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Diurnal Variation of Mood and the Cortisol Rhythm in Depression and Normal States of Mind

D. von Zerssen[1], P. Doerr[2], H. M. Emrich[1], R. Lund[3], and K. M. Pirke[1]

[1]Max-Planck-Institut für Psychiatrie, Kraepelinstrasse 2, D-8000 München 40
[2]Psychosomatic Department, City Hospital München-Bogenhausen, D-8000 München
[3]Department of Psychiatry, University of München, D-8000 München 2, Federal Republic of Germany

Summary. A large scale chronobiological investigation was undertaken in 20 drug-free psychiatric inpatients displaying RDC major depression (endogenous subtype) in comparison to 10 healthy control subjects and 10 of the patients after clinical recovery. A series of measurements was taken 6 times a day and, in 8 of a total of 14 variables, also once a night over a period of 10 to 14 days. The following variables were assessed: mood (three different scales), performance (two tests), motor activity (three measures), salivary flow, urinary excretion of water, sodium, potassium, and free cortisol (UFC), and rectal temperature. A phase chart of the acrophases of the 8 variables with measurements taken during day and night revealed two clusters in the depressives and three in the non-depressed subjects. In the depressives, the acrophases of the mood scales clustered around the time of awakening in the morning, together with the acrophase of UFC, whereas all other acrophases clustered in the afternoon. In the non-depressed subjects, however, the mood scales reached their circadian maxima in the middle of the night around the time when sleep was interrupted to take measurements. All other acrophases corresponded roughly with those found in the depressives. The coincidence of the time course of depressed mood and cortisol excretion in the patients was interpreted as reflecting a temporal relationship between diurnal mood swings in depression and the cortisol rhythm. This interpretation was supported by the significant correlation between the acrophases of the two respective rhythms in patients showing a significant diurnal variation in mood. The mood curves of non-depressed subjects seemed unrelated to the cortisol rhythm. Probably, they mirror diurnal fluctuations of vigilance rather than fluctuations of mood. According to the literature, this rhythm is temporally related to the rhythm of melatonin secretion.

Key words: Diurnal variation – Cortisol rhythm – Acrophase – Phase relations – Depression

Offprint requests to: D. von Zerssen

Introduction

Diurnal variation of mood, usually with the highest degree of severity of symptoms in the morning, is a typical clinical feature of endogenous depression (Mellerup and Rafaelsen 1979). Consequently, it is used as a criterion for the diagnosis of this subtype of depression (melancholia) in the most widely used operational diagnostic systems, the RDC (Spitzer et al. 1977) and DSM-III (American Psychiatric Association 1980). Even Sigmund Freud (1917) who attempted a psychological interpretation of the origin of melancholic symptomatology believed in an organic basis for this special characteristic of the disorder. Some authors have related it hypothetically to a hypothalamic dysfunction (e.g. Fink 1979). Nevertheless, the search for its somatic correlates has so far been rather limited.

Japanese authors (e.g. Chitani 1958; Takuma 1959) were among the first who attacked the problem empirically. Sakai (1960) reported an association of the "diurnal rhythm of 17-ketosteroids and diurnal fluctuation of depressive affect" with a displacement of the peak of 17-ketosteroid excretion in urine from

morning to noon, afternoon or evening and a relocation of the peak to morning when the depressive syndrome decreased and the diurnal fluctuation of depressive affect became obscure. In a more recent study of hormonal dysfunction in relation to diurnal variation of mood in endogenous depression, an American group (Grunhaus et al. 1985) failed to find a (positive) correlation between this and another clinical symptom of altered circadian rhythm (early morning awakening) with dexamethasone non-suppression of cortisol which they had expected on hypothetical grounds. However, a correlation between the temporal pattern of symptom severity in depression and the cortisol rhythm has, so far, not been investigated.

We have studied this relationship within a large scale project on circadian rhythms in endogenous depression performed by an inter-disciplinary research group at our institute over many years. The study included depressed patients, patients in remission and healthy controls so that a comparison of diurnal fluctuations in mood in a depressed and a normal state of mind was feasible. To our knowledge, it is the first investigation of this kind in which the time course of a large number of variables was measured simultaneously in a repetitive manner (six times a day and once a night) and night sleep was monitored over a period of 10 to 14 days according to the standards of chronobiological investigations of healthy subjects (Wever 1979).

The paradigm which was followed in the analysis presented here has been adopted from chronopathological studies in internal medicine (Reinberg and Smolensky 1983). Thus, our main question was not whether circadian rhythms of bodily functions are disturbed during depressive episodes (as in the chronobiological investigations in psychiatry by Halbreich et al. 1985; Jarett et al. 1983; Kripke et al. 1978; Linkowski et al. 1985; Mendlewicz 1984; Pflug et al. 1983; Sachar et al. 1973; Sherman and Pfohl 1985; Wehr and Goodwin 1983b; Wehr et al. 1985; Yamaguchi et al. 1978, and many others) but rather how these circadian rhythms were temporally related to diurnal mood swings. The latter were conceived as one circadian rhythm among others. In the case of melancholic patients, they were supposed to reflect diurnal fluctuations in the severity of the disorder, thus indicating temporal changes in the underlying disease process. Our question was therefore addressed to the relationship of the disease process to circadian rhythms in various somatic systems, including the hypothalamo-pituitary-adrenocortical axis.

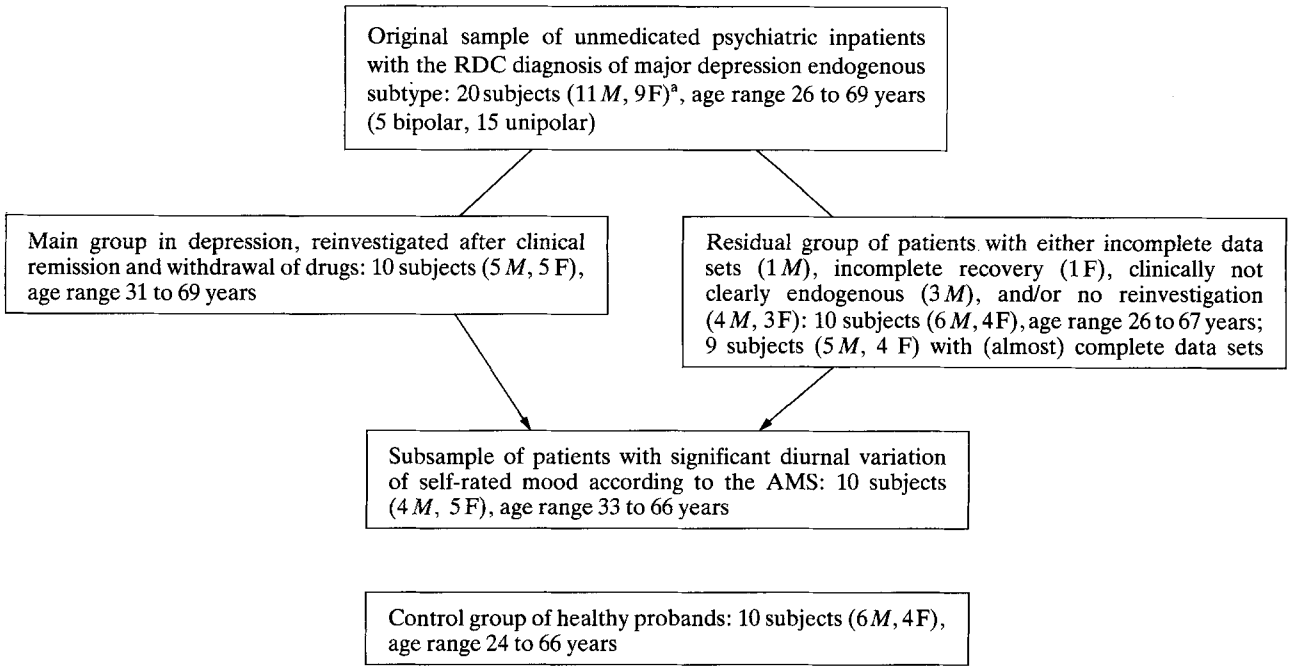
In the present study we investigated the phase positions of bodily functions in relation to the phase positions of symptom severity in depressed patients with marked diurnal variation. This question inevitably implies that the mood course and the circadian patterns of other variables must be followed throughout day *and* night. This can only be accomplished by measurements in a wakened state during the night in addition to those performed during the day. However, sleep deprivation of long duration has a marked influence on the severity of symptoms in a considerable proportion of patients with endogenous depression (Pflug and Tölle 1971; Schilgen and Tölle 1980) and repeated sleep deprivation for several nights may not be tolerable for many subjects, particularly for patients whose depression does not respond favourably to such a procedure. Therefore, a short interruption of night sleep at a fixed point in time appears to be the only adequate means to perform measurements during the night. Hypothetically, such a strict schedule could serve as an additional time cue for circadian systems and thus influence the results of the experiment. However, without a schedule of this kind it would hardly be possible to provide the database for a chronobiological analysis of the relationships among the variables in question. How far the results presented here might have been influenced by the procedure of awakening the subjects cannot be solved on the basis of our own investigation or the literature on circadian rhythms. It will require further empirical studies. For this reason, we will not refer to this point in the discussion of our results.

Method

Subjects. The investigation was performed on 20 psychiatric inpatients (11 males and 9 females) with the RDC diagnosis of major depression, endogenous subtype (definite or probable), 5 of them bipolar, the others unipolar. The age range was 26 to 69 years. Ten healthy subjects of similar sex and age distribution (6 males and 4 females, aged 24 to 66 years) served as controls. A further 10 patients with definite clinical and RDC diagnoses of endogenous depression (5 males and 5 females, aged 31 to 69 years) were reinvestigated after clinical recovery. These 10 patients formed the main group of the study allowing an intra- as well as an inter-individual comparison of the depressed and the non-depressed states the patients in remission and the control subjects, respectively). The other patients constituted a residual group for further (inter-individual) comparisons. From the total sample, we also selected a subsample of 10 patients (5 males and 5 females, aged 33 to 66 years) who exhibited diurnal variation of mood according to a self-rating mood scale (see below) (Table 1).

The age of the subjects was restricted to the range from above 20 to below 70 years in order to exclude the influence of adolescence or senescence on the results. Only males or postmenopausal females were included in the study to avoid the menstrual cycle as an intervening variable. Furthermore, relevant physical illnesses or psychiatric disorders except for the patients' depressions were exclusion criteria assessed by an intensive medical check-up. All subjects had to be drug-free not

Table 1. Description of the samples



[a] Males over-represented because of the exclusion of menstruating females
Modified from von Zerssen et al. 1985a

Table 2. Design of the study

1 to 2 Weeks	3 Days	14 Days	14 Days
Washout after withdrawal of medication before hospitalization	Adaptation to ward life and clinical screening	Observation of circadian rhythms during depression	Observation of circadian rhythms after remission

Times of measurement:
7 a.m., 10 a.m., 1 p.m., 4 p.m., 7 p.m., 10 p.m., 2:30 a.m.

Observed variables and techniques of assessment:

1. AMS (SR) = Adjective Mood Scale (self-rating) (von Zerssen 1976, 1986)
2. VAS (SR) = Visual Analogue Scale (self-rating) (Luria 1975)
3. VAS (OR) = Visual Analogue Scale (observers' rating)
4. UV = urine volume
5. Na = Urinary sodium, by filter flame photometry (Pirke and Stamm 1970)
6. K = urinary potassium, idem
7. UFC = urinary free cortisol, by protein binding (Köbberling and von zur Mühlen 1972)
8. BT = body temperature, by a rectal probe (Lund et al. 1983, 1985)

In addition, without rating/measurement at 2:30 a.m.: general activity (observers' rating), motor activity of left arm and leg (actometric recording), tapping speed (maximal), calculation (Pauli test), and during the night, from 10.30 p.m. to 6.30 a.m.: sleep, by continuous polygraphic recording (Schulz and Lund 1985)
1 to 3 Measures of severity of depression
4 to 8 Indicators of circadian processes

Modified from Lund et al. 1983 and von Zerssen et al. 1985a

only during the entire study period(s) but, if ethically permittable, for more than a week prior to the investigation of circadian rhythms. This was also true for the patients in remission. In the group of 20 depressives, 6 patients had been drug-free for 3 to 7 days before the beginning of the project, 3 others up to 2 weeks, 8 up to more than 4 weeks, and 3 had not yet received any antidepressants. In the group of 10 patients in remission, 1 had been drug-free for 12 days, the 9 others for at least 3 weeks. Informed consent was obtained from all subjects, patients as well as controls.

Variables and their assessment. The variables under study and the techniques for assessing them were: two self-rating-scales, (1) the Adjective Mood Scale (AMS[1], von Zerssen 1976, 1986), (2) the Visual Analogue Scale (VAS, Luria 1975), and (3) an observers' rating scale, a visual analogue scale similar to the patients' self-rating scale but filled in by the staff members in charge of the patients. These three scales served as measures of the time course of depressed mood.

The variables 4 to 8 were chosen as indicators of circadian rhythms, namely the renal excretion of: (4) water, (5) sodium, and (6) potassium (Pirke and Stamm 1970), (7) urinary free cortisol (UFC; Köbberling and von zur Mühlen 1972), and (8) core body temperature measured by a rectal probe (Lund et al. 1983, 1985) (Table 2).

The last three variables, urinary potassium (6), UFC (7) and body temperature (8), may be regarded as the best documented circadian parameters in man (Aschoff 1979; Krieger 1979; Lobban et al.1963; Wever 1979). This statement does not refer to oral temperature which has been usually assessed in chronobiological studies of psychiatric patients (e.g. Kripke et al. 1978; Pflug et al. 1976).

Six other variables (general motor activity rated by a clinician and motor activity of the left arm and leg measured by actometric recording, maximal tapping speed, calculation according to the Pauli test, and salivary flow) were also assessed, however, in most subjects not during the night; therefore, they were excluded from the present analysis. Night sleep was recorded polygraphically (Schulz and Lund 1985) and evaluated by means of a visual analysis using standardized criteria (Rechtschaffen and Kales 1968).

Design. All subjects, including the controls, were investigated over a period of up to 2 weeks (in one case even 3 weeks) on the same open psychiatric ward of our institute. In the depressives, an adaptation period of usually 2 to 3 days was used for medical check-up and an intensive psychiatric examination by means of standardized instruments (Möller et al. 1983), e.g., the Inpatient Multidimensional Psychiatric Scale (Hiller et al. 1986; Lorr and Klett 1967; von Zerssen 1985; von Zerssen and Cording 1978) and the Clinical Self-Rating Scales (von Zerssen 1976, 1986). During the study period, the variables were assessed at equidistant intervals of 3 h six times a day (from 7 a.m. to 10 p.m.) and, in the case of variables 1 to 8, also once a night after waking up the patient around 2:30 a.m. Rectal temperature was measured continuously during the night along with the polysomnographic recording.

Data analyses. Complete data sets for at least 10 consecutive 24-h periods were obtained from the vast majority of the subjects. Counting only the measurements actually performed at six or seven points during each of these periods and omitting the sleep data, an average of more than 1,000 measurements were obtained from each individual during one study period (i.e. altogether double the amount per patient of the main group after reassessment in remission). These data were stored in the data bank of a computer (DECSYSTEM 2060) and analysed according to several procedures approved in chronobiological research (Enright 1981; Otnes and Enochson 1978; Wever 1979). We thus obtained chronograms (plots of the data against time) for each variable per subject and educed waveforms (average curves for fixed 24 h sections of the chronograms) per subject and (as averaged group profiles) per sample (Dirlich et al. 1987). Furthermore, power spectra of the chronograms derived by means of Fourier analysis, and a series of parameters characterizing the educed waveforms (circadian maximum, minimum and mean, range of circadian variation etc.) as well as the power spectra (total power, i.e. variability of the chronograms, acrophase, i.e. time of maximum of the strongest component within the spectrum, usually the 24-h component[2], relative strength of the 24-h or the around 24 h, i.e. 22 h–26 h, component, and the ultradian and infradian components etc.) were computed. In order to analyse the phase relations between diurnal variations of mood and other variables, phase charts were drawn for the medians and the adjacent quartiles of the 24-h components of the variables per sample. However, this component of the power spectrum was computed only if it exceeded double the magnitude of white noise.

A series of statistical procedures was applied to the results thus obtained. In this context it is important to mention the evaluation of diurnal variation in the educed waveform of each variable per patient by means of the Friedman test[3] and the analysis of the relationship of diurnal variation of mood in depressives (according to the AMS[4]) to the diurnal rhythms of the other variables and to the time spent in rapid eye movement (REM) and the time awake during the third part of the night (the last variable indicating early morning awakening). Pearson's product-moment correlation was used to analyse the relationship between the acrophase of self-rated mood with the acrophases of the variables 2 to 8 and the two sleep parameters in patients with significant diurnal variation (Friedman test over the seven points of measurement per 24-h period: $p < 0.05$ in the values of the AMS). The relationship between mood swings and the cortisol rhythm in these patients was further analysed on the basis of a scatter diagram and Spearman's rank correlation in order to check the influence of outliers on the result.

Further details regarding the methodology of this study have been published by Dirlich et al. (1987). Statistical group comparisons of chronobiological parameters per variable have also been reported elsewhere (von Zerrsen et al. 1985a).

Results

In the upper part of Fig. 1 the phase chart of variables 1 to 8 is presented for two subsamples of depressed patients, the main group ($n = 10$) and the residual group minus 1 patient with incomplete data sets ($n = 9$). The lower phase chart contains the respective val-

[1] German: Befindlichkeits-Skala (Bf-S/Bf-S')

[2] For the sake of simplicity, this component was subsumed in this paper under the term "acrophase" even if it was, in some cases, not the strongest of all components of the power spectrum (e.g. in cases with pronounced trends in the data which led to the appearance of strong infradian components).

[3] This non-parametric statistical test (Siegel 1956) checks the significance of deviations of a set of dependent measurements (in this case: measurements of the variables at seven points in time during each 24-h interval of the observation period) from a random distribution.

[4] This self-rating instrument was clearly superior to the other two scales with respect to its validation as a measure of fluctuations in depressive mood (von Zerssen 1976, 1986). Those scales were only used to check the results obtained by means of the AMS (e.g. with respect to phase positions where there was sufficient agreement among the results to accept them as valid criteria of diurnal variation in mood).

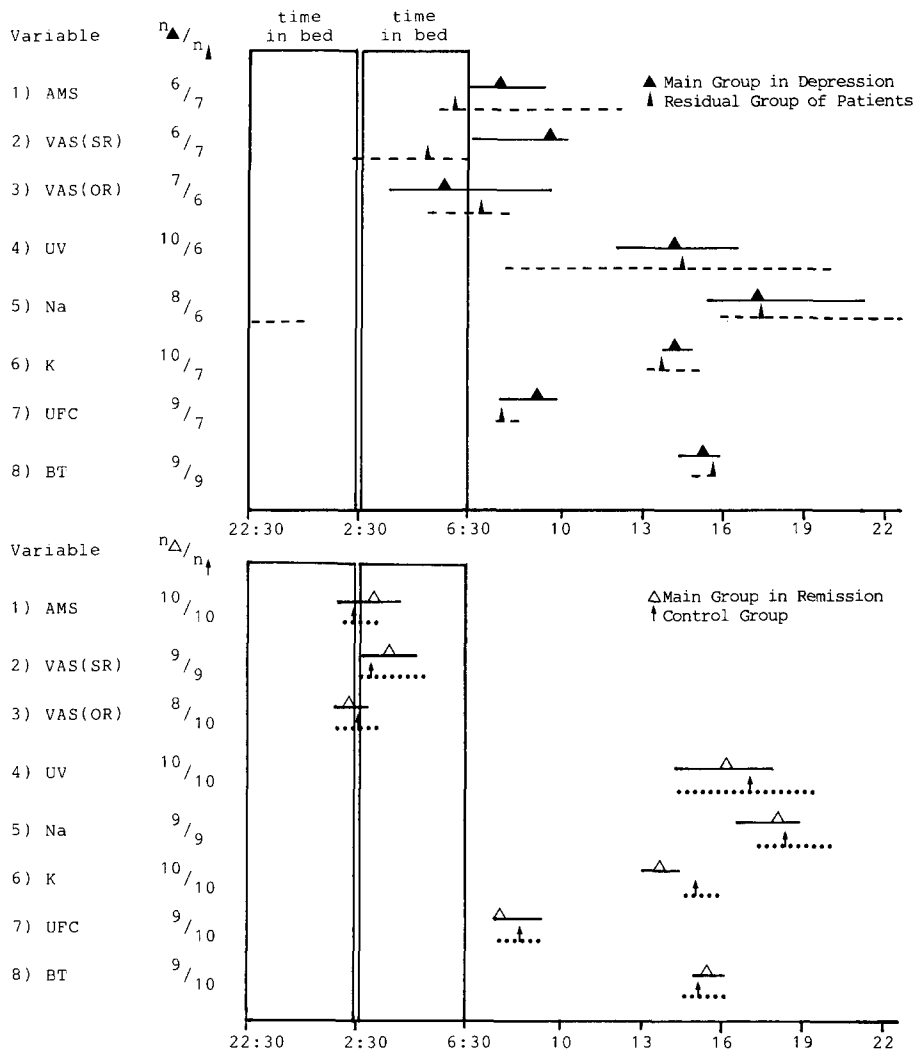


Fig. 1. Phase chart for maximum of 24-h component (derived by means of Fourier analysis: group median (e.g. ▲) and adjacent quartiles (e.g. ----) of 8 variables (for abbreviations see Table 2) in two groups of depressives *(upper part)* and in non-depressed subjects *(lower part)*

ues of the two groups of non-depressed subjects, i.e., the patients in remission ($n = 10$) and the healthy controls ($n = 10$). Only cases exhibiting diurnal variation in the respective variable were included in this analysis. It can be seen that, in all groups, the average phase positions of the variables representing circadian rhythms (4 to 6, and 8) clustered in the afternoon between about 1 p.m. and 7 p.m. The only exception was with respect to UFC which reached its maximum much earlier, around the time of awakening in the morning, compatible with previous studies (Krieger 1979). The phase positons were, on average, consistent for the two groups of depressed patients, on the one hand, and for the two groups of non-depressed subjects, on the other hand. However, the phase positions of the three depression scales differed markedly between depressed and non-depressed subjects. The maxima of the 24-h component clustered around the time of awakening at night (between 2 and 3 a.m.) in the latter and around the time of awakening in the morning in the former, i.e. around the time of the cortisol maximum. This difference in time averaged approximately 4 h per scale. A time shift in the opposite direction was observed with respect to urine volume and urinary sodium, but was much less pronounced and, due to the wide range of values in depression, did not reach statistical significance (von Zerssen et al. 1985a: Table 3).

In the depressives, the scatter of phase positons around the median was larger not only for the urinary excretion of water and sodium (4 and 5) but also for the mood scales (1 to 3). However, the same did not apply to the main criteria of circadian rhythms, namely urinary potassium (6), UFC (7), and body temperature (8). With respect to the mood scales, in particular the AMS (1), the larger scatter of acrophases could be explained on the basis of the educed waveforms (Fig. 2). Whereas in healthy subjects there was a rather circumscribed peak during the night, the respective mood curves of depressives with significant diurnal variation of mood exhibited a marked broadening of this peak into daytime, with the highest val-

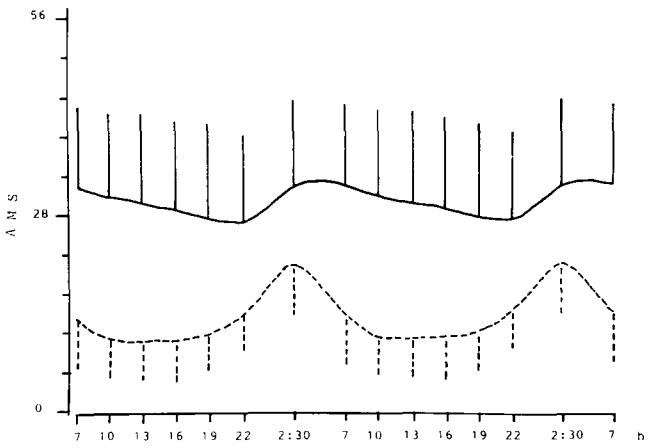


Fig. 2. Double plot of the educed waveforms of the AMS scores of 10 depressives *(dashed lines)* with significant dirunal variation in scores, and 10 healthy subjects *(dotted lines)*. SD indicated at points of measurement

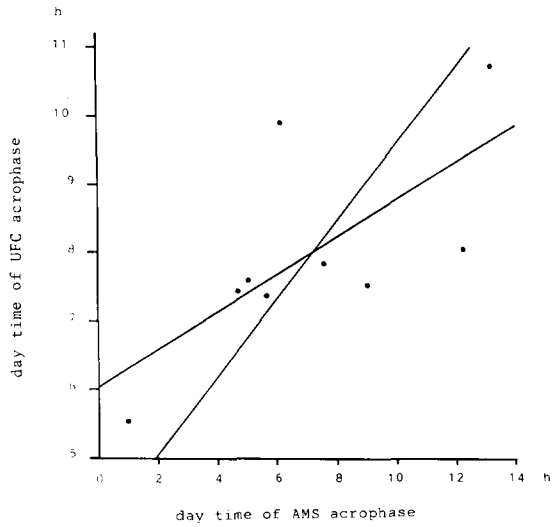


Fig. 3. Relationship between acrophases of UFC *(ordinate)* and self-rated mood (AMS: *abszissa*) in 9 patients with significant diurnal variation of mood and complete data sets. Regression lines indicated

ues sometimes occurring hours after awakening in the morning (see Fig. 3). Consequently, the acrophases, i.e. the maxima of the sinusoidal curves representing the 24-h component of these patients' chronograms, varied considerably between the middle of the night and early daytime.

We interpreted the typical mood curve of healthy subjects as predominantly reflecting fluctuations in vigilance with the peak of sleepiness, i.e. the trough of vigilance, occurring in the middle of the night. In depressives, the shape of the mood curve seemed to be modified by variations in the severity of depression which, usually, reached its maximum early in the morning, thereafter gradually declining until the night. Thus, the average mood curve of depressives with significant diurnal variation roughly paralleled the average curve of cortisol secretion/excretion (von Zerssen et al. 1985a: Figs. 1 and 2). For this reason, we predicted a significant temporal association between the mood curve of these patients and the curve representing the diurnal pattern of cortisol excretion. This was tested by means of the product-moment correlation between the acrophases of both rhythms in the nine subjects with significant diurnal variation of AMS in whom the assessment of UFC was complete enough for the evaluation of circadian parameters. The calculation resulted in a coefficient of 0.69 ($df = 8$) which was significant at the 2% level (one-tailed because of the prediction made beforehand).

In order to check the specificity of this association, the correlations of the acrophase of AMS (1) with the acrophases of the variables 2 to 6 and 8 as well as two sleep parameters (time in REM and time awake during the last third of the night), were also computed. In this case, only a temporal association between the time courses represented by the two self-rating scales (AMS and VAS) was elicited. This finding can be considered as trivial since both variables were reflections of the same phenomenon, i.e. subjectively perceived distress.

To make feasible a critical evaluation of the temporal association between diurnal variation in mood and the cortisol rhythm, the values of AMS and UFC in the subjects entering the correlational analysis are graphically represented in Fig. 3. According to a visual analysis of this graph, Pearson's correlation coefficient was not inflated by extreme values of statistical outliers. Indeed, Spearman's rank correlation resulted in a coefficient which was slightly higher ($\rho = 0.77$; $p < 1\%$, one-tailed) than that elicited by the product-moment correlation.

As may be noted on Figs. 1 and 3, the distributions of the acrophases of AMS and UFC in depressives covered different ranges with a much broader range for the AMS maxima than for the maxima of UFC. This is to say that there was not a close relationship between the temporal patterns of changes in AMS and UFC but rather a common tendency of their diurnal maxima to cluster around the time of awakening in the morning and/or to deviate from the median in the same direction (both either advanced or delayed in time).

Discussion

The study presented here differs from the majority of chronobiological investigations of psychiatric patients (Wehr and Goodwin 1981, 1983a) in several

respects: (1) a higher number of patients than usual, (2) reassessment in half of the patients after clinical recovery, (3) a truly comparable control sample investigated according to the same design in the same environment (open psychiatric ward), (4) a longer study period in a drug-free state, (5) a higher number of variables ($n = 14$) and a higher number of measurements (usually, more than 1,000) per subject, (6) continuous recording of rectal temperature and night sleep during bed rest, (7) assessment of 8 of the variables not only six times a day but also once a night after a short interruption of sleep, (8) more comprehensive data analyses according to various programmes used in chronobiological research of healthy subjects, and (9) a theoretical approach to the problem of circadian rhythms in endogenous depression that deviates from the one-sided search for abnormalities of biological rhythms, e.g., free-running periods in spite of the usual 24-h routine (Halberg 1968; Kripke et al. 1978; Pflug et al. 1976) or a general tendency towards phase-advance (Kripke 1983; Wehr and Goodwin 1981, 1983b, and others). Such abnormalities have been discussed in other reports (Doerr and von Zerssen 1983; Lund et al. 1983, 1985; Schulz and Lund 1985; von Zerssen 1983, 1987; von Zerssen et al. 1984, 1985a b, in press), whereas the main question of the present analysis was related to the coincidence of circadian fluctuations in the severity of depression with those of other, in particular physiological and biochemical, variables.

The main result of the study was a temporal relationship of the circadian variation of depression to the cortisol rhythm. Furthermore, a considerably larger scatter of the acrophases of mood and urinary excretion of water and sodium, but not potassium was ascertained in the depressed patients. Since the excretion rates of water and sodium are strongly influenced by the intake of fluids (which was not standardized in our investigation), the larger dispersion of maxima in the depressives probably does not indicate a disturbance in the circadian system during depressive episodes but changes in patients' drinking habits. The urinary excretion of potassium and cortisol (which are recognized as more valid indicators of endogenous rhythms than the excretion of water and sodium) did not exhibit a similar increase in the variation of circadian maxima. It seems noteworthy that this was also true for rectal temperature, a variable that had been continously recorded during the night. Therefore, the estimation of its time course appears particularly valid.

Our interpretation of the normal mood curves (in the ten healthy control subjects and the ten recovered patients) was that they represented mainly the increase in fatigue after the interruption of sleep during the night, compared with the minor fluctuations of this particular component of the general subjective state during day time. The mood scores of depressives were, however, assumed to be determined by the vigilance component *and* by an additional component reflecting the patients' specific mood disorder. This depression-specific mood component is probably not (or only slightly) present in healthy subjects. In depressives, it tends to increase later than the vigilance component, reaching its circadian maximum usually around awakening or during the first half of the day. This assumption would explain the phase-delay and the increased dispersion of the acrophases of the mood curves in depressives with significant diurnal variation.

According to this hypothesis, it is not a real phase-delay of mood that occurs during the depressed state. Rather, the vigilance component of the mood curves of depressives seems often obscured by the component reflecting diurnal changes in the intensity of depression. It is this particular component which we suspected to coincide with the cortisol rhythm. Consequently, a correlation of the acrophases of the AMS and the UFC rhythms was to be expected. This prediction was substantiated in our correlational analyses of the respective variables.

If the mood rhythms ascertained in the recovered depressives and the healthy probands of our study were indeed reflections of circadian fluctuations in vigilance, they were probably not only determined by the artificial time schedule of the study by awakening the subjects between 2 and 3 a.m. since they corresponded with the diurnal curves of fatigue and poor performance, respectively, as revealed in studies of healthy subjects in sleep deprivation experiments (Åkerstedt et al. 1979, 1982; Fröberg 1977) and shift workers (Bjerner et al. 1955). These curves also reached peak values a few hours after midnight although the subjects were awake during the whole night. According to the studies by Åkerstedt and his group and by Fröberg the peak of sleepiness/fatigue coincides not only with the trough of performance but likewise with the peak of melatonin (Åkerstedt et al. 1979, 1982; Wetterberg et al. 1979) and the trough of adrenaline excretion in urine (Åkerstedt et al. 1979; Fröberg 1977).

It is questionable whether hormonal rhythms trigger the mental state in a similar way as to be assumed for the cortisol and adrenaline rhythms with respect to asthma attacks (Reinberg and Smolensky 1983). Nevertheless, the temporal organization of these rhythms seems to be co-ordinated in some way. Particularly, diurnal fluctuations in the mood of patients with endogenous depression appear to be co-ordinated with the cortisol rhythm.

In cannot be ignored that one of these rhythms may trigger the other, e.g., the stress of severe depression after awakening in the morning may induce a rise in cortisol that modulates the circadian pattern of this hormone or, vice versa, the morning rise in cortisol may increase the severity of depressed mood and thereby impose a similar rhythm on an otherwise arhythmic disease process. In the terminology of chronobiologists (Wever 1979), such mechanisms would be designated as the masking of one peripheral rhythm by another one. However, if one variable correlates with another, one has to consider the possibility of a common denominator for both of them. With respect to diurnal variation of mood in depressives and the cortisol rhythm, it may well be that both depend partially on the same signal(s) from the internal clock governing circadian rhythms in man. Since, according to our investigation, there are no marked disturbances in circadian processes other than those directly related to the symptoms of the disorder (diurnal variation in the severity of depression, early morning awakening and other sleep abnormalities: Doerr and von Zerrsen 1983; Lund et al. 1985; Schulz and Lund 1985; von Zerssen 1987; von Zerssen et al. 1985a, b, in press), it appears unlikely that the main circadian pacemaker which is supposed to be located in the nucleus suprachiasmaticus (Kawamura and Inouye 1979; Moore 1979; Rusak and Zucker 1979; Schwartz et al. 1979) is involved in the disease process (von Zerssen 1983). Yet time signals from that pacemaker, which trigger the circadian modulation of production and release of corticotropin-releasing factor (CRF) in the hypothalamus, may also influence circadian fluctuations in the central disease process underlying episodes of melancholia.

Assuming that a disturbed balance of neurotransmitters in the hypothalamus is responsible for depressive symptomatology (Janowsky et al. 1972) and that this balance depends on time signals from the internal clock that modulates the cortisol rhythm via CRF and adrenocorticotropic hormone release (Carlsson et al. 1980; Krieger 1979), a coupling of fluctuations in symptom severity to the cortisol rhythm would occur and thoroughly explain our results. These speculations may stimulate further clinical and basic research on the inter-dependence of hormonal rhythms and diurnal variations of mood in depression and normal states of mind.

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