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Core Body Temperature in Narcoleptic and Normal Subjects Living in Temporal Isolation

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POLLAK, C. P. AND D. R. WAGNER. *Core body temperature in narcoleptic and normal subjects living in temporal isolation.* PHARMACOL BIOCHEM BEHAV **47**(1) 65–71, 1994.—The aim was to detect abnormalities in the circadian temperature rhythms of narcoleptic patients, as evidence of abnormal circadian pacemaker function. Six narcoleptic patients and nine normal controls lived in a time-isolation laboratory for 18–22 days. Rectal temperature was measured every minute and modeled by mean waveforms and cosine functions, which have complementary advantages. In this study, the two types of models gave similar results: The levels, periods, amplitudes, and phases of the circadian temperature rhythms of patients and controls did not significantly differ—evidence against an abnormality of circadian pacemaker function in narcolepsy. The increases of temperature that normally follow main sleep periods were smaller in narcoleptic subjects, and narcoleptic naps, which were involuntary, were heralded and accompanied by small decreases of mean temperature.

Core body temperature Narcolepsy Temporal isolation Circadian Cosinor Educed waveform

NARCOLEPSY is a chronic sleep disorder in which daily periods of wakefulness are interrupted by multiple naps, even when subjects have been instructed to avoid naps and no limit has been placed on bedrest periods (9). In addition, nocturnal sleep is often interrupted by brief awakenings (11). Inability to sustain periods of both wakefulness and sleep may be described as loss of the normal amplitude of the sleep–wake rhythm and explained as the failure of the circadian timing system to modify the expression of wakefulness and sleep by the brain. Among other possibilities, the necessary signals may not be generated by a circadian pacemaker. In that case, other circadian rhythms might also be affected. Body temperature has a robust circadian rhythm in humans and is often used as an index of circadian time [for a recent review, see (10)]. This study was therefore carried out to detect abnormalities in the circadian temperature rhythms of narcoleptic patients, as evidence of abnormal circadian pacemaker function.

METHOD

The findings reported here were obtained from six narcoleptic subjects (four females, two males, mean age 55.2 years) who lived continuously for 18–22 days in a special laboratory that provided no means of knowing the time of day or measuring the passage of time. Nine normal controls (six females, three males, mean age 54.7 years) were studied under the same conditions. All narcoleptic subjects complained of chronic, daily sleepiness and cataplexy and had abnormal multiple sleep latency tests (short sleep latencies & multiple REM-sleep periods). Controls had no symptoms of narcolepsy or other disorders affecting sleep. All subjects had been drug free for at least 2 weeks before entering the laboratory.

Core body temperature was monitored with rectal temperature probes (Yellow Springs Model 400 or 700, Yellow Spring Instruments, Yellow Springs, CO) that were worn continuously except when defecating. Subjects inserted the probes to a depth of 6 cm, as marked by heat-shrink tubing of contrasting color. Probe wires were brought up between the buttocks and securely taped by a technician to the lower back. The stability of measurements was checked while subjects bent over, walked, and sat, and probes were repositioned if necessary. Signals were led to a digital telethermometer and optoelectronic computer interface (Yellow Springs). Temperature was sampled once per minute and analyzed on a MicroVax 3400 computer (Digital Equipment Corp.) running UNIX (Ultrix-32) and the S interactive environment for data analysis and graphics (2).

Rhythms were synchronized with a 24.0-h schedule for the first 4–6 days and were then allowed to free-run for 9–13 days. During the scheduled phase, subjects were required to retire,

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arise, and eat meals at times assigned by the experimenters. When free-running, subjects were free to sleep and eat whenever they chose. All subjects were instructed to avoid napping, that is, to avoid sleeping outside of assigned or self-selected sleep periods. Additional details regarding subjects and laboratory procedures are provided elsewhere (9).

Circadian temperature rhythms were analyzed by fitting educed waveforms and cosine functions to the data. To speed computation, the measured values were replaced by values calculated by linear interpolation every 10 min. When plotted on a high-resolution device, the smaller data sets closely resembled the original data. To obtain an educed waveform, data were first averaged modulo P, P being 1 of 21 trial periods ranging from 22 to 26 h. Of the resulting average waveforms, the one that minimized the mean square deviation of the model from the data was selected and smoothed. The model period was the corresponding value of P. Peak–peak amplitude and phase were measured from the extrema of the model waveform. The general approach has been described by Enright (5), as well as Lamprecht and Weber (6,7). The educed waveforms of subjects of each group were also aligned by circadian time and averaged. Procedures for the cosine model were similar except that a best-fitting cosine function was found for each trial period, using the approximations given by Bloomfield (3).

Mean temperature responses to events such as sleep, exercise, and meals were calculated over the scheduled and free-running phases of the experiment. To accomplish this, temperature samples were sorted into 3-min time bins extending from 20 min before to 90 min after an event. The mean temperatures within corresponding bins of subjects of each group were then analyzed by two-way (group × time) analysis of variance (ANOVA) and averaged for graphical display (Fig. 5). When events such as naps occurred in close succession, temperature values falling within the overlapping intervals of successive events were excluded.

RESULTS

Examples of waveforms fitted to the temperature data of a narcoleptic subject are shown in Figs. 1 and 2. In the example, the educed waveform model produced a visibly closer fit to the data and a smaller mean-square error (mse) than the cosine model. The closer conformity of the educed waveform model to the data is especially obvious near the spike-like increases of temperature (to over 37°C) related to exercise, as well as the sharp decreases (to 36°C or below) during the early portions of the main sleep periods. This was true in general: Educed waveform models gave significantly smaller values of mse in both groups and under both the entrained and free-running conditions (Table 1).

Neither model gave evidence of significant differences in the level, period, amplitude, or phase of the circadian temperature rhythms between narcoleptic patients and controls (Table 1). Narcoleptic patients did tend to have lower temperature levels and smaller rhythm amplitudes, as shown by group average waveforms (Figs. 3 and 4) and numerical analysis (Table 1).

The possibility of such differences led us to analyze the mean temperature responses of narcoleptic subjects and controls to events that could affect body temperature, including the onsets and offsets of main sleep episodes, naps, exercise, and meals. As expected, temperature significantly decreased after the onsets of main sleep episodes, $F(35, 455) = 11.0$, $p < 0.001$ (Fig. 5), but the decrease was not significantly smaller in narcoleptic subjects. Awakenings from main sleep episodes were followed by increases of mean temperature, $F(35, 455) = 22.0$, $p < 0.001$, that were identical in the two groups during the first 40 min. The temperature of the narcoleptic group then stopped increasing, while that of controls continued to rise [group × time interaction, $F(29, 377) = 2.0$, $p < 0.01$; Fig. 5]. This divergence was not explained by delays in the decision to arise by narcoleptic subjects, who in fact tended to arise sooner after awakening than controls. Nor was it explained by narcoleptic naps, which were practically nonexistent within the first 1.5 h after sleep termination. Exercise-related increases of temperature were not significantly smaller in narcoleptic subjects (mean +0.188°C vs. +0.234°C in controls, n.s.), and exercise was an infrequent event soon after awakening. Meals, which occurred with comparable frequency in the two groups, also had negligible effects on core temperature.

Involuntary naps, which occurred in all narcoleptic subjects, were heralded by small decreases of core temperature that averaged 0.022°C from 5 min before nap onset to the time of nap onset, $F(4, 20) = 10.5$, $p < 0.001$. Nap onsets were followed by further temperature decreases that averaged 0.011°C after 5 min (n.s.) and 0.022°C after 10 min, $F(9, 45) = 6.5$, $p < 0.001$.

DISCUSSION

Two models of the core body temperature data were employed. One was based on an empirical waveform "educed" from the data of each subject; the other was based on the cosine function. The models have complementary advantages. The empirical model provides close fits to the data (perhaps the best fits that a circadian waveform model can provide), but the model waveform is complex, and measures of amplitude and phase are based on landmarks that are often closely related to local features of the data such as exercise-induced increases of temperature. Because the waveform is often asymmetrical, both the times of minimal and maximal temperature are needed as parameters. The cosine model, by comparison, provides inferior fits but does provide universally accepted measures of amplitude and phase that are less closely tied to local features of the time series. Because the cosine function is symmetrical, a single measure of phase (conventionally the acrophase) suffices.

Both models gave similar findings: Circadian body temperature rhythms were similar in time-isolated narcoleptic patients and normal controls both when subjects followed a 24-h routine and when they free-ran. This finding is evidence against an abnormality of circadian pacemaker function in a small but carefully studied sample of narcoleptic patients. Impaired circadian organization of sleep and wakefulness in this sample (and perhaps in narcoleptic subjects in general) might be explained by failure of circadian timing signals to reach or activate central neural systems that generate states of sleep and wakefulness.

Using cosine fits, Mosko et al. (8) found that non-time-isolated narcoleptic subjects had elevated temperature levels and acrophases that were early in relation to sleep onset. We were unable to confirm those findings and instead observed small group differences in the opposite direction. Findings similar to ours were recently obtained in a study of temperature in narcoleptic subjects and controls whose opportunities to sleep were restricted to 20 of every 90 min (4).

Awakenings from major sleep periods were followed by temperature increases that were identical in the two groups

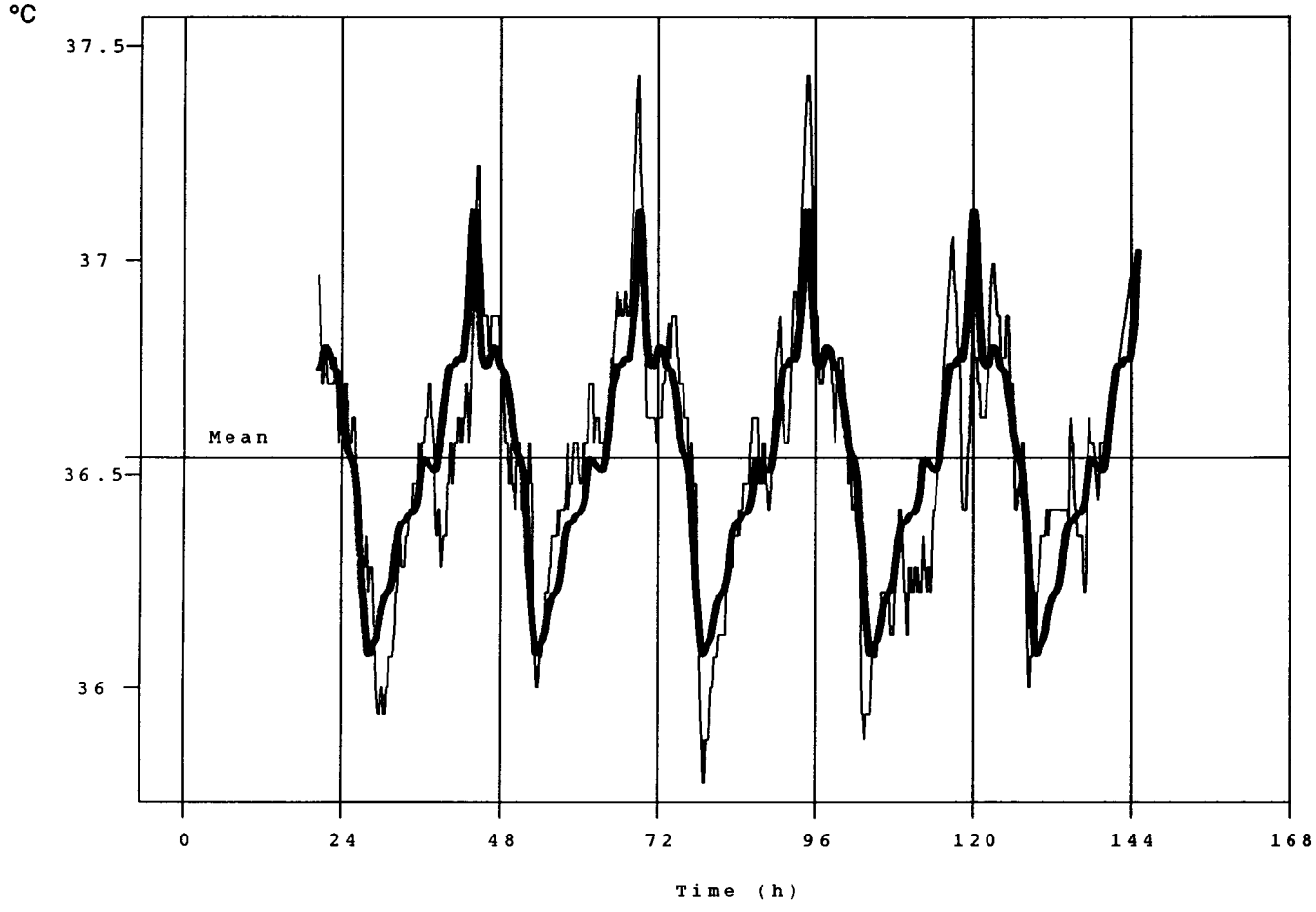

FIG. 1. Educed-waveform model fitted to the entrained temperature data of a narcoleptic subject ("zz06"). n = 740. Period = 1,500 min. Mean-square error (mse) = 0.036°C. 0, 24, . . . = midnight.

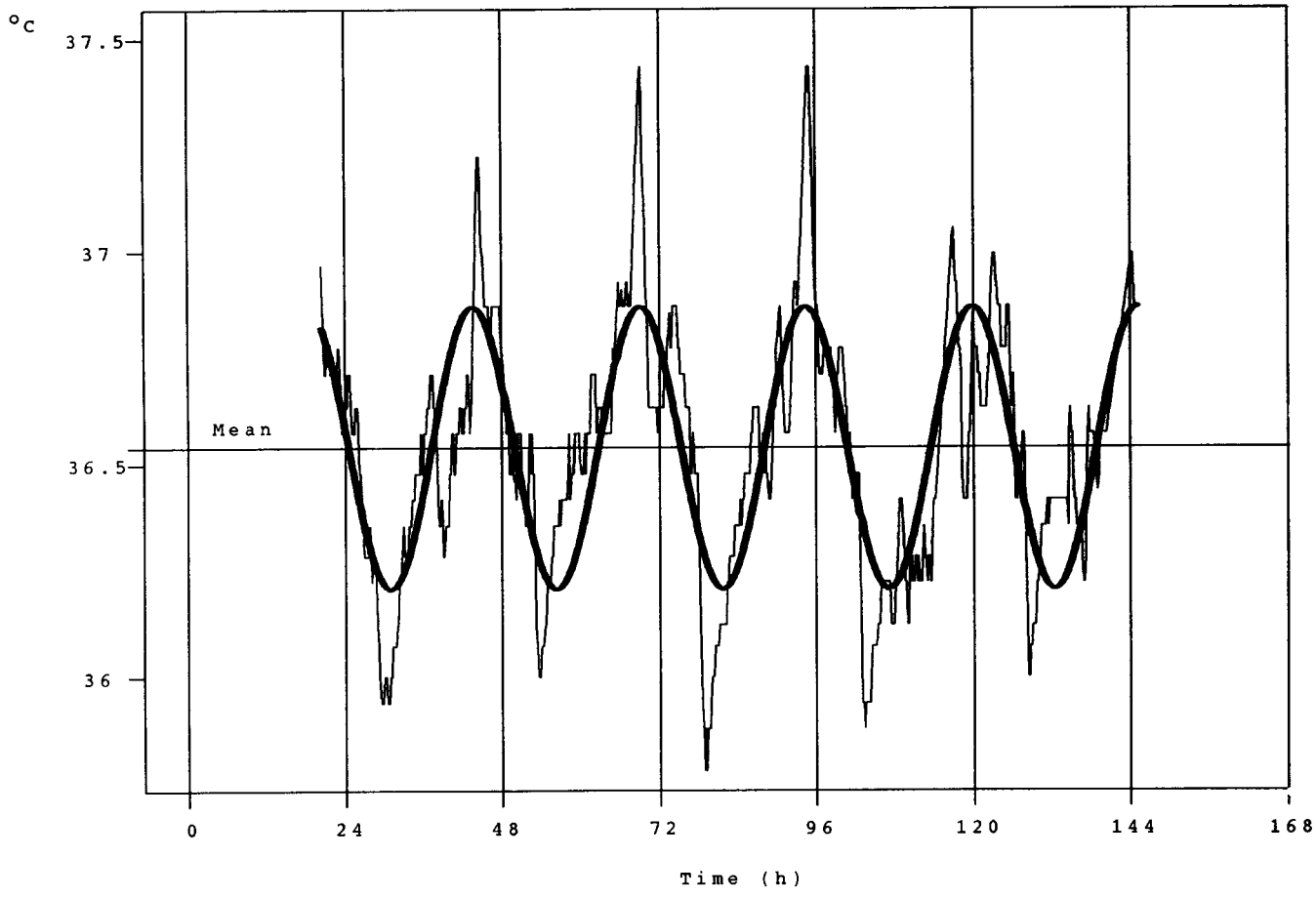

FIG. 2. Cosine model fitted to same data shown in Fig. 1. Period = 1,524 min. mse = 0.057°C.

TABLE 1

MEAN MODEL PARAMETERS

	Entrained			Free-running		
	Narc	Narc*	Ctr	Narc	Narc*	Ctr
Mean-square error (°C^2)						
Educed†	0.116	0.111	0.063	0.131	0.133	0.133
Cosine	0.142	0.139	0.108	0.139	0.143	0.138
Level (°C)	36.71	36.73	36.98	36.81	36.85	37.01
Period (min)						
Educed	1,456	1,457	1,444	1,474	1,466	1,468
Cosine	1,490	1,476	1,453	1,472	1,471	1,465
Peak-peak amplitude (°C)						
Educed	0.75	0.82	0.98	0.58	0.62	0.64
Cosine	0.43	0.48	0.61	0.44	0.48	0.57
Maximum (h)						
Educed	1424	1330	0909	–	–	–
Cosine	1554	1422	1511	–	–	–
Minimum (h)						
Educed	0046	0124	0312	–	–	–
Cosine	0329	0204	0305	–	–	–

No narcolepsy-control group comparisons were significant.
*Excludes one narcoleptic subject with low amplitude and poor model fits in the entrained phase.
†Significantly smaller ($p < 0.05$) for educed waveform model for every group and condition (paired t-test).

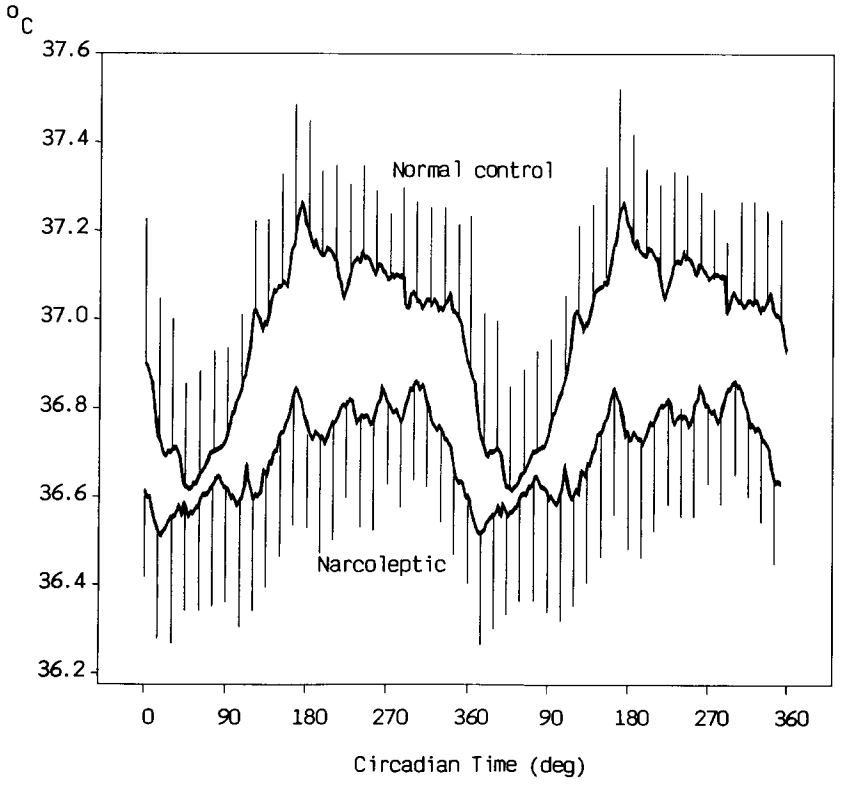

FIG. 3. Mean temperature of narcoleptic subjects and normal controls while they were following 24-h schedules are double plotted by circadian time of day (0°, 360° = midnight). Resolution = 10 min. Bars representing mean − SEM (narcoleptic subjects) and mean + SEM (controls) are shown at 60-min intervals.

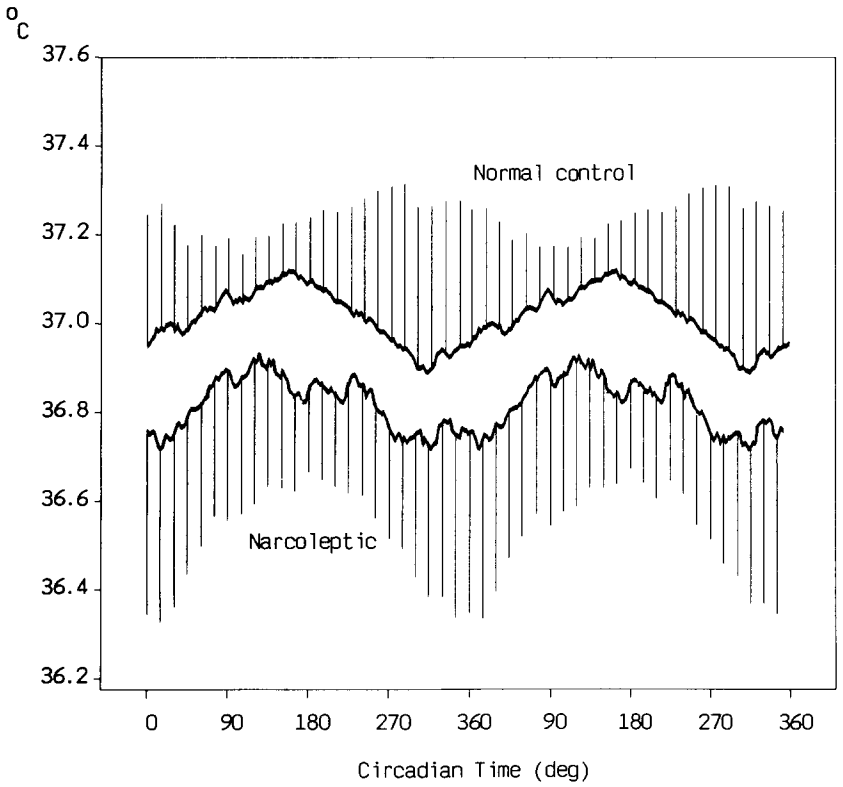

FIG. 4. Mean temperatures of free-running narcoleptic subjects and controls plotted in the same way as in Fig. 3.

for the first 40 min and then diverged, the temperatures of controls continuing to increase while those of narcoleptic subjects leveled off. The divergence was not fully explained by differences in arising behavior, naps, meals, or exercise. Another possibility, not directly assessed in this study, was that narcoleptic subjects were motorically less active and therefore generated less heat while they were awake.

Decreases of temperature were found to precede naps by up to 10 min. These decreases may have resulted from: a) decreasing heat production as narcoleptic patients became mo-

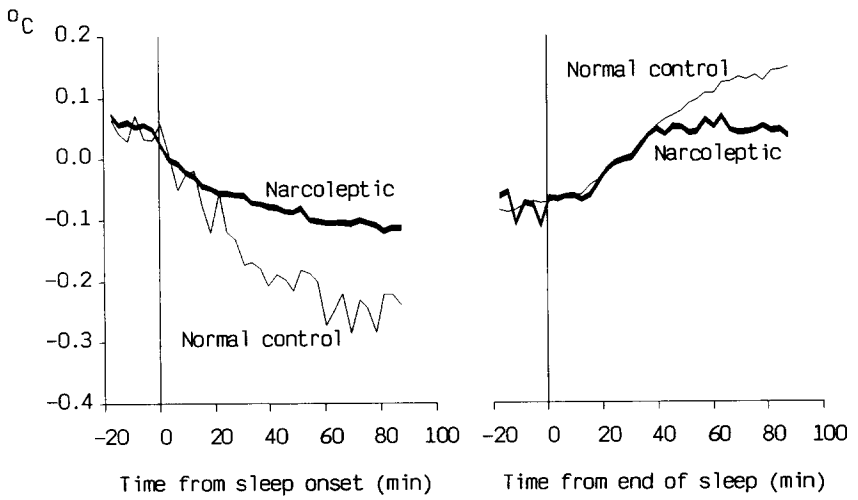

FIG. 5. Mean temperature responses to sleep onset (left) and end of sleep (right) in narcoleptic subjects (heavy line) and controls (light line).

torically inactive; b) increased thermal conductance associated with inactivity or sleep (1); or c) some combination of the two. In any case, the decreases imply that narcoleptic naps represent the culmination of a physiological process and do not begin abruptly, even when sleep is being actively resisted.

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