CHAPTER 5

Sleep in Seasonal Affective Disorder patients in forced desynchrony: An explorative study

Kathelijne M. Kooregevel\textsuperscript{1}, Domien G.M. Beersma\textsuperscript{2}, Johan A. den Boer\textsuperscript{1}, Rutger H. van den Hoofdakker\textsuperscript{1}

\textsuperscript{1}Department of Psychiatry
\textsuperscript{2}Zoological Laboratory of the University of Groningen, The Netherlands

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ABSTRACT

Background
The majority of winter-type Seasonal Affective Disorder (SAD) patients complain of hypersomnia and daytime drowsiness. Since human sleep is regulated by the interaction of circadian and homeostatic processes, sleep disturbances may be due to either one of these factors or both. The present study focuses on homeostatic aspects of sleep regulation in SAD.

Methods
Sleep was recorded polysomnographically in 7 SAD patients and 8 matched controls subjected to a 120-hour forced desynchrony protocol. In time isolation, subjects were exposed to 6 20-hour days, each comprising a 6.5-hour period for sleep. Patients participated while being depressed, while remitted after light therapy and in summer. Controls were studied in winter and in summer. In each condition, the data of each subject were averaged across all recordings. Thus, the influence of the effects of the circadian pacemaker on sleep was excluded mathematically.

Results
The comparison of patients with controls and with themselves in the various conditions revealed no abnormalities in homeostatic parameters: sleep stage variables, relative power spectra and time courses of power in various frequency bands across the first three NREM-REM cycles showed no differences.

Conclusions
The data suggest that homeostatic processes are not involved in the disturbance of sleep in SAD.
INTRODUCTION

Most SAD patients complain of hypersomnia and daytime drowsiness (Rosenthal et al 1984, Anderson et al 1994). This suggests that in SAD sleep regulation may be altered. Because of the seasonal recurrence of symptoms and the efficacy of light therapy the pathogenesis of SAD is thought to be linked to disturbances of the circadian pacemaker. The potential depressogenic role of dysregulation of sleep is relatively seldom addressed. Homeostatic, ultradian, and circadian pacemaker related mechanisms are all involved in the regulation of sleep (Borbély 1982; Daan et al 1984; Dijk and Czeisler 1994, 1995; Wyatt et al 1999). Therefore, the subjective and objective sleep abnormalities in SAD might be due to disturbances of either circadian or non-circadian components of sleep regulation. The present study is devoted to the exploration of the homeostatic and ultradian aspects of sleep regulation in SAD.

According to the generally accepted two-process model of sleep, the alternation of wakefulness and sleep is regulated by an interaction of a circadian pacemaker related process ‘C’ and a homeostatic, or sleep-wake cycle related, process ‘S’ (Borbély 1982; Daan et al 1984). Additionally, Dijk and Czeisler (1994) have postulated that the interaction of the circadian pacemaker and the sleep-wake cycle promotes wakefulness during the day and facilitates sleep during the night. The human circadian pacemaker, localized in the suprachiasmatic nuclei (SCN) of the brain, generates near-24-hour oscillations in many physiological and psychological processes (Aschoff 1965; Czeisler et al 1999). By its sensitivity to light, the circadian pacemaker synchronizes these oscillatory processes with the 24-hour environmental light-dark cycle. (Honma and Honma 1988; Minors et al 1991; Boivin et al 1996; Jewett et al 1997). However, overt circadian rhythms measured under normal conditions comprise a mixture of both pacemaker related and sleep-wake cycle related contributions. Forced desynchrony protocols have been designed to distinguish the influences of the circadian pacemaker from those of the sleep-wake cycle (Kleitman and Kleitman 1953; Czeisler et al 1986; Dijk et al 1992; Hiddinga et al 1997). Forced desynchrony studies have demonstrated circadian- and sleep-dependent components in the distribution of non-rapid eye movement sleep (NREMS), slow wave sleep (SWS), spindle activity, and the latency to the first episode of REM sleep (Dijk and Czeisler 1995; Wyatt et al 1999). In other words, the polysomnographically recorded sleep data obtained in forced desynchrony studies in healthy subjects have shown that sleep is regulated by the interaction of circadian and homeostatic influences (Dijk and Czeisler 1994, 1995; Wyatt et al 1999).

Sleep abnormalities are a prominent feature of mood disorders (Benca et al 1992). Most non-seasonally depressed patients complain of insomnia (i.e., difficulties falling
asleep, increased wakefulness during the sleeping period, early morning awakening) and do not feel restored after sleep (Benca et al 1997). Compared to those obtained in healthy controls, polysomnographic recordings in affective disorder patients have consistently revealed a decreased sleep continuity, a reduction in SWS, a shortening of the REM sleep latency and an increase of REM sleep in the first part of the night (reviewed in Benca et al 1992). In contrast, about 80% of the SAD patients suffers from hypersomnia with earlier sleep onset and later wake times (Anderson et al 1994). In several studies polysomnographically recorded sleep in SAD has been examined. Recordings of SAD patients in winter were compared with those in summer (Rosenthal et al 1984, 1985, 1989; Anderson et al 1994; Palchikov et al 1997; Endo et al 1992) and with those in control subjects in winter (Rosenthal et al 1989; Anderson et al 1994; Schwartz et al 2000). Furthermore, comparisons have been made between recordings of SAD patients in winter before and after light treatment (Brunner et al 1996; Rosenthal et al 1989; Kohsaka et al 1994; Anderson et al 1994; Palchikov 1997; Endo 1993; Kohsaka et al 1994; Partonen et al 1993). Sleep in SAD patients in winter was found to differ from sleep in matched controls, but the sleep pattern which is characteristic for non-seasonal depression has not been observed. One study of polysomnographic recordings of seasonal and non-seasonal affective disorder revealed that seasonality is not characterized by a particular pattern of EEG characteristics (Thase 1989). Furthermore, it was shown that light therapy or the change of season can correct some of the polysomnographic abnormalities observed in SAD, although in one study no such changes were found (Partonen et al 1993). Finally, a study should be mentioned in which baseline sleep and sleep following the total sleep deprivation of a 40-hour constant routine protocol were recorded in SAD patients and controls. The patients exhibited a normal homeostatic regulation of sleep (Brunner et al 1996). In contrast, the analysis of EEG theta-alpha activity of SAD patients and controls during the wakeful hours of a 40-hour constant routine procedure in both winter and summer suggested that SAD patients may have a trait deficiency of process S, as expressed by a deficient buildup of sleep pressure during extended wakefulness (Cajochen et al 2000).

The polysomnographic changes found in depression and the pronounced but temporary effects of sleep deprivation on depressive symptomatology led to hypotheses concerning the involvement of either process C (e.g. an abnormality of circadian phase relative to the timing of the sleep-wake cycle, or a blunted circadian amplitude), or process S (a deficiency in the homeostatic buildup of sleep pressure), or both in the pathogenesis of affective disorders (reviewed in for example Wirz-Justice 1995; Wirz Justice and Van den Hoofdakker 1999; Boivin 2000). The seasonality of symptoms and the efficacy of light therapy have especially favored hypotheses concerning the involvement of circadian pacemaker abnormalities in SAD. This led to the present...
forced desynchrony study in SAD patients and matched controls. In a previous analysis of core body temperature and melatonin obtained in the same protocol no differences were observed between SAD patients and controls with respect to the period and phase position of the circadian pacemaker (chapter 4). It was therefore concluded that process C was normal in these patients. The aim of the present analysis is to examine process S. During the forced desynchrony protocol sleep was scheduled at all circadian phases. Thus, by averaging the sleep data, the impact of circadian phase could be minimized, if not excluded completely. Additionally, to avoid differences between patients and controls due to differences in habitual sleep timing, subjects were instructed to sleep between midnight and 8 AM during four baseline days at home as well as subjected to a habituation night in the lab prior to the start of the experiment.

**METHODS AND MATERIALS**

**Recruitment and Selection Criteria**

SAD patients who in previous years responded favorably to morning bright light therapy were recruited from the outpatients clinic. Healthy control subjects who could be matched to one of the participating patients for age, sex, smoking habits and menstrual cycle phase (if appropriate) were approached through local newspaper and television advertisements. All subjects received written information about the study. Before entering the protocol, the study was explained verbally to the subjects. Thereafter, subjects gave written informed consent. The study was approved by the Medical Ethics Committee of the Groningen Academic Hospital. Subjects were paid for their participation.

Patients fulfilled the DSM-IV criteria for recurrent major depression with seasonal pattern (American Psychiatric Association 1994) and the Rosenthal criteria for SAD (Rosenthal et al 1984). Controls reported no psychopathological disturbances or sleeping problems. Before inclusion in the study, subjects rated their general mental health, depressive symptomatology, seasonality and the preference for morningness or eveningness by completing the following questionnaires: (1) the General Health Questionnaire (GHQ; Goldberg and Williams 1988), (2) the Beck Depression Inventory (BDI: Beck et al 1979) and the Structured Interview Guide for the Hamilton Rating Scale of Depression - self-rating version (SIGH-SAD-SR; Williams et al 1992), (3) the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal et al 1987), and (4) the Morningness-Eveningness questionnaire (M/E; Horne and Ostberg 1976). The SIGH-SAD-SR consists of the 21-item Hamilton Rating Scale for Depression (HRSD) and an 8-item atypical scale (ATYP) addressing atypical symptoms.
such as an increase in sleep. An M/E score below 30 and above 70 reflects eveningness and morningness respectively (Horne and Ostberg 1976). Controls required a score of below 3 on the GHQ, below 9 on the BDI and below 8 on the SIGH-SAD-SR as well as on the SPAQ (Kasper et al 1989).

Subjects were physically fit, not dependent on alcohol or other substances and medication-free at least one month prior to participation (with the exception of the sporadic use of NSAIDs). Patients had not used psychoactive medications during at least six months before entering the study. Menstrual cycle phase was assessed through self report. If appropriate, the use of oral contraceptives, a depot progesterone or estrogen replacement therapy was continued.

During the winter season, depressive symptoms were monitored in patients by means of weekly BDI and SIGH-SAD-SR ratings. Patients were invited for participation during a depressive episode (BDI ≥ 16), when remitted after light therapy (BDI<6) and in summer. After finishing the protocol during the depressive episode, 45 minutes of 10,000 lux morning light therapy was administered at the out-patients clinic for at least 5 consecutive days. Controls participated once in winter and once in summer.

**Subjects**

From 1997 until 1999, the winter and summer experiments were scheduled during the months October - March and May - August respectively. Seven SAD patients (1 male and 6 females) and 8 matched controls (1 male and 7 females) participated. Baseline scores on the GHQ, SPAQ and the M/E and the scores on the SIGH-SAD-SR and BDI completed on day 1 of the protocol are summarized in Table 5.1. For the SIGH-SAD-SR, the HRSD and ATYP scores are listed separately. Furthermore, for each condition the score on the hypersomnia item of the SIGH-SAD-SR is presented. During the depressive episode, 6 out of 7 patients reported to sleep at least 1 hour more than when not depressed. In general, the scores on the hypersomnia item revealed that during a depressive episode SAD patients were more hypersomnic than when remitted \((p = .011)\), than in summer \((p = .023)\) and than controls in winter \((p = .015)\). Furthermore, no differences were detected in hypersomnia scores between patients and controls in summer \((p = .172)\). After participating in summer, 1 female control subject canceled the second experiment and was therefore replaced by another matched control for the winter condition. In both groups, 3 subjects were cigarette smokers. Of the female patients, 4 were studied each time in the (pseudo-) follicular phase of their menstrual cycle and 1 in the pseudo-luteal phase. The female controls were matched for menstrual cycle phase, except for one control matched to a post-menopausal patient who participated in the pseudo-luteal phase while depressed and in the pseudo-follicular phase while remitted due to estrogen replacement therapy.
Protocol

The protocol took 10 days. The first 4 days were baseline days, which the subjects spent at home. They were instructed to restrict sleep to midnight till 8 AM, to refrain from daytime naps, heavy physical exercise and alcoholic beverages. Furthermore, they were asked to drink not more than 4 caffeine containing drinks a day. Compliance to the sleep-wake schedule was verified by an actometer, which the subjects continuously wore at the non-dominant wrist (Bakker and Beersma 1991).

On day 4, subjects were admitted to the time isolation unit of the Psychiatry Department of the Groningen Academic Hospital. This facility comprises a sound and light shielded apartment in which no information on time of day is available. A habituation period from 6 PM on day 4 till 8 AM on day 5 enabled the subjects to become acquainted with the experimental procedures during wakefulness and sleep. Subsequently, the participants were subjected to a 120-hour forced desynchrony

Table 5.1 Characteristics (mean ± SD) of subjects: age at times of first participation, scores on the General Health Questionnaire (GHQ), Seasonal Pattern Assessment Questionnaire (SPAQ), and Morningness/Eveningness Questionnaire (M/E) which were completed at baseline and scores on the Beck Depression Inventory (BDI), on the Structured Interview Guide for the Hamilton Rating Scale of Depression - self-rating version (SIGH-SAD-SR) at day 1 of the protocol. The SIGH-SAD-SR sub-scores on the Hamilton Rating Scale of Depression (HRSD), the atypical symptom list (ATYP) and SIGH-SAD-SR item 14 on complaints of hypersomnia are listed separately. Seasonal Affective Disorder (SAD) patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer.

<table>
<thead>
<tr>
<th></th>
<th>SAD patients</th>
<th>controls</th>
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<tbody>
<tr>
<td>age</td>
<td>36.3±13.9</td>
<td>38.1±12.8</td>
</tr>
<tr>
<td>GHQ</td>
<td>1.4±2.3</td>
<td>0.3±0.5</td>
</tr>
<tr>
<td>SPAQ</td>
<td>16.7±3.6</td>
<td>3.5±1.8</td>
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<tr>
<td>M/E</td>
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<td>51.4±13.7</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>depressed (n = 7)</td>
<td>remitted (n = 7)</td>
</tr>
<tr>
<td>BDI</td>
<td>20.3±6.1</td>
<td>1.7±1.8</td>
</tr>
<tr>
<td>SIGH-SAD-SR</td>
<td>32.3±11.8</td>
<td>3.7±4.3</td>
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<td>HRSD</td>
<td>21.3±7.9</td>
<td>2.0±2.0</td>
</tr>
<tr>
<td>ATYP</td>
<td>11.0±5.4</td>
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<tr>
<td>hypersomnia (item 14)</td>
<td>2.0±1.3</td>
<td>0.3±0.5</td>
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protocol. Without knowledge of the timing of the experimental procedures, subjects were scheduled on six 20-hour days consisting of 13.5 hours of wakefulness in dim light (<10 lux) and 6.5 hours of darkness in which they had to be in bed. Staff members (conscious of revealing no information about time of day) had brief contacts with the subjects to announce the moments for rising, having meals, showering, performing psychometric tests, sticking electrodes for polysomnographic recordings and to announce the moments for going to bed. Therefore, each subjective 20-hour day had the same temporal structure.

During time isolation, core body temperature and melatonin concentrations were assessed to study circadian pacemaker characteristics (period, phase, and amplitude). Core body temperature was measured continuously with a rectal probe and stored at 1 minute intervals (Bakker and Beersma 1991). The endogenous circadian period was calculated from the salivary dim light melatonin onset (DLMO) obtained on day 4 and 9. On these days, saliva was sampled hourly between 7 PM and midnight and between 7 PM and 2 AM respectively. To determine circadian phase and amplitude, the melatonin-derived value for circadian period was integrated into an iterative mathematical analysis of the temperature data (Hiddinga et al 1997). In addition, every two hours, starting 15 minutes after the scheduled wake-up time, subjects completed a psychometric test battery.

In between the scheduled activities during wakefulness, subjects could watch videos, listen to music or perform other leisure activities according to their own preference. In the subjective morning a maximum intake of 4 caffeine containing drinks was permitted. Subjects were continuously monitored by an infra-red camera.

**Polysomnography**

In time isolation, sleep was only allowed during 7 intervals, the first of which was scheduled from 23:45 on day 4 until 08:15 on day 5. This first period for sleep functioned as habituation period and was not included in further analyses. The other periods for sleep occurred during the forced desynchrony part of the study and were subsequently scheduled between 21:45 (day 5) – 04:15 (day 6), 17:45 (day 6) – 00:15 (day 7), 13:45 (day 7) – 20:15 (day 7), 09:45 (day 8) – 16:15 (day 8), 05:45 (day 9) – 12:15 (day 9), and 01:45 (day 10) – 08:15 (day 10). Each period for sleep in time isolation was evaluated by means of polysomnography (PSG), the preparations of which were scheduled 2.25 hours before the start of the registration. Two electroencephalograms (EEG), two electrooculograms and one submental electromygram were continuously recorded (Rechtschaffen and Kales 1968). EEG signals were derived with reference to the contralateral mastoid process (C3-A2 and C4-A1). EEG signals were low-pass filtered at 25 Hz (24 dB/oct). The time constant of the preamplifier was 1 second. EEGs were sampled at 128 Hz, and EOGs and EMGs at 64 Hz. Three raters visually scored the PSGs per 30-second epoch according to the criteria of Recht-
Schaffen and Kales (1968) assisted by VitaPort software (TEMEC Instruments, Kerkrade, Netherlands). Raters displayed an average agreement with assigned scores of 95.4% (range 94.1% - 96.3%), with an average largest disagreement interval of 3 minutes (range 1.5 - 4 minutes).

**Sleep Stage Parameters**

From each registration the following sleep stage parameters were computed: total sleep time (TST), sleep latency (SL), total minutes of NREM sleep during the recording (SNREM), total minutes of REM sleep during the recording (SREM), REM latency (REML), total minutes of stage 1 (S1), stage 2 (S2) and slow wave sleep (i.e., stage 3 and 4 combined) during the recording (SWS), and intermittent wakefulness (IW). TST was calculated by adding the minutes in sleep stage 1, 2, 3, 4 and REM. SL was defined as the latency from lights-off to the first page of any sleep stage (stage 1 included). REML was obtained by computing the time asleep between sleep onset (first page of any sleep stage, including stage 1) and first page of REM sleep. Furthermore, the amount of SWS, NREM and REM expressed as a percentage of TST (SWS%; NREM%; REM%) were calculated. To compare the parameters between the various conditions regardless of possible pacemaker related influences, the data of all six periods for sleep scheduled during one forced desynchrony experiment were averaged per subject before comparing the conditions in which the subjects participated. Because the sleeping periods during the forced desynchrony experiment were scheduled across all circadian phases, the impact of the circadian pacemaker could thus practically be excluded.

**The Spectral Composition of the NREM Sleep EEG Signal**

Each 4-second epoch of all EEG signals was subjected to Fast Fourier Transformation (FFT) with a cosine-tapered window. Each subsequent epoch in the FFT analysis started 3 seconds later than the previous one to account for the loss in power due to the tapering. The epoch duration of 4 seconds leads to a spectral resolution of 0.25 Hz. The frequencies included in the analysis ranged from 0.25 to 30 Hz. Except for one sleeping period containing 90 minutes of NREM sleep, all periods for sleep included at least 120 minutes of NREM sleep. Therefore, for each PSG recording during forced desynchrony, spectral power in each 0.25 Hz frequency bin was accumulated over the first 120 minutes of NREM sleep (i.e., the stages 1, 2, 3, and 4). For the one sleeping period of shorter duration, the results were proportionally corrected. For each subject, the power spectra obtained were normalized to the individual average power spectrum across all experiments. The 6 normalized spectra were averaged per condition to obtain the best estimate of the NREM power spectrum of the individual in that condition. Subsequently, the resulting individual mean power spectra were averaged per condition and the corresponding standard errors were calculated.
The Time Course of Power in the Various EEG Frequency Bands across the First Three NREM-REM Sleep Cycles

A problem with studying the time course of EEG variables is the fact that individual recordings differ in the timing of the sleep stages. Changes in the spectral composition of the EEG signal around the transitions to and from REM sleep, for instance, can only be studied when those transitions are superimposed across nights. To study the time course of power in the various EEG frequency bands, the method described by Brunner et al (1990) was used. The average duration of the first, second and third NREM and REM episodes were calculated for each sleeping period in forced desynchrony. A histogram plotting the number of NREM episodes as a function of their duration revealed a bimodal pattern with a clear trough at a duration of 30 minutes. NREM episodes shorter than 30 minutes in duration apparently are of a different nature as compared with NREM episodes longer than 30 minutes. Therefore those few (4.8%) NREM-REM cycles which incorporated a NREM episode shorter than 30 minutes were excluded from the analysis. Out of 210 nights 165 had 3 or more NREM-REM cycles. These nights were included in the analysis of the temporal course of power in the various frequency bands. In each condition, the missing data were replaced by the average values of the subjects who did complete 3 NREM-REM cycles in the sleeping period which occurred at that time of day. On average, the first NREM-REM cycles contained 62 minutes of NREM sleep and 23 minutes of REM sleep, the second cycle had 71 minutes of NREM sleep and 22 minutes of REM sleep and the third cycle had 65 and 22 minutes NREM and REM sleep respectively. For each individual EEG recording, the various NREM and REM episodes were subsequently compressed or stretched in time to match the template defined by the average durations. This leads to synchronous transitions between NREM sleep and REM sleep in all sleeping periods. The following frequency bands were studied: the delta band from 1.0 to 4.5 Hz; the theta band from 4.75 to 7.75 Hz; the alpha band from 8.0 to 11.75 Hz, the sigma band from 12.0 to 14.75 Hz and the beta band from 15.0 to 19.75 Hz. Since the relative power spectra are investigated separately, this analysis focuses on the time course of the signals. Therefore, for each night, the power in a certain frequency band on a certain moment was expressed relative to the average power in that band of the three NREM REM cycles of that recording.

Statistical Analysis

To reveal possible differences in sleep stage parameters between the various conditions in which SAD patients and controls participated, the following comparisons were made: (1) depressed patients versus themselves in the remitted state, (2) depressed patients versus themselves in summer, (3) remitted patients versus themselves in summer, (4) depressed patients versus controls in winter, (5) remitted patients versus controls in winter, (6) patients in summer versus controls in summer.
These comparisons were evaluated by means of two-tailed paired \( t \) tests. Significance was accepted at \( p < .05 \). Data on the spectral composition of the EEG were evaluated by means of sign tests.

## RESULTS

### Sleep Parameters Averaged across Circadian Phase

For each condition, the average values for the various sleep parameters are listed in Table 5.2. Paired \( t \) tests did not reveal significant differences neither between groups nor between the various conditions in which patients and controls participated in any

<table>
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<th>SAD patients</th>
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<td>depressed ( n = 7 )</td>
<td>remitted ( n = 7 )</td>
<td>summer ( n = 7 )</td>
</tr>
<tr>
<td>SL</td>
<td>10.0±0.9</td>
<td>8.5±1.4</td>
<td>9.1±1.5</td>
</tr>
<tr>
<td>REML</td>
<td>53.3±5.8</td>
<td>54.0±6.3</td>
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<tr>
<td>IW</td>
<td>41.5±11.7</td>
<td>36.6±12.4</td>
<td>34.1±10.6</td>
</tr>
<tr>
<td>S1</td>
<td>18.7±2.9</td>
<td>20.9±3.0</td>
<td>19.5±2.6</td>
</tr>
<tr>
<td>S2</td>
<td>135.6±11.6</td>
<td>144.7±10.3</td>
<td>147.2±9.2</td>
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<tr>
<td>SWS</td>
<td>88.0±14.8</td>
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<td>SREM</td>
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<tr>
<td>TST</td>
<td>324.1±18.6</td>
<td>330.7±13.8</td>
<td>334.2±11.7</td>
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<tr>
<td>SWS%</td>
<td>27.6±3.9</td>
<td>26.5±3.4</td>
<td>26.2±3.5</td>
</tr>
<tr>
<td>NREM%</td>
<td>75.6±1.6</td>
<td>76.5±1.2</td>
<td>76.1±1.1</td>
</tr>
<tr>
<td>REM%</td>
<td>24.1±1.5</td>
<td>23.3±1.2</td>
<td>23.7±1.2</td>
</tr>
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</table>
of these parameters (SL: $p = .413$; IW: $p = .100$; SWS: $p = .624$; SNREM: $p = .111$; SREM: $p = .205$; TST: $p = .391$; SWS%: $p = .370$; NREM%: $p = .241$; REM%: $p = .116$; REML: $p = .210$; S1: $p = .127$ and S2: $p = .092$). Patients exhibited shorter average REM latencies than controls in every condition. However, these differences were not significant. To test whether short REM latencies were more frequent in patients than in controls, the REM latencies obtained from each period for sleep in forced desynchrony were grouped in 10-minute bins. The distribution of the binned REM latencies showed two peaks separated by a trough at the 30-minute bin. Therefore, REM latencies were considered short when their duration was less than 30 minutes. Again, paired $t$ tests did not reveal significant differences in the prevalence of short REM latencies between patients and controls ($p = .182$), nor between the separate conditions in which they participated ($p = .078$).

**The Spectral Composition of the NREM Sleep EEG Signal**

For each condition, the log-transformed average power spectra of the first 120 minutes of NREM sleep are plotted in Figure 5.1. Except for the 5.75 – 12.5 Hz frequency range (i.e., the theta-alpha band), the average power spectra are remarkably similar in the various groups and conditions. In the control group, comparison of the mean power spectra in winter with those obtained in summer revealed no significant differences. Therefore, the winter and summer spectra of controls were averaged. Plots of the mean power spectra of patients in the depressed, remitted and summer condition relative to the average control spectrum showed that in each condition patients manifested twice as much power than controls in the theta-alpha band. This was due to the contribution of two patients who consistently exhibited power densities in the theta-alpha band far above average. Therefore, the large inter-patient differences are the reason that the differences observed in the average power spectra are not significant.

**Time Course of Power in the Various EEG Frequency Bands across the First Three NREM-REM Sleep Cycles**

Figure 5.2 depicts the time course of the power in (A) the delta band, (B) the theta band, (C) the alpha band, (D) the sigma band and (E) the beta band across the first three NREM-REM cycles for each condition. In each condition in which the subjects participated, the course of the various frequency bands show a robust rhythmicity. Both delta or slow wave activity (SWA) and theta activity exhibit an increase at the start and a sharp decrease just before the end of each NREM episode with an overall declining trend across the consecutive NREM-REM cycles (Figure 5.2A and 5.2B). Similarly, the curves representing the alpha and sigma activity rise towards a peak value at the start of the NREM episode and gradually decline thereafter (Figure 5.2C and 5.2D). Each time at the start of the REM episode, the amounts of alpha and sigma activity decrease even more and reach their lowest values at the end of the
Figure 5.1 Power spectra (mean ± SEM) obtained in Seasonal Affective Disorder (SAD) patients and healthy matched controls subjected to a 120-hour forced desynchrony experiment in which six 6.5-hour periods for sleep scanned through all circadian phases. SAD patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer. For the first 120 minutes of NREM sleep (stages 1, 2, 3 and 4 combined), the power in each 0.25 Hz frequency bin was calculated by means of Fast Fourier Transformation. The power spectra were normalized to the individual average total power across all experiments. For each subject, the 6 normalized spectra were averaged per condition to obtain the best estimate of the NREM power spectrum in that condition. Subsequently, the resulting individual mean power spectra were averaged per condition and plotted on a logarithmic scale.
Figure 5.2 Time course (mean ± SEM) of activity in (A) the delta (1.0-4.5 Hz; slow wave activity (SWA)) band, (B) the theta (4.75-7.75 Hz) band, (C) the alpha (8.0-11.75 Hz) band, (D) the sigma (12.0-14.75 Hz) band, and (E) the beta (15.0-19.75 Hz) band in the first three NREM-REM cycles obtained in Seasonal Affective Disorder (SAD) patients and healthy matched controls participating in a 120-hour forced desynchrony protocol. Per subject, six polysomnographic recordings were made during each experiment. Patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer. Powers within the various frequency bands were calculated for the first three NREM-REM cycles occurring during each scheduled sleeping period. The NREM-REM cycles were normalized to the average duration of each NREM- and REM episode, i.e., the NREM- and REM episodes were either stretched or compressed in time. The powers were normalized to the average power of the respective recording and subsequently averaged across each experiment and each condition.
respective episode. Furthermore, in most of the NREM episodes, the alpha activity shows an initial decline before rising, whereas the sigma activity demonstrates a temporary increase at the end of the episode. Finally, the beta activity (Figure 5.2E) exhibits a sharp diminution at the start of the NREM episode and a subsequent small rise towards the end of the episode. During the following REM episode, the beta activity drops again. Like the absolute power spectra, the curves representing the average time course of the various frequency bands appear to be similar in both groups. To detect possible differences between conditions, the same procedure as used in the evaluation of the absolute power spectra was applied. For each frequency band no
systematic differences were found when the results of controls in winter were compared with those obtained in summer. Therefore, for each condition in which patients participated, the individual average course of each frequency band was expressed as a percentage of the winter-summer average of controls. Sign tests revealed no significant differences between patients and controls in almost all time bins. The only consistent difference observed is the slightly slower increase of delta power in the second NREM episode in the patients, in particular in winter. Obviously, this difference may be a chance observation, given the large number of tests performed.

Figure 5.2C
Figure 5.2D
Figure 5.2E
DISCUSSION

Sleep is regulated by homeostatic, ultradian and circadian mechanisms. The present study focused on the exploration of the homeostatic and ultradian aspects of sleep in Seasonal Affective Disorder (SAD) patients and healthy matched controls.

Although data were collected in a relatively small number of subjects, the design of the present study provides some major advantages over the previous studies of sleep in SAD. First, the study was designed in such a way that the influences of prior wakefulness and circadian phase could be minimized. Secondly, for each condition in which a subject participated, polysomnographic data were averaged across 6 recordings. Thereby, an accurate estimate of the individual’s sleep characteristics was achieved. To the best of our knowledge, this is the first time in which sleep of SAD patients was studied in a forced desynchrony protocol.

Like the majority of SAD patients (Rosenthal et al 1984; Anderson et al 1994), 6 out of 7 patients in the present study reported to be hypersomnic during their depressive episode. Nevertheless, the comparisons between the various conditions in which patients and controls were studied did not reveal abnormalities in the sleep stage parameters, the power spectra and time course of power in various frequency bands across the first three NREM-REM cycles. Similar to the finding of Brunner et al (1996), the results of the present study suggest that in SAD the regulation of sleep is not affected. This absence of polysomnographical recorded sleep abnormalities is in contrast with the findings in most previous studies of sleep in SAD (Rosenthal et al 1984, 1985, 1989, Endo et al 1992, 1993; Kohsaka et al 1994; Anderson et al 1994, Palchikov et al 1997; Schwartz et al 2000). However, these studies have not provided a clear picture of sleep in SAD. In some studies unrestricted sleep was allowed, whereas in others sleep was restricted within certain times of the day. Because both prior wakefulness and circadian phase influence sleep, differences in sleep timing might be a confounding factor. It is conceivable that the discrepancies between our results and those of other studies are partly due to the differences in design. Furthermore, the scheduled sleep timing before the start of the experiment and the criteria for selecting the control group may also account for discrepancies in results. It is known that some of the sleep stage parameters and EEG characteristics vary with age, sex, or menstrual cycle phase (Dijk et al 1999; Dijk et al 1989; Driver et al 1997). Therefore, in the present study patients and healthy controls were matched for age and sex. Moreover, the pre-menopausal female subjects were matched for the menstrual cycle phase and were studied in the same phase of their menstrual cycle if possible. Only two of the previous studies of sleep in SAD patients and controls compared groups that were
matched for all these characteristics (Brunner et al 1996; Schwartz et al 2000).

The data regarding the time course of the various EEG frequency bands during the first three NREM-REM cycles are in accordance with data obtained in studies of polysomnographical recorded sleep in healthy subjects. Slow wave activity (SWA) recorded under baseline conditions has been found to decline during sleep (Brunner et al 1990; Achermann et al 1993; Werth et al 1997; Schwartz et al 2000). Similarly, in forced desynchrony studies SWA has been found to show a sleep-dependent decrease (Dijk and Czeisler 1995; Wyatt et al 1999). Schwartz et al (2000) reported that, when age and habitual sleep length are taken into account, SAD patients on average exhibit significantly more SWA per minute of NREM sleep than controls. In the present study absolute SWA values were not analyzed. Generally, subjects differ substantially in absolute SWA. Hence, a relatively large number of subjects is required to allow discrimination between SAD patients and controls in this respect.

To conclude, the present study of homeostatic and ultradian aspects of sleep did not reveal differences between SAD patients and controls. Therefore, the results do not support the hypotheses concerning the involvement of process S in the pathogenesis of (seasonal) affective disorder.

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