | 0.5 ± 0.3 | - | 1.35 | - | 5.1 | - | 0.36 |
| St1, % | 8.5 ± 3.3 | 5.3 ± 4.1 | 10.9 ± 3.4 | 5.2 ± 2.4 | 11.8 ± 5 | 8.7 ± 2.9 | - | 2.22 | *** | 51.59 | - | 2.38 |
| St2, % | 54.2 ± 5.9 | 50.1 ± 6.3 | 50.2 ± 5.7 | 46.1 ± 5.2 | 58.7 ± 13.9 | 54.8 ± 13.6 | - | 1.92 | *** | 17.02 | - | 0 |
| St3, % | 10.4 ± 2.9 | 11.4 ± 3.5 | 11.1 ± 2.8 | 13.2 ± 4.2 | 11.3 ± 5.3 | 15.0 ± 4.4 | - | 0.83 | *** | 14.6 | - | 1.7 |
| St4,% | 8.1 ± 5.9 | 16.8 ± 9.6 | 7.5 ± 6.1 | 15.1 ± 6 | 2.8 ± 2.5 | 6.4 ± 4.4 | * | 4.19 | *** | 69.71 | * | 3.83 |
| SWS, % | 18.4 ± 6.2 | 28.2 ± 9.3 | 18.7 ± 7.5 | 28.3 ± 6.7 | 14.1 ± 7.5 | 21.4 ± 8.5 | - | 1.59 | *** | 109.89 | - | 0.87 |
| NREM, % | 72.7 ± 5.9 | 78.3 ± 7.1 | 68.9 ± 4.5 | 74.4 ± 4.1 | 72.8 ± 8.9 | 76.2 ± 7.8 | - | 0.83 | *** | 38.46 | - | 0.88 |
| REM, % | 18.9 ± 3.8 | 16.4 ± 4.6 | 20.2 ± 2.3 | 20.4 ± 3.7 | 15.4 ± 6.4 | 15.1 ± 6.1 | - | 3.11 | - | 0.88 | - | 0.84 |

* *p* < 0.05.

** *p* < 0.01.

**** ^r p < 0.001.

frequency range 0.75–25 Hz for F, C, P, and O derivations were calculated in order to highlight EEG power modulation across the night in more detail (Fig. 3). Because mixed-model 3-way rANOVA with the factors *group*, *cycle*, and *derivation* showed significant interaction in only three frequency bins (7.25–7.75 Hz p < 0.05; $F_{12,126} = 1.37$) statistical analyses was performed for each cycle separately.

Mixed-model 2-way rANOVA with the factors group and derivation yielded significance for the factor group in some of the delta frequency bins in cycle 1 (1.5–2 Hz and 2.75–4.5 Hz; p < 0.05; $F_{2,21} > 4.37$) and in cycle 2 (2.75 Hz and 3.25–4.25 Hz; p < 0.05; $F_{2,21}$ > 3.48). Furthermore, EEG power values also differed significantly between groups in the theta/alpha frequency bins (4.75-8.25 Hz) and in some of the sigma frequency bins (13.5 Hz, 14-14.25 Hz) during cycle 1 (p < 0.05; $F_{2,21} > 3.74$), in the theta frequency range during cycle 2 (6.25 Hz, 7–7.5 Hz; *p* < 0.05; $F_{2,21}$ > 3.56), and in the theta/alpha frequency range (7.75– 8.25 Hz and 8.75 Hz; p < 0.05; $F_{2,21} > 3.57$) during cycle 3. Posthoc comparisons showed, therefore, higher values of young depressed (MDD) compared to healthy older (HO) women for cycle 1, for the frequency bins 1.5-2 Hz and 2.75-7.75 Hz (p < 0.01), and for higher values of MDDs compared to HY in the delta range (3.75-4 Hz; p = 0.05), in the theta frequency bins 4.5-4.75 Hz, in the alpha frequency bins 5.25-8.25 Hz, and in some bins of the sigma frequency range (13 Hz and 14–14.25 Hz) (p < 0.05; LSMEANS procedure, Tukey-Kramer adjusted). During cycle 2 MDD had significantly higher relative EEG power than healthy young women in some frequency bins of the delta range (3.75-4.25 Hz) and in some theta frequency bins (6.25 Hz and 7–7.5 Hz, p < 0.05). During cycle 3 young depressed women had higher relative spectra values than HO in one of the theta frequency bins (7.75 Hz; p < 0.05).

Significant interaction of the factors *group***derivation* was observed in some frequency bins of the delta range (1.5–1.75 Hz and 2.75 Hz) and in the theta range (7.25–7.5 Hz) during cycle 1 (p < 0.05; $F_{6,63} > 2.26$), in the delta frequency bins 1–2.75 Hz during cycle 2 (p < 0.05; $F_{6,63} > 3.07$), and in the frequency bins 1 Hz, 2 Hz, 8 Hz, 9.5 Hz, and 25 Hz during cycle 3 (p < 0.05; $F_{6,63} > 2.35$). Posthoc analysis for cycle 1 disclosed significantly higher relative EEG activity of young depressed women in F and C derivations com-

pared to HO for two delta frequency bins (1.75 Hz and 2.75 Hz) and one theta frequency bin (7.5 Hz) and in addition for the 1.5 Hz and 7.25 Hz frequency bins (p < 0.05) for the F derivations only. Moreover, higher relative EEG values were observed for the MDD compared to HY in the F and C derivations in some of the theta frequency bins (7.25–7.5 Hz, p < 0.01 for the F derivations, p < 0.05 for the C derivations) during cycle 1. During cycles 2 and 3 there was no significant interaction between groups per derivation after Tukey–Kramer adjustment of p-values.

In order to analyze the time course of EEG delta activity in more detail, percentiles (see Section 2) for the frequency range 1-3 Hz (=significant EEG frequency band between groups across the baseline and recovery nights; see Fig. 2) were calculated as a percentage of the mean delta value during the baseline night for NREM-REM sleep cycles 1-3 for the F, C, P, and O derivations (see Fig. 4). A mixed-model 4-way rANOVA disclosed significant effects of the main factors group (p < 0.01; $F_{2,22} = 5.58$), with higher delta power activity in young depressed compared to healthy older women (p < 0.01; post-hoc analysis based on LSMEANS procedure, Tukey-Kramer adjusted) and *night* (p < 0.001; $F_{1,26} = 111.43$), with higher values during the recovery night. The factor *derivation* (p < 0.001; $F_{3,420}$ = 92.69) revealed decreasing EEG delta activity along the antero-posterior axis and the factor cycle (p < 0.001; $F_{2,50} = 136.34$) showed its highest values during sleep cycle 1. Furthermore, a significant interaction of the factors group*night (p < 0.05; $F_{2.26} = 4.40$), group*derivation (p < 0.001; $F_{6,420} = 4.22$), group*cycle (p < 0.01; $F_{4,50} = 4.84$), group*night*cycle (p < 0.001; $F_{4,420} = 17.86$), and group*night*derivation*cycle (p < 0.001; $F_{42,420} = 6.27$) were observed. Significant within group comparisons for the 4-way interaction group*night*derivation*cycle are displayed in Fig. 4.

A significant increase in EEG delta power during the recovery night was observed for the first NREM sleep cycle within each group for the F and C derivations (MDD and HY p < 0.001, HO p < 0.01) and, for the MDD and HY, in the P and O derivations (p < 0.001) as well. During NREM sleep cycle 2 there was no significant difference in delta EEG power during the recovery and baseline nights in any of the derivations in HO. MDDs displayed higher delta activity during the recovery night in sleep cycle 2 in each derivation, whereas EEG delta power activity in HY was only signifi-



Fig. 2. Relative EEG spectra during the baseline and recovery nights (expressed in % of HY). Relative EEG spectra values for baseline and recovery nights with reference to respective levels of healthy young women (reference line at 100%; n = 8) are shown for healthy older women (HO; gray open circles; n = 8) and young depressed women (MDD; black circles; n = 9) between 0.75–25 Hz for F, C, P, and O derivations (collapsed left, central, and right values along the anterior posterior axis). Significant differences between the groups are indicated near the abscissa, as are respective post-hoc comparisons (black circles = significant group effect; open triangles = MDD vs HO; p < 0.05; analysis based on absolute EEG spectra values).

cantly higher in the F derivations. During NREM sleep cycle 3 no EEG delta activity differences occurred. Post-hoc analysis of the 4-way interaction disclosed significantly higher EEG delta power activity of the MDD and HY groups than of the HO group during the first NREM sleep cycle in the recovery night for the F derivation (p < 0.001), which was also present during the second NREM sleep cycle between MDD and HO (p < 0.001). Neither cycle duration nor NREM or REM duration per sleep cycles 1–3 differed between the three groups during the baseline and recovery nights (p > 0.1, mixed-model 2-way rANOVA; data not shown).

Delta ratios (delta EEG activity in the frequency range between 0.75 and 4.5 Hz during NREM sleep episode 1 in relation to the respective value during NREM sleep episode 2) during the recovery night of HY were significantly higher than the corresponding ratios of the MDD and HO groups (p < 0.05; $F_{2,22} = 4.7$; mixed-model 2-way rANOVA; data not shown) which is a reflection of a different time-dependent decrease of SWA in HY compared to the other two groups (see Figs. 4 and 5).

3.3. Decay of slow-wave activity during the baseline and recovery nights

The decay of the SWA for each group during the baseline and recovery nights was analysed by fitting a nonlinear regression function (see Section 2) to the individual mean spectra values centred at the middle of each sleep cycle of each participant in the relative EEG delta range (1–3 Hz; percentage of baseline night). Fig. 5 shows the fitted exponential decay function for each of the three groups during the baseline and recovery nights for lateral collapsed F derivations. The respective estimated parameters of the decay functions are displayed in Table 2.

The difference of the decay rates between groups was not significant (mixed-model 3-way rANOVA based on individual decay rates per subject; p > 0.6; $F_{2,21} = 0.52$) since the mean decay rates of each group reached the 95% confidence interval of the other two groups during the baseline night and during the recovery night. Furthermore, mean values of the baseline slopes overlapped



Fig. 3. Relative EEG power spectra per sleep cycle during NREM sleep for the recovery night. Relative EEG spectra values (EEG power values of the recovery night in % of the baseline values per cycle) are shown between 0.75–25 Hz for F, C, P, and O derivations (collapsed left, central, and right values) for healthy young (HY; gray filled circles; n = 8), healthy older (HO; gray open circles; n = 8), and major depressed subjects (MDD; black circles; n = 8) for sleep cycles 1–3. Post-hoc comparisons on the significant effect of the factor group (p < 0.05), as well as significant interaction effects of the main factors group*derivation, are indicated at the bottom line (mixed-model 2-way rANOVA p < 0.05).

with the 95% confidence interval of the recovery nights within the groups. Interestingly, although not significant, young depressed women and healthy older women exhibited a shallower decline of SWA during the recovery night, which contrasts with the steeper slope of healthy young women after sleep deprivation.

3.4. Time course of circadian variables

Salivary melatonin, as a reliable variable to measure endogenous circadian rhythmicity, was sampled every 30 min over the entire 40 h protocol. Samples were subsequently collapsed into 2.5 h bins per subject before averaging across groups (see Fig. 6). Mixed-model two-way rANOVA disclosed significant effects of the main factors group (p < 0.05; $F_{2,22} = 3.52$) and session (p < 0.001; $F_{15,330} = 34.44$), as well as of their interaction (p < 0.001; $F_{30,330} = 2.12$). Post-hoc analysis on the group effect showed, therefore, only a tendency toward significantly higher mean melatonin secretion in healthy young women compared to healthy older women (p = 0.057) during the 40 h protocol. However, healthy young women had significantly higher nocturnal melatonin levels compared to young depressed women in session

eight (p < 0.001) and healthy older women during sessions seven and eight (p < 0.05 and 0.001, respectively).

Subjective sleepiness ratings were derived from the Karolinska Sleepiness Scale (KSS) during the 40 h sustained wake episodes. The time course of mean subjective sleepiness per group as illustrated in Fig. 7 (top panel) is based on half-hourly ratings which were collapsed into 2.5-h bins. Mixed-model 2-way rANOVA disclosed only significance for the factor *session* (p < 0.001; $F_{15,330} = 43.67$), but not for the factor *group* or the interaction between these two factors (p at least >0.05).

The time course of subjective mood ratings during sustained wakefulness was significant (p < 0.001; $F_{15,330} = 4.18$; panel at the bottom of Fig. 7). Furthermore, mixed-model 2-way rANOVA yielded significance for the main factor group (p < 0.05; $F_{2,22} = 5.18$), with significantly worse mood of MDD when compared to the two healthy age groups (p < 0.05). Interestingly, no significant mood improvement occurred in MDD during sleep deprivation with respect to both the assessments before the baseline night (data not shown) and the start value during the sustained wakefulness protocol (p > 0.1). The interaction of the two factors group*session was not significant (p > 0.05).



Fig. 4. EEG delta activity per NREM-REM sleep cycles 1–3 during baseline and recovery night. EEG delta activity (1-3 Hz) per sleep cycle 1–3 for collapsed derivations (F, C, P, O) is expressed for each group separately as a percentage of the respective baseline value (young depressed, n = 8; healthy older, n = 8; healthy young, n = 8; mean ± SEM). Time of day as indicated on the abscissae corresponds to the mean onset time per group of the NREM-REM episodes. Black filled circles = baseline night, black open circles = recovery night. Asterisks indicate significant post-hoc comparisons of mean values per cycle and derivation between baseline and recovery night within each group (p < 0.05; LSMEANS procedure, Tukey–Kramer adjusted).



Fig. 5. Fitted exponential decay of relative delta power activity during the baseline and recovery night. Fitted exponential decay function [$delta_t = delta_{\infty} + delta_0 * e(-st)$] to relative EEG delta power (1–3 Hz; percentage of baseline night) NREM sleep across all NREM sleep episodes for lateral collapsed F derivations during the baseline (left hand panel) and recovery (right hand panel) nights. Major depressed women *n* = 8, black filled circles and black line; healthy young women *n* = 8, gray filled circles and gray line; healthy older women *n* = 8, gray open circles and dashed gray line.

Table 2

Estimated parameters for the nonlinear regression analysis of the decay of relative EEG delta power activity during the baseline and recovery nights. The estimated parameters of the nonlinear regression analysis for the decay of EEG delta power during the baseline and recovery nights for all three groups are indicated for the collapsed F derivations during all NREM sleep episodes (mean of all cycles ± SEM). 95% CI = 95% confidence interval, *R* = index for goodness of fit.

| Parameter | Young depressed won | nen | Healthy young wom | en | Healthy older wome | Healthy older women | | |
|---------------------------------|--|---|---|---|---|---|--|--|
| | Baseline night | Recovery night | Baseline night | Recovery night | Baseline night | Recovery night | | |
| Decay rate, /min 95% Cl R | 0.0076 ± 0.0033 0.000793-0.0144 0.84 | 0.005 ± 0.0024 0.000069-0.01 0.86 | 0.0098 ± 0.0023 0.00525-0.0145 0.93 | 0.0109 ± 0.0022 0.006-0.0155 0.94 | 0.0084 ± 0.0022 0.00402-0.0128 0.94 | 0.0079 ± 0.0019 0.00402-0.0119 0.94 | | |



Fig. 6. Mean salivary melatonin levels during the 40-h sustained wakefulness protocol. The figure displays mean salivary melatonin values (\pm SEM) for healthy young (HY, gray filled circles; *n* = 8), young depressed (MDD, black filled circles; *n* = 9), and healthy older (HO, gray open circles; *n* = 8) woman volunteers. Significant post-hoc comparisons of the interaction of the factors *group**session are indicated at the bottom line (open circle = HY > HO, filled square = HY > MDD; *p* at least <0.05; post-hoc analysis based on LSMEANS statement with Tukey–Kramer adjustment of *p* values).

4. Discussion

We have investigated the impact of high sleep pressure induced by 40 h of sustained wakefulness on sleep architecture and sleep EEG spectra in young unipolar moderately depressed women (MDD) and healthy young (HY) women as well as in older controls (HO). All three groups showed a typical increase of slow-wave activity (SWA) during the first part of the recovery night as a response to increased homeostatic sleep pressure [41]. Contrary to our expectations, young depressed women reacted with an even stronger absolute SWA response in the delta frequency range compared to healthy young women and healthy older women, particularly in frontal brain regions. Furthermore, relative EEG spectra also showed higher homeostatic response to sleep deprivation in depression compared to healthy young women and healthy older women, particularly in the first sleep cycle, but also in the second sleep cycle when compared to healthy young women. In both young groups the low frequency EEG response to sleep deprivation was accompanied by a hyperfrontality which not only confirms the fact that frontal brain areas are most susceptible to sleep deprivation [40], but also extends previous findings on this topographical feature of NREM sleep homeostasis in middle-aged depressed outpatients [47] to a younger moderately depressed cohort. In contrast, healthy older women exhibited not only attenuated SWA values compared to the other two groups, but also an absence of the frontal predominance of mean SWA during the recovery night along the antero-posterior axis, which confirms previous findings on age-related changes in homeostatic sleep regulation after sleep deprivation [69,70].

4.1. Homeostatic response to sleep deprivation

Our data on SWA response after sleep deprivation in young moderately depressed women contrast the predictions of the Sdeficiency hypothesis [37], which postulates a reduced SWA response during sleep in depression after sleep deprivation due to an impaired buildup of homeostatic sleep pressure during wakefulness. However, it has to be noted that the S-deficiency hypothesis was developed on the basis of two important clinical findings: first, the common occurrence of sleep disturbances in depression and, second, the clinical effect of sleep deprivation to improve mood in depressed patients. Our group of depressed women had none of the reported common sleep disturbances such as reduced sleep time, increased REM sleep, and shortened REM sleep latency. Moreover, we could not observe mood improvement in our depressed subjects during the 40-h sleep deprivation protocol [71]. Hence, the S-deficiency hypothesis may not apply to depressed subjects without sleep disturbances. Our findings add a caveat to the S-deficiency hypothesis rather than refute it. A homeostatic deficiency in sleep regulation may be related to the presence of



Fig. 7. Time course of subjective sleepiness and mood during 40-h of sustained wakefulness. Mean subjective sleepiness (top panel) and mean mood (bottom panel) ratings are shown for each group over the 40-h period between the baseline and the recovery night whereby half-hourly given subjective ratings were binned in 2.5-h segments (means \pm SEM). Subjective sleepiness ratings are derived from the Karolinska Sleepiness Scale whereas subjective mood ratings are based on the visual analogue scale. HY = healthy young women (gray filled circles; *n* = 8), HO = healthy older women (gray open circles; *n* = 8), MDD = young depressed women (black filled circles; *n* = 9). Groups did not differ significantly with reference to sleepiness (mixed-model 2-way rANOVA; *p* > 0.05). In contrast, MDD exhibited significantly lower mood ratings than HY and HO (*p* < 0.05; post-hoc analysis based on LSMEANS statement, Tukey–Kramer adjusted).

sleep disturbances associated with depression such as insomnia, rather than to depression per se. This argumentation would need validation by a 40-h sleep deprivation study of age-matched depressed women *with* sleep disturbances under the same stringent conditions of a constant routine protocol.

Our results on homeostatic SWA response to sleep deprivation in young depressed women corroborate previous findings in depressed female outpatients aged 18–40 y, where an enhanced SWA response to a relatively small homeostatic sleep pressure after a 3-h sleep delay was found in comparison to healthy controls [46,72]. As our study included outpatients of approximately the same age range, it still remains unclear whether older depressed women would exhibit a similar EEG delta response to sleep deprivation compared to healthy age-matched controls. Furthermore, as only women were included in our study, it remains to be elucidated under the same stringent constant routine conditions whether depressed male subjects would also show an enhanced SWA response to sleep deprivation compared to healthy controls. So far, studies on the effect of sex in depression have shown ambiguous results such as depressed men exhibiting lower homeostatic response during NREM sleep compared to depressed women and healthy controls [20,21,46] or no differences in slow-wave sleep between depressed men and women being detected [47].

The stronger frontal SWA response during the recovery night in our depressed group after sleep deprivation shows not only that homeostatic sleep regulation is different from that in healthy aging, but also points toward higher homeostatic sleep pressure in moderately depressed women compared to age-matched healthy controls. The latter was not caused by less sleep prior to sustained wakefulness, as total sleep time during the baseline night was not different between the groups. Our recent findings of higher delta and theta EEG activity during sustained wakefulness, as a marker of sleep homeostasis and sleep propensity [73,74], in the same cohort of depressed subjects compared to healthy young women provide further evidence for this conclusion [75].

Different aspects may contribute to higher homeostatic sleep pressure in depression such as neural, chemical, and genetic processes. According to the synaptic homeostasis hypothesis SWA during sleep serves to downscale synaptic strength acquired during prior wakefulness, and its amount is correlated to the extent of cortical activation and, thus, synaptic potentiation [76]. Although not well-understood vet, rumination in depression, as one of the key factors for the onset and maintenance of the illness [77], may reflect higher cognitive demand and, thus, lead to additional cortical activation [78] during wakefulness and higher SWA during the subsequent sleep episode as observed in our group of young depressed women compared to the two healthy groups. However, it remains to be shown whether rumination may increase synaptic potentiation during wakefulness and lead to higher SWA during subsequent NREM sleep. From a chemical perspective, higher levels of adenosine, a nucleoside proposed to act as an endogenous somnogen [79,80], may entail higher SWA in depression. Studies so far have shown both decreased and increased levels of adenosine deaminase levels in depression [81,82]. Beside these altered neural and chemical processes, genetic alterations may also contribute to differences in slow-wave sleep (SWS) and SWA. Studies on clock genes have shown that alterations in the Period3 gene, for instance, influence individual differences in SWA and sleep phase preference in humans [83].

4.2. Ultradian modulation of EEG slow-wave activity during NREM sleep

The dynamics of SWA with reference to its exponential decline during the night did not show significantly different time constants between the three groups and the high correlation coefficient values confirmed a good quality of fit of the decay functions. Although not significant, it is noteworthy that the decay rate during the recovery night, when compared to the respective value of the baseline night, showed a decreasing trend in young depressed women and healthy older women, while in healthy young women there was an opposite pattern observed. The decreasing time constant in MDD and HO may be explained by a different ultradian modulation of NREM delta activity after sleep deprivation compared to HY, as indicated by a rather stable slow-wave activity rebound during the first three sleep cycles of the recovery night in MDD and HO compared to a consecutive declining trend over the sleep cycles in HY. Additionally, even more pronounced differences in ultradian delta sleep modulation became obvious by inspection of the delta sleep ratios where young depressed women and older women exhibited significant lower values after sleep deprivation compared to healthy controls. The occurrence of lower delta sleep ratios in depression has first been described by Kupfer and colleagues and they also found a positive correlation between the level of the delta sleep ratio and the duration of the remission times in depression [84]. Other studies showed an age-dependency of delta sleep ratios in depression, as reduced values were found in depressed female adolescents compared to healthy controls but not in depressed women aged 18-40 y [46,85]. Furthermore, lower delta sleep ratios were found in older depressed women regardless of their remission state [86]. In contrast to these other findings, where mean SWA values were lower during the first NREM sleep cycle compared to the second, low delta sleep ratios in our group of depressed women after sleep deprivation came about through a higher temporal preponderance of SWA during sleep cycle 2 compared to healthy young controls. This different temporal pattern of NREM delta activity is under circadian control, as are other temporal related aspects of sleep regulation [32,52,87]. Hence, lower delta sleep ratios may point towards circadian alterations in sleep regulation, which, at least for our older group, would be supported by previous suggestions of a reduced ability of the hypothalamic circadian master clock to synchronize endogenous rhythms [88].

4.3. Melatonin secretion and subjective sleepiness

We observed lower mean melatonin levels in depressed and older subjects compared to healthy controls. These findings coincide with other reports of low melatonin levels for both groups [89–92]. Reduced melatonin levels may mirror a reduced circadian signal responsible for the promotion of wakefulness during the biological day according to the two-process model of sleep regulation [32]. There are many reports of circadian disturbances in depression [18,31], but, to date, the only studies to elucidate unmasked circadian aspects of sleep-wake regulation in depression have been performed in winter depression [54,55,93,94] and in patients remitted from major depression [95]. In healthy older women there is some evidence for a weaker circadian signal in sleep-wake regulation as shown under constant routine conditions [69]. More sleep occurs in older healthy women compared to young healthy women in the so-called forbidden zone for sleep [96], which refers to the period of wakefulness immediately prior to the increase of sleep propensity.

We observed no significant differences in subjective sleepiness between young depressed women, healthy young women, and older women during the 40 h of sustained wakefulness. However, visual inspection of the time course of subjective sleepiness showed a marked increase of sleepiness in healthy older women in the early evening after approximately 10 h of wakefulness compared to the other two groups and in young depressed women after approximately 14 h compared to healthy young women. Both increases may reflect a deficiency of the circadian arousal for wakefulness. While in aging a weakening of the circadian arousal system has been shown [69,88], an increase in subjective sleepiness after 14 h of wakefulness in our depressed subjects does not evidently indicate a deficiency in the circadian wake-promoting signal. However, results on low frequency EEG during wakefulness as an objective marker for sleepiness in the same cohort showed higher values in young depressed women compared to healthy young women during 40 h of sustained wakefulness [75]. Thus, it could be that the young moderately depressed women became habituated to higher sleep pressure levels.

5. Conclusions

Our results show that homeostatic sleep regulation as well as sleep architecture in young unipolar moderately depressed women is not the same as premature aging, as has been proposed by some authors [23,25]. Young unipolar moderately depressed women live on higher homeostatic sleep pressure and we hypothesize that an imbalance of the opponent interaction between the circadian and homeostatic processes in depression due to an attenuated circadian wake promoting signal combined with a process (e.g., rumination) that leads to increased homeostatic sleep pressure levels may contribute to this. A caveat to this conclusion is that not all variations of the circadian sleep–wake cycle could be studied in our design because sleep occurred at habitual bedtime. In addition, rumination was not measured in our study. However, a parallel investigation in an independent age-matched group of young depressed women studied in a low sleep pressure protocol (nap protocol) under constant routine conditions also revealed elevated homeostatic sleep pressure combined with attenuated melatonin secretion, providing a confirmation of our findings [97].

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2012.03.008.

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