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Testing the Hypothesis of a Circadian Phase Disturbance Underlying Depressive Mood in Nonseasonal Depression

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Abstract In a crossover design, 8 nonseasonal depressed subjects, selected on the presence of diurnal mood variations, and 8 sex- and age-matched controls were exposed to dim light (< 10 lux) in the evening (18:00-21:00 h) and bright light (2500 lux) in the morning (ML, 6:00-9:00 h), to dim light in the morning and bright light in the evening (EL), or to dim light both in the evening and in the morning (DL) during 3 consecutive days in each of these conditions. There were no initial phase differences between depressed and healthy subjects in the timing of dim light melatonin onset, sleep termination, and body temperature. The phase shifts after EL and ML in both healthy and depressed subjects were as expected on the basis of a human phase response curve. On average, there was no therapeutic effect of the light exposure in the depressed patients. Two patients improved, but these effects do not seem to be related to shifts in the circadian system.

Key words circadian rhythms, nonseasonal major depression, light, sleep, melatonin, mood

INTRODUCTION

The appealing hypothesis of a causal link between the disorganization of circadian rhythms and disturbed mood in affective disorders still is open to discussion (Van den Hoofdakker, 1994; Healy and Waterhouse, 1995; Wirz-Justice, 1995). Internal dissociation of rhythms driven by the biological clock in relation to the sleep-wake cycle is one of the options, proposed already by Papoušek (1975). In the "internal coincidence model" (Wehr and Wirz-Justice, 1981), a causal link is postulated between a phase advance of circadian rhythms and mood. Evidence consistent with such a causal relationship was obtained in (uncontrolled) experimental studies on the effects of

phase-advancing sleep, relative to internal rhythms (Wehr et al., 1979; Sack et al., 1985; Souëtre et al., 1987), with a beneficial effect on mood. Wehr and Goodwin (1983) reviewed evidence for a phase advance of circadian rhythms in depressives compared to healthy controls. Since then, however, many contradictory results have been presented, for example, those reviewed by Checkley (1989) and Van den Hoofdakker (1994). It is still unclear whether or not dissociated rhythms occur during depression and, if so, whether they are cause or effect of the mood disturbance or whether dissociated rhythms and mood disturbance are determined by an unknown common factor. In addition, the question of whether disturbed rhythms are due to a disorder of the biological clock or to

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changes in the phasing of external zeitgebers still is unanswered (Healy and Waterhouse, 1995).

In view of the inconsistency of the evidence for the existence and the pathogenetic significance of chronobiological disturbances in depression, it has been proposed that such disturbances might play a role in subgroups of depressed patients. One often mentioned possible indicator of chronobiological disturbances in depressed patients is diurnal mood variation. Recently, it has been reported that there are no clear subgroups of patients with and without diurnal mood variations and that the mood swings do not commonly show a clear 24-h pattern (Gordijn et al., 1994). However, the presence of daily mood swings, and especially the variability thereof, is highly related to the response to total sleep deprivation, in other words, to a manipulation of the sleep-wake cycle. Because of the relationship between diurnal mood variation and the sleep-wake cycle, it is supposed that patients with high daily mood variability are likely to suffer from underlying chronobiological disturbances. This idea is supported by the results of Volz et al. (1991); in their study, patients with diurnal variations of mood (feeling better in the evening) responded slightly better to 7 days of bright light therapy in the morning than did patients without diurnal mood variations.

The purpose of the present study is to test whether circadian phase disturbances play a causal role in the presence of depressive mood in a group of patients with large daily mood variations.

Theoretically, the "cause or effect" problem can be solved in two ways. The first possibility is to shift circadian rhythms relative to sleep and investigate the effects on mood. This can be achieved by exposing subjects to light at sensitive phases of the circadian system, that is, times at which it may be expected to produce phase shifts. In healthy subjects, 2 or 3 days of bright morning or evening light produced substantial shifts (Czeisler et al., 1986; Dijk et al., 1987) and amplitude changes (Jewett et al., 1991, 1994) in circadian rhythms. The second possibility to induce phase-angle differences between circadian rhythms and sleep is to force a sleep shift while keeping the other clock-related rhythms unchanged. This should be possible by controlling the light-dark cycle while sleep time is changed. As noted earlier, phase shifts of sleep resulted in mood changes in depressed subjects (Wehr et al., 1979; Sack et al., 1985; Soutre et al., 1987), but in these studies the light-dark cycle was shifted as

well. In the present study, we chose the first procedure; that is, subjects were exposed to bright light at particular times of the day to produce phase shifts while sleep time was fixed.

Exposing depressive subjects to bright artificial light is very common, especially in winter depressives, because of the "renewed" discovery of its beneficial effect in this group of patients (reviewed in Terman et al., 1989). The beneficial effect of "light therapy" in nonseasonal depressives is less clear. The effects reported are controversial because most studies have some serious drawbacks. For a recent review of the effects of light therapy in nonseasonal depression, see Van den Hoofdakker and Gordijn (1997). In all studies, various times and durations of light exposure, as well as different designs, were used. The possibility that only a subgroup of the nonseasonal depressed patients responds favorably to light treatment is proposed, but the possible predicting characteristics are unknown. Deltito et al. (1991) reported superiority of light in bipolar patients, Kripke et al. (1992) mentioned a "trend for better response among bipolars," and Bauer (1993) reported a large beneficial effect of light in three bipolar patients. Stewart et al. (1990) tested whether the selection on atypical symptoms in nonseasonals predicted response to light, but they found no significant therapeutic effect of 2 weeks of light therapy. Although the hypothesis of a circadian phase disturbance underlying depression is discussed in most of the literature, a controlled study of light exposure with the purpose of shifting circadian rhythms in nonseasonal depressives hardly ever is carried out. Either light is given both in the morning and in the evening (Dietzel et al., 1986; Peter, 1986; Kripke et al., 1987, 1992) or light exposure at other sensitive phases of the biological clock is not avoided (Deltito et al., 1991; Bauer, 1993; Thaln et al., 1995). Obviously, both approaches are inadequate to induce systematic shifts in circadian rhythms. In three studies, the effects of controlled light exposure on the depressive symptomatology in relation to shifts in circadian rhythms were tested. With the exception of the case study by Lewy et al. (1985), the two recent large studies by Rao et al. (1992) and Yamada et al. (1995) provided no evidence for a relationship between clinical change and chronobiological variables. This conclusion was based on comparisons between groups of patients, not selected for possible predicting characteristics.

In the present study, we selected depressive subjects with large diurnal mood variations. In a cross-

over paradigm, they received either dim light both in the morning and in the evening, dim light in the morning and bright light in the evening, or bright light in the morning and dim light in the evening. The effects on circadian rhythms and mood were recorded and compared to the effects of the same procedure in healthy age- and gender-matched controls.

METHODS

Subjects

A total of 10 depressed patients entered the study. Due to physical illness of 1 patient after 2 days in the study and a change in diagnosis of another patient at the end of the study, results are presented for 8 subjects. Of these, 7 patients were outpatients and 1 was admitted to the hospital. DSM-III-R diagnoses were major depression ($n = 7$) and dysthymic disorder ($n = 1$). No subject reported seasonal variations in mood. The patients were free of any use of medication, had no major somatic disease, and did not abuse drugs or alcohol. They showed extreme diurnal variations of depressed mood in a 1-week observation period. During this week, self-ratings were completed three times daily (9:00, 17:00, and 22:00 h) by means of the Dutch version of Von Zerssen's Adjective Mood Scale (AMS) (Von Zerssen, 1976; Elsenga, 1988). The ratings range from 56 (most severely depressed) to 0 (not depressed). "Extreme diurnal variations of depressed mood" was defined by a difference of at least 10 points between two daily ratings on at least 3 out of 7 days. At least one rating on these 3 days had to be higher than 25. The decision of including a patient was made during that selection week. Once included, every subject underwent all experimental conditions regardless of the depression score at the start of each of these conditions. Controls were recruited by newsletter advertisement. They were selected on having no history of depression or any other mental illness. They had to be physically healthy and not on medication or drugs. Their sleep-wake behavior had to be regular without habitual naps. After they were informed about the experimental procedure, they were on call and notified when an appropriate depressed subject was selected. Healthy subjects were matched to depressed subjects on age and gender. Except for 2 subjects, the healthy subjects took part in the experiment in the same season of the year in which the depressives were

studied. The design of the experiment and the measurements performed were exactly the same for both groups. The study was approved by the ethical committee. Both depressed subjects and healthy subjects signed written informed consents.

Design

The experimental period lasted 4 weeks. During the first, second, and fourth weeks (further referred to as experimental weeks), all subjects came to the laboratory on 4 days at 18:00 h and stayed there until 9:00 h the next morning. The third week served as a washout period. In this week, no laboratory visits were scheduled. On experimental weeks, between 9:00 and 18:00 h, subjects followed their normal daily routines; only intensive sporting, drinking alcohol, and daytime sleeping were not allowed. From 18:00 until 9:00 h, the subjects stayed individually in a dimly lit room (one 15-watt light bulb, at 1 m eye distance, less than 10 lux). During walks inside the building, they wore dark goggles. They were allowed to read or watch television and were visited regularly by one of the researchers to prevent them from sleeping. Sleep time was fixed from 22:00 until 6:00 h during the first 3 nights of each experimental week while lights were off. The first week served as control with dim light exposure (DL) both in the morning and in the evening. During the second and fourth weeks, subjects were exposed to bright light (2500 lux) either in the morning (ML, 6:00-9:00 h) or in the evening (EL, 18:00-21:00 h) on 3 consecutive days in a crossover design. In each group, 4 subjects started in the second week with ML and 4 with EL. The light fixtures contained 8 full-spectrum fluorescent light tubes (Duro-lite, 40 watts) in a light box of 110 × 120 cm placed vertically at an eye distance of 60 cm; ultraviolet light (< 400 nm) was filtered out. In the fourth night of each experimental week, circadian rhythms and sleep were recorded. In this night, subjects stayed in dim light until midnight. At that time, they went to bed and were instructed to sleep until spontaneous wake-up time.

Measurements

To assess the phase of the circadian pacemaker, three variables were measured—dim light melatonin onset (DLMO), core body temperature, and sleep timing. All these variables were obtained during the

fourth evening and night. During this evening, with dim light and bedtime at midnight, the direct influence of the experimental condition and related behavior on the variables under study were considered to be equal for all individuals in all conditions.

Dim light melatonin onset. To assess the DLMO, hourly saliva samples were collected from 18:00 until midnight while the subjects stayed in dim light (< 10 lux). No coffee or tea was served, and teeth brushing was postponed because of the possible contaminating effects of these substances for assessing melatonin in saliva (Gordijn et al., 1991). Subjects were sitting in a chair while producing the saliva to control for the influence of posture on melatonin concentration (Deacon and Arendt, 1994). Limited eating, drinking, and smoking was allowed in the first quarter of each hour, after which the mouth was rinsed with water. Three quarters of an hour later, saliva was collected. Immediately after collection, the saliva was frozen at -20°C for later analysis. Melatonin was assessed by radioimmunoassay in our laboratory. The method was, in essentials, described by Vakkuri et al. (1984) and Vakkuri (1985) and was performed with [^3H]melatonin. Through the melatonin results, a sigmoid-shaped curve was fitted using a four-parameter logistic function with the form

$$f(x) = \frac{a}{1 + e^{b(x-c)}} + d.$$

DLMO was arbitrarily defined as the time when the fitted curve exceeded a melatonin level of 20 pmol/liter. For 3 depressed and 2 healthy subjects, it appeared to be necessary to lower or increase this level (until 10 or 30 pmol/liter) to obtain paired data for all conditions.

Core body temperature. Core body temperature was recorded in each experimental week during the third and fourth night and the day in between by an ambulatory recording system—either a Vitalog with a sample rate of 0.25 min or a homemade three-channel recording system (JOBLOG; Bakker and Beersma, 1991) set to a 1-min sample rate. Subsequently, each set of four 0.25-min samples of the Vitalog system was averaged, also resulting in a sampling interval of 1 min. Small intervals of missing data (≤ 15 min) due to removal of the temperature probe were linearly inter-

polated. For the present analysis, the average temperature per 10-min blocks was calculated from midnight until 7:00 h during the fourth night. The median body temperature was calculated over this period. The time of the midcrossing point between the first interception of decreasing body temperature with the median and the last interception of increasing body temperature with the median was used as an indicator of circadian phase.

Sleep timing. During the third and fourth nights of each experimental week, sleep recordings were made. Nine electrodes were attached with collodium 1 or 2 h before bedtime (Jasper, 1958)—EEG derived from C4-A1 and C3-A2, 2 EOG, submental EMG, and one earth electrode on the forehead. EEG signals were digitized with a sample rate of 128 Hz, EOG and EMG with a sample rate of 64 Hz, and they were stored on magnetic tape of a micro-Vax VMS system. Afterward, EEG, EOG, and EMG could be replayed on a 17-inch screen, and visual scoring per 30-sec epoch according to Rechtschaffen and Kales (1968) was performed. In the third night, time in bed was planned from 22:00 until 6:00 h. Only wake-up time was assessed in this night (the end time of the last page of Stage 2, 3, or 4 or rapid eye movement [REM] sleep). (Dim) Lights off in the fourth night was set to midnight, and subjects were instructed to sleep until they felt refreshed. Sleep timing in the fourth night was assessed on the basis of time of sleep onset (the start time of the first page of Stage 2 or REM sleep) and wake-up time.

Depressed mood, various aspects of activation, and sleep quality were assessed by multiple self-ratings during the entire 4-week period. The Dutch version of Von Zerssen's AMS (Von Zerssen, 1976; Elsenga, 1988), which measures depressed mood; the Activation-Deactivation Adjective Checklist (Thayer, 1967), which measures four components of activation (energy, tension, calmness, and tiredness); the Stanford Sleepiness Scale (Hoddes et al., 1973); and a Visual Analog Scale (VAS), which measures depressed mood, anger, anxiety, and elation (Albersnagel, 1988), were completed three times daily at 9:00, 17:00, and 22:00 h. The Sleep Quality Scale (Mulder-Hajonides v.d. Meulen et al. 1980) was completed daily at 9:00 h. Depressed mood also was assessed with the Beck Depression Inventory (BDI) (Beck and Steer, 1987) on the mornings of Day 1 (the first day of EL and last day before ML) and Day 4 (the first day after EL and last

day of ML) of each experimental week and on the morning of the first day of Week 6. This last BDI, together with the BDI at Day 1 of Week 4, made it possible to compare mood 11 days after ML with mood 12 days after EL.² In addition, severity of depression was assessed by the 21-item version of the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). The interview was held between 9:00 and 11:00 h on Day 1 and Day 4 of each experimental week and was scored by two independent, experienced raters. The final score was calculated by averaging the scores of the two raters. In the present study, average self-ratings of mood and activation on Day 1 and Day 4 were calculated and analyzed. Terman et al.'s (1989) criteria for improvement after light therapy in seasonal affective disorder (> 50% reduction of the HRSD rating and a final score of less than 8) were used to define response. Moreover, an expectations questionnaire concerning the effects on mood, general activation, anxiety, and sleepiness was presented on Day 1 of each experimental week.

Statistics

Statistical procedures included analysis of variance (ANOVA), multiple analysis of variance (MANOVA) with repeated measures with planned comparison for statistical significant differences, Wilcoxon matched pairs signed rank test, and Kendall correlations. A probability level of $p < .05$ was taken as the level of statistical significance for all tests. Because of the small group size ($n = 8$ in both groups), trends in the data with p values between .05 and .10 also are presented.

RESULTS

Subject Characteristics

The groups consisted of 5 females and 3 males. Average ages of depressed subjects (38.3 ± 12.2 years) and healthy controls (38.7 ± 12.9 years) did not differ significantly; the individual differences between patients and matched controls range from -0.7 to 1.5 years. Average severity of depression (HRSD) as mea-

sured at the first day of the DL week was 18.4 ± 3.3 in depressed subjects and 2.1 ± 1.9 in healthy controls. In 6 of 8 cases, we managed to study the matched controls in the same month (± 1) as the depressed subjects. The last 2 healthy subjects were measured 6 and 4 months later than the matched depressed subjects. Due to the 4-week duration of the experiment, it was impossible to avoid particular phases of the menstrual cycle. We did not control the start of the experiment for menstrual phase.

Circadian Variables

Effects on Melatonin Profile

In healthy and depressed subjects, the profile of melatonin concentrations after ML is shifted to an earlier phase than after EL, whereas in the DL condition it is in between (Fig. 1, left panels). In the depressed group, the melatonin concentration at 21:00 h was significantly higher after ML than in the DL condition (Wilcoxon matched pairs, $p < .05$). At 21:00 and 22:00 h, the melatonin concentration after ML also was higher compared to EL, although this difference was not statistically significant ($ps = .05$ and .06, respectively). In the group of healthy subjects, there was a significantly higher level of melatonin after ML compared to EL at 21:00 and 22:00 h ($p < .05$) and a significantly higher level after ML compared to DL at 21:00 h. In addition, there were some differences that showed nonsignificant trends (Fig. 1, left panels).

Curve fitting through the average curves yielded DLMO values that confirm the interpretation that these differences were the result of shifts of the melatonin profiles. In depressed subjects, DLMO after DL occurred at 21:08 h, after EL at 21:55 h, and after ML at 20:24 h. In healthy subjects, DLMO values were 21:24 h, after DL, 21:49 h after EL, and 19:55 h after ML. A comparison of the melatonin profiles in depressed subjects with the profiles in healthy subjects yielded no significant differences in all three conditions (Fig. 2, upper panels). This means that the effects of the three lighting conditions on the melatonin profiles were not different between depressed and healthy subjects.

Next, we compared the two most extreme conditions with respect to the timing of melatonin—the ML and EL conditions within individuals. The comparison of DLMO after EL and ML was possible in 6

2. The 1-day difference is due to the fact that ML is given from Tuesday until Thursday, whereas EL is given from Monday until Wednesday.

Figure 1. Profiles of melatonin concentration in saliva during the evening after various lighting conditions in depressed ($n = 8$) and healthy ($n = 8$) subjects (left panels) and accumulation of wakefulness after sleep onset during the night after various lighting conditions in depressed ($n = 8$) and healthy ($n = 7$) subjects (right panels). Statistics (Wilcoxon matched pairs): $+p < .10$, $*p < .05$, indicated at the appropriate times.

healthy and 7 depressed subjects; in the other subjects, melatonin concentrations were so low that DLMO could not be determined reliably in one or both conditions. In 4 depressed and 4 healthy subjects, the melatonin level of 20 pmol/liter was used as a criterion to assess DLMO; in 1 depressed and 1 healthy subject, a higher criterion level was necessary; and in 2 depressed subjects and 1 healthy subject, a lower level was used. Because the criterion level for DLMO differed between subjects, the absolute times of DLMO after EL and ML cannot be compared across individuals.

The shifts of DLMO after ML compared to EL were in the expected direction in all individuals; the onsets after ML were earlier than those after EL (Fig. 3, left panels). On average, in healthy subjects, DLMO after ML started 87 min earlier than after EL ($p < .05$, Wilcoxon test); in depressed subjects, it started 85 min earlier after ML than after EL ($p < .05$).

Effects on Sleep Variables

Wake-up times in the third night did not differ significantly between conditions or between groups

Figure 2. Profiles of melatonin concentration in saliva during the evening after various lighting conditions in depressed ($n = 8$) and healthy ($n = 8$) subjects (upper panels) and accumulation of wakefulness after sleep onset during the night after various lighting conditions in depressed ($n = 7$) and healthy ($n = 7$) subjects (lower panels). $+p < .10$.

(patients: DL = 5:58 h $\pm$ 5 min, EL = 5:53 h $\pm$ 14 min, ML = 5:50 h $\pm$ 28 min; controls: DL = 5:56 h $\pm$ 15 min, EL = 5:48 h $\pm$ 35 min, ML = 5:59 h $\pm$ 4 min).

During 1 registration night (fourth night), all electrodes were torn loose by 1 of the healthy subjects. For this reason, the precise wake-up time according to the EEG measures is missing in 1 night after ML. However, times of lights off and sleep onset are available. Also, spontaneous rising time is known. Because in

this individual's other 2 registration nights there were only 2 and 2½ min, respectively, between wake-up time and rising time, an estimate of wake-up time was derived by subtracting 2 min from rising time in the night under consideration.

No statistical main effect (MANOVA with repeated measurements, two factors, two and three levels, respectively) between depressed and healthy subjects was found for the sleep variables presented (Table 1).

Figure 3. Timing of dim light melatonin onset, sleep termination, and time of temperature midpoint after 3 days of evening light and 3 days of morning light in depressed ($n = 8$) and healthy ($n = 8$) subjects. Paired data from individual subjects are interconnected by straight lines; unpaired data are shown by symbols only. Left panels: individual melatonin levels were used to obtain paired data: $\bullet$ $\circ$ level = 20 pMol/liter, $\blacksquare$ $\square$ level = lower than 20 (10 or 15) pMol/liter, $\blacktriangle$ $\triangle$ level = higher than 20 (25 or 30) pMol/liter. Middle panels: *estimated wake-up time (see text). Right panels: time of temperature midpoint, defined as the midpoint between downward and upward crossing of body temperature through the median value.

Times of lights off were the same for both groups in all conditions, as was intended. There was a significant Group $\times$ Condition interaction effect for sleep onset time ($p < .05$). Planned comparison yielded a significant difference between controls and patients in sleep onset after ML compared to DL; patients showed an earlier sleep onset after ML compared to DL, whereas controls showed the opposite ($p < .05$). Controls showed a trend in earlier sleep onset after EL compared to ML where patients showed the opposite ($p = .06$). The largest difference, however, is found in wake-up times. A significant main effect for condition was found, but no interaction effect was found. On aver-

age, wake-up time after ML was 78 min earlier than wake-up time after EL in depressed subjects and 50 min earlier in healthy subjects. Wake-up time in DL was situated in between, but was not significantly different from, wake-up times after both ML and EL.

The right panels in Fig. 1 present the average accumulation of "wakefulness after sleep onset" in the three conditions. This figure suggests that the tendency for sleep termination speeds up earlier after ML than after EL (significantly different at 9 and 10 h since sleep onset in patients, $p < .05$, and at 6, 8, 9, and 10 h since sleep onset in controls). The data for DL are in between. During the first hour of sleep, controls were

Table 1. Effects ($\pm$ SD) on sleep variables (mean hours and minutes $\pm$ min) in the fourth night after 3 days of different light exposures.

Sleep Variable	Depressed Subjects			Healthy Subjects		
	DL	ML	EL	DL	ML	EL
Lights off	00:05 $\pm$ 3	00:05 $\pm$ 5	00:06 $\pm$ 7	00:06 $\pm$ 5	00:08 $\pm$ 8	00:08 $\pm$ 8
Sleep onset ^a	00:21 $\pm$ 10	00:14 $\pm$ 9	00:19 $\pm$ 11	00:17 $\pm$ 7	00:21 $\pm$ 8	00:18 $\pm$ 8
Wake-up time ^b	08:31 $\pm$ 88	07:44 $\pm$ 42	09:02 $\pm$ 54	07:39 $\pm$ 87	07:30 $\pm$ 86	08:20 $\pm$ 72

NOTE: DL = dim light (< 10 lux 18:00-21:00 h and < 10 lux 6:00-9:00 h); ML = morning light (< 10 lux 18:00-21:00 h and 2500 lux 6:00-9:00 h); EL = evening light (2500 lux 18:00-21:00 h and < 10 lux 6:00-9:00 h). Multiple analysis of variance with repeated measurements (Factor 1: subject group, 2 levels; Factor 2: condition, 3 levels, Wilks's lambda), $n = 8$ in both groups.

a. Significant interaction effect: Group versus Condition, $p < .05$ —Group $\times$ DL-ML, $F(1, 14) = 7.79$, $p < .05$; Group $\times$ ML-EL, $F(1, 14) = 4.26$, $p = .06$.

b. Main effect of condition, $p < .001$: ML-EL, $F(1, 14) = 19.61$, $p < .001$.

significantly less awake after EL than after DL, but the difference was very small (5.5 min).

After DL and ML, the accumulation of wakefulness slightly differs between patients and healthy subjects (Fig. 2, lower panels). After DL, healthy subjects showed a few minutes more wakefulness after 3, 4, 7, and 9 h since sleep onset ($n = 7$, $p < .10$). After ML, the accumulation of wakefulness increased earlier in healthy subjects after 7, 8, 9, and 10 h since sleep onset ($n = 7$, $p < .10$). The accumulation of wakefulness after EL was not significantly different.

The individuals' wake-up times after EL and ML are presented in the middle panels of Fig. 3. In the group of depressed subjects, wake-up times were later after EL than after ML in all 8 subjects. In the group of healthy subjects, 1 subject showed later wake-up time after ML than after EL; the data of the other 7 subjects confirmed the expectations.

Effects on Body Temperature

Unfortunately, several registrations of body temperature are missing, mainly due to improper positioning of the temperature probe. Therefore, the results have to be interpreted with caution. The right panels of Fig. 3 represent the phase of the midpoint between downward and upward crossing of body temperature through the median value in individuals after EL and ML. In both depressed subjects ($n = 4$) and healthy subjects ($n = 6$), the timing of this midpoint was later after EL than after ML. ANOVA with repeated measurements revealed no significant difference between the two groups (difference between ML and EL: in depressed subjects, 70 min; in healthy subjects, 30 min, n.s.). However, there was a significant

difference between lighting conditions; the phase of the temperature midpoint was significantly earlier after ML compared to EL in the group of healthy subjects (30 min, $n = 6$, $F = 28.07$, $p < .01$) as well as in the combined group of depressed and healthy subjects (41 min, $n = 10$, $F = 12.29$, $p < .01$).

Finally, we examined the interrelationship between the shifts of the three variables—DLMO, wake-up time, and body temperature midcrossing. Linear regression revealed no significant intercorrelations (depressed and healthy subjects combined, n ranges from 7 to 13).

Effects on Mood and Activation

Tables 2 and 3 present the average scores of the self-ratings and the HRSD on Day 1 and Day 4 in the depressed and healthy subjects.

Except for the ratings on the VAS for "anger," the depressed subjects differed significantly from the healthy subjects on all ratings (ANOVA). MANOVA with repeated measurements was carried out within groups.

Within the group of depressed subjects, MANOVA revealed only one significant main effect for the factor "Day 1/Day 4"; this means that the HRSD ratings at Day 4 were lower compared to those at Day 1. No significant interaction effect was found. Thus, the magnitude of the reduction in HRSD ratings (2.2 points on average) did not differ between conditions. Also, no differences between conditions were observed when we tested the HRSD ratings at Day 4 of each condition with the HRSD ratings at Day 1 as a covariate; this means that there was no difference in severity of depression at Day 4 between conditions if

Table 2. Average ($\pm$ SD) mood ratings in depressed subjects 1 day before (Day 1) and 1 day after (Day 4) 3 consecutive days of (dim) light exposure.

	DL		ML		EL	
	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
AMS depression	36.5 $\pm$ 8.6	32.0 $\pm$ 13.5	29.5 $\pm$ 12.9	27.9 $\pm$ 14.7	29.9 $\pm$ 16.7	32.2 $\pm$ 12.4
AD-ACL energy	8.1 $\pm$ 1.5	9.6 $\pm$ 2.7	9.5 $\pm$ 2.4	10.9 $\pm$ 2.4	10.3 $\pm$ 3.3	10.1 $\pm$ 1.3
AD-ACL tiredness	15.4 $\pm$ 3.0	14.2 $\pm$ 2.7	14.8 $\pm$ 2.6	14.4 $\pm$ 2.2	14.0 $\pm$ 2.4	14.4 $\pm$ 1.5
AD-ACL tension	12.0 $\pm$ 2.2	11.7 $\pm$ 1.8	11.4 $\pm$ 2.6	11.1 $\pm$ 2.2	11.2 $\pm$ 1.7	12.2 $\pm$ 1.8
AD-ACL calmness	13.1 $\pm$ 1.8	13.0 $\pm$ 1.9	13.6 $\pm$ 2.5	14.0 $\pm$ 2.2	12.9 $\pm$ 1.2	12.9 $\pm$ 1.6
SSS sleepiness	4.1 $\pm$ 0.7	3.4 $\pm$ 0.7	3.4 $\pm$ 0.7	3.4 $\pm$ 0.6	3.3 $\pm$ 1.0	3.5 $\pm$ 0.4
SQS sleep quality	8.5 $\pm$ 2.8	6.5 $\pm$ 4.4	6.8 $\pm$ 4.3	5.0 $\pm$ 3.1	6.1 $\pm$ 4.3	6.3 $\pm$ 3.9
VAS anxiety	33.8 $\pm$ 20.4	32.9 $\pm$ 12.4	28.0 $\pm$ 13.9	25.1 $\pm$ 17.3	30.9 $\pm$ 17.0	32.8 $\pm$ 15.5
VAS anger	8.5 $\pm$ 11.0	8.2 $\pm$ 9.1	12.6 $\pm$ 14.9	18.5 $\pm$ 18.8	12.1 $\pm$ 13.3	18.3 $\pm$ 19.7
VAS depression	49.3 $\pm$ 18.7	43.5 $\pm$ 26.2	36.4 $\pm$ 27.7	39.8 $\pm$ 31.0	39.5 $\pm$ 26.6	41.2 $\pm$ 21.9
VAS elation	26.0 $\pm$ 10.0	31.8 $\pm$ 13.8	39.8 $\pm$ 13.8	37.4 $\pm$ 20.0	37.1 $\pm$ 17.0	35.1 $\pm$ 9.6
BDI depression	18.3 $\pm$ 8.6	15.6 $\pm$ 9.1	14.5 $\pm$ 7.6	13.6 $\pm$ 11.3	14.4 $\pm$ 8.3	16.4 $\pm$ 11.1
HRSD depression ^a	18.4 $\pm$ 3.3	13.6 $\pm$ 3.6	14.8 $\pm$ 4.7	14.3 $\pm$ 5.9	16.2 $\pm$ 5.7	15.0 $\pm$ 4.6

NOTE: DL = dim light (< 10 lux 18:00-21:00 h and < 10 lux 6:00-9:00 h); ML = morning light (< 10 lux 18:00-21:00 h and 2500 lux 6:00-9:00 h); EL = evening light (2500 lux 18:00-21:00 h and < 10 lux 6:00-9:00 h). MANOVA with repeated measurements (Factor 1: condition, 3 levels, Wilks's lambda; Factor 2: Day 1/Day 4, 2 levels). AMS = Adjective Mood Scale; AD-ACL = Activation-Deactivation Adjective Checklist; SSS = Stanford Sleepiness Scale; SQS = Sleep Quality Scale; VAS = Visual Analog Scale; BDI = Beck Depression Inventory; HRSD = Hamilton Rating Scale for Depression.

a. Main effect factor: Day 1/Day 4, $F(1, 7) = 21.88$, $p < .01$.

Table 3. Average ($\pm$ SD) mood ratings in healthy subjects 1 day before (Day 1) and 1 day after (Day 4) 3 consecutive days of (dim) light exposure.

	DL		ML		EL	
	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
AMS depression ^a	5.6 $\pm$ 3.2	3.9 $\pm$ 3.8	3.5 $\pm$ 3.7	5.3 $\pm$ 5.3	4.0 $\pm$ 4.1	5.7 $\pm$ 6.2
AD-ACL energy	16.2 $\pm$ 2.6	17.0 $\pm$ 3.2	17.0 $\pm$ 3.1	16.6 $\pm$ 3.4	16.5 $\pm$ 3.1	16.0 $\pm$ 3.7
AD-ACL tiredness	9.8 $\pm$ 2.4	8.6 $\pm$ 2.8	8.7 $\pm$ 3.0	8.9 $\pm$ 3.6	9.0 $\pm$ 3.2	9.3 $\pm$ 3.4
AD-ACL tension	7.4 $\pm$ 2.0	7.2 $\pm$ 2.3	7.4 $\pm$ 2.8	7.9 $\pm$ 3.5	7.1 $\pm$ 2.8	7.3 $\pm$ 3.5
AD-ACL calmness	16.2 $\pm$ 1.6	15.9 $\pm$ 1.3	16.0 $\pm$ 1.5	16.3 $\pm$ 1.8	16.5 $\pm$ 1.8	16.3 $\pm$ 1.8
SSS sleepiness	2.3 $\pm$ 1.2	1.6 $\pm$ 0.6	1.5 $\pm$ 0.5	1.6 $\pm$ 0.6	1.8 $\pm$ 0.8	1.8 $\pm$ 0.6
SQS sleep quality	2.3 $\pm$ 1.9	1.9 $\pm$ 1.9	1.0 $\pm$ 1.1	2.3 $\pm$ 2.9	2.0 $\pm$ 2.3	3.0 $\pm$ 3.1
VAS anxiety ^b	13.9 $\pm$ 12.3	7.5 $\pm$ 8.4	6.6 $\pm$ 9.6	6.6 $\pm$ 8.7	5.2 $\pm$ 7.7	4.7 $\pm$ 7.0
VAS anger	11.1 $\pm$ 11.5	5.9 $\pm$ 6.6	5.3 $\pm$ 6.5	4.4 $\pm$ 4.8	4.0 $\pm$ 5.3	3.3 $\pm$ 7.0
VAS depression	15.1 $\pm$ 14.3	7.5 $\pm$ 6.8	5.5 $\pm$ 7.8	6.1 $\pm$ 7.2	5.2 $\pm$ 5.7	6.8 $\pm$ 6.2
VAS elation ^c	64.4 $\pm$ 14.8	73.6 $\pm$ 17.2	77.2 $\pm$ 16.8	74.1 $\pm$ 19.6	71.0 $\pm$ 16.4	71.1 $\pm$ 17.6
BDI depression	1.4 $\pm$ 1.5	2.0 $\pm$ 3.2	0.3 $\pm$ 0.5	1.0 $\pm$ 1.2	0.1 $\pm$ 0.4	0.6 $\pm$ 0.9
HRSD depression	2.1 $\pm$ 1.9	1.8 $\pm$ 1.2	1.4 $\pm$ 1.6	2.3 $\pm$ 1.8	1.5 $\pm$ 1.3	2.3 $\pm$ 1.5

NOTE: DL = dim light (< 10 lux 18:00-21:00 h and < 10 lux 6:00-9:00 h); ML = morning light (< 10 lux 18:00-21:00 h and 2500 lux 6:00-9:00 h); EL = evening light (2500 lux 18:00-21:00 h and < 10 lux 6:00-9:00 h). MANOVA with repeated measurements (Factor 1: condition, 3 levels, Wilks's lambda; Factor 2: Day 1/Day 4, 2 levels). AMS = Adjective Mood Scale; AD-ACL = Activation-Deactivation Adjective Checklist; SSS = Stanford Sleepiness Scale; SQS = Sleep Quality Scale; VAS = Visual Analog Scale; BDI = Beck Depression Inventory; HRSD = Hamilton Rating Scale for Depression.

a. Significant interaction effect: Condition versus Day 1/Day 4, $p = .05$ —DL-ML/day, $F(1, 7) = 11.61$, $p < .05$; DL-EL/day, $F(1, 7) = 9.22$, $p < .05$.

b. Main effect of condition, $p < .05$: DL-ML, $F(1, 7) = 9.77$, $p < .05$; DL-EL, $F(1, 7) = 13.70$, $p < .01$; ML-EL, $F(1, 7) = 5.58$, $p = .05$. Main effect of Day 1/Day 4, $p = .05$. Significant interaction effect: Condition versus Day 1/Day 4, $p = .05$ —DL-ML/day, $F(1, 7) = 10.92$, $p < .05$; DL-EL/day, $F(1, 7) = 11.41$, $p < .05$.

c. Main effect of condition, $p < .05$: DL-ML, $F(1, 7) = 8.94$, $p < .05$; ML-EL, $F(1, 7) = 5.97$, $p < .05$.

controlled for possible differences in severity of depression at Day 1. Not one of the self-ratings differed between conditions or from Day 1 to Day 4. BDI ratings 11 days after ML were not significantly different from BDI ratings 12 days after EL (not in Table 2 [1 BDI missing]), BDI ratings 11 days after ML (15.9 ± 9.0) were not significantly different (1 BDI missing, $n = 7$, n.s.) 12 days after EL (13.4 ± 6.3).

Observation of the individual data revealed 1 subject who was improved after the DL condition and 1 who was improved after the ML condition, according to HRSD criteria—a pre-post difference $> 50\%$ and a final rating < 8 . Both subjects remained rather well over the subsequent light conditions—HRSD ratings of 10 before and 8 after ML and 9 before and after EL in the first subject and HRSD ratings of 9 before and 11.5 after EL in the second subject.

Within the group of healthy subjects, some significant differences were found. Planned comparison after the significant interaction effect in the AMS depression ratings revealed that the decrease after DL differed significantly from the increase after ML and from the increase after EL (for significance, see Table 3). However, the raw data show that the scores are quite different from those of the depressed subjects. Depressive mood increased only slightly, and the scores after ML and EL are comparable with the values before DL. Anxiety differed significantly between all conditions. The highest values were found before and after DL and the lowest before and after EL, with the ratings before and after ML in between. Anxiety decreased significantly over the experimental weeks and showed a significant interaction effect. The decrease of anxiety after DL was largest compared to the decrease after EL and the absence of change after ML. Elation ratings differed only between conditions, with slightly higher ratings before and after ML than before and after DL and EL.

Summarizing the effects of morning and evening light, in depressive subjects there is no effect on any of the self-rating variables, whereas in healthy subjects there is a minor difference (i.e., elation and anxiety are somewhat higher before and after ML than before and after EL).

The overall subjective expectation at the beginning of the experimental weeks did not differ between the three conditions, both for depressed subjects and for healthy subjects. There was a trend in healthy subjects

of a different expectation of ML effects compared to EL effects ($p = .06$). This difference was caused mainly by the expectation to become more sleepy by EL.

Relationship between Mood and Circadian Phase

The question of whether there is a direct relationship between mood and circadian phase is difficult to answer. Although all three variables showed shifts in the same direction after EL compared to ML, the magnitude of the shifts differed. This resulted in the absence of significant interrelationships. Therefore, it is unclear which variable should be chosen as a marker of circadian phase. In addition, the group size ($n = 8$) is too small to justify a statistical approach.

However, it is interesting to observe the phase shifts in the 2 subjects who were improved, 1 after the ML condition and 1 after the DL condition. The first subject, who had received ML as the first condition after DL, showed a relatively large phase advance of wake-up time (94 min earlier than after DL) but shifted back completely after EL (wake-up time 4 min later than after DL) without deterioration of mood. DLMO in this subject showed phase delays after ML (–41 min) as well as after EL (–148 min) relative to the phase after DL. Unfortunately, the phase of the body temperature rhythm could not be determined after ML. The second subject who was improved after DL showed phase delays in wake-up time both after EL (–77 min, the first condition after DL) and after subsequent ML (–21 min) relative to the phase after DL without deterioration of mood. DLMO was not shifted after EL compared to DLMO after DL but shifted in advance after ML compared to DL (+43 min). The phase of the body temperature rhythm showed a large phase delay after EL compared to the phase after DL (–175 min) and also a phase delay after ML relative to the phase after DL (–91 min).

DISCUSSION

Limitations of the Study

The aim of this study was to determine whether circadian phase disturbances play a role in the pathogenesis of depressive mood. To induce a clear shift in circadian rhythms, 3 days of bright light exposure at the appropriate time of day, while preventing light

exposure during the other sensitive parts of the phase response curve, are sufficient in healthy subjects (Czeisler et al., 1986; Dijk et al., 1987). Light therapy induces quick mood changes in seasonal affective disorders in about the same time span (3-5 days) (Meesters et al., 1995), although longer treatment durations have been reported to result in further improvement (Bauer et al., 1994; Labbate et al., 1995). Usually, improvement of nonseasonal depressive patients takes far more time. For instance, pharmacological treatment with tricyclic antidepressives takes at least 3 weeks to induce therapeutic effects. On the other hand, also in nonseasonal depressives, fast improvement is actually possible as demonstrated by the immediate effects of total sleep deprivation (for a recent review, see Van den Hoofdakker, 1994). In the course of our study, it became clear that the overall responses of our nonseasonal depressed patients to the short-lasting light conditions were clinically negligible. Moreover, data were being published suggesting that in those cases in which nonseasonal depressives were reported to benefit from light therapy, longer periods of treatment were used (Kripke et al., 1992; Rao et al., 1992; Wetterberg, 1992). For those reasons, we limited the study to 8 patients. This small group size raises the possibility of insufficient power to detect differences. The strong point of the present study is that it is a within-subjects comparison, in contrast to the between-subjects comparison of two other studies that examined clinical change in relation to chronobiological variables (Rao et al., 1992; Yamada et al., 1995). In this context, the present study might play a role in the discussion on the possible pathogenic role of circadian phase disturbances in depression.

Effects on Circadian Rhythms

The time courses of the three physiological variables—DLMO, core body temperature, and sleep termination—are supposed to be under the control of the circadian pacemaker. After DL, no clear differences in phase positions of these variables were found between healthy and depressed subjects. This result does not indicate an abnormal phase position of the biological clock in our sample of depressives. The accumulation of wakefulness after sleep onset differs between depressives and controls after DL and ML, but these differences were significant only at a level of $p < .10$

and were observed not only at the end of the night but also at various times during the night (after DL). Therefore, we do not interpret this finding as an indication of a different phase position. Controls were slightly more awake than depressives. Because sleep disturbances normally are found in depressive patients, this result seems contradictory to what would be expected. However, our depressive subjects did not, on average, report severe sleep complaints.

In general, both in the healthy subjects and in the patients, the phase shifts brought about by EL and ML were as expected on the basis of our knowledge of the human phase response curve. Phase positions were assessed at the end of each condition only. According to empirical (Czeisler et al., 1986; Minors et al., 1994) and simulated data (Daan and Beersma, 1992), the washout period of 11 to 12 days in between ML and EL was considered to be long enough to recapture baseline phase positions at the start of the next condition. Not 1 subject showed an unexpected phase shift of DLMO after bright light exposure. The average melatonin profile after EL shifted -47 min with respect to DL in depressed subjects and -25 min in healthy subjects. After ML, the average melatonin profile shifted $+44$ min in depressed and $+89$ min in healthy subjects with respect to DL. Also, the timing of the body temperature rhythms after EL and ML was as expected. With respect to the timing of sleep termination in the fourth night, there was only 1 healthy subject with a later wake-up time after ML compared to EL; all other subjects, both healthy and depressed, woke up earlier after ML than after EL. The conclusion must be that the circadian rhythms studied showed quite normal reactions to EL and ML in both healthy and depressed subjects. Yamada et al. (1995) obtained similar conclusions, although in their study the shifts were somewhat larger in patients than in controls.

Wake-up time in the third night was not different between groups. Therefore, we conclude that we induced phase relation differences between circadian rhythms and sleep in the third night, and probably in all 3 nights, as we intended.

Between variables, there were some differences in the magnitude, and occasionally in the direction, of the shifts, and they were not significantly correlated. If rhythms were not completely entrained after 3 days, this still can be understood to be caused by one pacemaker (Daan and Beersma, 1992). However, Shanahan

and Czeisler (1991) reported that 3 days with light exposure induced equivalent shifts in melatonin rhythm and core body temperature rhythms in a constant routine protocol the next day. The discrepancy between these authors' data and ours most likely is explained by the small group size in our study and the noise in our data induced by the "semi-naturalistic" experimental circumstances; our temperature data are not recorded in a constant routine protocol and, consequently, were influenced by sleep and activity. Nevertheless, this means that within individuals, shifts of various variables can differ between each other. Overall, the observed shifts in DLMO, sleep termination, and body temperature seem robust and in line with theoretical predictions. For this reason, the shifts are interpreted as valid indicators of shifts of the circadian pacemaker.

Effects on Mood and Activation

Except for anger, the average mood and activation ratings of depressed subjects differed from those of healthy subjects. This means that the 2 groups were in quite different mood states at the start of the experiment (as was intended) as well as during the experimental weeks.

On average, the group of depressed subjects did not benefit from the various light conditions, although there were 2 individuals who clearly improved during the 4 weeks. The only significant overall effect was a slight decrease in depression, as measured with the HRSD, during the experimental weeks regardless of whether it was measured after EL, ML, or DL. This decrease was only minor and without substantial clinical relevance. An explanation of these mood changes in terms of effects of shifts in circadian rhythms is not very plausible. If a shift in circadian rhythms would be the mechanism underlying the mood changes, then one would expect that these changes would be different, even opposite, for the ML and EL conditions. The effects on the HRSD ratings, however, were similar regardless of the type of treatment. The positive responses of the 2 individuals after DL and ML, respectively, were not reversed in the subsequent conditions despite the concomitant shifts (both advances and delays) of the three physiological variables. In our opinion, there is no plausible explanation for the minor mood changes observed over the

conditions other than in terms of placebo mechanisms or spontaneous temporal fluctuations. The finding that the largest improvement occurred during the first week with DL probably is due to the high ratings at the start of the experiment, possibly caused by initial unacquaintedness with the situation. Because we analyzed many mood factors, both self-ratings and the HRSD, it is remarkable that not more mood measurements turned out to be significantly different just by chance.

In the group of healthy subjects, there were a number of significant changes in self-ratings. These effects are mainly interaction effects and attributable to the relatively large change after DL. For instance, the decrease in depression rating (AMS) after DL differed from the increase after EL and ML. These "increases," however, are very small and not clinically relevant. The healthy subjects did not become really "depressed." In the elation and anxiety ratings, there were significant main effects of condition. Again, this is caused mainly by high anxiety and low elation ratings at the start of the experiment. Just as seems the case with the depressed subjects, inclusion in the experimental procedure caused high ratings at the start and a rapid decline after DL. There also are minor differences in anxiety and elation ratings between ML and EL regardless of whether it was at the start or the end of the experimental weeks, with both variables being somewhat higher both before and after ML. This suggests that healthy subjects, although somewhat more anxious, liked the ML condition more than the EL condition. The tendency of a different expectation of the effects of ML compared to EL—the expectation of becoming more sleepy due to the EL condition—is in agreement with this interpretation, although there are no actual significant effects on sleepiness ratings.

Depressive Mood and Circadian Rhythms

In earlier studies, we found that the response to total sleep deprivation is strongly related to the presence and variability of diurnal mood variations (Reinink et al., 1993; Gordijn et al., 1994). One interpretation might be that patients with diurnal mood variations are those with chronobiological disturbances. Sleep deprivation effects in this reasoning might be explained by avoiding the coincidence of sleep with a particular phase of the circadian system (Wehr and

Wirz-Justice, 1981). An alternative interpretation is that manipulation of the sleep-wake cycle can act as a mood-changing stimulus for those subjects who are highly susceptible to stimuli in general, reflected in diurnal mood variability (Gordijn et al., 1994) and variability in the sleep deprivation effect (Gordijn et al., 1995). Both interpretations predict that patients' mood may be changed by manipulations of the circadian system by light. This idea was supported by data of Volz et al. (1991), who reported a small predictive value of diurnal mood variation with respect to the success of light therapy.

The results from the present study do not indicate circadian phase abnormalities in this group of depressives. This finding supports most of the recent data from other studies (for reviews, see Checkley, 1989; Van den Hoofdakker, 1994; Wirz-Justice, 1995) but now for a selected group of depressives with diurnal mood variations. Second, the shifts of the circadian rhythms measured in this study, induced by light exposure, were not different between depressives and controls. This indicates that not only the phase position but also the sensitivity of the biological clock to light probably is not different between depressives and controls. Furthermore, there is no indication of any relationship between a mood change and an induced phase relation difference (1-2 h) between circadian rhythms and sleep. The result that opposite phase shifts within the same subject do not result in opposite mood changes strengthens the conclusion that no clear relationship between shifts of the circadian system and mood exists in the present group of depressives and healthy subjects. This is the third study that concludes that the possible effects of light in nonseasonal depressives are not mediated by chronobiological mechanisms (Rao et al., 1992; Yamada et al. 1995). Alternative explanations for the lack of a mood change in the present study are that the phase shifts induced were too small to obtain effects or that the duration of the shifts did not last long enough. It must be mentioned, however, that 1 night of sleep deprivation can have immediate large effects.

In summary, a subgroup of nonseasonal depressive subjects characterized by large diurnal mood variations turned out to be insensitive to short-lasting moderate phase shifts of the circadian system relative to sleep phase. The phase shifts induced by light were not different from the phase shifts achieved in healthy controls. This suggests that the sensitivity of the bio-

logical clock to light is not different between depressives and controls. In contrast to sleep deprivation, moderate shifts of circadian rhythms do not act as mood-changing stimuli. The present results do not plead for an important role of circadian phase disturbances underlying depressive mood in depressive illness.

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