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Barbara Barbini · Francesco Benedetti
Cristina Colombo · Emanuela Guglielmo
Euridice Campori · Enrico Smeraldi

Perceived mood and skin body temperature rhythm in depression

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Abstract Eighteen inpatients affected by recurrent major depression were monitored in their clinical and biological features during the acute episode of illness. Diurnal mood variations rated with Visual Analogue Scale (VAS) and diurnal variations of skin body temperature were measured every 2 h consecutively for 2 days. Circadian rhythmicity of the two parameters was evaluated by cosinor analysis separately for each patient. The inspection of the individual cosine fitting shows that patients with a high circadian rhythmicity in perceived severity of symptomatology tend to show low circadian rhythmicity in skin body temperature, whereas patients with a low VAS oscillation tend to display a higher diurnal variation in skin body temperature. A chi-square test confirmed a statistical significance of the discordance between the two rhythms. We discuss our findings hypothesizing a different degree of entrainment of the disease process to the main circadian pacemaker.

Key words Mood disorder · Major depression · Circadian rhythms · Temperature

Introduction

Patients affected by major depression often report to the clinician an important variation in the intensity of perceived symptomatology during the day. Typically, mood is reported to be worse in the morning, and behavioral observation confirms the clinical relevance of this perceived circadian fluctuation (Leibenluft et al. 1992).

Several physiological variables show a clear-cut circadian rhythmicity, which is thought to be due to the influence of a biological circadian pacemaker. Since mood fluctuation in depressive state exhibits a circadian period, it is possible to hypothesize that it is due to an entrainment of mood to the same master clock which rules biological variables (for a review see Von Zerssen 1987). This hypothesis is, however, still lacking adequate experimental support. Although chronobiological studies have previously revealed several alterations in the physiological rhythmicity of biological variables in depressed patients, few studies, on the other hand, have recorded diurnal mood variations in depressed patients during distinct time periods, and no shared model is available on the subject.

If diurnal variation of biological parameters and symptomatological intensity in depressed patients are ruled by the same circadian biological clock, then it should be possible to define a kind of interaction between these two kinds of fluctuations. Only few studies have tried to link the diurnal variation of autonomous parameters with that of symptomatological intensity, reporting preliminary results which support the hypothesis of an interaction between the two fluctuations (e.g., Rechlin et al. 1995). The possibility of a quantitative definition of this interaction could be of great clinical importance, since positive correlations exist between the occurrence of diurnal mood variations and response to sleep deprivation (Reinink et al. 1990).

Following this point of view, we were challenged to define an individual chronobiological profile of depressed patients which could take into account both the biological and symptomatological rhythmicity during the depressive state. Among biological fluctuations, we chose to study the skin body temperature rhythm, which is known to exhibit a strong entrainment to the main circadian pacemaker (Aschoff et al. 1982).

Subjects and methods

We studied 18 inpatients (5 males and 13 females) affected by recurrent major depression according to DSM-III-R criteria. Axis-I diagnosis was assessed by means of the diagnostic interview schedule (DIS; Robins 1989) for DSM-III-R. Clinical and demographic characteristics of the patients are summarized in Table 1. Females were in postmenopausal phase and only 2 patients were in

B. Barbini (✉) · F. Benedetti · C. Colombo · E. Guglielmo
E. Campori · E. Smeraldi
Department of Neuropsychiatric Sciences, School of Medicine, University of Milan, Via Prinetti N 29, I-20127 Milan, Italy

Table 1 Characteristics of sample. HRSD Hamilton Rating Scale for Depression

Age (years)	50.8 ± 13.1
Age of onset (years)	40.1 ± 14.1
Duration of illness (years)	10.6 ± 7.6
No. of previous episodes	7.1 ± 6.5
Recurrence index	0.78 ± 0.48
Duration of current episode (weeks)	14.9 ± 10.3
HRSD total score	24.4 ± 4.4

Values are mean ± standard deviation

the luteal phase of the menstrual cycle. Exclusion criteria were organic disease, which could induce an alteration of body temperature regulation, and maintenance therapy including lithium salts and carbamazepine. Patients were free from antidepressant and benzodiazepine drugs for at least 2 weeks before the experiment.

The experimental design was approved by the ethical committee of our hospital; all patients gave their written informed consent to participate in the study.

Data collection

Body temperature was monitored every 2 h for a period of 48 h starting from 8 a.m. on the first day (Tsujimoto et al. 1990). Because of the possible confounding effects of continuous rectal measurement (Von Zerssen 1983), we monitored body temperature oscillations from the skin surface using a probe connected to an electronic thermometer (Data Logger Grant) sited to the chest near to the xyphoidean process.

Patients were rated on the first day of the study with a 21-item version of Hamilton Rating Scale for Depression (HRSD; Hamilton 1964). In order to quantify fluctuations in perceived mood levels, patients were rated on self-administered Visual Analogue Scale (VAS; Aitken 1969) every 2 h from 8 a.m. to 10 p.m. every day during the 2 days of the monitoring period (excluding night sleep periods). Raw VAS scores were converted to a 0–100 rating scale; since patients were unipolar, 0 and 100 denoted euthymia and extreme depression, respectively.

Social "zeitgebers" during the experimental period were carefully controlled. Patients woke up at 7 a.m. and went to bedrooms at 10 p.m. Meals took place at 7:30 a.m., 12 a.m., and 6 p.m., composition of the meals was the same for all subjects. During the recording period all subjects were not allowed to leave the ward; they could spontaneously watch television, read, and talk to each other, but were not allowed to stay in bed during daytime hours. Daytime clinical activities included an interview with a member of the medical staff every morning and with a member of the nursing staff every afternoon; no instrumental examination was performed during the recording period. Visitors were allowed to enter the ward from 6:30 p.m. to 8:30 p.m.; all subjects were paid regular visits by their relatives during the two experimental days.

Data analysis and statistics

Circadian rhythmicity of skin body temperature and VAS scores were evaluated by cosinor analysis (Rice and Rosenblatt 1988) separately for each patient. Two descriptive parameters were calculated: mesor (mean level of the sinusoid), and amplitude (height of the sinusoid peak above the mean level). The fitness of the cosine model was estimated by means of ordinary least-squares regression (Piletz 1994). The percentage of variability in the data which was accounted for by the fitted sinusoid (percentage rhythm) was calculated as an index of the goodness of fit of the 24-h fixed-period sinusoid curve, and thus as an index of the weight of the circadian oscillation in determining the observed data pattern (Minors and Waterhouse 1989).

Cluster analysis was then performed to classify patients into two groups on the basis of percentage rhythms of VAS and skin body temperature; differences in the selected variables between the two groups were compared by a one way ANOVA. Since the two clusters of patients were characterized by a discordance between VAS and skin body temperature percentage rhythms (see Results), patients were post hoc classified on the basis of "presence" or "absence" of circadian rhythmicity in the evaluated parameters. Cut-off values were fixed at 20% for VAS percentage rhythm and at 15% for skin body temperature percentage rhythm. Frequencies in the four resulting groups were then tested by means of chi-square test.

Data were analyzed through a commercially available software (Stat Soft Statistica for Windows 4.5).

Table 2 Characteristics of observed rhythms. *VAS* Visual Analogue Scale

VAS scores:	Percentage rhythm	21.52 ± 18.49
	Amplitude	7.48 ± 4.88
	Mesor	60.14 ± 16.95
	Percentage rhythm	21.78 ± 15.82
Skin body temperature:	Amplitude	0.43 ± 0.28
	Mesor	35.09 ± 0.45

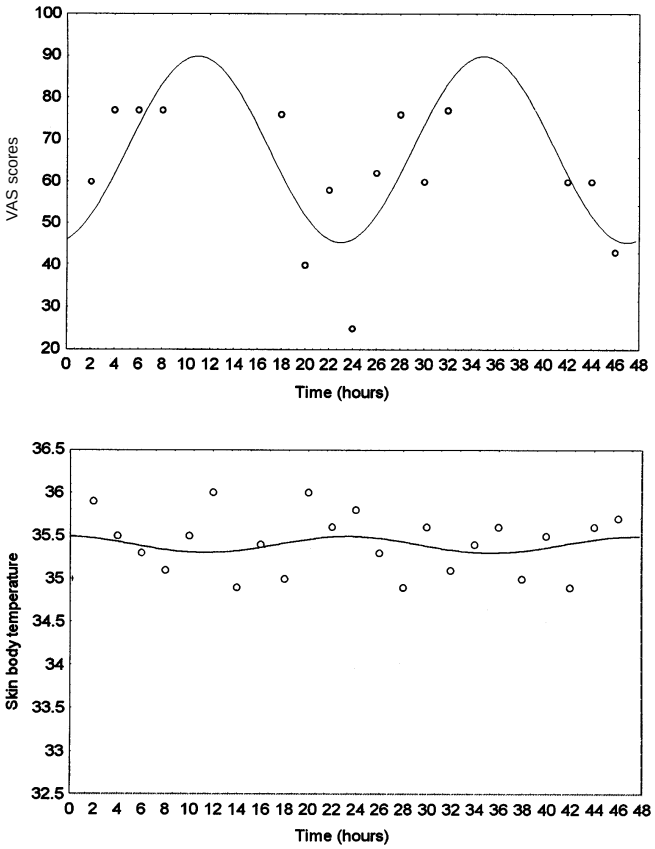

Fig. 1 Data from a 32-year-old unipolar patient at his sixth episode of major depression. Each *point* represents a single measurement of Visual Analogue Scale (VAS) scores and skin body temperature levels; *continuous line* represents the 24-h fixed-period fitted sinusoid curve. The patient exhibits a high circadian rhythmicity in VAS fluctuations (percentage rhythm = 79.2), with a low circadian rhythmicity in temperature oscillations (percentage rhythm = 3.8)

Results

Mean values of the estimated parameters in our experimental sample are summarized in Table 2. Inspection of Table 2 shows that, considering our patients as a group, the mean variance explained by a fixed-period 24-h sinusoid curve is less than 25% of the observed variance in both biological and symptomatological data sets, with a widespread distribution in the sample of percentage rhythms.

Inspection of individual cosine fitting shows that patients with a high circadian rhythmicity in perceived severity of symptomatology tend to show low circadian rhythmicity in skin temperature (see Fig. 1), whereas patients with low VAS oscillations tend to display higher diurnal variations in skin temperature (see Fig. 2).

Cluster analysis using VAS and body temperature percentage rhythms divided the patients into two subgroups with the following characteristics: Group 1 includes 5 patients with high percentage rhythms in VAS (mean ± SD; 41.46 ± 24.12) and low skin temperature fluctuations (5.00 ± 1.37), whereas group 2 includes 13 patients with low percentage rhythm in VAS (13.84 ± 7.83) and high skin body temperature percentage rhythm (28.23 ± 13.85). A one-way ANOVA showed that the two subgroups differed significantly for VAS ($F(1,16) = 14.39$; $p = 0.001$) and skin body temperature ($F(1,16) = 13.51$; $p = 0.002$) percentage rhythms.

Discordance between the two parameters was confirmed to be statistically significant by chi-square test (5.51; *df* 1, $p = 0.0189$; see Table 3).

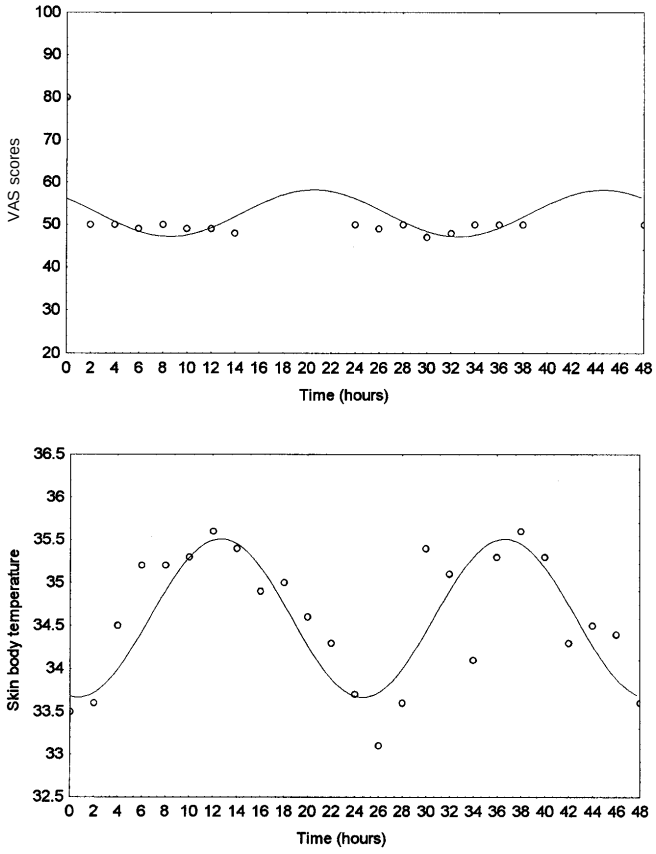

Fig. 2 Data from a 72-year-old unipolar patient at her seventh episode of major depression. Each *point* represents a single measurement of VAS scores and skin body temperature levels; *continuous line* represents the 24-h fixed-period fitted sinusoid curve. The patient exhibits a low circadian rhythmicity in VAS fluctuations (percentage rhythm = 19.1), with an high circadian rhythmicity in temperature oscillations (percentage rhythm = 63.5)

Table 3 Classification of patients on the basis of presence/absence of circadian mood and temperature rhythmicity: excess of discordant subjects

	VAS circadian rhythm[a]	
	+	–
Skin body temperature	+ 3 (16.7%)	9 (50.0%)
Circadian rhythm	– 5 (27.8%)	1 (5.6%)

[a] Chi-square (*df* = 1) 5.51, $p = 0.0189$

Discussion

Considering our patients as a group, our data confirm previous findings of chronobiological studies in patients affected by mood disorders. We observed a poor mean fitting of a fixed-period 24-h sinusoid curve in both biological and VAS data sets. The observation of a low mean circadian rhythmicity in skin temperature regulation is consistent with the well-known flattening of circadian biological rhythms in depressed patients (e.g., Von Zerssen 1987), which has been reported to lead, in some patients, to a disappearance of the endogenous body temperature rhythm (Beersma et al. 1983). In the same way, the observation of a low mean circadian rhythmicity in perceived symptomatology is in agreement with the reported irregular occurrence of diurnal mood variations in a random sample of depressed patients (e.g., Gordjin et al. 1994). Moreover, percentage rhythms were significantly correlated with the amplitude of the sinusoid in all data sets (for temperature data set, Pearson's $r = 0.54$, $p < 0.05$; for VAS scores, $r = 0.61$, $p < 0.01$): This observation supports the proposal of amplitude as an index of the strength of the circadian oscillation (Aschoff 1983).

What is new in our approach is the analysis of individual circadian chronobiological profiles shown by the subjects by means of cluster analysis and chi-square test. We observed that patients with a high circadian rhythmicity in perceived symptomatology tend to show low circadian fluctuations in skin body temperature, whereas patients with low symptomatological circadian rhythmicity show high fluctuations of skin body temperature. This observation suggests the presence of an interaction between the two chronobiological patterns and then the possible entrainment of both rhythms to the circadian biological clock: Recent findings of different diurnal fluctuations of parasympathetic tone in depressed patients with or with-

out circadian mood variations (Rechlin et al. 1995) are in accordance with this hypothesis.

Several models have been proposed to explain circadian chronobiological patterns in depressed patients by hypothesizing a primary or secondary dysfunction of circadian clocks, but contradictory results hampered the reaching of a general agreement on the proposed dysfunctions (for a review, see Monk 1993). An alternative view conceives circadian phenomena in depression as a modulation of the disease process, conceptualized as being separate from the main circadian pacemaker, by the basically intact circadian clock (Von Zerssen 1987). While the disease process is entrained to the main circadian pacemaker and thus the symptomatology shows a circadian fluctuation, overt symptomatology caused by the disease process should exert, in turn, a masking effect on overt chronobiological rhythms.

Following this perspective, differences in chronobiological profile of clinical and biological parameters among the patients of our sample could be explained by a different degree of entrainment of the disease process to the main circadian pacemaker. Alternative hypotheses cannot be ruled out. In particular, we collected data on skin temperature fluctuations without following a constant routine protocol, i.e., without keeping under constant conditions light levels, motor activity, vigilance state, and food intake (Kräuchi and Wirz-Justice 1994). Constant routine involves marked manipulations of spontaneous behavior, and we chose a "naturalistic" approach to avoid an interference of these manipulations with the clinical mood fluctuations in depressed patients; in particular, we avoided the well-known antidepressant effect of sleep deprivation (e.g., Wu and Bunney 1990) which has been reported to appear after approximately 18–20 h of prolonged wakefulness (Haugh and Faehndrich 1988). In this respect, to our knowledge, the well-documented circadian mood fluctuations in depression have never been studied under constant routine conditions (e.g., Haugh and Faehndrich 1990; Rechlin et al. 1995). Further research with different "unmasking" protocols will clarify these points.

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