Circadian rhythms and sleep regulation in seasonal affective disorder

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"If I may offer just one more summary, otherwise we won't get anywhere." *Rutger Kopland*

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INTRODUCTION AND METHOD

Seasonal affective disorder (SAD) is characterised by recurrent episodes in autumn and winter of depression, hypersomnia, augmented appetite with carbohydrate craving, and weight gain, and can be successfully treated with bright light.[1] Circadian rhythm hypotheses (summarized in[2]) have stimulated research into the pathophysiology of SAD, postulating that:

1. The illness is a consequence of delayed phase position,
2. It is correlated with diminished circadian amplitude, or
3. It results from changes in the nocturnal duration between dusk and dawn e.g. of low core body temperature or melatonin secretion. Light is considered to act directly on the circadian pacemaker ('Process C') and not on sleep dependent processes ('Process S').[3] Thus successful treatment of SAD must act via mechanisms within known retinohypothalamic pathways. Conversely, emergence of SAD symptoms may reflect inappropriate neurobiological response to decreasing daylength.

It is difficult to test these circadian hypotheses under normal nychthemeral conditions, due to 'masking' of the expression of the circadian pacemaker to varying degrees by activity, sleep, meals, light, and ambient temperature. If there is an underlying dysfunction of biological timing in SAD, the 'Constant Routine' (CR) protocol may be the most stringent method to uncover it.[4] The CR consists of 40h of sleep deprivation while sitting in bed under controlled photic and thermal conditions. In winter, we carried out a CR protocol in 11 women with SAD and 8 healthy controls (24-66y) during the follicular phase of their menstrual cycle (if present), before and after 5 days of 6000 lux light therapy from 10-14h. A large battery of psychological ratings, physiological and neuroendocrine measurements revealed significant circadian rhythms under unmasked conditions. Additionally, the sleep EEG was recorded before and after the controlled sleep deprivation of the CR. Four parameters are briefly summarized here.

RESULTS

Mood follows a circadian rhythm

Depressed SAD patients improved after the total sleep deprivation of the CR (self-rated visual analogue scales at half-hourly intervals permitted a very precise analysis of the kinetics of this sleep deprivation response). They relapsed after recovery sleep. Light therapy induced more stable improvement. Both controls and SAD patients showed a circadian rhythm of mood (Fig. 1).[2,5] The 'unmasked' rhythm revealed a more complex wave form ('afternoon dip' as well as circadian trough) than prior studies of diurnal variation of mood would suggest. The afternoon dip was particularly clear on the day after sleep deprivation. The presence of a circadian rhythm in both controls and SAD patients suggests an important endogenous component to changes in affect: indeed, strong evidence for this has been obtained in the forced desynchrony protocol.[6]

Core body temperature

The rectal temperature rhythm is a validated marker of the circadian pacemaker[4], with which the three circadian hypotheses of SAD pathophysiology can be directly tested.[7,8] For characterising the rhythm of each subject, least-squares regression analysis was applied to calculate the best fit to a combined 24-h-period cosine function, its 12-h-period harmonic and a linear component. As shown in figure 2 and table I, the 'classical' marker of phase, the circadian minimum, did not significantly differ between SAD patients and controls; nor was there a difference in amplitude or duration of the nocturnal temperature minimum between the mid-range crossings. None of these parameters were modified by midday light.

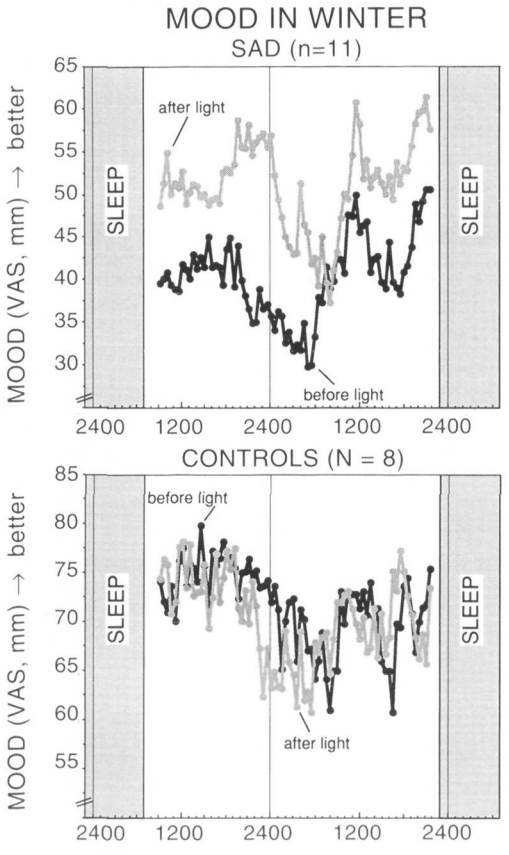

Figure 1. Half-hourly VAS self-ratings of mood during the 40-hour constant routine in winter. SAD patients are depressed (50 mm = euthymia) and switch out of their depression in the morning (6 a.m.) of the second day of sleep deprivation. After light treatment (6000 lux, 10-14 h, 5 days), their average mood is increased. Control subjects have higher mood ratings, but also show a circadian rhythm, which is not modified by light treatment. Note the afternoon dip of mood on the second day of the constant routine. The scales for SAD and controls are different to show the rhythms more clearly.

Figuur 1. Zelfbeoordelingen van stemming met behulp van een visual analog scale elk half uur gedurende de 40 uur van een constant routine in de winter. SAD patienten komen uit hun depressie op de ochtend (6 a.m.) van de tweede dag met slaapdeprivatie (50 mm = normale stemming). Na lichtbehandeling (6000 lux, 10-14 h, 5 dagen) is de gemiddelde stemming verbeterd. Controle personen hebben hogere stemmingsscores waar ook een circadiaan ritme in zit, dat niet verandert door lichtbehandeling. Let op de daling van stemming in de middag van de tweede dag van de constant routine. De verticale schalen zijn verschillend voor de twee figuren om de ritmes duidelijker te laten zien.

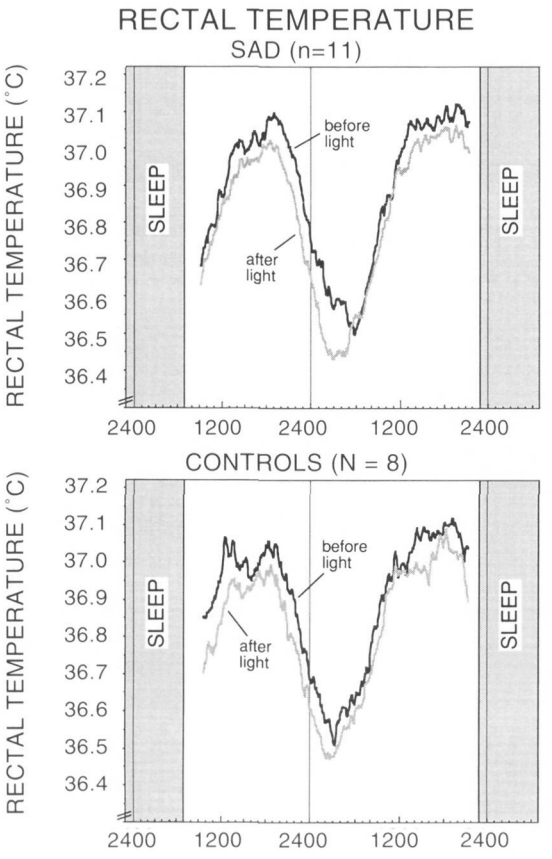

Figure 2
Circadian rhythms of rectal temperature during the 40-hour constant routine in winter. The timing of the minimum in SAD patients tends to be later than in controls, and significantly advances after light treatment. The amplitude in SAD is surprisingly robust. In both groups, light induces a small but significant decrease in temperature (–0.07°C).

Figuur 2
Circadiane ritmen van lichaamstemperatuur gdurende de 40 uur van een constant routine in de winter. Het minimum in de curve van de SAD patiënten lijkt wat later te komen dan bij de controles, en het verschuift significant naar voren na lichtbehandeling. De amplitude van het ritme bij de SAD patiënten is opvallend constant. In beide groepen verlaagt de lichtbehandeling de temperatuur significant (–0,07°C).

The morning mid-range crossing of temperature rise was significantly delayed in SAD patients compared with controls (by 81'). Only in SAD patients did light treatment significantly phase advance certain parameters of the temperature rhythm: the 24-h component by 61 ± 20' ($p < 0.02$), the circadian maximum by 108 ± 26' ($p < 0.005$), and the mid-range crossings - morning by 68 ± 24' ($p < 0.02$), evening by 41 ± 14' ($p < 0.005$).

Salivary melatonin

The melatonin rhythm has also been validated as hand of the biological clock in the CR.[9] Amplitude, phase, and duration of melatonin secretion were similar in SAD patients and controls, and were not modified by light (e.g. melatonin onset and nocturnal duration, table I).

Sleep EEG and sleep regulation

Sleep EEG parameters were not disturbed in winter SAD.[10-13] Recovery sleep after the sleep deprivation of the CR showed the well-known regulatory responses of sleep stage parameters and of the EEG power spectrum under all seasonal and light treatment conditions. Irrespective of diagnosis, midday light treatment induced some improvement in sleep (sleep latency and efficiency, REM sleep). In SAD patients, but not in controls, light treatment slightly increased EEG power density in the delta and theta frequencies.

Table I.
Tabel I.

	CONTROLS (n=8, 50 ± 13 y)		SAD (n=11, 46 ± 13 y)		
	Before	*After light*	*Before*	*After light*	*ANOVA*
Depression self rating (v. Zerssen)	3.5 ± .8	2.6 ± .8	16.0 ± 2.1	8.0 ± 1.2	**,§§ ++
Core body temperature					
Circadian amplitude (°C)	0.265 ± .018	0.273 ± .018	0.298 ± .026	0.291 ± .014	ns
Circadian minimum (time)	3:39 ± 26'	3:23 ± 35'	4:28 ± 28'	3:59 ± 23'	ns
24-hour component (time)	15:57 ± 29'	15:51 ± 32'	17:14 ± 28'	16:13 ± 22'	§,(+)
Mid-range crossing (morning)	9:50 ± 25'	9:55 ± 34'	11:11 ± 24'	10:30 ± 22'	ns
Mid-range crossing (evening)	21:57 ± 31'	21:43 ± 28'	23:02 ± 31'	21:54 ± 21'	§
Duration of minimum	11h53' ± 18'	12h12' ± 17'	12h9' ± 21'	12h36' ± 14'	ns
Salivary melatonin					
melatonin onset (time)	22:47 ± 21'	22:51 ± 29'	23:21 ± 30'	22:43 ± 18'	ns
duration of secretion	8h ± 16'	7h30' ± 44'	6h42' ± 45'	7h47' ± 27'	ns

mean ± sem; 2-way ANOVA for repeated measures: controls vs. SAD ** $p<0.001$; before vs. after light § $p<.05$, §§ $p<0.001$; interaction (+) $p=.1$ + $p<0.05$ ++ $p<0.002$

CONCLUSIONS

This CR study provides evidence that:

- SAD patients improve during sleep deprivation (as do patients with other depressive syndromes), but show a more robust improvement after light treatment.
- Certain parameters of the circadian temperature rhythm are phase-delayed in SAD patients and phase advanced by light treatment.
- The melatonin rhythm does not differ between SAD patients and controls, nor is it significantly modified by light treatment.
- The circadian amplitude of both temperature and melatonin rhythms is normal in SAD patients, and is not modified by light treatment.
- There is no difference between SAD patients and controls in the nocturnal duration of the temperature minimum or melatonin secretion.
- There is no abnormality of process 'S' as measured by the EEG power density in the delta frequencies in SAD patients; the small effects of light on sleep parameters are unlikely to mediate the antidepressant effect.

Analysis of further parameters measured in this study are necessary to support the statement that there appears to be no abnormality of process 'C' or of process 'S' in SAD patients that can explain their recurrent winter depression and the antidepressant effect of midday light.

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