EEG and Subjective Sleepiness during Extended Wakefulness in Seasonal Affective Disorder: Circadian and Homeostatic Influences

Christian Cajochen, Daniel P. Brunner, Kurt Kräuchi, Peter Graw, and Anna Wirz-Justice

Background: *Seasonal affective disorder (SAD) may reflect a disturbance of circadian phase relationships or a disturbance of sleep–wake dependent processes, both of which change daytime energy and sleepiness levels.*

Methods: *Under the unmasking conditions of a 40-hour constant routine protocol (CR), self-rated sleepiness and waking electroencephalogram (EEG) power density were assessed in women with SAD (n = 8) and in age-matched healthy control subjects (n = 9).*

Results: *There was no significant effect of season or light treatment in any of the measures. The time course of subjective sleepiness was characterized by a circadian modulation and an overall increase during extended wakefulness in both SAD patients and control subjects. A prominent circadian rhythm of subjective sleepiness was not different in SAD patients and control subjects; however, the progressive buildup of sleepiness, as quantified by nonlinear regression analysis, was significantly reduced in SAD patients, mainly because they were sleepier than control subjects during the first 12 hours of the CR. The time course of waking EEG theta-alpha activity showed a more rapid increase during the first 10 hours of the CR in SAD patients. In contrast to control subjects who showed a progressive increase in the course of the 40-hour episode of extended wakefulness, EEG theta-alpha activity in SAD patients did not further increase over the remainder of the CR.*

Conclusions: *The data suggest that SAD patients may have a trait (rather than state) deficiency in the homeostatic buildup of sleep pressure during extended wakefulness as indexed by subjective sleepiness and EEG theta-alpha activity.* Biol Psychiatry 2000;47:610–617 © 2000 Society of Biological Psychiatry

The winter recurrence of depressive episodes in patients suffering from seasonal affective disorder (SAD) has been linked to abnormalities in the regulation of biological rhythms (for a review see Wirz-Justice 1995). Treatment of SAD patients with light, the major synchronizer of human circadian rhythms, results in a rapid improvement of their depressive symptoms (for a review see Partonen and Lönqvist 1998). Recent studies confirm that the beneficial effects of light treatment in SAD patients are greater than with placebo (Eastman et al 1998; Terman et al 1998b). In addition, whereas SAD patients improve during sleep deprivation (Graw et al 1998), as do patients with other depressive syndromes, they show a more robust and stable improvement after light treatment (Wirz-Justice et al 1995).

The underlying mechanisms of these treatments (i.e., light exposure and sleep deprivation) and their relation to the pathophysiology of SAD are still unclear. It has been hypothesized that SAD may reflect a disturbance of circadian phase relationships, such as a phase delay (Lewy et al 1987), reduced amplitude (Czeisler et al 1987), or a disturbance of a sleep–wake-dependent process (i.e., S-deficiency; Borbély and Wirz-Justice 1982), or SAD may result from a complex interaction of circadian and sleep–wake cycle-dependent processes (Koorengevel et al 2000; for a review see Wirz-Justice 1995).

Recent data in healthy subjects (Boivin et al 1997; Van den Hoofdakker 1997) imply that mood state is modulated as a function of simultaneous changes in circadian phase and prior sleep–wake history. Therefore even moderate changes in the timing of the sleep–wake cycle may have profound effects on mood. A number of studies have investigated whether sleep times, sleep structure, and sleep electroencephalogram (EEG) in depressed SAD patients differ from those of control subjects. None found the typical pattern of EEG changes characterizing sleep in

major depression, nor did they report consistent or large effects on sleep duration (Anderson et al 1994; Brunner et al 1996; Palchikov et al 1997). One previous study has addressed the question of whether sleep regulatory mechanisms are altered in SAD patients (Brunner et al 1996). Sleep deprivation, which activates sleep regulatory mechanisms by extending wakefulness from 16 to 40 hours resulted in a similar increase of low frequency EEG activity during recovery sleep in both SAD patients and control subjects (Brunner et al 1996); however, detailed time course analysis of EEG slow wave activity (SWA) during sleep has not yet been performed.

Whereas changes in sleep regulation and sleep structure have been difficult to demonstrate in SAD patients, altered daytime energy, fatigue, sleepiness, and activity levels are associated with depressive symptoms (Meesters et al 1993; Terman et al 1998a). Moreover, these changes may be correlated with a deficiency in the homeostatic buildup of Process S as suggested by Borbély and Wirz-Justice (1982) for depressive patients. Recent reports indicate that the increase in EEG power density in the theta-alpha frequencies accumulating during extended wakefulness may be associated with a homeostatic buildup of sleepiness (Cajochen et al 1995, 1999). Therefore, EEG recorded during extended wakefulness from the same SAD patients as reported by Brunner et al (1996) were analyzed across the 40-hour constant routine (CR) and compared with the time course of self-rated sleepiness. It was hypothesized that the daytime increase of sleep propensity is different in SAD patients as compared to control subjects, and that this difference is reflected in an altered time course of EEG activity and of subjective sleepiness during extended wakefulness.

Methods and Materials

Subjects and Study Design

Eight women (48.8 ± 13.1 years of age [SD], range 27–66) diagnosed with SAD, with unipolar major depression (DSM-III-R; American Psychiatric Association 1987), were mildly depressed in winter (Hamilton Depression rating [Hamilton 1967] 13.4 ± 3.0), improved after light therapy (3.3 ± 2.0), and were asymptomatic in summer. None of the nine matched healthy women (52.7 ± 12.9 years of age [SD], range 24–66) experienced seasonality or reported a history of depression. Body mass index and demographic variables were not significantly different between the two groups. Premenopausal women entered the study between the first and fourth day of their menstrual cycle in order to complete the entire experiment within the follicular phase. All subjects were nonsmokers, free of medication, including contraceptives, and underwent a medical examination prior to the study. A 3-month period free of shift work, time zone travels, and antidepressant medication was required. All subjects were requested to refrain from alcohol and caffeine

for the 10 days of the experiment and to reduce the consumption of such beverages in the week prior to the study. Subjects were asked to keep their habitual bedtimes constant for the duration of the entire study. They kept a detailed sleep diary and wore actometers on the nondominant wrist for 1 week before, during, and after the experiment, to document compliance to the above instructions.

The experiment lasted for 10 days and included two pairs of nightly sleep recordings separated by 5 days of light treatment (10 AM to 2 PM; 6000 lux) in summer and winter. Immediately before and after the 5 days of light treatment, the subjects underwent two identical 40-hour CRs in both winter and summer (four CRs in total).

EEG Recordings and Data Analysis

Throughout the CR, half-hourly self-ratings of sleepiness were obtained on 100 mm visual analogue scales. During each of the four CR protocols, the waking EEG signal was recorded after 3 hours (day 1 at 10:00 hours), 10 hours (day 1 at 17:00 hours), 27 hours (day 2 at 10:00 hours), 34 hours (day 2 at 17:00 hours) and after 40 hours (day 2 at 22:30 hours) of wakefulness. The last recording took place immediately before the start of recovery sleep. Since subjects were aroused by the ongoing preparations for the sleep recording and by the approaching end of sleep deprivation, the conditions during the last waking EEG recording clearly differed from the four recordings on the CR protocol. This last recording was therefore excluded from the analysis. This number of EEG recordings is sufficient to explore homeostatic influences on the EEG during extended wakefulness. Each recording lasted for 4 minutes, during which the subjects were instructed to relax, to watch a small picture on the wall, to keep their eyes open and to avoid movement. These instructions were intended to maximize signal quality. Throughout the CR protocol, subjects were sitting in bed in a propped-up body position (45° angle) under dim light conditions (<80 lux). They were kept awake by a technician, who was constantly with the subject and enforced adherence to the stringently timed procedures of the CR protocol (for protocol details see Brunner et al 1996). In order to ensure wakefulness the subjects were not allowed to close their eyes at any time during the CR protocol. During the entire 4-min episode of an EEG recording, an experimenter was in the bedroom with the subject in order to control wakefulness and proper execution of the task. At incipient behavioral signs of sleep (lowering of eyelids, drowsiness, gazing, or rolling eyes) the instructions were repeated or the subject was verbally entertained. During these 4-min episodes, one EEG signal (C3-A2), two electro-oculogram signals, and one electromyogram and electrocardiogram signal were recorded on polygraph paper (Nihon Kohden; 10mm/sec paper speed). The EEG signal was high-pass filtered with a time constant of 1.0 seconds and low-pass filtered at 35 Hz (12 dB/octave), on-line digitized at a sampling rate of 128 Hz, and subjected to spectral analysis by a fast Fourier routine. Power spectra were computed for consecutive 4-sec epochs and 0.25 Hz frequency bins by applying a Kaiser-Bessel window.

By computing the mean values over adjacent frequencies, the data were reduced to 0.5 Hz bin width for frequencies between 0.25

and 5.0 Hz, and to 1 Hz bin width for frequencies between 5.25 and 25.0 Hz. Bins are referred to and plotted by the highest frequency included (e.g., the 2.5 Hz bin refers to the averaged values of 2.25 and 2.5 Hz; the 6 Hz bin refers to the averaged values of 5.25, 5.5, 5.75, and 6.0 Hz). In connection with the on-line calculation of the 4-sec spectra, a time mark was written on the polygraph paper in 4-sec intervals in order to allow synchronization of EEG spectra and paper recording. All records of waking EEG were visually inspected on a 4-sec basis. Four-second epochs with eye blinks or artifacts due to body movements, slow eye movements, and sweating were excluded from subsequent analyses.

Statistics

For statistical analyses the statistical package SAS (SAS Institute Inc., Cary, NC, Version 6.12) was used. Absolute EEG power densities in the frequency range of 1.0–25 Hz were log-transformed within each subject. Subjective sleepiness ratings (VAS) were binned in 30-min, 1-hour or 2-hour intervals; averaged within these intervals per subject and then averaged over subjects (SAD patients and control subjects separately).

If no consistent significant effects of *season* (winter vs. summer) and *light therapy* (before and after light therapy) were found, data were averaged within subjects. Two-way analyses of variance for repeated measures (rANOVA) with the repeated factor *elapsed time awake* and the nominal factor *group* (SAD vs. control subjects) were performed for each variable separately. All p values derived from rANOVAs were based on Huynh-Feldt's (H-F) corrected degrees of freedom, but the original degrees of freedom are reported. The least significant difference (LSD) test for planned comparisons or the unpaired t test was used for post-hoc comparisons.

Changes in subjective sleepiness ratings during a 40-hour CR reflect circadian and homeostatic influences. The circadian modulation can be modeled by applying a sinusoidal function (24-hour component) with its first harmonic, whereas the homeostatic component is usually fitted by an exponential or linear function (Jewett 1997). In the present report, we used a sinusoidal function comprising the fundamental oscillation and its first harmonic for the circadian component and a linear function for the homeostatic component. Nonlinear regression analysis was performed on z-transformed sleepiness ratings for each subject separately using the function: $f(t) = A + B \times t + C \times \sin(t \times 2\pi/t_{24} - \phi_{24}) + D \times \sin(t \times 2\pi/2 \times t_{24} - \phi_{12})$.

The time course of EEG theta-alpha activity during extended wakefulness was fitted with a nonlinear regression analysis using the exponential function: $f(t) = S_{max} - (S_{max} - f(0)) \times e^{-t/18.18}$ for each subject separately. This was based on the assumption that the buildup of theta/alpha power in the waking EEG across wakefulness follows an exponential function analogous to that of sleep propensity, which is conceptualized in the two-process model of sleep regulation as Process S (Daan et al 1994). Parameter estimates were performed according to the Gauss-Newton method.

Results

Subjective Sleepiness (VAS)

Subjective sleepiness ratings as assessed on the VAS were analyzed with a three-way rANOVA with the factors
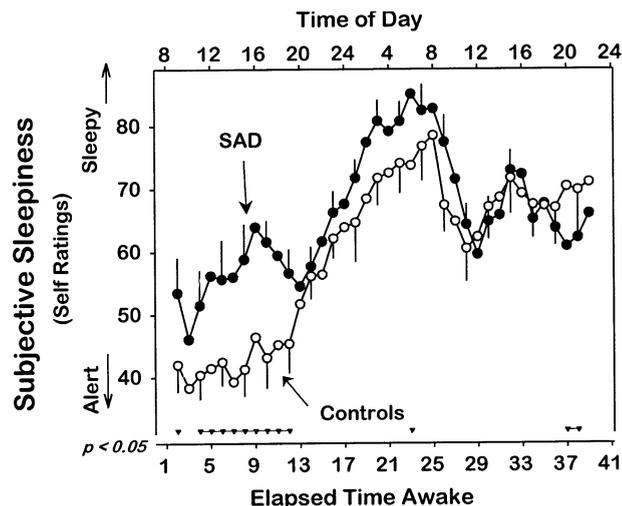

Figure 1. Time course of subjective sleepiness ratings as assessed on a visual analogue scale (VAS) during extended wakefulness in seasonal affective disorder (SAD) patients ($n = 8$, filled symbols) and control subjects ($n = 9$, open symbols). Hourly mean values $\pm$ 1 SEM. Triangles near the abscissa indicate significant differences between SAD and control subjects ($p < .05$, least significant difference test). Higher numbers indicate greater sleepiness.

season, *light treatment*, and *elapsed time awake* for SAD patients and control subjects separately. Surprisingly, unlike the VAS for mood (Wirz-Justice et al 1995), there was no significant effect on sleepiness of *season*, *light treatment* or interaction between these two factors in either the SAD patients or control subjects ($p > .2$, in all cases). Therefore, data were averaged within subjects.

Subjective sleepiness ratings for SAD patients and control subjects during the 40-hour CR protocol are illustrated in Figure 1. A two-way rANOVA with the factors *group* (SAD vs. control subjects) and *elapsed time awake* revealed a significant effect for the factor *elapsed time awake* ($F_{73, 1095} = 18.3; p < .001$, on 30-min binned values) and the interaction *group* $\times$ *elapsed time awake* ($F_{73, 1095} = 2.2; p < .04$). SAD patients rated their sleepiness significantly higher than control subjects during the first 12 hours of the CR (see line above the abscissa in Figure 1). In addition, on the second day of the CR, SAD had a significantly higher value at hour 23 and significantly lower values during the hours 37 to 38 ($p < .05$, post-hoc comparisons; LSD test).

By applying nonlinear regression analysis, the underlying rhythmic and linear components in the time course of subjective sleepiness were quantified (Figure 2). Sleepiness was quantified for each subject separately by fitting a sinusoidal function comprising a linear component, a fundamental oscillation and its first harmonic (see methods section). The mean time course of the fitted sleepiness curves are shown for SAD patients and control subjects in
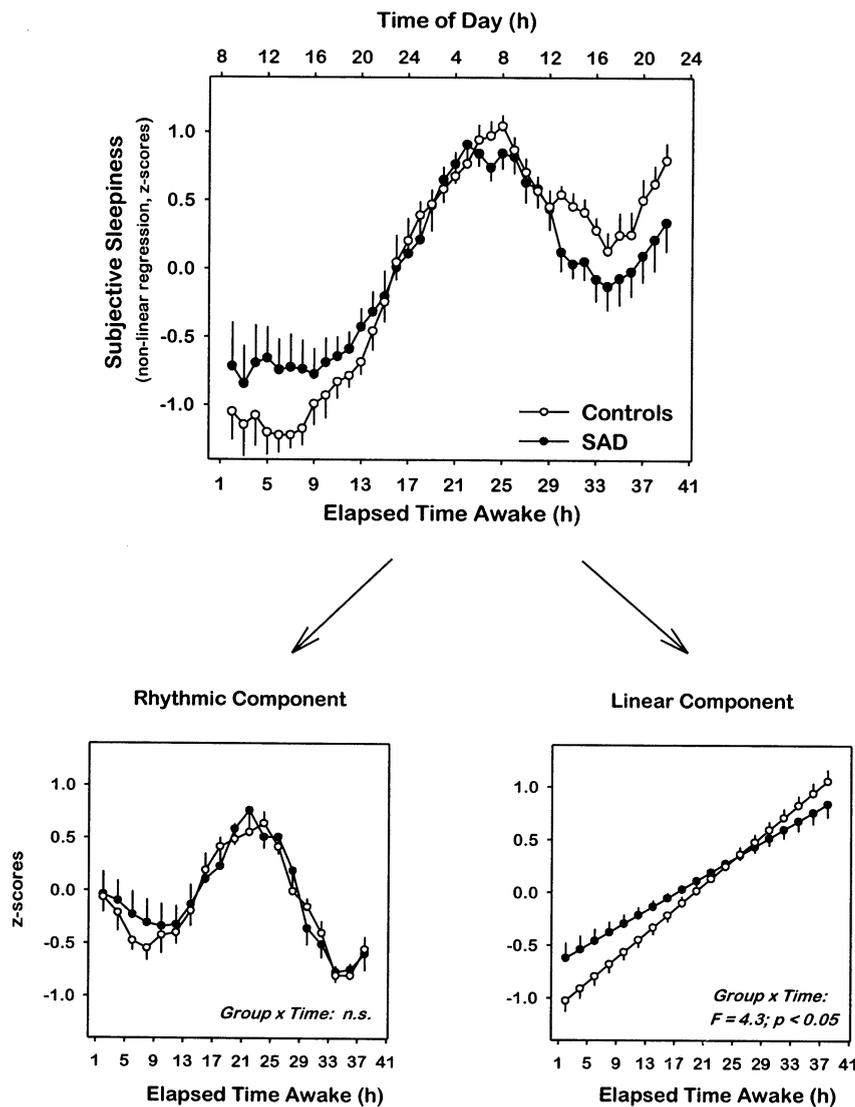
Time of Day (h)

Figure 2. Top panel: Time course of fitted z-transformed sleepiness ratings in seasonal affective disorders (SAD) patients ($n = 8$, filled symbols) and control subjects ($n = 9$, open symbols; mean hourly values $\pm$ 1 SEM). For nonlinear regression analysis see methods section. Bottom panel, left: Time course of the extracted rhythmic component in SAD and control subjects. The interaction *group* (SAD vs. control subjects) $\times$ *elapsed time awake* was not significant (see text; mean 2-hourly values $\pm$ 1 SEM). Bottom panel, right: Time course of the extracted linear component in SAD and control subjects. The interaction *group* (SAD vs. control subjects) $\times$ *elapsed time awake* was significant (see text; mean 2-hourly values $\pm$ 1 SEM). Higher numbers indicate greater sleepiness.

Figure 2 (first panel). For statistical analysis the fitted rhythmic component (Figure 2, bottom left panel) and the fitted linear component (Figure 2, bottom right panel) were subjected to a two-way rANOVA with the factors *group* and *elapsed time awake*. For the rhythmic component no significant differences were found between SAD and control subjects (factor *group*; $p > .2$, *group* $\times$ *elapsed time awake*: $p > .5$), whereas the factor *elapsed time awake* yielded significance ($F_{18,270} = 11.3$; $p < .001$, on 2-hour binned values); however, the same statistical analysis for the linear component (Figure 2, bottom right panel) revealed a significant interaction *group* $\times$ *elapsed time awake* ($F_{18,\ 270} = 4.3$; $p < .05$). In addition, the slopes of the lines were significantly different between SAD and control subjects ($p < .03$, unpaired t test).

EEG during Wakefulness

EEG power density in each frequency bin was analyzed with a three-way rANOVA with the factor *season, light treatment* and *elapsed time awake* for SAD patients and control subjects separately. Again, there was no consistent significant effect of *season, light treatment,* or interaction between these two factors in either the SAD patients or control subjects ($p > .2$, in all cases). Therefore, data were averaged within subjects.

Figure 3 illustrates waking EEG power spectra recorded after 3, 10, 27, and 34 hours of elapsed time awake. A two-way rANOVA revealed a significant factor *group* and *elapsed time awake* for EEG power density (log transformed) in the following frequency bins: 6.25–7, 7.25–8, 8.25–9 Hz (p at least $< .03$). Post-hoc comparisons
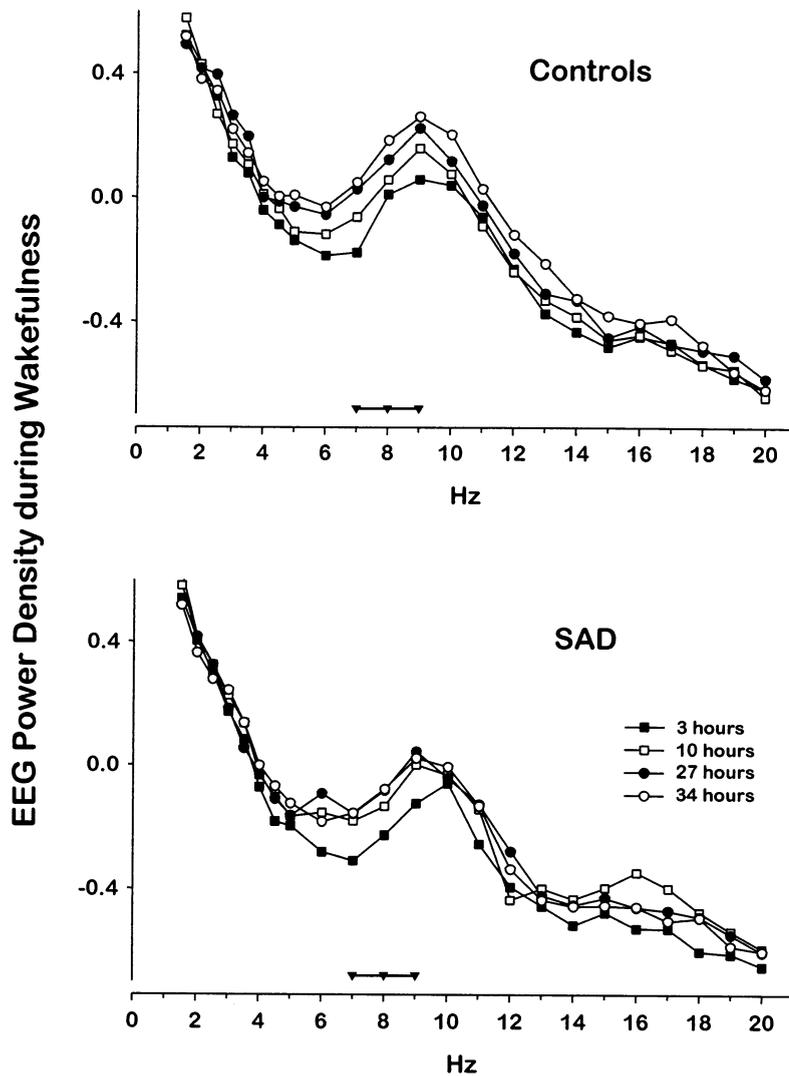
Figure 3. Electroencephalogram power density (μV^2/Hz, log transformed) in single frequency bins (1.5–20 Hz) recorded after 3, 10, 27, and 34 hours of elapsed time awake for seasonal affective disorder patients ($n = 8$) and control subjects ($n = 9$). Triangles above the abscissa indicate frequency bins for which significant changes over time were present.

revealed significantly lower values in SAD patients as compared to control subjects ($p < .05$, LSD test).

EEG theta-alpha activity (EEG power density in the 6.25–9 Hz range) exhibited a progressive increase during extended wakefulness in control subjects (Figure 4, first panel). This time course could be closely fitted by an exponential curve (see methods section). In SAD patients the temporal evolution of EEG theta-alpha activity during extended wakefulness was different than in control subjects and the values were lower at all times. The same exponential fitting procedure as used for the control subjects resulted in a poorer fit for the SAD patients (Figure 4, first panel). For statistical analysis, theta-alpha activity was expressed as a percentage of the EEG recorded after 5 hours of elapsed time awake for each subject in each group (Figure 4, bottom panels). A one-way rANOVA for each group

separately revealed a significant time effect (factor: *elapsed time awake*: SAD: $F_{3,18} = 4.7$; $p < .03$; control subjects: $F_{3,24} = 5.0$; $p < .02$). The progressive increase in EEG theta-alpha activity in control subjects was validated by post-hoc analyses, which showed significantly higher theta-alpha activity in the EEG after 27 hours and 34 hours versus the EEG after 3 hours (Figure 4, bottom left panel). In addition, theta-alpha activity in the EEG after 34 hours was also significantly higher when compared with the EEG after 10 hours ($p < .03$ at least, for all comparisons, LSD test). In contrast, in SAD patients only the theta-alpha activity after 3 hours was significantly lower when compared to the EEG after 10, 27, and 34 hours (Figure 4, bottom right panel). After 10 hours of elapsed time awake no significant further increase in EEG theta-alpha activity could be observed in SAD patients ($p > .2$).
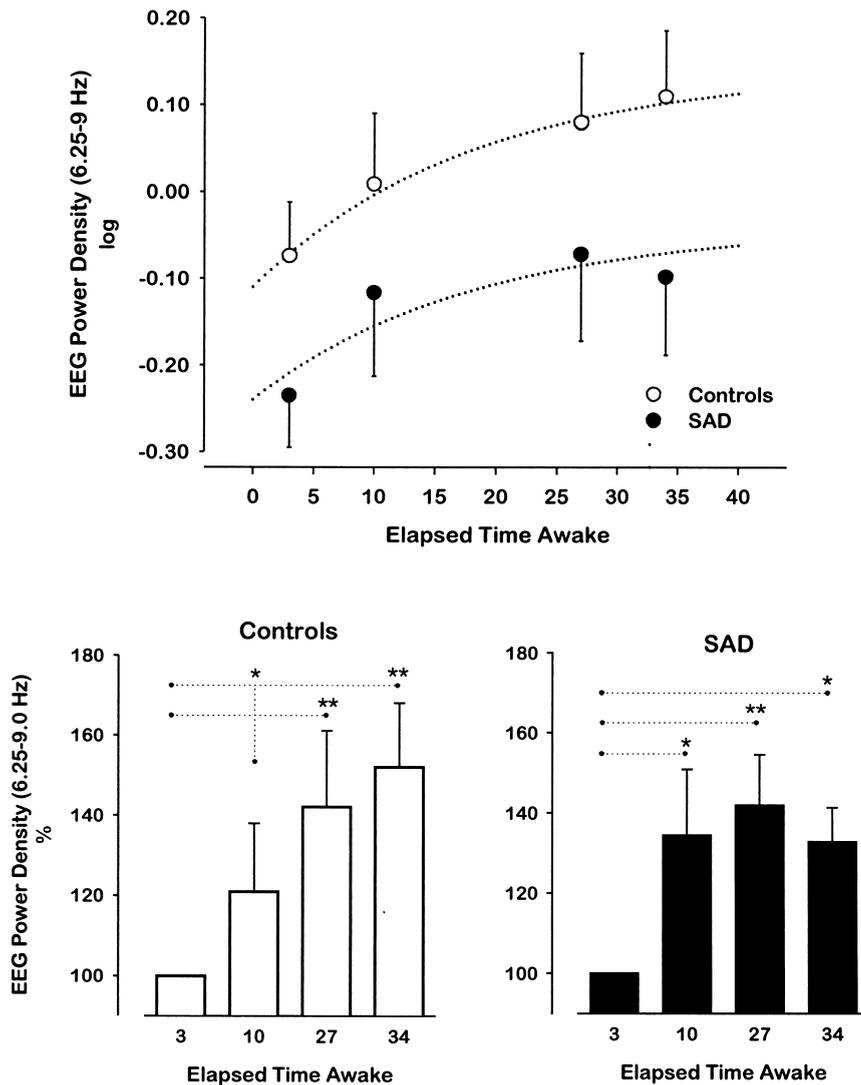
Figure 4. Top panel: Time course of electroencephalogram (EEG) theta-alpha activity (6.25–9.0 Hz, log transformed) during extended wakefulness in seasonal affective disorder (SAD) patients ($n = 8$, filled symbols) and control subjects ($n = 9$, open symbols; mean hourly values $\pm$ 1 SEM). Stippled lines indicate the fitted exponential function for SAD and control subjects (for details see text). Bottom panels: Theta-alpha activity during extended wakefulness expressed as a percentage of EEG activity (6.25–9.0 Hz) after 3 hours of elapsed time awake in SAD (right) and control subjects (left). Mean values + 1 SEM. Asterisks and stippled lines indicate significant differences (** $p < .002$; * $p < .03$; least significant difference test).

Discussion

The present data indicate that the overall level of EEG theta-alpha activity during sustained wakefulness is lower in SAD patients in comparison with control subjects, but the relative increase is more rapid. Paradoxically, this suggests that their arousal level is higher than in control subjects, in spite of being sleepier and attaining maximal EEG theta-alpha activity already during the first 12 hours of the CR protocol. How much do these changes in SAD patients reflect a disturbance of circadian rhythms or a disturbance of sleep–wake dependent processes?

Circadian Component

Extending the widely supported concept that two processes govern the mammalian sleep–wake cycle (Daan et al 1984), Edgar et al (1993) proposed that the sleep–wake

cycle results from the opponent interaction of suprachiasmatic nuclei (SCN)-dependent alerting and homeostatic sleep drive. As SCN-dependent alerting increases to high levels late in the day, a *forbidden zone for sleep* or *wake maintenance zone* occurs (Lavie 1986; Strogatz et al 1987). In the present data, the interaction of these two hypothetical processes is clearly reflected in the time course of subjective sleepiness. Although SAD patients had higher sleepiness values during the first 12 hours of the CR, sleepiness decreased at the time of the wake-maintenance zone, reaching the same levels as seen in the control subjects. This indicates that the circadian SCN-dependent alerting effect was intact in our SAD patients. In addition, the circadian component of subjective sleepiness was similar in SAD patients and control subjects. This is in accordance with other variables, such as the circadian rhythms of core body temperature and salivary

melatonin measured during the same CR that did not show any significant difference between control subjects and SAD patients (Wirz-Justice et al 1995). Taken together, it seems that there were no significant changes in either phase or amplitude of the circadian rhythm in the SAD patients.

Homeostatic Component

It is widely accepted that the output of the human circadian pacemaker can be measured under the unmasking conditions of a constant routine protocol, which represents the gold standard. In contrast, such a standard for the assessment of the homeostatic drive for sleep pressure during wakefulness does not exist. However, computerized analysis of the EEG during sleep have demonstrated that the power of low frequency (0.75–7.0 Hz) components declines across the sleep episode and increases with the duration of wakefulness preceding sleep (Borbély et al 1981; Dijk et al 1987). More recent data indicate that low-frequency activity in the EEG during extended wakefulness, particularly in frontal areas, is primarily determined by a homeostatic process (Cajochen et al 1999). This exponential rise in EEG theta-alpha activity with time awake, as clearly seen in the control women, may therefore represent the waking EEG correlate of a validated measure of the homeostatic drive for sleep. SAD patients showed lower theta-alpha activity than control subjects in the waking EEG throughout the CR. In addition, the relative increase in theta-alpha activity after 34 hours of wakefulness was lower in SAD patients (33%) than in control subjects (52%). The latter could imply that the increase in SWA and slow wave sleep (SWS) during the subsequent recovery sleep episode might be smaller in SAD patients than in control subjects; however, SWS levels during sleep in the same SAD patients have been reported not significantly different from control subjects (Brunner et al 1996). Since others have reported lower SWS values in the sleep EEG of SAD patients (Anderson et al 1996; Palchikov et al 1997), our rather poor-sleeping control group (Brunner et al 1996) may have biased these findings. If one focuses on the first 12 hours of the CR protocol as exhibiting the most significant differences between SAD patients and control subjects, we find a close parallel between the linear component underlying the buildup of sleepiness and the relative rate of buildup of EEG theta-alpha activity. Taken together, the present data indicate a change in the homeostatic buildup of sleep drive during extended wakefulness in SAD patients. Given that the data are drawn from averages over season and light treatment, they suggest a trait-dependent homeostatic abnormality in patients with SAD.

It is important to note another difference between patients with SAD and control subjects: the progressive antidepressant effect of sleep deprivation in the former and mood deterioration in the latter (Graw et al 1998; Wirz-Justice 1995; Wirz-Justice et al 1995). One could argue that this mood amelioration counteracted the increase in sleepiness. Yet both SAD patients and control subjects showed identical changes in sleepiness on the second day of the CR, quite different from their mood ratings. This provides further validation for the assumption that individuals can indeed well differentiate when rating their mood or sleepiness. It is now known that many such self-ratings are dependent on nonadditive circadian and sleep–wake dependent processes, but that the time course of each component and their relative importance differs for each item (Boivin et al 1997; Dijk et al 1992; Koorengevel et al 2000).

Conclusions

In summary, our data indicate that in comparison to control subjects, patients with SAD manifest a state-independent deficiency in the homeostatic buildup of theta-alpha frequencies during extended wakefulness that is not reflected in their homeostatic sleep regulation. They do not show differences in circadian phase or amplitude. When analyzed as relative values, SAD patients show a faster buildup of theta-alpha activity in the EEG during the first 12 hours of the wake episode, concomitant with higher sleepiness.

References

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders*, 3rd rev. ed. Washington, DC.

Anderson Jl, Rosen LN, Mendelson WB, Jacobson FM, Skwerer RG, Joseph-Vanderpool JR, et al (1994): Sleep in fall/winter seasonal affective disorder: Effects of light and changing season. *J Psychosom Res* 38:323–337.

Boivin DB, Czeisler C, Dijk DJ, Duffy JF, Folkard S, Minors DS, et al (1997): Complex interaction of the sleep–wake cycle and circadian phase modulates mood in healthy subjects. *Arch Gen Psychiatry* 54:145–152.

Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D (1981): Sleep deprivation: Effect of sleep stages and EEG power density in man. *Electroenceph Clin Neurophysiol* 51:483–493.

Borbély AA, Wirz-Justice A (1982): Sleep, sleep deprivation and

depression: A hypothesis derived from a model of sleep regulation. *Human Neurobiol* 1:205–210.

Brunner DP, Kräuchi K, Dijk DJ, Leonhardt G, Haug HJ, Wirz-Justice A (1996): Sleep EEG in seasonal affective disorder and control women: Effects of midday light treatment and sleep deprivation. *Biol Psychiatry* 40:485–496.

Cajochen C, Brunner DP, Kräuchi K, Graw P, Wirz-Justice A (1995): Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep* 18:890–894.

Cajochen C, Khalsa, SB, Czeisler CA, Wyatt JK, Dijk DJ (1999): EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *Am J Physiol* 227:R640–R650.

Czeisler CA, Kronauer RE, Mooney JJ, Anderson JL, Allan JS (1987): Biologic rhythm disorders, depression, and phototherapy: a new hypothesis. *Psychiatr Clin North Am* 10:687–709.

Daan S, Beersma DGM, Borbély AA (1984): Timing of human sleep: Recovery process gated by a circadian pacemaker. *Am J Physiol* 246:R161–R178.

Dijk DJ, Duffy JF, Czeisler CA (1992): Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J Sleep Res* 1:112–117.

Dijk DJ, Beersma DGM, Daan S (1987): EEG power density during nap sleep: Reflection of an hourglass measuring the duration of prior wakefulness. *J Biol Rhythms* 2:207–219.

Edgar DM, Dement WC, Fuller CA (1993): Effect of SCN lesions on sleep in squirrel monkeys: Evidence for opponent processes in sleep–wake regulation. *J Neurosci* 13:1065–1079.

Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM (1998): Bright light treatment of winter depression: A placebo-controlled trial. *Arch Gen Psychiatry* 55:883–889.

Graw P, Haug HJ, Leonhardt G, Wirz-Justice A (1998): Sleep deprivation response in seasonal affective disorder during a 40-h constant routine. *J Affect Disord* 48:69–74.

Hamilton M (1967): Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278–296.

Jewett M (1997): Models of circadian and homeostatic regulation of human performance and alertness [PhD thesis]. Cambridge, MA: Harvard University, pp 1–276.

Koorengevel KM, Beersma DGM, Gordijn MCM, den Boer JA,

van den Hoofdakker RH (2000): Body temperature and mood variations during forced desynchronization in winter depression: A preliminary report. *Biol Psychiatry* 47:355–358.

Lavie P (1986): Ultrashort sleep-waking schedule. III. "Gates" and "forbidden zones" for sleep. *Electroencephalogr Clin Neurophysiol* 63:414–425.

Lewy AJ, Sack RL, Miller LS, Hoban TM (1987): Antidepressant and circadian phase-shifting effects of light. *Science* 235:352–354.

Meesters Y, Jansen JHC, Lambers PA, Bouhuys AL, Beersma DGM, Van den Hoofdakker RH (1993): Morning and evening light treatment of seasonal depressive disorder: Response, relapse and prediction. *J Affect Disord* 28:165–167.

Palchikov VE, Zolotarev DY, Danilenko KV, Putilov AA (1997): Effects of the seasons and of bright light administered at different times of day on sleep EEG and mood in patients with seasonal affective disorder. *Biol Rhythm Res* 28:166–184.

Partonen T, Lönqvist J (1998): Seasonal depressive disorder. *Lancet* 352:1369–1373.

Strogatz SH, Kronauer RE, Czeisler CA (1987): Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia. *Am J Physiol* 253:R172–178.

Terman M, Levine SM, Terman JS, Doherty S (1998a): Chronic fatigue syndrome and seasonal affective disorder: Comorbodity, diagnostic overlap, and implications for treatment. *Am J Med* 28:115S–124S.

Terman M, Terman JS, Ross DC (1998b): A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry* 55:875–882.

Van den Hoofdakker RH (1997): Total sleep deprivation: clinical and theoretical aspects. In: Honig A, van Praag HM (editors). *Depression: Neurobiological, Psychopathological and Therapeutic Advances.* Chicester: John Wiley & Sons, pp 563–589.

Wirz-Justice A (1994): Biological rhythms in mood disorders. In: Bloom FE, Kupfer DJ (editors). *Psychopharmacology. The Fourth Generation of Progress.* New York: Raven Press, pp 999–1017.

Wirz-Justice A, Kräuchi K, Brunner DP, Graw P, Haug JH, Leonhardt G, et al (1995): Circadian rhythms and sleep regulation in seasonal affective disorder. *Acta Neuropsychiatrica* 7:41–43.