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## Mood regulation in seasonal affective disorder patients and healthy controls studied in forced desynchrony

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### Abstract

In healthy subjects, both the duration of wakefulness and the circadian pacemaker have been demonstrated to be involved in the regulation of mood. Some features of affective disorders suggest that these two factors also play a role in the dysregulation of mood. In particular, disturbances of the circadian pacemaker have been proposed to be a pathogenetic factor in Seasonal Affective Disorder, winter type (SAD). This report presents a test of this proposition. To this end seven SAD patients and matched controls were subjected to a 120-h forced desynchrony protocol, in which they were exposed to six 20-h days. This protocol enables us to discriminate the extent to which the course of mood is determined by the imposed 20-h sleep–wake cycle from the influence of the circadian pacemaker on that course. Patients participated during a depressive episode, after recovery upon light therapy and in summer. Controls were studied in winter and in summer. Between SAD patients and controls no significant differences were observed in the period length nor in the timing of the endogenous circadian temperature minimum. In both groups, sleep–wake cycle- and pacemaker-related components were observed in the variations of mood, which were not significantly different between conditions.

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**Keywords:** Circadian pacemaker; Sleep–wake cycle; Melatonin; Core body temperature; Depressive mood

### 1. Introduction

In major depression, a diurnal variation of mood and a temporary alleviation of symptoms by the deprivation of sleep have often been observed.

These clinical features gave rise to several hypotheses relating to the involvement of processes controlled by the circadian pacemaker, the sleep–wake cycle, or an interaction between these processes in the dysregulation of mood (reviewed in, for example, Van den Hoofdakker, 1994; Wirz-Justice, 1995; Buysse et al., 1999; Boivin, 2000). In the present experiment the regulation of mood in seasonal affective disorder, winter type (SAD) is explored, specifically the contributions of the

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circadian pacemaker and the sleep–wake cycle to this regulation.

The strongest evidence for the involvement of the duration of prior wakefulness in the regulation of mood has been found in sleep deprivation experiments. In depressed patients, sleep deprivation often results in a pronounced improvement while recovery sleep is frequently followed by relapse (Wirz-Justice and Van den Hoofdakker, 1999). In contrast, healthy subjects experience a deterioration of mood when they are deprived of sleep (Gerner et al., 1979; Brendel et al., 1990). Thus, the regulation of mood is affected by manipulation of the sleep–wake cycle in both depressed patients and controls.

Hypotheses about the involvement of abnormal functioning of circadian processes in depression have especially gained interest with respect to SAD. As in non-seasonal depression, in SAD both diurnal variation (Graw et al., 1991; Krauss et al., 1992) and a sleep deprivation-induced improvement of mood (Graw et al., 1998) have been observed. The annual recurrence of depressive symptoms in autumn and/or winter (Rosenthal et al., 1984) and the efficacy of bright light therapy (Terman et al., 1989) provide additional support for the involvement of the circadian pacemaker in this disorder. The pros and cons concerning proposed circadian explanations of the pathogenesis of depressive disorders including SAD are described more extensively by Boivin (2000).

The human circadian pacemaker, localized in the suprachiasmatic nuclei of the brain, generates endogenous physiological and psychological rhythms with a near 24-h period (Campbell et al., 1993; Czeisler et al., 1999). The daily exposure to light synchronizes these endogenous circadian rhythms with the exogenous 24-h light–dark cycle (Boivin et al., 1996; Jewett et al., 1997). Thus, the pacemaker enables adequate adaptation to the alternation of light and darkness caused by the earth's rotation and is involved in the regulation of seasonal changes in behavior. It has been postulated that a phase delay of the circadian pacemaker relative to the timing of the sleep–wake cycle underlies the pathogenesis of SAD (Lewy et al., 1987) and that an advance phase shift is required for improvement (Lewy et al.,

1998; Terman et al., 2001). According to this phase-shift hypothesis, light therapy applied in the morning is effective because of its phase-advancing properties. Alternatively, the amplitude hypothesis (Czeisler et al., 1987) postulates that SAD patients might show a diminished circadian amplitude and that the amplitude-enhancing effect of light applied in daytime accounts for the efficacy of light therapy in SAD.

Overt circadian rhythms always represent a mixture of circadian pacemaker and sleep–wake-related processes. Constant routine and forced desynchrony protocols have been designed to reveal unmasked circadian rhythms. In the constant routine (CR) protocol, participants are subjected to a regime of more than 24 h of wakefulness in dim light. Subjects stay in a semi-recumbent position. Hourly iso-caloric snacks provide a constant energy supply (Mills et al., 1978; Czeisler et al., 1985). Physiological circadian rhythms measured under these constant conditions are considered to reflect unmasked circadian pacemaker activity. In a forced desynchrony (FD) protocol, subjects are living on a schedule of artificial 'days' that are either shorter or longer than 24 h, i.e. 20 or 28 h (Kleitman and Kleitman, 1953; Czeisler et al., 1986). In the present study artificial days lasted 20 h: 13.5 h of wakefulness in dim light (<10 lux) and 6.5 h of darkness in which subjects could sleep. In dim light, the circadian pacemaker is not able to adapt to this unusual schedule of wakefulness and sleep and starts to oscillate according to its endogenous period (Klerman et al., 1996), which is close to 24 h (Campbell et al., 1993; Czeisler et al., 1999). As a result of the desynchronization between the sleep–wake cycle and the circadian pacemaker, the scheduled activities occur at all endogenous circadian phase positions. The contributions of the sleep–wake cycle and the pacemaker to the circadian variation of a variable can be disentangled by a mathematical method (Dijk et al., 1992; Hiddinga et al., 1997).

So far, two CR studies have been performed in female SAD patients and matched controls. In both studies, certain characteristics of the circadian rhythm in body temperature (Dahl et al., 1993; Wirz-Justice et al., 1995), melatonin (Dahl et al., 1993) and cortisol (Avery et al., 1997) were shown

to be phase delayed in patients compared with those found in controls. After light therapy, a phase-advance of some of the circadian temperature characteristics (Dahl et al., 1993; Wirz-Justice et al., 1995) and of the secretion of melatonin were observed (Dahl et al., 1993). Neither study revealed disturbances of circadian amplitude.

Besides a circadian variation in physiological variables, CR studies have also demonstrated a circadian modulation of mood in both healthy subjects and SAD patients (Wirz-Justice et al., 1995; Monk et al., 1997). The CR-induced sleep deprivation affected the circadian mood variation in both groups differently. In the 40-h CR study in which both SAD patients and controls participated, 52% of the patients and 29% of the controls showed an improvement of mood (Graw et al., 1998). Additionally, the circadian variation of 'well-being' measured in healthy subjects showed a declining linear trend in the course of a 36-h CR protocol (Monk et al., 1997).

An obvious distinction between CR and FD protocols is that sleep deprivation effects are nearly completely avoided by the latter. In FD protocols in healthy subjects, circadian and sleep-wake dependent influences on core body temperature have been shown (Hiddinga et al., 1997; Czeisler et al., 1999). Moreover, a complex interaction between these two components has been demonstrated in many respects: the production of melatonin (Wyatt et al., 1999), the regulation of sleep (Dijk and Czeisler, 1995; Wyatt et al., 1999), and the regulation of subjective alertness, cognitive performance (Dijk et al., 1992), and mood (Boivin et al., 1997). Like the circadian modulation of alertness and performance (Dijk et al., 1992), also that of mood was found to be closely associated with the circadian oscillation of core body temperature (Boivin et al., 1997). Mood respectively improves and worsens with the ascending and descending limbs of the endogenous circadian temperature curve, which reaches its minimum in the early morning. Additionally, mood was found to gradually deteriorate with the duration of prior wakefulness.

The aim of the present study was to investigate the contributions of the circadian pacemaker and the duration of prior wakefulness to the regulation

of mood in SAD patients. Therefore, SAD patients were studied in a forced desynchrony protocol during a depressive episode, while recovered upon light treatment, and in summer. For comparison, also healthy matched control subjects were studied in winter and summer.

## 2. Methods

### 2.1. Subject's recruitment and characteristics

SAD patients who in previous years responded favorably to morning bright light therapy administered at the out-patients clinic, received general written information about the study. Healthy controls were approached through local newspaper and television advertisements. Those who were interested received a detailed description of the protocol. If participation was considered, the study was verbally explained to all SAD patients and those controls that could be matched to one of the participating patients for age, sex, smoking habits and menstrual cycle phase (if appropriate). All subjects gave written informed consent and were paid for their participation. The study was approved by the Medical Ethics Committee of the Groningen Academic Hospital. 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 had to have no psychopathological disturbances or sleeping problems.

To assess general mental health, depressive symptoms, seasonality and preference for morningness or eveningness, the following instruments were used: the General Health Questionnaire (GHQ; Goldberg and Williams, 1988), the Beck Depression Inventory (BDI; Beck et al., 1979), the Structured Interview Guide for the Hamilton Rating Scale of Depression-self-rating version (SIGH-SAD-SR; Williams et al., 1992), the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal et al., 1987) and 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 eight-item atypical scale (ATYP)

addressing atypical symptoms such as an increase in appetite and sleep. An M/E score below 30 and above 70 reflects evening and morning types, respectively. 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 (including leisure drugs) for at least one month prior to participation (with the exception of the sporadic use of NSAIDs). Patients had not used psychoactive medications for 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. Subjects did not cross more than one time zone in the month prior to the study, nor did they work night shifts.

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 completion of the protocol during the depressive episode, 45 min of 10 000 lux morning light therapy were administered at the out-patients clinic for at least 5 consecutive days. Controls participated in winter and in summer.

## 2.2. Protocol

The protocol took 10 days. During the first 4 days subjects were at home. They were instructed to restrict sleep to night until 08.00 h, to refrain from daytime naps, heavy physical exercise and alcoholic beverages and to drink not more than four caffeine-containing drinks a day. Compliance to the regular sleep–wake schedule was verified by an actimeter, which was continuously worn 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 consists of a small sound and light shielded apartment

in which no information on time of day is available. A habituation period from 18.00 h on day 4 until 08.00 h on day 5 enabled the subjects to become acquainted with the experimental procedures. Subjects went to bed at midnight. Subsequently, the participants were subjected to a 120-h forced desynchrony protocol. Without knowledge of the timing of the experimental procedures, subjects were scheduled on six 20-h days consisting of 13.5 h of wakefulness in dim light (<10 lux) and 6.5 h of darkness (0 lux) 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, and attaching electrodes for polysomnographic recordings, and to announce the times for going to bed. As a result, each subjective 20-h day had the same temporal structure. 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 four caffeine-containing drinks was permitted. Subjects were continuously monitored by an infra-red camera.

## 2.3. Melatonin and core body temperature

For each experiment, period length and phase position of the circadian pacemaker were assessed from salivary melatonin and core body temperature data (Koorengevel et al., 2002). While the subjects were in time isolation, core body temperature was recorded at 1-min intervals by means of a rectal probe connected to a portable device (Bakker and Beersma, 1991). Saliva was sampled hourly from 19.00 h until midnight on day 4 and from 19.00 h until 02.00 h on day 9 of the protocol. Salivary melatonin concentrations were measured by radioimmunoassay (Bühlmann, Allschwill, Switzerland) and expressed as a percentage of the maximum melatonin value in the first sampling period (day 4). The dim-light melatonin onset (DLMO) was defined as the last time within the sample interval at which this normalized melatonin curve passed the 25% level. In all but one occasion, this was also the first time that the crossing

occurred. Temperature data showed that five circadian oscillations had passed between day 4 and 9. Therefore, an estimation of circadian period ( $\tau$ ) could be derived from the DLMO data. However, different subjects may have very different melatonin profiles. The arbitrary definition of DLMO can therefore result in different definitions of circadian phase in different subjects. To avoid misinterpretation, circadian phase was therefore derived from the endogenous circadian temperature cycle. The method by which this endogenous cycle was obtained is based on the assumption that overt body temperature is the result of the additive contribution of a sleep–wake-related and a pacemaker-related component (see Hiddinga et al., 1997). A first impression of the sleep–wake-related component was obtained by averaging for each minute the six body temperature values measured during the six 20-h subjective days. The thus obtained mean sleep–wake-related component of the temperature curve was subtracted from the raw data for each of the six consecutive subjective days. The residual curve is relatively unmasked by the activities of the 20-h protocol. It shows the endogenous temperature modulation with a period close to 24 h. Next, these residual body temperature data were divided into approximately five epochs with the length of the melatonin derived  $\tau$ -values. Again, for each minute of the cycle, the five corresponding datapoints were averaged. This procedure yields an estimate of the mean circadian curve of body temperature. Computer simulation revealed that the estimate can be further improved by subtracting the obtained circadian curve from the raw data and repeating the above-described procedures (Hiddinga et al., 1997). This iterative approach finally yields stable estimations of the endogenous and exogenous components of core body temperature.

The timing of the minimum of the endogenous temperature component nearest to the start of the forced desynchrony protocol can be used as an estimate of circadian phase during the entrained conditions which existed prior to the forced desynchrony study. Yet, the timing of this minimum is strongly influenced by fluctuations of the temperature signal. The impact of those fluctuations can be reduced by transposing the data from the

subsequent unmasked circadian temperature cycles back to the first circadian cycle and calculating the average time course. The timing of the minimum of this curve served as the reference phase (CT0). In more detail, CT0 was assessed by computing the timing of the midpoint between the upward and downward crossings of the endogenous temperature curve through the mean, after filtering the signal by means of a 1-h moving average procedure.

#### 2.4. Mood ratings

On days 1 and 10 of the protocol, subjects completed the BDI and SIGH-SAD-SR to evaluate the severity of depressive symptoms. During the baseline days at home, mood was rated three times daily. At 09.00 h, 17.00 h and 22.00 h, subjects attributed a score between 1 and 10 to their mood (worst and best possible, respectively) and completed the Adjective Mood Scale (AMS; Von Zerssen, 1986) and a Visual Analogue Scale (VAS; Albersnagel, 1987) for depression (VAS-D) and elation (VAS-E).

During wakefulness in the time isolation unit, similar mood ratings were obtained at 2-h intervals, the first of which occurred 15 min after rising. The effects of the pacemaker and the sleep–wake cycle on mood were computed from the raw data by the same method as already described for body temperature. Again the estimation of the effects of these components on mood is based on the assumption that the raw course of mood is composed of the sum of these two components. First, mean mood scores were calculated as a function of duration of wakefulness. This initial estimation of the mean sleep–wake-related influence was subtracted from the original raw data points obtained during the 6 subjective days. Next, circadian time was attributed to each resulting data point. This was done on the basis of the circadian phase and period length derived from temperature and melatonin data of the same experiment. Subsequent epochs with a length of  $\tau$  h were superimposed to obtain an estimation of the mean circadian modulation of mood. This average pacemaker-related mood curve was then subtracted from the raw data to obtain a more accurate

estimation of the specific influence of the duration of wakefulness on mood. This procedure was repeated until stable estimations of the effects of circadian phase and duration of wakefulness were established for each experiment. Five repetitions turned out to be sufficient.

### 2.5. Polysomnography

Since sleep deprivation induces changes of mood, each sleeping period in time isolation was evaluated by means of polysomnography (PSG). PSGs were recorded and visually scored according to the criteria of Rechtschaffen and Kales (1968). This was done in 30-s intervals by three raters with the computerized aid of 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 min (range 1.5–4 min). Total sleep time (TST) per scheduled sleeping period was calculated by adding the min in sleep stages 1, 2, 3, 4 and REM.

### 2.6. Statistical analysis

The severity of depression before and after finishing the protocol, the sleep–wake- and pacemaker-related variations of mood, the circadian pacemaker period and phase, and the respective TSTs obtained in forced desynchrony were evaluated by means of analysis of variance with repeated measures (ANOVA) to detect differences between patients and controls or between conditions. Significance was accepted at  $P < 0.05$ . Data on mood presented in figures were  $z$ -transformed to account for inter-subject variability.

## 3. Results

### 3.1. Subjects

From 1997 until 1999, the winter and summer experiments were scheduled during the months October–March and May–August, respectively. In total, seven SAD patients (one male and six females) and eight matched controls (one male and seven females) participated. Ages at the first

participation, and scores on the GHQ, SPAQ and M/E questionnaire completed at the introduction meeting are summarized in Table 1. After participating in summer, one female control subject canceled the second experiment and was therefore substituted by another matched control for the winter condition. In both groups, three subjects were cigarette smokers. Of the female patients, four were studied each time in the (pseudo-) follicular phase of their menstrual cycle and one in the pseudo-luteal phase ('pseudo' is referring to situations induced by oral contraceptives). The participation of female controls was matched for menstrual cycle phase, except for the control subject matched to a post-menopausal patient participating in the pseudo-luteal phase while depressed and in the pseudo-follicular phase while remitted due to estrogen replacement therapy.

### 3.2. Severity of depression prior to and after the 120-h forced desynchrony experiment

The severity of depression before (day 1) and after the experiment (day 10) was assessed by the BDI and the SIGH-SAD-SR (Table 1). On day 1, depressed SAD patients had a minimum score of 14 on the BDI and of 19 on the SIGH-SAD-SR, whereas in the other conditions for all subjects scores were less than 6 and less than 11, respectively. The SIGH-SAD-SR and the 21-item HRSD sub-score exhibited a significant deterioration of mood after the end of the protocol. Two repeated measures ANOVAs were applied. In both cases a before/after by season interaction repeated measures ANOVA was applied in which the patient/control distinction was entered as a between-subject factor. In one test the depressed state of the patients in winter was considered; in the second test, the remitted state was used. The repeated measures ANOVAs yielded  $F > 12.1$ ,  $P < 0.003$ . A similar trend was observed for the BDI ( $F > 3.51$ ,  $P < 0.09$ ). However, the deterioration was not very large (Table 1) and showed no significant difference between patients and controls ( $F < 1.07$ ,  $P > 0.32$ ). The eight-item atypical symptom scale (ATYP) only showed an overall significant effect of time if the patients in winter were considered

Table 1

General characteristics of subjects, severity of depression before and after finishing the forced desynchrony protocol, and circadian pacemaker characteristics (mean  $\pm$  S.D.)

	SAD patients		Controls		
Age	36.3 $\pm$ 13.9		38.1 $\pm$ 12.8		
GHQ	1.4 $\pm$ 2.3		0.3 $\pm$ 0.5		
SPAQ	16.7 $\pm$ 3.6		3.5 $\pm$ 1.8		
M/E	44.7 $\pm$ 10.4		51.4 $\pm$ 13.7		
	Depressed (n=7)	Remitted (n=7)	In summer (n=7)	In winter (n=7)	In summer (n=7)
Depression scores before FD					
BDI	20.3 $\pm$ 6.1	1.7 $\pm$ 1.8	0.6 $\pm$ 0.8	0.3 $\pm$ 0.8	0.3 $\pm$ 0.5
SIGH-SAD-SR	32.3 $\pm$ 11.8	3.7 $\pm$ 4.3	1.1 $\pm$ 1.9	1.4 $\pm$ 2.1	1.6 $\pm$ 1.6
21-item HRSD	21.3 $\pm$ 7.9	2.0 $\pm$ 2.0	0.9 $\pm$ 1.5	0.9 $\pm$ 0.9	1.3 $\pm$ 1.5
ATYP	11.0 $\pm$ 5.4	1.7 $\pm$ 2.2	0.3 $\pm$ 0.5	0.6 $\pm$ 1.5	0.3 $\pm$ 0.8
Depression scores after FD					
BDI	23.6 $\pm$ 10.4	2.6 $\pm$ 2.9	2.6 $\pm$ 3.1	0.7 $\pm$ 0.8	1.7 $\pm$ 2.6
SIGH-SAD-SR	30.7 $\pm$ 12.1	8.3 $\pm$ 7.7	8.1 $\pm$ 5.4	5.4 $\pm$ 3.6	6.7 $\pm$ 5.0
21-item HRSD	23.0 $\pm$ 9.6	5.9 $\pm$ 5.5	6.3 $\pm$ 4.2	3.9 $\pm$ 2.2	5.1 $\pm$ 4.0
ATYP	7.7 $\pm$ 3.5	2.4 $\pm$ 2.6	1.9 $\pm$ 1.3	1.6 $\pm$ 1.7	1.6 $\pm$ 1.6
Pacemaker characteristics					
Period	24:02 $\pm$ 0:11	24:08 $\pm$ 0:13	24:10 $\pm$ 0:15	24:13 $\pm$ 0:13	24:16 $\pm$ 0:16
Phase	4:31 $\pm$ 1:02	4:26 $\pm$ 1:17	4:43 $\pm$ 1:11	5:12 $\pm$ 1:51	4:47 $\pm$ 0:58

General characteristics: age (in years) at times of first participation, score on the General Health Questionnaire (GHQ), Seasonal Pattern Assessment Questionnaire (SPAQ) and Morningness/Eveningness questionnaire (M/E). For a more detailed description of these ratings, see the Methods section. Severity of depression before and after finishing the forced desynchrony (FD) was assessed by the Beck Depression Inventory (BDI) and the Structured Interview Guide for the Hamilton Rating Scale for Depression—self-rating version (SIGH-SAD-SR) consisting of the 21-item Hamilton Rating Scale for Depression (HRSD) and an 8-item atypical symptom scale (ATYP). The period length ( $\tau$ ) of the circadian pacemaker (in hours) was obtained from salivary melatonin assessed on days 4 and 9 of the protocol. The phase of the circadian pacemaker is expressed as the timing (h:min) of the unmasked temperature minimum on the first morning in the time isolation unit.

in their recovered state. Contrary to the other experimental conditions in which the atypical symptom score slightly increased, the ATYP demonstrated a small decrease (i.e. improvement) over the experiment only in depressed patients. Six out of seven patients reported sleeping on average at least 1 h more when depressed than when not depressed. Two patients reported early morning awakenings in the depressed state.

### 3.3. Circadian pacemaker characteristics

The average course of core body temperature during the 120-h forced desynchrony protocol, for both groups of subjects in each condition, is depicted in Fig. 1. The analysis of pacemaker characteristics, i.e. circadian period ( $\tau$ ), phase position and amplitude, from salivary melatonin

and core body temperature data is described in detail elsewhere (Koorengevel et al., 2002). Table 1 lists the observed average values for  $\tau$  and phase of the circadian pacemaker for each condition. In patients and controls, melatonin-derived  $\tau$ -values of slightly longer than 24 h were observed in each condition. In both groups, the first circadian temperature minimum under time isolation (after correction for masking) occurred in the early morning of day 5. Repeated measures ANOVAs with season as the repeated measures factor and patient/control status as the between-subjects factor did not reveal significant differences between patients and controls nor between conditions in circadian pacemaker period ( $F < 1.89$ ,  $P > 0.19$ ) and phase ( $F < 0.58$ ,  $P > 0.57$ ). The amplitude of the endogenous component of core body temperature was slightly smaller in the patients in winter, irrespective of



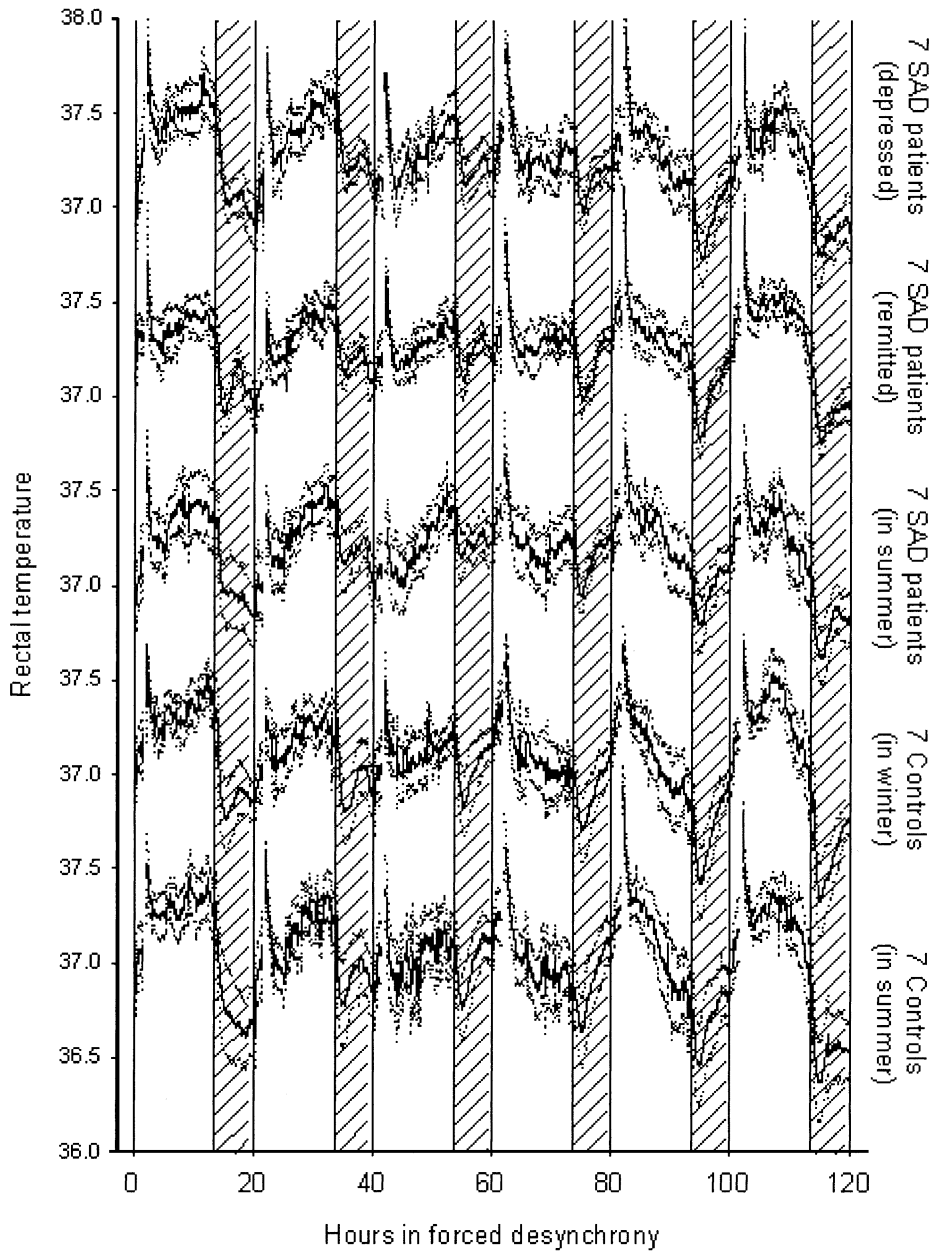


Fig. 1. Course of core body temperature (mean  $\pm$  S.E.M.) measured rectally at 1-min intervals during the 120-h forced desynchrony protocol. This protocol was composed of six 20-h days, consisting of 13.5 h of wakefulness in dim light (<10 lux) and 6.5 h of darkness, which had to be spent in bed (indicated by the shaded areas).

whether they were depressed or recovered (paired samples tests:  $P=0.050$  and  $P=0.031$ , respectively). The significant relationship between the ampli-

tude of the circadian component of body temperature and the average level of body temperature (Koorengel et al., 2002) renders it likely

that the reduced amplitude is not caused by the circadian pacemaker but by thermoregulatory mechanisms.

#### 3.4. Sleep–wake cycle-related and pacemaker-related variations of mood

Fig. 2 illustrates the average course of mood during the waking hours of the 120-h FD protocol assessed by means of the AMS. The average raw scores (before the transformation to  $z$ -scores) of the AMS, the VAS-D, the VAS-E and the self-attributed mood scores obtained at 2-h intervals during forced desynchrony are summarized in Table 2. As expected, patients rated their mood significantly worse in the depressed state than when remitted and than in summer. The same holds for the comparison with controls in winter. (Repeated measures ANOVAs with season as repeated measures factor and patient vs. control status as between-subjects factor revealed  $F > 8.13$  and  $P < 0.015$  for the effects of season and of subject status when patients in winter were considered in their depressed state. If, in contrast, patients were considered in winter in the recovered state, ANOVAs yielded  $F < 3.45$ ,  $P > 0.09$ .)

For each mood scale, the 42 consecutive raw scores were subjected to the iterative mathematical procedure described in the methods section, to disentangle the influences of the sleep–wake cycle and the pacemaker on mood. Two repeated measure ANOVAs were applied to assess the influence of time of day, circadian phase, season and affective state of the subjects. In both cases, a time by season interaction repeated measures ANOVA was applied in which the patient/control distinction was entered as a between-subjects factor. In one test the depressed state of the patients in winter was considered; in the second test the remitted state was used. A significant variation of mood as a function of time since awakening was revealed for the AMS in both tests ( $F(6) > 6.01$ ,  $P < 0.001$ ), the self-attributed mood score ( $F(6) > 3.14$ ,  $P < 0.014$ ) and the VAS-E ( $F(6) > 3.83$ ,  $P < 0.005$ ), but not for the VAS-D. Significant effects of season ( $F > 8.11$ ,  $P < 0.015$ , all scales) were observed when patients in winter were studied in the depressed state, but not in the remitted state ( $F <$

$3.48$ ,  $P > 0.09$ , all scales). There were no significant interaction effects between time since awakening and patient vs. control status ( $F < 2.02$ ,  $P > 0.073$ , all scales). Similarly, significant relationships of mood with circadian time were found (AMS:  $F(11) > 6.0$ ,  $P < 0.001$ ; self-attributed mood score:  $F(11) > 5.17$ ,  $P < 0.001$ ; and VAS-E:  $F(11) > 2.37$ ,  $P < 0.016$ ). The VAS-D scores did not systematically reveal a significant relationship with circadian time. Significant effects of season ( $F > 7.86$ ,  $P < 0.02$ , all scales) were observed when patients in winter were studied in the depressed state, but not in the recovered state ( $F < 3.61$ ,  $P > 0.08$ , all scales). Again there were no significant interaction effects between circadian time and patient vs. control status ( $F(11) < 1.29$ ,  $P > 0.24$ , all scales).

Fig. 3 depicts the average course of the AMS scores per condition both as a function of time since awakening and of circadian time. In each condition, the sleep–wake-related variation of mood shows an improvement during the first 4 h of wakefulness. Thereafter, mood gradually deteriorates. In the depressed patients only, mood improves just before bedtime. The pacemaker-related variation in mood shows an almost sinusoidal course in each condition. In healthy subjects, the circadian variation of mood has been found to parallel the circadian variation of body temperature (Boivin et al., 1997). In Fig. 3, the sleep–wake cycle-related and the pacemaker-related variations in core body temperature are plotted. Since the pacemaker's period length and phase position did not differ between conditions, the temperature data were averaged across all forced desynchrony experiments. The sleep–wake cycle-related variation of body temperature shows an increase in temperature after awakening, with a sharp peak induced by showering. After a subsequent drop, the temperature level remains relatively stable during the remaining hours of wakefulness. Finally, at the start of the sleeping period, a decrease in temperature can be observed. The pacemaker-related variation of body temperature has a sinusoidal shape. CT0 refers to the timing of the circadian temperature minimum (see Table 1). Globally, the pacemaker-related variation in mood runs parallel

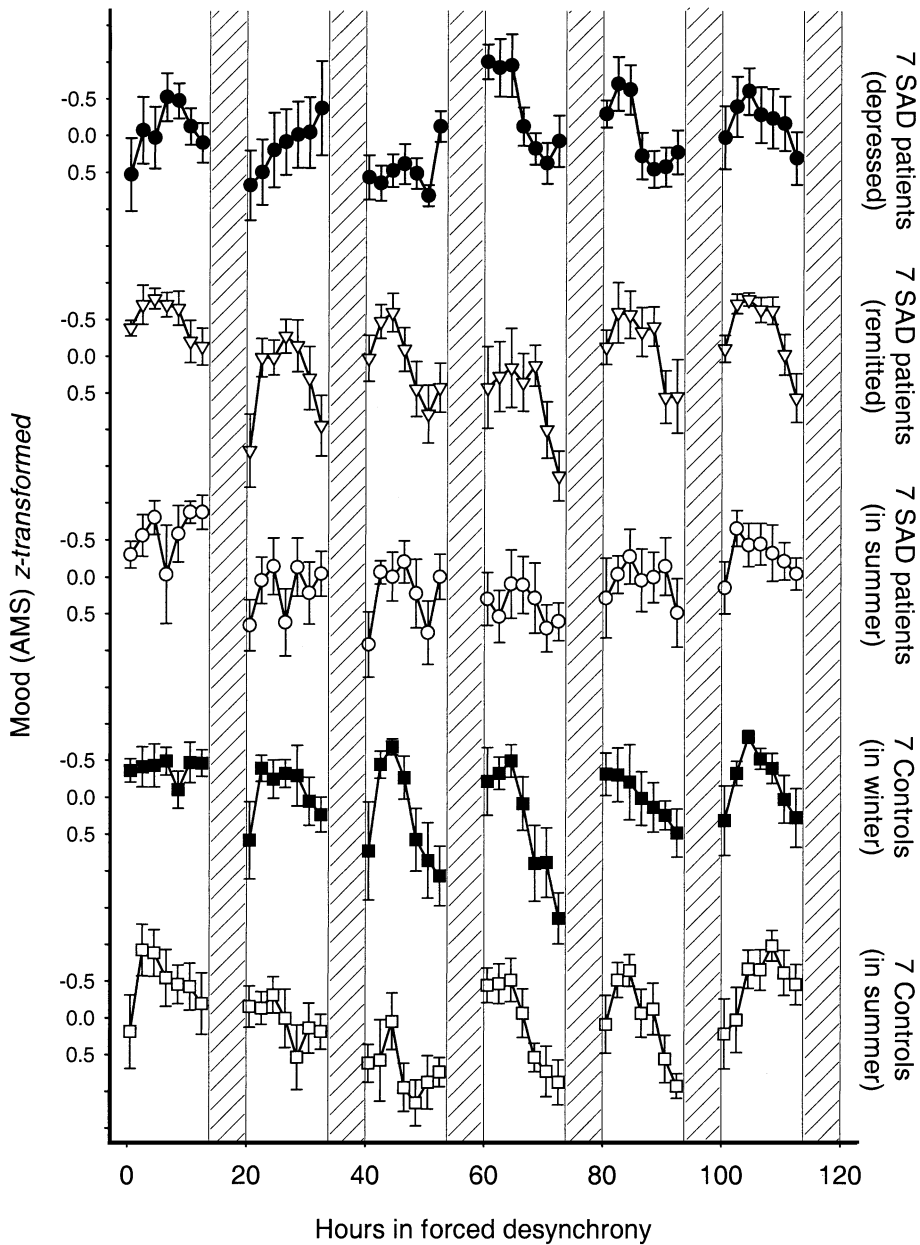


Fig. 2. Course of mood (mean  $\pm$  S.E.M.) as assessed by the Adjective Mood Scale (AMS), completed at 2-h intervals during the entire 120-h forced desynchrony protocol. The AMS ranges from 0 (not depressed)—56 (severely depressed). Negative  $z$ -scores represent better mood and are therefore plotted at higher levels.

with the circadian temperature curve, with an improvement of mood when the curve rises and a worsening when it descends. The absence of a

clear relationship between the sleep–wake-related components of mood and body temperature is the reason that the raw course of mood (Fig. 2) differs

Table 2  
Mood ratings during the forced desynchrony experiment (mean  $\pm$  S.D.)

	SAD patients			Controls	
	Depressed ( <i>n</i> = 7)	Remitted ( <i>n</i> = 7)	In summer ( <i>n</i> = 7)	In winter ( <i>n</i> = 7)	In summer ( <i>n</i> = 7)
AMS	31.9 $\pm$ 10.6	9.9 $\pm$ 4.4	10.3 $\pm$ 6.2	5.9 $\pm$ 2.7	8.5 $\pm$ 3.0
Self-attributed mood score	5.3 $\pm$ 0.9	7.3 $\pm$ 0.5	7.4 $\pm$ 1.0	7.4 $\pm$ 0.5	7.2 $\pm$ 0.5
VAS-D	48.3 $\pm$ 10.4	9.5 $\pm$ 8.3	9.5 $\pm$ 9.5	8.9 $\pm$ 8.8	4.8 $\pm$ 3.8
VAS-E	37.7 $\pm$ 12.3	62.2 $\pm$ 9.4	65.8 $\pm$ 14.6	60.5 $\pm$ 12.0	55.4 $\pm$ 6.3

Scores on the Adjective Mood Scale [AMS; 0 (not depressed)–56 (severely depressed)], on the Visual Analogue Scale for Depression (VAS-D) and on the Visual Analogue Scale for Elation (VAS-E), both ranging from 0 (not at all depressed/elated) to 100 (extremely depressed/elated). The self-attributed mood score consists of a score ranging from 0 to 10 (worst and best possible, respectively). Of each rating, the mean of all ratings is computed by averaging the 42 scores obtained throughout the 120-h forced desynchrony protocol.

considerably from the raw course of body temperature (Fig. 1).

### 3.5. Reconstruction of the daily course of mood

It was investigated whether the average course of mood during the baseline days could be explained from the two factors involved in mood regulation. To this end the course of mood during the baseline period was reconstructed by adding both components at the appropriate phase positions. Fig. 4 depicts the average course of the AMS ratings both as collected at home and as reconstructed. Baseline data are available for 09.00 h 17.00 h and 22.00 h. within the interval between 17.00 h on day 1 and 9.00 h on day 4. In each condition, there is a close correspondence between the reconstructed course of mood and the average baseline data.

### 3.6. Effect of forced desynchrony experiment on sleep

Sleep deprivation can have effects on mood. Hence, TST was determined for each subjective night in forced desynchrony (Table 3). A significant effect of night sequence number in forced desynchrony on TST was observed when repeated measures ANOVAs were applied with a night sequence number by season interaction and patient vs. control as between-subject factors, once including patients in the depressed state and once in the remitted state ( $F > 4.99$ ,  $P < 0.001$ ). However, no

significant interaction between night sequence number and patient/control group was detected ( $F < 0.36$ ,  $P > 0.87$ ). In all conditions, sleep duration was shortest in the second night of forced desynchrony (scheduled from 17:45 to 00.15 h).

## 4. Discussion

Recently, an FD study in healthy subjects has demonstrated that two factors influence mood by means of a complex non-additive interaction: a circadian factor and the duration of wakefulness (Boivin et al., 1997). Several clinical features of affective disorders (reviewed in, for example, Van den Hoofdakker, 1994; Wirz-Justice, 1995; Boivin, 2000) suggest that these two factors are involved in the dysregulation of mood in depressed patients. The aim of the present study was to explore the contributions of the sleep–wake cycle and the circadian pacemaker to the course of mood in SAD patients.

Only a few studies of mood in depressed patients isolated from time cues have been performed. In one of these studies a male patient with 48-h manic-depressive mood cycles was subjected to twelve 22-h days (Jenner et al., 1968). The period length of the otherwise remarkably regular 48-h mood cycles changed to 44-h. It was concluded that the environment, and not a ‘metabolic clock’ within the patient, is important in the regulation of mood. However, from a free-run experiment in another male patient with 48-h

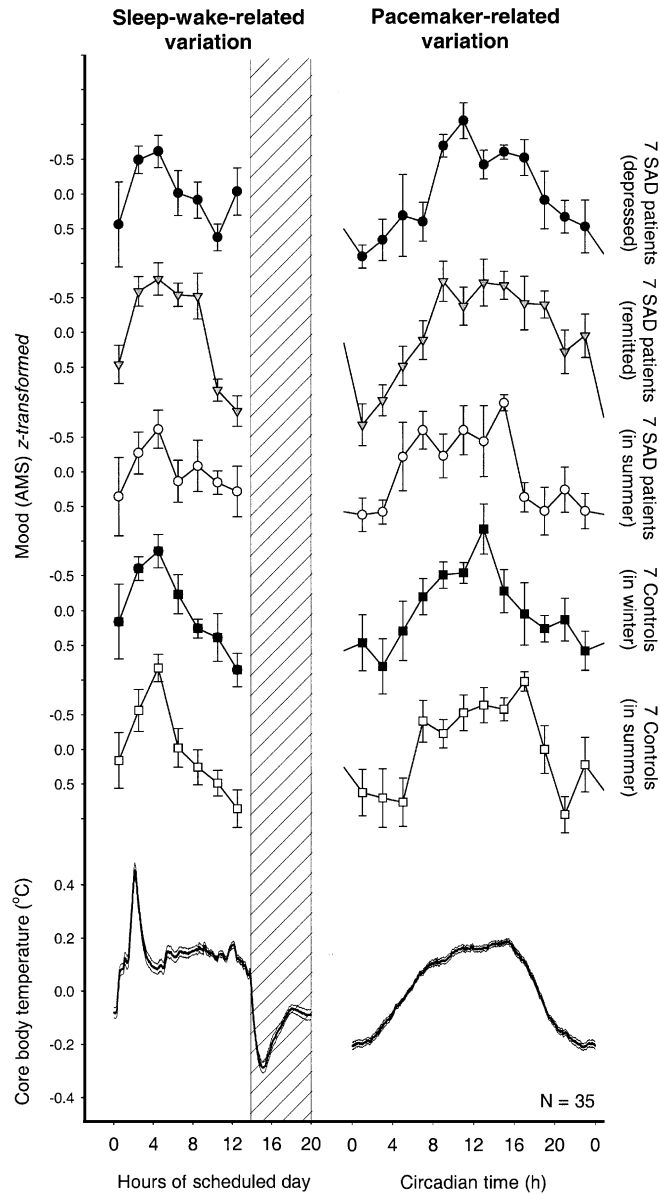


Fig. 3. Sleep–wake cycle related and pacemaker-related modulation of mood and core body temperature (mean  $\pm$  S.E.M.) in SAD patients and matched controls. The  $z$ -transformed data on the circadian and sleep–wake-related components of mood were calculated from the Adjective Mood Scale (AMS), completed at 2-h intervals during wakefulness in forced desynchrony. Negative scores represent better mood. Throughout the protocol, core body temperature was measured at 1-min intervals. The temperature data are averaged across all forced desynchrony experiments.

unipolar depressive cycles, the opposite was concluded (Dirlich et al., 1981). That study showed that the circadian organization of mood remained

unaffected under time isolation, while the duration of the rest–activity cycle shortened to approximately 19.5 h. Finally, in a third study three female

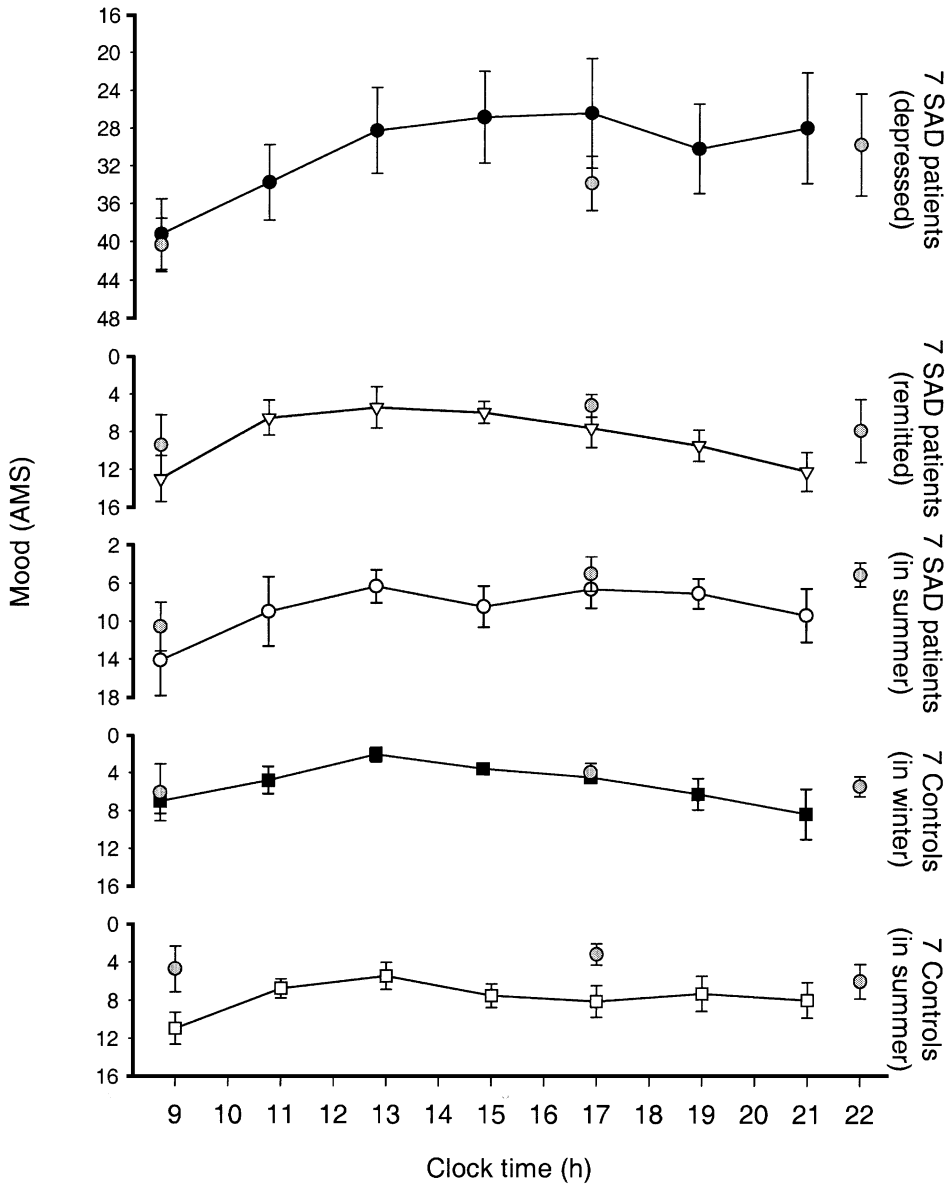


Fig. 4. Reconstruction of daily course of mood during baseline from the sleep-wake-related and pacemaker-related variation of mood obtained in forced desynchrony. For each condition, the daily course of mood (mean  $\pm$  S.E.M.) during baseline, calculated by averaging the mood scores obtained at 09.00, 17.00 and 22.00, respectively, is illustrated by the gray circles. The Adjective Mood Scale (AMS) ranges from 0 (not depressed) to 56 (severely depressed). The plotted curve represents the reconstruction of the daily course of mood obtained by adding the sleep-wake cycle- and pacemaker-related modulation of mood (mean  $\pm$  S.E.M.) at 2-h intervals.

manic-depressive patients and one female unipolar depressive patient were isolated from time cues for 3–4 weeks (Wehr et al., 1985). In none of

these patients did the clinical state remain stable. It was hypothesized that the clinical instability might have resulted from changes of phase rela-

Table 3  
Total sleep time per subjective night in forced desynchrony

	Total sleep time (min)					
	Night 1	Night 2	Night 3	Night 4	Night 5	Night 6
Patients (depressed; $n=7$ )	322 ± 75	279 ± 97	310 ± 69	316 ± 81	356 ± 43	356 ± 5
Patients (remitted; $n=7$ )	346 ± 39	314 ± 75	319 ± 47	302 ± 71	349 ± 34	351 ± 21
Patients (summer; $n=7$ )	352 ± 12	308 ± 82	308 ± 60	336 ± 41	334 ± 36	362 ± 13
Controls (winter; $n=7$ )	347 ± 33	326 ± 49	311 ± 65	348 ± 41	339 ± 38	356 ± 15
Controls (summer; $n=7$ )	349 ± 25	289 ± 66	315 ± 66	338 ± 53	332 ± 54	359 ± 24
Average	344 ± 42	304 ± 73	313 ± 59	329 ± 59	343 ± 41	358 ± 17

Total time in stages 1, 2, 3, 4, and REM (mean ± S.D.) per subjective night in forced desynchrony. The consecutive subjective nights were scheduled at 21.45–04.15 (night 1), 17.45–00.15 (night 2), 13.45–20.15 (night 3), 09.45–16.15 (night 4), 05.45–12.15 (night 5) and 01.45–08.15 h (night 6).

tionships between the circadian pacemaker and the sleep–wake cycle. It may be concluded from these studies that the contributions of the sleep–wake cycle and the pacemaker to the regulation of mood in depression were far from established.

The aim of the present FD study was to assess the contributions of the pacemaker and the sleep–wake cycle to the variation of mood in SAD patients and matched controls. The data show that with seven subjects in each group, the influences of the pacemaker and the sleep–wake cycle on mood in SAD patients do not differ sufficiently from those in healthy subjects to be detected in this experiment. In all conditions, the protocol was tolerated quite well and did not induce strong lasting effects on mood in patients or controls. Scores on the BDI and the SIGH-SAD-SR completed prior to and directly following the 10-day protocol revealed that the experiment induced only a small deterioration of mood in both groups.

The only way by which the influence of the circadian pacemaker on mood can be distinguished from the influence of rhythmic sleep–wake-behavior-related processes is by desynchronizing these two types of rhythms. In our study this was done by using a forced desynchrony protocol with an imposed cycle of 20 h. The facts that imposed cycles of 20 h and of 28 h yielded similar values of the intrinsic periods of healthy subjects (Wyatt et al., 1999), and that the endogenous component of mood in healthy subjects in our study is similar to the one obtained by Boivin et al. (1997), demonstrate that these aspects can reliably be

measured with such a protocol independent of the length of the imposed period. They also show that the impact of the behavioral cycles on circadian rhythmicity is very small, as has recently been confirmed by Wright et al. (2001) and Danilenko et al. (2002). Given that most diurnal mammals respond to light by changing the period of their circadian pacemaker (Beersma et al., 1999), a true intrinsic period of the pacemaker probably does not exist. The values of the circadian period determined by forced desynchrony are the values that belong to the dimly lit environment in which the measurements are performed. It cannot be excluded that those values are different under conditions of normal light exposure.

Light is the major synchronizer of circadian rhythmicity in humans (Czeisler et al., 1981). Since variation in sleep timing leads to a concomitant variation in the timing of light–dark cycles, it was important to schedule sleep at the same time during the days prior to the experiment for all subjects. Given that many SAD patients tend to sleep long, this instruction may have been more difficult to meet for the patients than for the controls. Yet, we expect 4 days to be sufficient for the circadian pacemaker to adapt to the situation. Notably, the resulting phase position of the pacemaker belongs to the thus entrained situation, and not to the habitual circumstances.

There were changes of mood during the protocol: the course of self-rated mood varied across the consecutive periods of wakefulness in each condition (Fig. 2). Comparison of the data of Figs.

1 and 2, however, clearly shows that depressed mood is not related to core body temperature. The days showing the largest modulation of mood are the days in which body temperature varies the least and vice versa. Sleep recordings were examined to test whether sleep duration influenced mood. The PSG data showed that the protocol affected TST similarly in patients and controls (Table 3). Average TST was shortest in the second period for sleep in FD, scheduled from 17.45 h until 00.15 h. This corresponds with the data of another FD study in which healthy subjects were scheduled on 20-h subjective days (Wyatt et al., 1999), which showed that sleep was disrupted most when centered around CT16 (which approximates 21.00 h in the present study). Comparison of mood scores before and after the night with shortest TST reveals a slight (but non-significant) deterioration of mood in the depressed patients. Since in depression sleep deprivation on average induces a mood improvement, sleep deprivation effects cannot explain the observed course of mood.

Mood scores were obtained at 2-h intervals. Clear systematic changes of mood could be observed both as a function of the 20-h timescale and of circadian period. These findings show that the applied mood-sampling rate was adequate. Yet, it must be noted that changes within the 2-h intervals cannot be detected.

During the protocol, subjects were allowed a maximum of 4 cups of coffee per subjective morning. In an attempt to protect sleep quality, no caffeinated beverages were allowed during the rest of the day. On average, the actual consumption turned out to be 2.6 cups per day. There was no significant effect of time in study nor between conditions. As a result, we consider it unlikely that caffeine consumption masked intrinsic differences between conditions and groups.

As in the FD study in healthy subjects (Boivin et al., 1997), the present study shows both sleep–wake cycle- and pacemaker-related components in the course of mood. No significant differences were observed between patients and controls. For three of the four mood scales, the circadian and sleep–wake-related mood swings reached significance. Differences in the composition of the four

rating scales and possible ceiling effects in some of the scales used are likely explanations for the differences. Following the first 4 h of wakefulness in which mood was found to improve, in all conditions a subsequent worsening was observed with increasing duration of wakefulness. The circadian variation of mood in turn globally followed the sinusoidal circadian variation in core body temperature in all conditions. The observed minimum mood scores were centered near the circadian temperature minimum, which occurs in the early morning under entrained conditions. Unfortunately, due to the restricted length of the design, the possibility of differences in interaction between the two components (Boivin et al., 1997) could not be studied. For each condition, the reconstruction of the daily variation of mood by means of addition of the two components closely followed the average mood scores obtained at 09.00, 17.00 and 22.00 h during baseline.

The present study does not support the notion of an abnormal influence of the pacemaker on both psychological and physiological variables in SAD. Comparisons between SAD patients and controls revealed no significant differences in period or phase of the pacemaker assessed by salivary melatonin and the endogenous circadian variation in core body temperature. The observed reduction of endogenous circadian body temperature amplitude in the patients in winter is probably due to thermoregulatory mechanisms. Since the patients still had a low body temperature amplitude after light therapy, these data are inconsistent with the amplitude hypothesis by Czeisler et al. (1987). Contrary to previous constant routine studies (Dahl et al., 1993; Wirz-Justice et al., 1995; Avery et al., 1997), these results suggest that a disturbance of the circadian pacemaker is not likely to be involved in the pathogenesis of SAD. In view of the small number of subjects and the relatively short experimental period, the power of the statistical analysis is limited and the conclusions must be taken with care. Obviously, participation in this experiment, especially during a period of depression is very demanding. Nevertheless, the limited amount of data show no indication that the circadian regulation of mood is abnormal in SAD



patients. A replication study is required to corroborate this preliminary conclusion.

The present results might contribute to a better understanding of the mechanisms underlying the beneficial effects of light therapy. Although some authors have concluded that the timing of light therapy is not crucial (Wirz-Justice et al., 1993; Meesters et al., 1995), most studies show a slight superiority of morning light over evening light (e.g. Lewy et al., 1998; Terman et al., 2001). From circadian studies in healthy subjects, it is clear that morning light advances the circadian pacemaker (Honma and Honma, 1988; Czeisler et al., 1989; Minors et al., 1991; Jewett et al., 1997). It has also been observed that shifts of the pacemaker are accompanied by proportional shifts in psychological variables such as subjective alertness and cognitive performance (Czeisler et al., 1990). Thus, morning light therapy in SAD will not only phase-advance the pacemaker but also the rising limb of the pacemaker-related mood variation. Therefore, the rising part of the circadian mood variation will shift to an earlier clock time and might even occur during sleep. As a result, morning light therapy in SAD patients might provide a slightly better mood in the first part of the day.

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