Similar Sleep EEG Topography in Middle-Aged Depressed Patients and Healthy Controls

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Objectives: One of the early hypotheses relating sleep disturbances in depression to a model of sleep regulation is the S-deficiency hypothesis. It is postulated that, in depressed patients, sleep propensity during wakefulness does not rise to the level attained by nondepressed subjects, resulting in altered sleep structure or changes in the electroencephalogram during sleep. We aimed to test this hypothesis by assessing topographic changes in the sleep electroencephalogram associated with depression.

Design: Cross-sectional clinical study.

Setting: Mental Health Clinical Research Center.

Participants: Sixteen unmedicated depressed outpatients (mean age: 41.2 years) and 16 pair-matched healthy controls (mean age: 41.1 years).

Interventions: None.

Measurements: Baseline sleep electroencephalogram recordings were obtained from a central referential electrode and from 3 bipolar derivations (frontocentral, centroparietal, parietooccipital) along the anteroposterior axis.

Results: Symptoms of depression at the time of sleep recordings were moderate (24-item Hamilton Rating Scale of Depression range: 16–31).

INTRODUCTION

In historical references to what today would be considered major depression, mood disorders have long been associated with changes in sleep patterns. Using the term melancholia, Hippocrates (460-377 BC) already described many features, including “loss of sleep,” by which we define major depressive disorder (MDD) today. Subjective sleep complaints are frequently present in depressed patients, and insomnia or hypersomnia are among 9 diagnostic criteria for MDD. Patients with depression typically complain of prolonged sleep latency, frequent arousals with early-morning awakenings, short and nonrestorative sleep, and disturbing dreams. These subjective symptoms may be accompanied with objective sleep alterations such as disturbed sleep continuity, abnormalities of rapid-eye-movement (REM) sleep, loss of deep non-REM (NREM) sleep (ie, slow-wave sleep), and changes in variables derived from quantitative sleep electroencephalogram (EEG) analysis (eg4-8).

Several models have been proposed to account for the relationship between depressed mood and disturbed sleep in patients with MDD. For example, it has been suggested that REM sleep is excessively increased,9 the balance between cholinergic and monoaminergic neurotransmission is abnormal,10,11 and the phase-relationship between sleep and the circadian system is altered12 in depressed patients. Moreover, Borbély and Wirz-Justice13 hypothesized that depression is associated with a deficient build up of a sleep-regulatory process that accumulates during waking and dissipates during sleep. This process reflects NREM sleep intensity, depending on the history of prior sleep and wakefulness, and has been referred to as the homeostatic Process S in the 2-process model of sleep regulation.14 The dynamics of Process S can be reliably tracked by the time course of slow-wave (or delta) activity (SWA)(~ 0.5-5 Hz) in the NREM sleep EEG. In healthy adults, delta activity declines ROUGHLY exponentially during a sleep episode, is enhanced after sleep deprivation, and is reduced after a daytime nap (see15 for recent overview).

In early studies of untreated depressed patients and healthy controls, the level of delta activity in the initial part of sleep was reduced, and its decline across consecutive NREM sleep episodes was altered in accordance with the S-deficiency hypothesis.5,16 These changes, however, were not confirmed in all further studies. They are present in some patients, but not in others (eg8,17,18; see19 for discussion). Thus, the question whether Process S is deficient or not in individuals with depression remained unanswered.

A novel approach to detect subtle changes in sleep regulation is the investigation of fronto-occipital EEG power gradients dur-
ing sleep. Recent studies have demonstrated that activity in distinct frequency bands exhibits prominent state-related and sleep-wake dependent (ie, homeostatic) regional changes along the anteroposterior axis. Werth et al20,21 observed in baseline nights that EEG power in the delta range recorded from an anterior derivation was higher than in more posterior derivations. This ‘hyperfrontality’ was present initially after sleep onset and vanished in the second half of the night, yet it was even more pronounced in recovery sleep after total and partial sleep deprivation.22-25 These findings suggested that frontal parts of the cortex pronounced in recovery sleep after total and partial sleep deprivation. This derivation was higher than in more posterior derivations. This topography of power spectra along the anteroposterior axis revealed that these changes showed regional specificity and included an anteroposterior shift of delta/theta (3.75- to 7-Hz) and low spindle-frequency activity (10- to 12-Hz) in NREM sleep, and of 3.25- to 7-Hz activity in REM sleep.

Possible alterations in sleep EEG topography in patients with depression are currently unknown. To investigate whether changes in sleep homeostasis are indeed associated with the pathophysiology of depressed mood, we compared the brain topography of power spectra along the anteroposterior axis between depressed patients and healthy controls. Because earlier studies based on a central referential derivation reported changes between depressed patients and healthy controls. Because earlier studies expected to find alterations in sleep EEG topography in depressed patients that are similar to those found with advanced age.

METHODS
Patients and Controls

The baseline sleep recordings of 16 nonsuicidal outpatients with MDD (8 women, 8 men; age range: 29.4-53.5 years) and 16 age- and sex-matched healthy controls (age range: 27.6-54.6 years) were analyzed. The data of 8 patients have been included in our previous reports of the effects of phenelzine on sleep and mood.29,30 All participants were recruited by the University of California, San Diego, Mental Health Clinical Research Center, via advertisements searching for individuals with depression and healthy volunteers. After telephone screening, respondents were administered the Structured Clinical Interview for DSM-IV by a trained staff member of the Mental Health Clinical Research Center and were evaluated by medical and psychiatric history, physical examination, standard laboratory tests (chemistry panel, complete blood cell count, human immunodeficiency virus screen, urine analysis, and drug screen), and electrocardiography. Severity of depression was measured in all subjects with the Hamilton Rating Scale of Depression,31 the Beck Depression Inventory32 and the Profile of Mood States.33 All diagnoses were presented to and arrived at by consensus conferences of the Mental Health Clinical Research Center. Patients with psychotic features, current alcohol and/or substance abuse, bipolar disorder, and recent or current major medical disorders were excluded. A detailed personal and family history was obtained from all participants. All patients had an Axis-2 disorder or a physical condition requiring medical treatment, except for 2 patients being treated for hypertension. None of the patients had been treated with any psychoactive or sleep medication, or had received psychotherapy, at least 2 weeks before the study. One patient, however, did not disclose the use of a centrally acting agent (St. John’s wort) until after the sleep recording. On recording days, moderate caffeine consumption was limited to the morning hours, and no alcohol was permitted.

Depressive Symptoms, Subjective Sleep Quality, and Polysomnographic Recordings

The data presented here are based on 1 nocturnal sleep recording per subject. Symptoms of depression were rated during the day before or after the sleep episode. Subjective sleep quality and self-rated state were assessed 15 minutes after awakening by a questionnaire and 100-mm visual analog scales.

Subjects slept in the completely darkened bedrooms of the sleep laboratory at their habitual bedtimes. Each recording was preceded by at least 1 adaptation night. Adaptation and study nights were consecutive. The EEG, submental electromyogram, electrooculogram, and electrocardiogram were recorded by a portable polygraphic amplifier (PS1, Institute of Pharmacology and Toxicology, University of Zürich, Switzerland). EEG electrodes were placed at frontal, central, parietal, and occipital locations. The data of the F4C4, C4P4, P4O2, and C3A2 derivations are reported. The bioelectric signals were digitized and transmitted via fiberoptic cables to a notebook computer with a digital-signal processor board. The analog signal was conditioned by at least 1 adaptation night. Adaptation and study nights were consecutive. The EEG, submental electromyogram, electrooculogram, and electrocardiogram were recorded by a portable polygraphic amplifier (PS1, Institute of Pharmacology and Toxicology, University of Zürich, Switzerland). EEG electrodes were placed at frontal, central, parietal, and occipital locations. The data of the F4C4, C4P4, P4O2, and C3A2 derivations are reported. The bioelectric signals were digitized and transmitted via fiberoptic cables to a notebook computer with a digital-signal processor board. The analog signal was conditioned by at least 1 adaptation night. Adaptation and study nights were consecutive.
NREM/REM sleep cycles were defined as in previous studies. With the exception of 1 patient who completed only 2 cycles, all subjects completed at least 3 NREM/REM sleep cycles.

Data Analyses

For statistical analyses, the SAS General Linear Model procedure (SAS Institute Inc., Cary, NC) was used. Exploratory statistics revealed no significant main effect of factor Sex or interactions involving the factor Sex for clinical variables, visually scored sleep variables, or sleep EEG measures. The groups of men and women were, therefore, pooled. Statistical models included terms for the factors Group (depressed patients, healthy controls), Derivation (F4C4, C4P4, P4O2) and 2-Hour Interval (1-3), as described in detail in the Results section. The significance level was set to \( \alpha < .05 \). If a factor had more than 2 levels, the presented probability values are based on Greenhouse-Geisser corrected degrees of freedom, but the original degrees of freedom are reported. Clinical characteristics, visually scored sleep variables, EEG power spectra in NREM and REM sleep, the dynamics of SWA (power within 0.75-4.5 Hz), regional differences along the anteroposterior axis, and the time course of the F4C4/C4P4 power ratio across consecutive 2-hour intervals were analyzed. Values of sleep latency and REM-sleep latency and absolute EEG power values and power ratios between derivations were log-transformed prior to statistical tests.

RESULTS

Depressive Symptoms, Subjective Sleep Quality, and Sleep Variables Derived From Visual Scoring

A minimum score of 14 on the 17-item Hamilton Rating Scale of Depression at the time of Structured Clinical Interview for DSM-IV diagnosis was used as the inclusion criterion of the study. While the current depressive episode was the first for 4 patients, the mean number of episodes was 3 ± 0.5 (range: 1-7). The mean duration of depression was 152.3 ± 74.5 weeks (range: 6-1144 weeks). The average age of the first onset of depression was 22 ± 2.8 years (range: 9-49 years).

At the time of sleep recordings, both clinician- and self-rated symptoms of depression were moderate on average (Table 1). With the exception of the Profile of Mood States anger subscale, the differences between patients and controls were highly significant for all mood measures.

Fifteen minutes after lights-on in the morning, patients’ mood was worse, and they felt more tense and less able to concentrate compared with the controls (Table 2). Other aspects of state after arising and self-rated sleep quality did not differ between the groups.

The time of lights off for sleep recordings was similar, yet the time in bed, thus, tended to be longer in the patients (range: 410-522 minutes) than in the controls (range: 298-525 minutes; \( P = .06 \), 1-way repeated-measures analysis of variance [ranova] with factor Group). Objective measures of sleep supported the absence of differences in subjective sleep quality. Sleep latency, total sleep time, sleep efficiency, and waking time after sleep onset were similar in both groups. Moreover, no differences were present in NREM sleep stages, slow-wave sleep, and REM-sleep latency. The patients had a slightly lower percentage of REM sleep per total sleep time, whereas REM-sleep duration did not differ between the groups (patients: 73.5 ± 4.8 minutes, controls: 82.0 ± 4.7 minutes, \( F_{1,15} = 1.4, P > .25 \)).

Dynamics of SWA in NREM Sleep

The dissipation of sleep propensity during sleep in patients and controls was quantified on the basis of SWA (C3A2 derivation).

### Table 1—Demographic and clinical characteristics of patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>F[1,15] (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset, y</td>
<td>22.3 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number previous episodes</td>
<td>3.2 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of current episode, wks</td>
<td>152.3 (74.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41.2 (2.0)</td>
<td>41.1 (2.1)</td>
<td>0.0 (.94)</td>
</tr>
<tr>
<td>HRSD, 17 items</td>
<td>16.1 (0.9)</td>
<td>0.7 (0.3)</td>
<td>211.9 (.001)</td>
</tr>
<tr>
<td>HRSD, 24 items</td>
<td>22.3 (1.1)</td>
<td>0.7 (0.3)</td>
<td>282.2 (.001)</td>
</tr>
<tr>
<td>BDI</td>
<td>23.3 (2.3)</td>
<td>0.5 (0.2)</td>
<td>922.2 (.001)</td>
</tr>
<tr>
<td>POMS Depression</td>
<td>26.8 (3.7)</td>
<td>1.1 (0.7)</td>
<td>518 (.001)</td>
</tr>
<tr>
<td>Tension</td>
<td>11.6 (1.6)</td>
<td>3.5 (0.7)</td>
<td>17.2 (.001)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12.4 (2.0)</td>
<td>2.7 (0.8)</td>
<td>23.8 (.001)</td>
</tr>
<tr>
<td>Confusion</td>
<td>11.9 (1.6)</td>
<td>3.3 (0.5)</td>
<td>25.9 (.001)</td>
</tr>
<tr>
<td>Vigor</td>
<td>4.4 (1.1)</td>
<td>15.1 (1.7)</td>
<td>30.1 (.001)</td>
</tr>
<tr>
<td>Elation</td>
<td>2.0 (0.5)</td>
<td>10.8 (1.1)</td>
<td>57.5 (.001)</td>
</tr>
<tr>
<td>Friendliness</td>
<td>12.7 (1.7)</td>
<td>20.9 (1.4)</td>
<td>15.8 (.001)</td>
</tr>
<tr>
<td>Anger</td>
<td>6.4 (2.0)</td>
<td>4.3 (1.1)</td>
<td>0.8 (.39)</td>
</tr>
</tbody>
</table>

Values represent means (SEM) of 16 depressed patients and 16 individually matched healthy controls. BDI refers to Beck Depression Inventory; HRSD, Hamilton Rating Scale of Depression; POMS, Profile of Mood States.

\( F \) and \( P \) values: repeated-measures analysis of variance with factor Group (patients, controls).

\( \text{df} = 15, \text{HRSD and BDI data were missing in 1 control (F1,14).} \)

### Table 2—Self-rating of sleep quality and state in the morning 15 minutes after lights-on

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated sleep latency, min</td>
<td>20.2 (5.4)</td>
<td>14.3 (2.4)</td>
<td>.51</td>
</tr>
<tr>
<td>Perceived number of awakenings</td>
<td>4.4 (1.4)</td>
<td>2.3 (0.5)</td>
<td>.32</td>
</tr>
<tr>
<td>Estimated wake time after sleep onset, min</td>
<td>23.9 (7.2)</td>
<td>11.9 (2.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Visual analog scales, 100 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sound, 100, vs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fragmented, 0, sleep</td>
<td>49.4 (7.4)</td>
<td>69.3 (4.8)</td>
<td>.10</td>
</tr>
<tr>
<td>Superficial, 100, vs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deep, 0, sleep</td>
<td>37.7 (6.3)</td>
<td>30.6 (4.5)</td>
<td>.50</td>
</tr>
<tr>
<td>Recuperated, 100, vs tired, 0</td>
<td>42.0 (5.5)</td>
<td>54.3 (7.7)</td>
<td>.18</td>
</tr>
<tr>
<td>Bad mood, 100, vs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>good mood, 0</td>
<td>39.0 (5.0)</td>
<td>24.2 (4.5)</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Full of energy, 100, vs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lack of energy, 0</td>
<td>45.7 (4.2)</td>
<td>56.3 (6.8)</td>
<td>.18</td>
</tr>
<tr>
<td>Tense, 100, vs relaxed, 0</td>
<td>38.9 (5.5)</td>
<td>21.2 (3.7)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Unable, 100, vs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>able, 0, to concentrate</td>
<td>44.9 (3.6)</td>
<td>28.7 (4.4)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Values are means (SEM) of 16 depressed patients and 16 individually matched healthy controls.

\( P \) values: 2-tailed Wilcoxon matched-pairs signed-ranks test

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In both groups, SWA was modulated by the NREM/REM sleep cycles and declined across consecutive NREM sleep episodes (Figure 1). The mean delta sleep ratio, i.e., the quotient of absolute SWA of the first and second NREM sleep episodes,7,18 was very similar in patients (1.35 ± 0.08, n = 16) and controls (1.35 ± 0.11, n = 16) and did not differ (P = 0.97, 1-way rANOVA with factor Group). To compare the dynamics of Process S during sleep in more detail, an exponential function was fitted to individual SWA data of the 2 groups. The time constants of the decline did not differ, as indicated by overlapping asymptotic 95% confidence intervals (patients: 200.7 ± 59.4 minutes [82.1-319.4 minutes], controls: 191.1 ± 67.7 minutes [56.5-327.4 minutes]). The high asymptotic r² values (0.77 and 0.72, respectively) confirmed that the quality of fit was good.

**Regional Differences in Sleep EEG Spectra**

All-night EEG power spectra were calculated in NREM (stages 2, 3 & 4) and REM sleep for 3 bipolar derivations on the right hemisphere. In patients and controls, EEG power showed the typical frequency- and state-related characteristics. Highest power occurred below 1 Hz and decreased as frequency increased (Figure 2). Secondary peaks were present in the theta range (~7-9 Hz) in REM sleep, and in the spindle frequency range (~11-15 Hz) in NREM sleep. No significant differences between patients and controls emerged.

Regional power gradients along the anteroposterior axis are illustrated in Figures 3 and 4. To represent the differences between adjacent derivations, the power in each 0.25-Hz bin was expressed as the ratio of F4C4 and C4P4, and of C4P4 and P4O2. Positive values indicated higher power in the more anterior derivation, while negative values indicated higher power in the more posterior derivation. Significant effects of a 2-way rANOVA with the factors Group (patients, controls) and Derivation (F4C4, C4P4, P4O2) were restricted to a main effect of Derivation in most bins in NREM sleep (except the 0.25- to 10.5- to 12.25-, and 17.0- to 17.25-Hz bins), and in the 0.25- to 2.5- to 14.25-, and 19.75- to 25.0-Hz range in REM sleep.

For follow-up statistics, the spectral data were collapsed into 6 frequency bands that were previously shown by cluster analysis to be characterized by a distinct topographic pattern.23 An anterior dominance in the low delta range (0.75-2 Hz) in NREM sleep was present in both groups in the F4C4/C4P4 ratio (Figure 4). In the controls, power in the F4C4 derivation was also higher than in the C4P4 derivation in the high delta (2- to 4-Hz), sigma (12- to 15-Hz), and beta (15- to 25-Hz) bands. In the C4P4/P4O2 ratio, a posterior dominance was found in both groups in the high delta, theta, and alpha range (2-11 Hz), as well as in the low delta range in the controls.

**Time Course of Frontal Predominance in the 0.75- to 2-Hz Band in NREM Sleep**

To investigate the temporal changes of the frontal predominance in low delta power in NREM sleep, the time course of the F4C4/C4P4 spectral ratio in the 0.75- to 2-Hz band was analyzed across consecutive 2-hour intervals. A 2-way rANOVA with the factors Group (patients, controls) and Interval (1-3) revealed a significant effect of Interval (F2,28 = 20.6, P < .001), yet no significant effect of Group nor a significant Group × Interval interaction. The frontal predominance of low delta activity in NREM sleep was present in the first 2-hour interval in the depressed patients (F1,15 = 7.6, P < .02), and in all three 2-hour intervals in the healthy controls (minimum F1,15 = 8.0, P < .02).

**DISCUSSION**

Patients with depression frequently complain of superficial nonrestorative sleep.1,2 The main findings of this study, that depressed patients showed no subjective sleep difficulties nor changes in the dynamics of EEG delta activity during sleep or the fronto-occipital power gradients along the anteroposterior axis in NREM and REM sleep, were thus unexpected. Our study, however, does not allow the conclusion that sleep changes are generally absent in depressed patients.

Early studies indeed found lower SWA or delta-wave counts in depressives than in healthy controls.5,16 Moreover, studies suggested that Process S during sleep may decay at a lower rate, or even increase from the first to the second NREM sleep period in certain clinical subgroups of depressed patients.7,8,18,19,35 To account for these sleep alterations, the S-deficiency hypothesis posulates that during wakefulness in depressed patients a homeostatic process underlying sleep regulation (i.e., Process S)14 does not rise to the same level that is attained by nondepressed subjects.13 Our findings do not corroborate the previous results to support the existence of an S deficiency during sleep. Various reasons could underlie the discrepancy. All patients in our study were outpatients, the majority had previous MDD episodes, and the level of depression was moderate. It is possible that more severe depressive symptoms, such as those usually found in an inpatient setting, are related to changes in sleep regulation.

To detec possibly subtle changes in sleep homeostasis in mod-

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### Table 3—All-night sleep variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Controls</th>
<th>F1,15 (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lights-off, h:min</td>
<td>22:49 ± 7</td>
<td>22:38 ± 10</td>
<td>0.8 (.38)</td>
</tr>
<tr>
<td>Lights-on, h:min</td>
<td>6:42 ± 6</td>
<td>6:04 ± 12</td>
<td>7.8 (.01)</td>
</tr>
<tr>
<td>Time in bed, min</td>
<td>473.9 (7.1)</td>
<td>439.0 (13.8)</td>
<td>4.3 (.06)</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>403.1 (10.3)</td>
<td>387.7 (11.8)</td>
<td>0.8 (.39)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>85.3 (2.4)</td>
<td>88.6 (1.6)</td>
<td>1.0 (.34)</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>20.0 (5.3)</td>
<td>12.5 (3.4)</td>
<td>2.1 (.17)</td>
</tr>
<tr>
<td>REM latency, min</td>
<td>78.1 (11.6)</td>
<td>59.5 (8.1)</td>
<td>2.8 (.12)</td>
</tr>
<tr>
<td>WASO, %</td>
<td>11.9 (3.2)</td>
<td>8.7 (1.6)</td>
<td>0.6 (.44)</td>
</tr>
<tr>
<td>Stage 1, %</td>
<td>11.2 (1.0)</td>
<td>11.4 (1.0)</td>
<td>0.0 (.91)</td>
</tr>
<tr>
<td>Stage 2, %</td>
<td>61.8 (1.9)</td>
<td>59.4 (1.6)</td>
<td>0.8 (.39)</td>
</tr>
<tr>
<td>Stage 3, %</td>
<td>5.1 (1.0)</td>
<td>5.7 (0.9)</td>
<td>0.2 (.64)</td>
</tr>
<tr>
<td>Stage 4, %</td>
<td>3.9 (1.4)</td>
<td>2.5 (0.7)</td>
<td>0.7 (.41)</td>
</tr>
<tr>
<td>Slow-wave sleep, %</td>
<td>8.9 (2.0)</td>
<td>8.1 (1.4)</td>
<td>0.1 (.75)</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>18.1 (0.9)</td>
<td>21.0 (0.9)</td>
<td>4.6 (.05)</td>
</tr>
</tbody>
</table>

Values of 16 depressed patients and 16 individually matched healthy controls represent means (SEM) in minutes or a percentage of total sleep time (except lights-off, lights-on and sleep efficiency). Time in bed refers to time between lights-out and lights-on; Sleep efficiency, total sleep time per time in bed; Sleep latency, time from lights-off to the first occurrence of Stage 2; REM sleep, rapid-eye-movement sleep; REM latency, time from sleep onset to the first occurrence of REM sleep; WASO, wakefulness after sleep onset (stage 2); Stage 1, 2, 3, and 4: non-REM sleep stages; Slow wave sleep, stages 3 & 4. F and P values: 1-way repeated-measures analysis of variance with the factor Group (patients, controls).
In moderately depressed patients, a topographic sleep EEG analysis was performed. We found that the power spectra derived from bipolar derivations along the anteroposterior axis did not differ between patients and controls (Figure 2). The absolute power spectra in NREM and REM sleep were very similar to those previously described. Moreover, the analyses of power gradients between adjacent derivations in NREM sleep revealed in both groups a striking ‘hyperfrontality’ in the low delta range (Figures 3 and 4). The topographic differences within this frequency band are particularly relevant as markers of NREM sleep homeostasis. In agreement with the notion that ‘frontal deactivation’ is most prominent in the beginning of the night when sleep propensity is highest, the anterior predominance of delta power diminished across consecutive 2-hour intervals. Thus, our study extends the previous findings in healthy young and middle-aged subjects of regional differences in NREM sleep homeostasis and to a clinical cohort of moderately depressed patients.

Sleep complaints are also common in older people in whom sleep consolidation is impaired, and the dissipation of delta activity in NREM sleep occurs more slowly than in young people. These findings suggest that increasing age is associated with an attenuation of the homeostatic sleep-regulating process. Because the effects of aging on sleep may be particularly pronounced in depressed patients, we expected to find changes in the time course of Process S in depression that are similar to those found in older people. Nevertheless, the dynamics and time constants of the decrease of SWA across NREM sleep episodes did not differ between patients and controls (Figure 1). We found for mean values of 3.3 and 3.2 hours, respectively. These values are very similar to those previously obtained in healthy young short and long sleepers (3.1 hours), as well as in middle-aged (mean age: 39 years) control subjects (2.9 hours) and patients with winter depression (2.7 hours). Our study thus adds to more recent work indicating that the sleep EEG and the kinetics of Process S during sleep are unchanged in major depression as well as in seasonal affective disorder. While these studies included predominantly women, it was recently suggested that depressed men, but not depressed women, show impaired SWA regulation. Our exploratory analyses of sleep variables and EEG spectra did not reveal significant Group by Sex interactions (data not shown). On the other hand, the suggestion that the homeostatic facet of sleep regulation within sleep is not changed in patients with moderate depression is also supported by the simulation of Process S in a pharmacologic study. After almost complete elimination of REM sleep with the monoamine oxidase inhibitor, phenelzine, the time course of SWA was consistent with Process S in the 2-Process model. It could be simulated with a good fit in the absence of REM sleep without the need for major adjustments in the model parameters derived from healthy adults.

Although we observed no changes in homeostatic sleep regulation during sleep, it remains possible that depressed patients and controls differ in the homeostatic build up of sleep propensity during wakefulness. Sleep deprivation, or “wake therapy,” rapidly improves depressive symptoms in about 60% of all depressed patients. It needs to be established with regularly timed waking EEG recordings whether the increase of sleep propensity during wakefulness is altered in patients with MDD. Moreover, it remains to be investigated whether sleep deprivation promotes the ‘hyperfrontality’ in SWA similarly to healthy adults, and whether the challenge of Process S has distinct repercussions on EEG topography in waking and sleep in “wake therapy” responders and nonresponders. It is interesting to note that a recent imaging study employing low-resolution electromagnetic topography (LORETA) based on 28 EEG electrodes revealed that 6.5- to 8-Hz activity during sleep deprivation, which was not reflected in different sleep structure or changes in NREM sleep EEG. It needs to be investigated whether sleep deprivation promotes the ‘hyperfrontality’ in SWA similarly to healthy adults, and whether the challenge of Process S has distinct repercussions on EEG topography in waking and sleep in “wake therapy” responders and nonresponders. It is interesting to note that a recent imaging study employing low-resolution electromagnetic topography (LORETA) based on 28 EEG electrodes revealed that 6.5- to 8-Hz activity during sleep deprivation, which was not reflected in different sleep structure or changes in NREM sleep EEG. It needs to be investigated whether sleep deprivation promotes the ‘hyperfrontality’ in SWA similarly to healthy adults, and whether the challenge of Process S has distinct repercussions on EEG topography in waking and sleep in “wake therapy” responders and nonresponders. It is interesting to note that a recent imaging study employing low-resolution electromagnetic topography (LORETA) based on 28 EEG electrodes revealed that 6.5- to 8-

Figure 1—Upper panel: Time course of electroencephalogram (EEG) slow-wave activity (SWA, power density in 0.75- to 4.5-Hz band) in depressed patients (open circles, n = 16) and healthy controls (filled circles, n = 16). Relative SWA was expressed as a percentage of the mean all-night value in non-rapid-eye-movement (NREM) sleep. Individual NREM sleep episodes were subdivided into 12 and rapid-eye-movement (REM) sleep episodes and the interval between lights-out and sleep onset into 4 equal time bins, respectively. Data were aligned with respect to sleep onset (ie, first occurrence of stage 2 sleep) and plotted against the mean timing of all NREM and REM sleep episodes. Vertical bars represent ± 1 SEM; dashed vertical lines indicate sleep onset and delimit REM sleep episodes. Lower panel: Dynamics of relative SWA across the sleep episodes. Individual SWA values per NREM sleep episode were plotted at episode midpoint times relative to sleep onset. Lines represent exponential functions for depressed patients (open circles, interrupted line) and healthy controls (filled circles, uninterrupted line). In each group, an exponential function SWA(t) = SWA0 x e^-t/τ + SWA∞ with an initial value (SWA0), an asymptotic value (SWA∞) and a time constant (τ) was fitted to the data. The time constant did not differ between patients (200.7 ± 59.4 minutes, asymptotic 95% confidence interval: 82.1 – 319.4 minutes, r^2 = 0.77) and controls (191.9 ± 67.7 minutes, asymptotic 95% confidence interval: 56.5 – 327.4 minutes, r^2 = 0.72).

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Hz activity during wakefulness was related to clinical outcome. More specifically, MDD patients with better response to nor-triptiline treatment showed 6.5- to 8-Hz hyperactivity before treatment within a rostral region of the anterior cingulate cortex when compared with patients with poor response.

The latter finding is in accordance with the notion that imbalances within limbic-thalamocortical circuits are associated with mood disorders. Considering the view that slow waves and sleep spindles in NREM sleep are generated by thalamocortical mechanisms, the lack of changes in the sleep EEG in our patients was unexpected. Among the most consistent results derived from brain imaging studies in patients with MDD are reduced volume, and abnormal regional cerebral blood flow and cerebral glucose metabolic rate in multiple areas of amygdala and prefrontal cortex. Moreover, local cerebral glucose metabolic rate in NREM sleep was diminished in the frontal cortex in depressed patients compared with healthy controls. On the other hand, the available evidence for structural and functional abnormalities in the thalamus is more controversial. For example, no statistically significant group effect in cerebral glucose metabolic rate was found in NREM sleep, and, in another study, thalamic size was normal in patients with MDD.

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Figure 3—Regional differences in all-night electroencephalogram (EEG) power spectra in non-rapid-eye-movement (NREM) sleep (stages 2, 3 & 4; left) and rapid-eye-movement (REM) sleep (right). Difference in log. spectral power of F4C4 and C4P4 (upper panel), and of C4P4 and P4O2 (lower panel) bipolar derivations in depressed patients (gray bars, n = 16) and healthy controls (black line, n = 16).

Figure 4—Regional differences in all-night electroencephalogram power spectra in non-rapid-eye-movement (NREM) sleep (stages 2, 3 & 4). Difference in log. spectral power of F4C4 and C4P4 (upper panel), and of C4P4 and P4O2 (lower panel) bipolar derivations in depressed patients (gray bars, n = 16) and healthy controls (white bars, n = 16). Error bars represent 1 SEM. Asterisks indicate frequency bands, which differed significantly between F4C4 and C4P4, and between C4P4 and P4O2, respectively (1-way repeated-measures analysis of variance with factor Derivation, df = 1,15, *** p < .001, ** p < .01, * p < .05).


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