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## Challenging the sleep homeostat does not influence the thermoregulatory system in men: evidence from a nap vs. sleep-deprivation study

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**Kräuchi, Kurt, Vera Knoblach, Anna Wirz-Justice, and Christian Cajochen.** Challenging the sleep homeostat does not influence the thermoregulatory system in men: evidence from a nap vs. sleep-deprivation study. *Am J Physiol Regul Integr Comp Physiol* 290: R1052–R1061, 2006. First published November 23, 2005; doi:10.1152/ajpregu.00381.2005.—The purpose of our study was to understand the relationship between the components of the three-process model of sleepiness regulation (homeostatic, circadian, and sleep inertia) and the thermoregulatory system. This was achieved by comparing the impact of a 40-h sleep deprivation vs. a 40-h multiple nap paradigm (10 cycles with 150/75 min wakefulness/sleep episodes) on distal and proximal skin temperatures, core body temperature (CBT), melatonin secretion, subjective sleepiness, and nocturnal sleep EEG slow-wave activity in eight healthy young men in a “controlled posture” protocol. The main finding of the study was that accumulation of sleep pressure increased subjective sleepiness and slow-wave activity during the succeeding recovery night but did not influence the thermoregulatory system as measured by distal, proximal, and CBT. The circadian rhythm of sleepiness (and proximal temperature) was significantly correlated and phase locked with CBT, whereas distal temperature and melatonin secretion were phase advanced (by  $113 \pm 28$  and  $130 \pm 30$  min, respectively; both  $P < 0.005$ ). This provides evidence for a primary role of distal vasodilatation in the circadian regulation of CBT and its relationship with sleepiness. Specific thermoregulatory changes occur at lights off and on. After lights off, skin temperatures increased and were most pronounced for distal; after lights on, the converse occurred. The decay in distal temperature (vasoconstriction) was significantly correlated with the disappearance of sleep inertia. These effects showed minor and nonsignificant circadian modulation. In summary, the thermoregulatory system seems to be independent of the sleep homeostat, but the circadian modulation of sleepiness and sleep inertia is clearly associated with thermoregulatory changes.

circadian rhythm; skin and core body temperature; electroencephalogram slow-wave activity

SLEEPINESS CAN BE DEFINED AS a physiological need for sleep with a behavioral measure of the subject's tendency to fall asleep at a certain time (sleep propensity) (3, 25). Sleepiness, and its converse “alertness” (in this study only sleepiness is used), is a regulated and important determinant of psychomotor vigilance and performance (19). Three major processes are considered to be involved in regulating sleepiness: 1) a homeostatic process that is manifested in a growing increase of sleep propensity during the course of wakefulness that is dissipated during sleep (7, 14); 2) a circadian process controlled by the circadian pacemaker in the suprachiasmatic nuclei that produces a maximum drive for alertness during the subjective day and a maximum drive for sleepiness during the subjective night

(7, 14); and 3) a process of “sleep inertia,” which describes the phenomenon of low vigilance on awakening even though sleepiness should be lowest at the end of a sleep episode (24). These three processes represent the compartments of the mathematical three-process-model for sleepiness (2, 18).

Many studies have shown that the level of EEG slow-wave activity (SWA) is a robust measure of non-rapid eye movement (NREM) sleep intensity and may serve as an objective physiological indicator of sleep homeostasis (6). A close relationship between the duration of prior waking and SWA in subsequent sleep episodes has been demonstrated and mathematically described (1). A sleep deficit elicits a compensatory response of increased SWA, with excess sleep having the opposite effect. This regulatory mechanism is referred to as sleep homeostasis.

An elegant way to assess the contribution of homeostatic and circadian components of sleepiness and sleep EEG measurements is by scheduling subjects to non-24-h sleep-wake cycles (days much longer or shorter than 24 h, e.g., 28 or 20 h, outside the range of entrainment) (16, 17). In these so-called “forced desynchrony” protocols, sleep occurs at many different circadian phases, whereas the sleep homeostat can be assumed to be in a near steady state.

The phase and amplitude of the circadian pacemaker cannot be measured directly. However, the circadian rhythm of core body temperature (CBT) is considered a good indicator when measured under the controlled conditions of a “constant routine” protocol (CR; Ref. 41). In normal life, CBT is differentially “masked” by various behaviors (e.g., food and fluid intake, motor activity, muscular exertion, postural changes), as well as by external conditions (e.g., light, sound, room temperature, humidity). The CR was developed to reduce such masking effects and serves therefore as an excellent method to measure circadian aspects of thermoregulation. To exclude the effects of sleep on the CBT, sleep is not allowed during the CR. Therefore, with increasing duration of sleep deprivation (e.g., for 40 h), the sleep homeostat is challenged and sleep pressure increases, which itself induces changes in other output variables.

A general relationship between thermoregulation and sleep regulation has been long hypothesized, e.g., sleep as an energy conservatory state (23, 49). In humans, sleep is typically initiated on the declining portion of the CBT curve when its rate of change is maximal (11, 21, 38, 50, 51). We have shown that body heat loss via distal skin regions (measured by the distal-proximal skin temperature gradient; DPG) is the variable most closely linked to subjective sleepiness and predicts sleep

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onset latency (30, 31). More recently, we have also shown that distal vasoconstriction after a nap (between 4:00 and 8:00 PM) or after night sleep (between 11:00 PM and 7:00 AM) is correlated with disappearance of sleep inertia after lights on (34). Conversely, the evidence for a thermoregulatory role of sleep in humans is surprisingly weak. Some studies have demonstrated that sleep propensity can be modulated by circadian and behavior-induced changes in cutaneous temperature (for review, see Ref. 47). However, most studies that show that correlations of CBT decline with slow-wave sleep have not been carried out under controlled conditions, particularly posture: subjects usually lie down just before lights off (16, 43). Although this may appear to be a minor detail, for thermoregulation, it is not. Such a change in body position alone decreases CBT and increases skin temperatures for at least 2 h (27). This masking phenomenon has been entirely neglected in interpreting prior data on thermoregulation and sleep. Thus, for understanding the relationship between the thermoregulatory system and sleepiness (sleep) regulation, studies under controlled unmasking conditions before, during, and after sleep episodes are needed.

The aim of our study was to understand the relationship between the components of the three-process model of sleepiness regulation (2, 18) and the thermoregulatory system. Therefore, in a 40-h crossover study under constant posture conditions, we attempted to combine the advantages of the CR (unmasking conditions for the circadian CBT rhythm) with the forced desynchrony protocol in a very much shortened form (10 cycles with 150 min of scheduled wakefulness and 75 min of scheduled sleep episodes), allowing separation (for discussion of this expression, see DISCUSSION) of homeostatic and circadian aspects. The nap protocol (NP) also allows a systematic comparison of sleep and sleep inertia on thermoregulation at different circadian phases. Finally, a comparison of 8-h sleep episodes before and after the two protocols allows for an evaluation of the effects of high- vs. low-sleep pressure on the thermoregulatory system in relation to SWA decay kinetics.

**METHODS**

*Subjects*

Subjects were recruited via poster advertisements at the University of Basel. After successfully completing a brief telephone screening, subjects received detailed information on the study and three questionnaires: a morning-evening-type questionnaire (46), the Pittsburgh Sleep Quality Index (8), and an extensive questionnaire covering sleep habits, sleep quality, life habits, physical health, and medical history. Subjects with self-reported sleep complaints (Pittsburgh Sleep Quality Index score  $\geq 5$ ) as well as extreme morning or evening types (score  $< 12$  or  $> 23$ ) were excluded from participation. Other exclusion criteria were chronic or current major medical illness or injury, smoking, medication or drug consumption, shift work within 3 mo or transmeridian travel within 1 mo before the study, excessive caffeine consumption, and excessive physical activity. Subjects who did not fulfill any of the above exclusion criteria were invited to the laboratory and interviewed. A physical examination excluded medical disorders. Subjects spent an adaptation night in the laboratory to test the ability to sleep in a new environment and to exclude primary sleep disorders (e.g., insomnia, apnea). All subjects gave signed, informed consent. The local Ethical Committee approved the study protocol, screening questionnaires, and consent form. All procedures conformed with the Declaration of Helsinki.

Sixteen healthy young subjects (8 men and 8 women) completed the study. Because of the influence of the menstrual cycle and contraceptives on the thermoregulatory system, only results of the eight men [age: range 21–29 yr, mean  $25.1 \pm 1.0$  (SE); body-mass index: range 19.60–24.69 kg/m<sup>2</sup>, mean  $21.90 \pm 0.46$  (SE)] are presented. The entire data set was used for analyses of neurocognitive functions and sleep (9, 10, 26, 42). During the week preceding the study, subjects were instructed to maintain a regular sleep-wake schedule (bed and wake times within  $\pm 30$  min of self-selected target times, verified by sleep logs and a wrist activity monitor; Cambridge Neurotechnology). Subjects were also instructed to refrain from excessive physical activity, caffeine, and alcohol consumption. Drug-free status was verified after admission with the use of urine toxicological analysis (Drug-Screen Card Multi-6 for amphetamines, benzodiazepines, cocaine, methadone, opiates, and tetra-hydro-cannabinole; von Minden). All subjects completed the study without any complaints.

*Design*

Subjects underwent two study blocks in a balanced crossover design (see Fig. 1): a sleep-deprivation protocol (SD; constant dim light,  $< 8$  lux) and a NP [10 alternating sleep-wake cycles (or nap cycles, naps 1–10) of 150 min of scheduled wakefulness (light phase,  $< 8$  lux) and of 75 min of scheduled sleep (dark phase, 0 lux)] (for details, see Refs. 9, 26). The low-light intensity ( $< 8$  lux) was chosen because it is below the threshold for suppressing melatonin secretion.

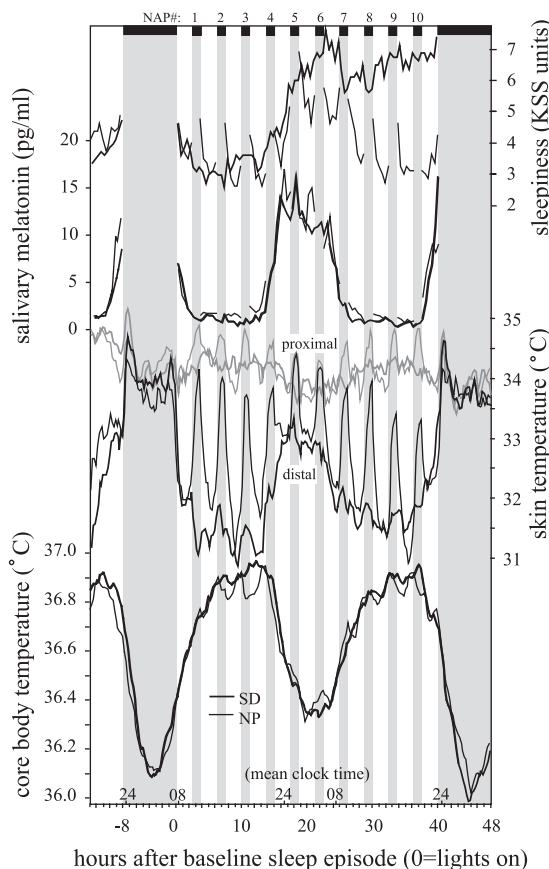


Fig. 1. Mean time course of all measured variables of 8 subjects for the entire protocol. Temperature data are binned in 15-min intervals. For better visualization, SE values were omitted [mean SE values/time bin did not differ between sleep deprivation (SD) and nap protocol (NP), data not shown]. The large black and gray areas indicate dark phase (nocturnal sleep) for both protocols; the black and gray areas between 0 and 40 h indicate dark phase only for NP. KSS, Karolinska Sleep Scale.

Subjects reported to the laboratory in the evening for an 8-h sleep adaptation episode. The timing of the sleep-wake schedule was calculated in such a way that the sleep episode was centered at the midpoint of each subject's habitual sleep episode, which was assessed by actigraphy during the baseline week. On the next afternoon, electrodes and thermocouples were attached. After a second 8-h sleep episode at habitual bedtime (baseline sleep), subjects remained in bed for 40 h (semirecumbent during wakefulness and supine during scheduled sleep episodes) under controlled CR conditions (room temperature 22°C, humidity 60%, light bedcover, 100-kcal sandwiches, and 100 ml of water at 1-h intervals; for details, see Ref. 28). They either remained awake for a 40-h total sleep deprivation, or they completed 10 nap cycles. The protocol ended with a third 8-h sleep episode (recovery sleep) starting again at habitual bedtime. After a 1- to 4-wk interval, the subjects carried out their second study block.

#### Thermometry

Temperature data were continuously recorded by thermocouples (Interstar, Cham, Switzerland) at 20-s intervals using a computerized system (System Hofstetter, SHS Allschwil). CBT was measured with a probe inserted 10 cm into the rectum. Skin temperature probes were fixed with thin air-permeable adhesive surgical tape (Fixomull, Beiersdorf, Hamburg, Germany). Distal temperatures were measured on the center of the back of the left and right hand and the middle of the left and right foot instep (all later averaged). Proximal temperatures were defined as the weighted mean of midforehead, weighting factor ( $f$ ) = 0.093; midthigh on the right musculus rectus femoris,  $f$  = 0.347; right infraclavicular area,  $f$  = 0.266; and stomach, 1 cm above the navel,  $f$  = 0.294. We did not present the DPG (30) results because it would extend our results section too much (see comments below).

#### Salivary Melatonin

Saliva samples were collected at 0.5-h intervals for measurement of melatonin using a highly specific direct double-antibody RIA (48).

#### Subjective Sleepiness Ratings

During the wake episodes, subjective sleepiness was self-assessed at 0.5-h intervals on the Karolinska Sleepiness Scale (KSS; Ref. 3).

#### Sleep Recording and Analyses

Sleep was recorded polysomnographically using the VITAPORT digital ambulatory sleep recorder (Vitaport-3 digital recorder; TEMEC Instruments, Kerkrade, The Netherlands). Twelve EEGs, two electrooculograms, one submental electromyogram, and one ECG signal were recorded. All signals were on-line digitized (12-bit analog-to-digital converter, 610  $\mu$ V/bit; storage sampling rate at 128 Hz for the EEG) and digitally filtered at 30 Hz (fourth-order Bessel-type anti-aliasing filters, total 24 dB/octave) using a time constant of 1.0 s; EEG artifacts were detected by an automated detection algorithm (CASA; 2000 Phy Vision, Kerkrade, The Netherlands). The EEGs were referenced against linked mastoids that were off-line subjected to spectral analysis using a fast Fourier transform (10% cosine 4-s window) resulting in a 0.25-Hz bin resolution (26). SWA during NREM sleep in the frequency range from 0.75 to 4.5 Hz was averaged every 2 h throughout the nights. To analyze the time course of sleep EEG power density, the 8-h sleep episodes were subdivided into 2-h intervals after lights off.

#### Data Analysis

The statistical packages StatView 5.0 and SuperANOVA (Abacus Concepts, Berkeley, CA) and STATISTICA 6 for Windows (StatSoft, Tulsa, OK) were used. Raw data from each subject were inspected visually, and data segments that were affected by removal or malfunctioning of the temperature sensors were removed. These missing data (<0.5%) were replaced by values derived from a linear interpo-

lation procedure. To reduce short-term fluctuations and the number of time segments, data were averaged either in 5-min bins [used for detailed analysis of time courses within a nap (75/150 min sleep/wake) cycle] or in 15-min bins (used for the overall analysis over 37.5 h). Because the protocols were identical for the first 150 min after baseline sleep, the analysis was performed only for the following 37.5 h.

The circadian time course was analyzed as follows: original data were purified from sleep/wake cycle-induced changes by subtracting the effects of mean nap cycles after data folding in 10 225-min cycles. Before results were averaged, naps at a similar circadian phase were first averaged (*naps 1 and 7, naps 2 and 8, naps 3 and 9, and naps 4 and 10*). To adjust for individual levels, the mean of the last 30 min of data (the last two 15-min bins) of the weighted mean nap cycle was taken as zero (at these time points, sleep inertia from the preceding nap had disappeared). We analyzed the circadian time course using this purified data set by cross-correlation analysis (according to Ref. 12). To purify original sleepiness data from additional long-term trends (see RESULTS), residuals to a linear regression line were taken for the cross-correlation analysis. Cross-correlations were calculated for time lags of  $\pm 480$  min. Time lags of maximum and minimum  $r$  values were extracted from smoothed (225-min moving average) individual curves. Mean cross-correlation curves were calculated after Fisher  $z$ -transformation, which were retransformed for Fig. 3.

The associations between the time course of subjective sleepiness ratings and temperature data with respect to sleep inertia were calculated using a multiple regression analysis for repeated measures. The between-subject differences were taken into account, as well as the nap number, using dummy coded subjects and nap number as forced variables in the model (20). Temperature values (5-min bins) were taken at the same time as KSS ratings and melatonin samples. Correlations between distal, proximal, and CBT or melatonin and sleepiness were calculated for the six time points of the ten 75/150 min sleep/wake cycles (60 values/subject).

Analyses of time courses were performed by one-, two-, and three-way ANOVA for repeated measures (rANOVA). All  $P$  values derived from rANOVAs were based on Greenhouse-Geisser-corrected degrees of freedom, but the original degrees of freedom are reported. For post hoc comparisons, Fishers paired least significant differences with  $\alpha$ -correction for multiple comparisons (12) were calculated.

In a first step, we analyzed the data with respect to differences between the protocols (*protocol*; SD vs. NP), the time course within a nap cycle (*time*; e.g., 15  $\times$  15-min temperature bins/nap), and the number of nap cycles (*nap*; 10 nap cycles). Because in all variables no significant three-way interaction term (*time*  $\times$  *nap*  $\times$  *protocol*) was found (see below), we analyzed in a second step the effects within a mean nap cycle in more detail with a higher time resolution of the temperature measurements [two-way rANOVA; *time* (5 min bins)  $\times$  *protocol*]. Third, to compare the circadian phase between the variables and between the protocols, we carried out cross-correlation analyses. In the last section, we analyzed thermoregulatory effects during an 8-h sleep episode under different sleep pressure conditions (high or low levels of SWA).

## RESULTS

### Comparison Between the Two Protocols (SD vs. NP)

This section describes the results for each variable between 1.5 and 40 h after the 8-h baseline sleep episode (Fig. 1). The raw data of all temperatures were averaged in 15-min bins over both the SD and NP. The only difference between the two protocols was that sleep was allowed in the 75-min lights off episodes during the NP (statistical analysis in Table 1). All data within the first 150-min time segment after the baseline night did not statistically differ with respect to SD and NP (statistics not shown), indicating similar starting conditions before the two different protocols began [i.e., the first nap cycle (*nap 1*)

Table 1. Statistical analysis of thermoregulatory variables and sleep pressure across the two protocols

Factor	CBT		Proximal Temperature		Distal Temperature		Melatonin			KSS	
<i>Prot</i>	<i>F</i> (1,7)	0.59 NS	1.54 NS	23.7 <i>P</i> < 0.005	<i>F</i> (1,7)	0.96 NS	<i>F</i> (1,7)	29.2 <i>P</i> < 0.001			
<i>Time</i>	<i>F</i> (14,98)	4.41 <i>P</i> < 0.05	19.9 <i>P</i> < 0.0001	18.2 <i>P</i> < 0.005	<i>F</i> (5,35)	5.72 <i>P</i> < 0.005	<i>F</i> (5,35)	10.6 <i>P</i> < 0.005			
<i>Nap</i>	<i>F</i> (9,63)	31.2 <i>P</i> < 0.0001	3.44 <i>P</i> < 0.05	11.3 <i>P</i> < 0.0001	<i>F</i> (9,63)	19.5 <i>P</i> < 0.0001	<i>F</i> (9,63)	20.9 <i>P</i> < 0.0001			
<i>Time</i> × <i>nap</i>	<i>F</i> (126,882)	12.7 <i>P</i> < 0.0001	1.17 NS	5.43 <i>P</i> < 0.005	<i>F</i> (45,315)	6.60 <i>P</i> < 0.001	<i>F</i> (45,315)	2.10 NS			
<i>Time</i> × <i>prot</i>	<i>F</i> (14,98)	2.40 NS	11.9 <i>P</i> < 0.005	25.9 <i>P</i> < 0.0001	<i>F</i> (5,35)	0.85 NS	<i>F</i> (5,35)	13.5 <i>P</i> < 0.005			
<i>Nap</i> × <i>prot</i>	<i>F</i> (9,63)	0.51 NS	0.50 NS	3.14 ( <i>P</i> < 0.1)	<i>F</i> (9,63)	0.26 NS	<i>F</i> (9,63)	15.7 <i>P</i> < 0.0001			
<i>Time</i> × <i>nap</i> × <i>prot</i>	<i>F</i> (126,882)	1.10 NS	1.01 NS	1.20 NS	<i>F</i> (45,315)	2.04 NS	<i>F</i> (45,315)	1.41 NS			

Three-way repeated measures ANOVAs with factors protocol [*prot*, sleep deprivation (SD) vs. nap protocol (NP)], time within a nap cycle (*time*, 15 × 15 min-bins/nap), and nap number (*nap*, 10 nap cycles) are given. Melatonin and Karolinska Sleep Scale (KSS) were measured only during the wake phase; therefore, *df* of factor *time* is 5 for these variables. NS, not significant; CBT, core body temperature.

started with a 75-min scheduled nap in dark followed by 150-min scheduled wakefulness in <8 lux].

**CBT.** CBT mean values over the 37.5 h did not differ between SD and NP [main effect: *protocol*, not significant (NS)]. The main effect *nap* was highly significant, with highest values in *naps* 3 and 9 and lowest values in *naps* 5 and 6, describing the circadian time course. The significant interaction term *time* × *nap* reflects CBT changes during the naps, which were strongly influenced by the uprising or falling part of the circadian CBT rhythm. During nap cycles, only minor nonsignificant differences in CBT occurred between NP and SD. Compared with SD, NP showed the largest reduction in CBT in the middle of the light phase (for detailed analysis, see Fig. 2), although statistical significance was not reached.

**Proximal skin temperature.** Mean proximal skin temperature values over the 37.5 h did not differ between SD and NP. The significant factor *nap* showed highest values in *naps* 1, 2, 3, and 9 and lowest values in *nap* 5. Significant changes occurred during nap cycles with highest SD vs. NP differences in the middle of the dark phase and smallest differences at the end of the light phase (*time* × *protocol*, significant) (for detailed analysis, see Fig. 2).

**Distal skin temperature.** All three main effects (*protocol*, *time*, and *nap*) reached levels of statistical significance. Compared with SD, the main effect *protocol* showed elevated mean values of distal temperature over the 37.5 h in NP. However, this elevation was modulated during the nap cycle. Highest SD vs. NP differences were found in the middle of the dark phase, and smallest differences were found at the end of the light phase within each nap cycle (for detailed analysis, see Fig. 2). The *nap* × *protocol* interaction showed only a trend to statistical significance (*P* < 0.1), indicating only small changes between NP and SD with respect to preceding duration of the protocols. The significant interaction term *time* × *nap* reflects changes during the naps, which are strongly influenced by the uprising or falling part of the circadian rhythm in distal skin temperature. The time course of DPG (data not shown) was very similar to distal skin temperature (statistics in Table 1).

**Salivary melatonin.** Mean melatonin values over the 37.5 h did not differ between SD and NP. The main effect *nap* was highly significant, with highest values in *naps* 4–7 and lowest values in *naps* 1–3 and *naps* 8–10, describing the circadian time course. The significant interaction term *time* × *nap* reflects salivary melatonin changes during the naps, which are strongly influenced by the uprising or falling part of the circadian melatonin rhythm. During the scheduled wakefulness

episode within the nap cycles, only minor nonsignificant differences occurred between NP and SD, indicating negligible effects of light (<8 lux) on melatonin secretion after a 75-min dark episode.

**Subjective sleepiness (KSS).** Subjective sleepiness showed clear differences between the two protocols with respect to *nap* and *time*. All three main effects were statistically significant; however, significant two-way interactions indicate more complex interpretations. The sleep deprivation led to an increased mean sleepiness level of 1.2 KSS units compared with that shown in NP; however, this difference was clearly modulated by the circadian rhythm (for detailed analysis, see Fig. 2). The significant interaction *nap* × *protocol* reflects the gradual increase of sleepiness in SD with proceeding duration of wake time as well as a circadian component and a different circadian pattern in NP with maximum values at *naps* 5 and 6.

#### Nap-Induced Effects

This section describes the results of the nap-induced effects in a mean 75/150 min sleep/wake cycle in 5-min bins (Fig. 2). To adjust for interindividual differences, data of the last 30 min of the light cycle were taken as zero (see METHODS). Because there were no significant three-way interactions in any of the variables (Table 1), detailed two-way ANOVAs (factors were *protocol* and *time*) could be performed. To study in detail the nap-induced effects, 45 × 5-min binned data (total 225 min) were analyzed (each bin previously averaged over all 10 nap cycles; see METHODS). Nearly identical statistical results were obtained, as shown in Table 1, with 15-min bins; therefore, a detailed ANOVA table is not shown.

A significant *time* effect in CBT reflected the influence of the protocols (however, the maximal variations were only 0.05°C). The apparent difference (0.05°C) between NP and SD in the middle of the light phase of a nap cycle did not reach statistical significance. Proximal skin temperature showed a significant *time* × *protocol* interaction. In NP, proximal skin temperature was significantly increased 10 min after lights off (maximum change of 0.5°C) and were decreased 5 min after lights on (no significant differences between SD and NP). Distal skin temperature also showed a significant *time* × *protocol* interaction. In NP, distal skin temperature was significantly increased 10 min after lights off (maximum change of 1.7°C at the end of the dark phase). This elevation in distal skin temperature during the dark phase of a nap cycle thereafter steadily de-

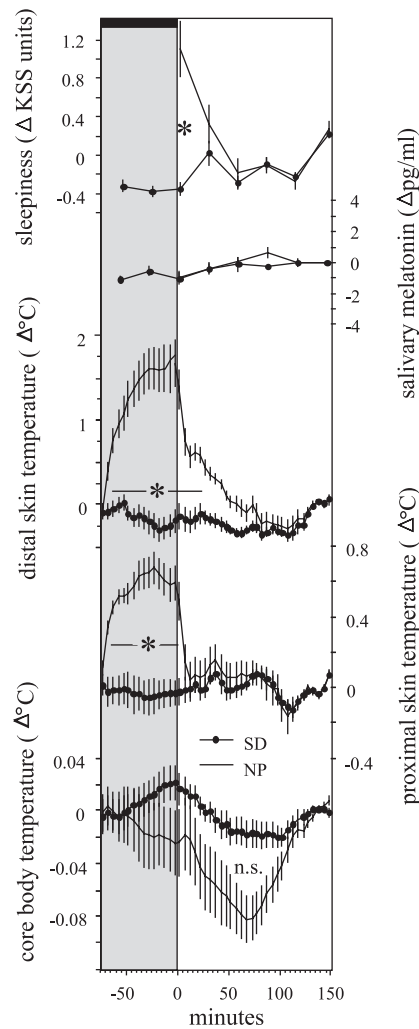


Fig. 2. Time course ( $\Delta$ mean  $\pm$  SE;  $n = 8$  subjects; 5-min bins) of all measured variables during an overall averaged 75/150 min sleep/wake cycle. To adjust for interindividual differences, data of the last 30 min of the light cycle were taken as zero (see METHODS). \*Significant differences ( $P$  at least  $<0.05$ , see text) between the 2 protocols. Black and gray areas indicate dark phase.

clined until the end of the light phase (with no differences between the 2 protocols after 25 min).

Sleepiness showed highest SD vs. NP differences at the beginning of the light phase (sleep inertia) and lowest at the end [ $time \times protocol$ ,  $F(5,35) = 12.28$ ,  $P < 0.0001$ ]. In NP, highest sleepiness ratings were found 5 min and lowest values 120 min after lights on. SD showed small but significant modulations of sleepiness during the 225-min cycle [ $time$  course,  $F(7,49) = 11.64$ ,  $P < 0.001$ ]. Because sleep was not

allowed, these variations can be related to the various tasks within the protocol.

A multiple regression analysis for repeated measures revealed that the intraindividual time course of subjective sleepiness was significantly correlated with distal skin temperature [standardized coefficient (std b) =  $+0.293$ ,  $P < 0.0001$ ] and CBT (std b =  $-0.132$ ,  $P < 0.005$ ) but not with proximal skin temperature (std b =  $+0.055$ , NS) and melatonin (std b =  $-0.041$ , NS).

#### Comparison Between Circadian Time Courses

To compare the circadian time course of SD and NP, it was necessary to purify the data from the significant nap cycle-evoked effects (see *Data Analysis* and Table 1). Therefore, data of the weighted mean nap cycle data were subtracted from the original data (see METHODS). The resulting residuals included changes induced by, e.g., circadian modulation and sleep pressure but no longer by nap-evoked effects (e.g., the increased skin temperatures after lights off, sleep inertia effects). All temperature variables were successfully detrended from the nap cycle-evoked effects, as indicated by nonsignificant statistical ANOVA terms for *protocol*, *time*, and *time  $\times$  protocol* (Table 1 shows  $F$  and  $P$  values for *nap*, *time  $\times$  nap*, *nap  $\times$  protocol*, and *time  $\times$  nap  $\times$  protocol* did not change; data not shown). Residuals of distal and proximal skin temperatures and CBT followed a significant circadian pattern, and CBT and proximal skin temperature had inverse phase relationships to distal skin temperature (see below), all being similar for both protocols. Although sleepiness was significantly detrended (as indicated by nonsignificant statistical ANOVA terms for *time* and *protocol  $\times$  time*), the protocols remained different [ $protocol$ :  $F(1,7) = 36.6$ ,  $P < 0.0005$ ] and *nap  $\times$  protocol* [ $F(9,63) = 15.7$ ,  $P < 0.0001$ ]. In NP, sleepiness clearly follows a circadian pattern with maximal values at naps 5 and 6. In SD, the time course of sleepiness shows a circadian pattern, which is overlapped with an increasing trend on the second day (for detrending of this effect, see below).

To compare circadian phase relationships between the variables or protocols, cross-correlation analyses were performed (see Table 2). Because subjective ratings of sleepiness showed a significant increase during SD (see above and Fig. 1), KSS data were detrended by linear regression analysis (see METHODS). For no variables was a significant phase lag between NP and SD curves observed, indicating no differences in circadian phase between the two protocols. The phase relationships between distal skin temperature, proximal skin temperature, melatonin, and KSS compared with CBT are shown in Fig. 3. In NP and SD, no phase differences between KSS and CBT curves were found, indicating inverse phase-locked patterns.

Table 2. Phase relationships between variables and between protocols

Variable	SD vs. NP Lag, h	$t$ -Test $P$	NP vs. CBT, Lag, h	SD vs. CBT Lag, h	Pooled NP and SD vs. CBT Lag, h	$t$ -Test (vs. 0 lag) $P$
CBT	$-0.09 \pm 0.38$	NS				
Distal skin temperature	$+0.47 \pm 0.56$	NS	$+1.89 \pm 0.84$	$+1.87 \pm 0.56$	$+1.88 \pm 0.46$	$< 0.005$
Proximal skin temperature	$+0.85 \pm 0.47$	NS	$-0.26 \pm 1.58$	$-1.12 \pm 1.72$	$-0.69 \pm 1.25$	NS
KSS	$-0.35 \pm 0.71$	NS	$+0.17 \pm 0.38$	$+0.38 \pm 0.51$	$+0.27 \pm 0.29$	NS
Melatonin	$+0.06 \pm 0.35$	NS	$+2.09 \pm 0.50$	$+2.24 \pm 0.57$	$+2.17 \pm 0.51$	$< 0.005$

Values are means  $\pm$  SE. Maximum or minimum lags were extracted from individual cross-correlation curves. +Lag values, phase advances; -lag values, phase delays.

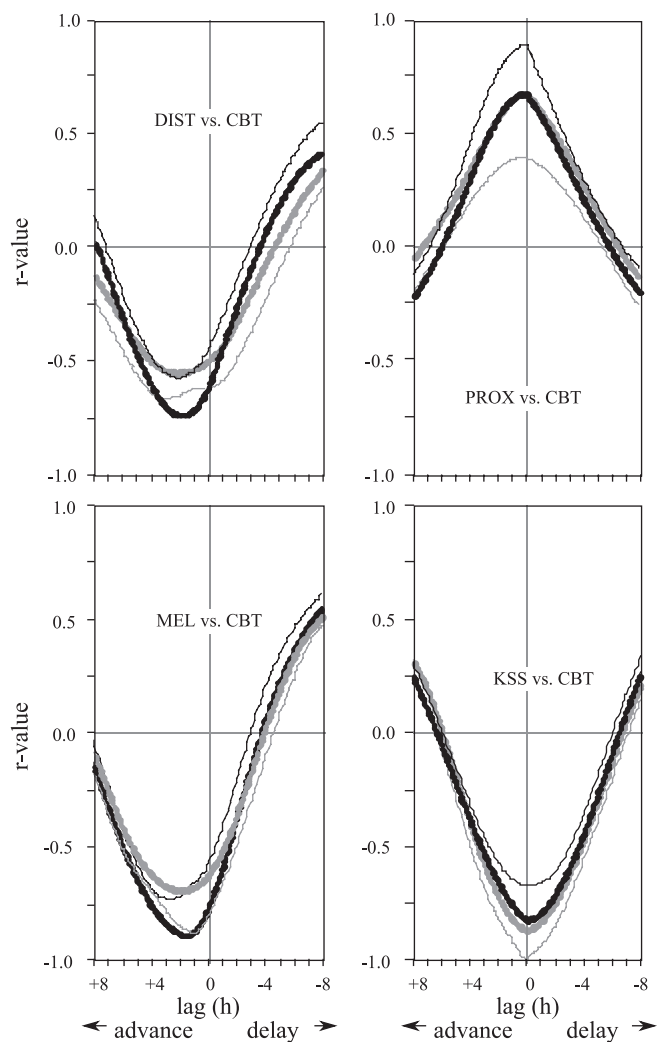


Fig. 3. Cross-correlation curves (5-min bins) between skin temperatures [proximal (PROX); distal (DIST)], subjective sleepiness (KSS), and core body temperature (CBT). To receive equidistance in time for all variables, KSS and melatonin (MEL) were linearly interpolated. Mean (thick lines)  $\pm$  SE (thin lines), after retransformation of Fishers  $z$ -values;  $n = 8$  subjects; black lines show SD results, and gray lines show NP results. Note that distal skin temperature and melatonin are significantly phase advanced by  $\sim 2$  h with respect to CBT (see Table 2).

Similarly, no phase differences were found between proximal skin temperature and CBT. In contrast, distal skin temperature and melatonin compared with CBT showed similar significant phase advances by 113 and 130 min, respectively. Similarly, distal skin temperature and melatonin were also phase advanced with respect to KSS [ $+96 \pm 29$  min,  $F(1,7) = 10.7$ ,  $P < 0.05$  and  $+114 \pm 40$  min,  $F(1,7) = 8.27$ ,  $P < 0.05$ ].

*Comparison Between Baseline, “Second,” and Recovery Night*

To disclose differences between the two protocols in the time course of temperatures during nocturnal sleep in the first [baseline (BN)] and third [recovery (RN)] night (Fig. 4), as well as during the second night (*night 2* = without sleep in SD, 2 short sleep episodes in NP; nap-purified data), 30-min binned data of CBT and skin temperatures were analyzed by three-way rANOVA (Table 3). This analysis tests the effects of low- vs.

high-sleep pressure (NP vs. SD) on thermoregulatory changes within an 8-h nocturnal recovery sleep episode in relation to SWA measured in NREM sleep. Additionally, the comparison with *night 2* allows an analysis of thermoregulatory effects with or without sleep at the same circadian phase (to simplify matters, an endogenous circadian phase of 24 h was assumed; Ref. 13).

There were no significant differences between the two protocols in CBT, distal skin temperature, and proximal skin temperature (Table 3). Significant main factors of *time* and *night* were found. The two protocols did not differ between BN and RN, allowing a combined testing against *night 2* (2-way rANOVA: BN vs. RN and *time*, NS). In *night 2*, overall higher values in CBT ( $+0.18 \pm 0.04^\circ\text{C}$ ,  $P < 0.005$ ; maximal difference 5 h after lights off:  $+0.31 \pm 0.05^\circ\text{C}$ ; difference at the end of the 8-h sleep episode:  $+0.18 \pm 0.05^\circ\text{C}$ ) and lower values in distal and proximal skin temperatures (distal skin temperature

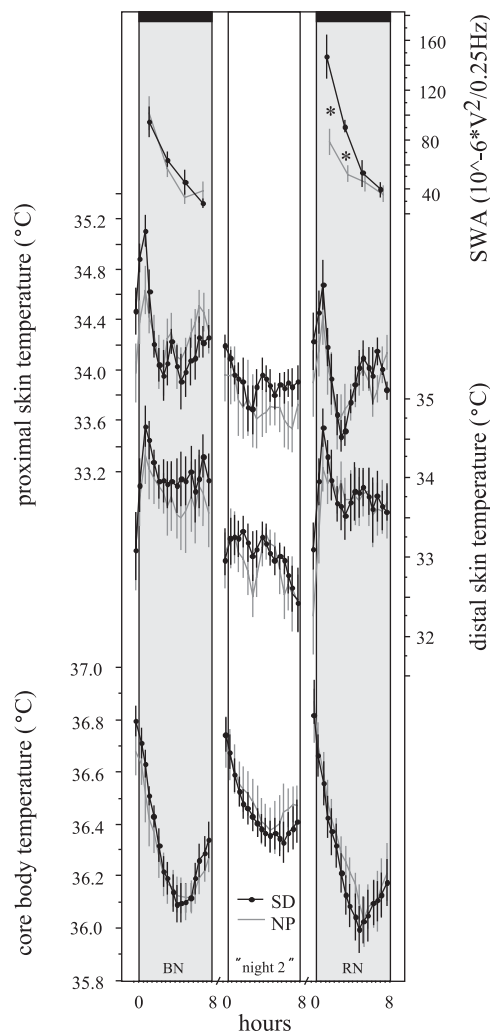


Fig. 4. Time course (mean  $\pm$  SE;  $n = 8$  subjects; 30-min bins) of slow-wave activity (SWA), distal and proximal skin temperatures, and CBT during the baseline night (BN), the time segment on *day 2* at the same circadian phase (*night 2*) without sleep, and the recovery night (RN). Note that, in contrast to SWA, no significant differences were found in any body temperature measures between NP and SD. \*Significant differences between the 2 protocols ( $P$  at least  $< 0.05$ , see text). Black and gray areas indicate dark phase of nocturnal sleep.

Table 3. Statistical analysis of thermoregulatory variables and SWA across the two protocols by three-way repeated measures ANOVA

Factor	CBT		Proximal Skin Temperature		Distal Skin Temperature		SWA			
<i>Prot</i>	<i>F</i> (1,7)	0.25	NS	1.31	NS	5.03	( <i>P</i> < 0.1)	<i>F</i> (1,7)	27.6	<i>P</i> < 0.005
<i>Time</i>	<i>F</i> (16,112)	42.4	<i>P</i> < 0.0001	11.5	<i>P</i> < 0.0001	9.21	<i>P</i> < 0.0001	<i>F</i> (3,21)	79.1	<i>P</i> < 0.0001
<i>Night</i>	<i>F</i> (2,14)	8.19	<i>P</i> < 0.005	8.63	<i>P</i> < 0.05	34.7	<i>P</i> < 0.0001	<i>F</i> (1,7)	95.4	<i>P</i> < 0.0001
<i>Time</i> × <i>night</i>	<i>F</i> (32,224)	5.97	<i>P</i> < 0.01	2.16	( <i>P</i> < 0.1)	2.44	( <i>P</i> < 0.1)	<i>F</i> (3,21)	1.02	NS
<i>Time</i> × <i>prot</i>	<i>F</i> (16,112)	0.80	NS	0.41	NS	0.57	NS	<i>F</i> (3,21)	5.88	<i>P</i> < 0.01
<i>Night</i> × <i>prot</i>	<i>F</i> (2,14)	1.87	NS	1.50	NS	0.21	NS	<i>F</i> (1,7)	44.1	<i>P</i> < 0.0001
<i>Time</i> × <i>night</i> × <i>prot</i>	<i>F</i> (32,224)	0.74	NS	1.22	NS	1.37	NS	<i>F</i> (3,21)	7.31	<i>P</i> < 0.001

SWA, slow-wave activity.

$-0.96 \pm 0.11^\circ\text{C}$ ,  $P < 0.05$ ; proximal skin temperature  $-0.31 \pm 0.10^\circ\text{C}$ ,  $P < 0.05$ ) occurred. The first significant reduction of CBT was found 2 h after lights off ( $-0.08 \pm 0.03^\circ\text{C}$ ) and thereafter.

The time course of distal and proximal skin temperatures during BN and RN did not statistically differ from *night* 2, indicating a general upregulation of distal and proximal skin temperatures after switching lights off (see above), even though distal and proximal skin temperatures tended to increase faster during the first 2 h when subjects were asleep [BN, RN vs. *night* 2 × *time*,  $F(16,112) = 2.70$ ;  $P < 0.1$ ].

The time course of SWA during BN did not differ between the two protocols. Both curves declined in an exponential manner. Compared with NP, SD showed a clear increase in SWA at the beginning of RN, confirming the well-known rebound effects of sleep deprivation on SWA. This increase gradually disappeared until the end of RN (fourth 2-h time segment: SD vs. NP, NS).

Together, during BN (including the succeeding 150-min light phase; statistics not shown), all measured variables did not differ with respect to the two protocols, indicating similar starting points. During RN, SWA activity was increased in SD after 40-h sleep deprivation; however, CBT and distal and proximal skin temperatures were not changed. Compared with the time segment at the same circadian phase without sleep (*night* 2), an 8-h sleep episode increases distal and proximal skin temperatures and conversely reduces CBT.

## DISCUSSION

This NP vs. SD under constant routine conditions provided the necessary controlled situation for measuring changes in thermoregulatory variables related to time of day, sleep pressure, sleep itself, and after waking from a nap. Reducing masking effects of behavior and light allowed a partial separation of the influence of the three processes determining sleepiness (2, 18) and their relationship to the thermoregulatory system. We have found an important difference between the circadian and homeostatic processes in this respect. This study supports our previous hypothesis that the circadian modulation of sleepiness is primarily related to the circadian regulation of distal vasodilatation (and hence to heat loss and CBT reduction), whereas the homeostatic-regulated increase of sleepiness is nearly independent thereof (32). The findings also suggest that this close relationship between distal vasodilatation and sleepiness also holds for the process of sleep inertia, thus confirming and extending our published data (30). This means that both the evening increase in sleepiness, which leads to

maximum sleep propensity in the middle of the night, and the exponential decline of sleepiness upon awakening can be described as a function of changes in distal vasodilatation. In contrast, the homeostatic increase in sleepiness related to duration of prior time awake is not related to a thermoregulatory function. This homeostatic buildup process of sleepiness has been related to topographic EEG correlates in the frontal cortex (10). From these different physiological correlates, two “kinds” of sleepiness can be postulated (thermoregulatory related and unrelated).

The following discussion is structured with respect to the three-process model of sleepiness as related to thermoregulation. Our study permits comparison of the buildup of sleepiness (or sleep propensity) and its disappearance during sleep. We have presented distal and proximal skin temperature data to show the thermoregulatory effects as it occurs and not the derivative DPG, which has been shown to be a reliable predictor of sleep-onset propensity.

### *Thermoregulatory Effects Related to Circadian and Homeostatic Regulation of Sleepiness*

The 40-h sleep-deprivation CR protocol has the disadvantage that the endogenous circadian modulation cannot be separated from the influence of the homeostatic rise in sleep pressure. Any overt circadian rhythm measured during CR, even with no obvious homeostatic rise or fall, may still be a masked rhythm. Such a masking component could be either sleepiness, which could lead to distal vasodilatation, or the counteractions taken by a subject to keep awake as sleep pressure increases, which could lead to distal vasoconstriction. A nonassociation of the homeostatic rise in sleep pressure during sleep deprivation with thermoregulatory changes (e.g., distal skin temperature) could be due to equilibrium of the two counterregulatory mechanisms. The NP was designed to reduce the buildup of sleepiness to a low level. Comparison of the two protocols therefore provides a good estimate of homeostatic sleep pressure. Sleepiness increased with increasing duration of time awake and reached significantly higher levels than in NP after 20 h. Previous CR studies found significantly higher subjective sleepiness ratings after ~16 h of wakefulness. The discrepancy can be explained by the fact that after 16 h of wakefulness the circadian increase of sleepiness overlaps with the homeostatic increase of sleepiness. Subjects may not be able to adequately differentiate (add) these two “kinds” of sleepiness, which could lead to a nonadditive interaction at this circadian phase.



The finding that the circadian pattern of all measured body temperatures did not differ between the two protocols indicates that they were independent of the homeostatic buildup of sleepiness (sleep pressure). This allows the conclusion that all the measured circadian patterns are not influenced by a masking process via the sleep homeostat, i.e., counteractions taken by a subject to keep awake. The buildup process of sleep pressure over 40 h has in fact no, or only minor, thermoregulatory consequences. This finding confirms a previous CR study in which our group (36) found nonsignificant changes in body temperatures (proximal, distal, and CBT) at the same circadian phase 24 h after a sleep-deprivation episode. This does not preclude the possibility that, with longer than 40-h SD protocols, the thermoregulatory system may no longer be independent of sleep pressure.

Proximal skin temperature exhibited a circadian profile similar to CBT, whereas distal skin temperature showed an inverse circadian pattern phase advanced by 113 min. As previously noted (Ref. 36 and Fig. 1), the falling limb of the CBT rhythm in the evening is steeper than the rising limb in the morning. Similarly, the rising limb of the distal skin temperature and DPG (data not shown) rhythm in the evening is also steeper (Fig. 1) than the falling limb in the morning. This indicates an asymmetrical regulation of heat loss and heat production in the evening and morning. Heat loss seems to be dominant in the evening, and heat production seems to be dominant in the morning (36). We could also define the temporal relationship between the circadian rhythm of sleepiness and the thermoregulatory system. Sleepiness was significantly phase delayed by  $-96$  min and  $-114$  min with respect to distal skin temperature and salivary melatonin and phase locked to CBT with a negative correlation coefficient. Because the circadian rhythm of distal skin temperature precedes both sleepiness and CBT, this could be the reason why distal skin temperature is a better predictor for sleepiness (and hence for sleep-onset latency) than CBT (30, 31). Interestingly, sleepiness shows not only a close phase relationship to distal skin temperature and CBT but also a similar asymmetrical circadian pattern, with a faster rise in the evening than decline in the morning.

The phase relationship between the circadian rhythm of distal skin temperature and CBT may also provide a thermophysiological explanation of the so-called “wake maintenance zone” in the evening just before endogenous melatonin secretion and distal vasodilatation begins (39). At this circadian phase, the circadian system counterregulates with high effort the homeostatically increased sleepiness and sleep pressure to maintain wakefulness (17). In thermophysiological terms, the “wake maintenance zone” can be characterized as the most vasoconstricted state of distal skin regions in relation to CBT over the entire circadian cycle (i.e., low inner heat conductance with high CBT and low distal skin temperature; Ref. 4).

#### *Thermoregulatory Effects Related to Lights Off in a Nap*

As found in earlier studies (5, 29, 30, 34, 37), thermoregulatory changes induced by lights off do influence CBT but slowly. In contrast, distal and proximal skin temperatures increase immediately after lights off and before the onset of sleep stage 2 (5, 29, 30, 34, 37). This indicates that redistribution of body heat from the core to the shell occurs shortly after lights off via relaxation.

The well-known circadian modulation of sleep onset latency (SOL to sleep stage 1 or 2; Ref. 16) yielded the shortest values near the CBT trough in naps 5 and 6 and longest values in naps 4 and 10 (42) just before distal skin temperature increased and CBT decreased. Similarly, an analysis of the time awake during a nap revealed maximal time awake values in naps 4 and 10 and minimal values during naps 5 and 6 (42). However, independent of the differences in SOL and time awake in each nap, the skin temperatures increased at a similar rate (see Fig. 1), indicating that the subjects relaxed after lights off, although without necessarily falling asleep. An important factor for the relaxation-induced effects could be eye closure occurring before sleep onset, which deserves to be investigated separately.

The extent of the increase in distal skin temperature exhibited a trend toward circadian modulation; the nonsignificance can be explained by a ceiling effect. When distal skin temperature reaches its circadian maximum, it is difficult to increase distal skin temperature above proximal skin temperature. The large and rapid increase in skin temperatures after lights off ( $0.7^{\circ}\text{C}$  in proximal and  $1.6^{\circ}\text{C}$  in distal skin temperature) only led to small decreases in CBT ( $\sim 0.027^{\circ}\text{C}/75$  min), with a time lag such that the lowest value actually occurred 75 min after lights on (Fig. 2). Therefore, it is not possible to extrapolate the reduction of CBT from a short sleep episode (75 min) to that during an 8-h dark (sleep) episode (see below). Furthermore, had subjective ratings of sleepiness after lights off until occurrence of sleep been measured, one could speculate that it would increase in parallel with relaxation, withdrawal of the sympathetic nervous system, redistribution of heat from the core to the shell, and increase of distal skin temperature. Thus these changes after lights off can be interpreted as an inverse process of sleep inertia (see below). What we see are thermoregulatory effects mainly induced by relaxation, most probably via a decrease in sympathetic tone, and not by the occurrence of sleep per se (33). In real life situations, it can be assumed that many effects on sleepiness and sleep, e.g., induced by exercise, hot or warm bathing, intake of food, hot or cold fluids, may occur via redistribution of heat from the core to the shell or vice versa.

#### *Thermoregulatory Effects Related to Sleep Inertia*

After lights on, we found converse thermoregulatory effects to those after lights off (see above). Because no significant suppression of melatonin secretion was found after lights on ( $<8$  lux), these effects cannot be explained by alterations in the retino-hypothalamic-pineal axis. Redistribution of blood from the shell to the core occurs via vasoconstriction, mainly in distal skin regions. However, this takes awhile, in the hands faster than in the feet (data not shown). It is most rapid in proximal skin regions. Sleep inertia, as measured by sleepiness (22, 24, 34), shows a close temporal relationship exclusively with distal but not with CBT and proximal skin temperature. A significant intraindividual correlation of the time course between distal skin temperature and sleepiness reveals a close functional relationship between the decay of sleep inertia and distal vasoconstriction. Most interestingly, we did not find a circadian modulation either in distal skin temperature or in sleep inertia (as measured by subjective sleepiness) after naps taken throughout the 24 h despite large differences in sleep duration within a nap independent on circadian phase (42). This finding supports the notion that sleep per se is not crucial for sleep inertia (22, 34). We could show in two sets of



experiments with either a nocturnal sleep episode (between 11:00 PM and 7:00 AM) or an afternoon nap (between 4:00 and 6:00 PM) that vasodilatation of hands and feet increased after lights off and that this was reversed after lights on. The time course of the distal skin temperature was significantly and positively correlated with subjective sleepiness, reflecting similar temporal relationships in both studies. The extremities cooled at a rate very closely parallel to the decay of sleepiness. The symmetry between the thermoregulatory processes related to the increase in sleepiness and those related to its dissipation is striking. However, to directly test these relationships, further studies with thermophysiological interventions (e.g., cooling the extremities) are required. From these findings, it can be hypothesized that redistribution of heat from core to shell during sleep could actually counteract the waking signal that grows as sleep pressure declines (mirrored in the SWA decline). This inertia may help to maintain sleep or to fall asleep again more easily after a wake bout.

#### *Effect of an 8-h Sleep Episode on Thermoregulation*

If we compare the same circadian phase awake and asleep, the maximum reduction of 0.31°C occurs after 5 h of sleep. In a similar CR study, a reduction of 0.46°C was found (5). The discrepancy can be explained by the higher light intensity level during the wake situation (40 vs. <8 lux in our study), leading to a suppression of melatonin secretion and consequently to higher CBT values.

The CBT minimum during sleep was masked by the process of redistribution of heat from the core to the shell, initiated immediately after lights off and not by sleep per se (see above). In the first 2.5 h after lights off, distal and proximal skin temperatures increased to a peak with a similar maximum value. Sindrup et al. (45) described this hyperemic reaction as an effect that occurs with sleep. However, our method has a much higher time resolution than the radioisotope method used by these authors, and thus we could clearly separate the relaxation from the sleep-induced effects. This leads to the conclusion that onset of sleep stage 2, and herewith onset of increased SWA, does not have additional thermoregulatory effects (see also Ref. 35). We have also shown that after lights off, when distal vasodilatation increases, heart rate falls in parallel, indicating a decrease in cardiac output, which could explain why the increase in distal vasodilatation does not induce an efficient heat loss with a consequent decrease in CBT (35). Furthermore, after the acute hyperemic response to lights off, proximal and distal temperatures remained at a comparable high value, indicating a loss of the core-shell dichotomy (4) of the body during sleep. This one-compartment state makes the body more vulnerable to heat loss or heat uptake, which could be a reason that a thermoneutral environment is preferred for sleep as a protection against external cooling and warming.

#### *Effect of High and Low Sleep Pressure on Thermoregulation in the Succeeding 8-h Sleep Episode*

In addition to the nap-related evidence, the nocturnal recovery sleep provided conclusive evidence that increased SWA (particularly during the first 4 h) that resulted from increased sleep pressure does not influence the thermoregulatory system. Previous studies claimed that high SWA has a thermoregulatory role, e.g., downregulation of CBT for energy conservation

(40, 43, 44). Dijk et al. (17) found the inverse, a relative increase of CBT during the recovery sleep after a 40-h CR. These findings unfortunately cannot be used as arguments because none has used posture-controlled protocols. Our protocols allow not only comparisons between BL and RN of a complete 40-h CR under controlled body position but also a comparison of the RN after conditions of relative high vs. low sleep pressure (SD vs. NP). This latter comparison controls for any possible confounding effect of the long period of 54 h in bed on the influence of SWA on thermoregulation.

Together, this is the first study that details the complex interactions between circadian phase, sleep pressure, and thermoregulatory effects in healthy young subjects kept under controlled posture, food intake, and environmental conditions. We have disproved the long-held belief that sleep, or more precisely NREM sleep, causes CBT to decline. Because lying down and relaxation after lights off evoke an increase in skin temperatures and a decline in CBT, these major masking effects have confounded prior studies and rendered their conclusions doubtful. This is not to deny the importance of such masking in real-life conditions. Thus it appears that the circadian pacemaker drives the circadian propensity for sleep via a circadian rhythm in heat loss (vasodilatation). A similar but inverse mechanism is responsible for the sleep inertia upon awakening. These thermoregulatory mechanisms underlying circadian sleepiness and sleep inertia are not related to changes in “homeostatic sleepiness” resulting from being awake over longer periods.

#### *Perspectives*

The corollary of these findings has important consequences in sleep medicine. Independent of circadian phase, sleepiness is augmented by conditions of warming and diminished by cooling of distal skin regions (leading to increased and reduced convective body heat loss, respectively). This knowledge supports the simple old-fashioned methods to speed up falling asleep (e.g., warm bath) or to rapidly dissipate sleep inertia (e.g., cold shower). In contrast, sleepiness related to extended episodes of prior wakefulness cannot be thermally manipulated and require a different strategy, such as a short nap, to diminish sleep pressure (a “power nap” that does not induce subsequent sleep inertia).

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#### **REFERENCES**

1. Achermann P, Dijk DJ, Brunner DP, and Borbély AA. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. *Brain Res Bull* 31: 97–113, 1993.
2. Åkerstedt T and Folkard S. A model of human sleepiness. In: *Sleep '90*, edited by Horne J. Bochum: Pontenagel, 1990, p. 310–313.
3. Åkerstedt T and Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 52: 29–37, 1990.
4. Aschoff J. Wechselwirkungen Zwischen Kern und Schale im Wärmehaushalt. *Archiv Physikalische Therapie H* 3: 113–133, 1956.

5. Barrett J, Lack L, and Morris M. The sleep-evoked decrease of body temperature. *Sleep* 16: 93–99, 1993.
6. Borbély AA. From slow waves to sleep homeostasis: new perspectives. *Arch Ital Biol* 139: 53–61, 2001.
7. Borbély AA. A two-process model of sleep regulation. *Hum Neurobiol* 1: 195–204, 1982.
8. Buysse DJ, Reynolds CF, Monk TH III, Berman SR, and Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 28: 193–213, 1989.
9. Cajochen C, Knoblauch V, Kräuchi K, Graw P, Wirz-Justice A, and Wallach D. Sequence learning depends on sleep, the level of sleep pressure and circadian phase. *J Sleep Res* 11, Suppl 1: 30–31, 2002.
10. Cajochen C, Knoblauch V, Kräuchi K, Renz C, and Wirz-Justice A. Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure. *Neuroreport* 12: 2277–2281, 2001.
11. Campbell SS and Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow? *Chronobiol Int* 11: 126–131, 1994.
12. Curran-Everett D. Multiple comparisons: philosophies and illustrations. *Am J Physiol Regul Integr Comp Physiol* 279: R1–R8, 2000.
13. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, and Kronauer RE. Stability, precision, and near-24-h period of the human circadian pacemaker. *Science* 284: 2177–2181, 1999.
14. Daan S, Beersma DG, and Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol Regul Integr Comp Physiol* 246: R161–R183, 1984.
15. Dijk DJ and Czeisler CA. Body temperature is elevated during the rebound of slow-wave sleep following 40-h of sleep deprivation constant routine. *J Sleep Res* 2: 117–120, 1993.
16. Dijk DJ and Czeisler CA. Contribution of circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves and sleep spindle activity in humans. *J Neurosci* 15: 3526–3538, 1995.
17. Dijk DJ, Duffy JF, and Czeisler CA. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J Sleep Res* 1: 112–117, 1992.
18. Folkard S and Åkerstedt T. A three-process model of the regulation of alertness-sleepiness. In: *Sleep, Arousal, and Performance*, edited by Broughton RJ and Ogilvie RD. Boston: Birkhäuser, 1992, p. 11–26.
19. Folkard S and Åkerstedt T. Trends in the risk of accidents and injuries and their implications for models of fatigue and performance. *Aviat Space Environ Med* 75: A161–A167, 2004.
20. Glanz SA and Slinker BK. *Primer of Applied Regression and Analysis of Variance*. New York: McGraw-Hill, 1990.
21. Gradisar M and Lack L. Relationships between the circadian rhythms of finger temperature, core temperature, sleep latency, and subjective sleepiness. *J Biol Rhythms* 19: 157–163, 2004.
22. Hofer-Tinguely G, Achermann P, Landolt HP, Regel SJ, Rétey JV, Dürri P, Borbély AA, and Gottselig JM. Sleep inertia: performance changes after sleep, rest and active waking. *Cogn Brain Res* 22: 323–331, 2005.
23. Horne JA. *Why We Sleep: the Functions of Sleep in Humans and Other Mammals*. Oxford: Oxford Univ. Press, 1988.
24. Jewett ME, Wyatt JK, Ritz-De Cecco A, Khalsa SB, Dijk DJ, and Czeisler CA. Time course of sleep inertia dissipation in human performance and alertness. *J Sleep Res* 8: 1–8, 1999.
25. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14: 540–545, 1991.
26. Knoblauch V, Martens W, Wirz-Justice A, Kräuchi K, and Cajochen C. Regional differences in the circadian modulation of human sleep spindle characteristics. *Eur J Neurosci* 18: 155–163, 2003.
27. Kräuchi K, Cajochen C, Danilenko KV, and Wirz-Justice A. The hypothermic effect of late evening melatonin does not block the phase delay induced by concurrent bright in human subjects. *Neurosci Lett* 232: 57–61, 1997.
28. Kräuchi K, Cajochen C, Möri D, Graw P, and Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol Regul Integr Comp Physiol* 272: R1178–R1188, 1997.
29. Kräuchi K, Cajochen C, Werth E, Renz C, von Arb M, and Wirz-Justice A. Thermoregulatory changes begin after lights off and not after onset of sleep stage 2. *Sleep* 24: 165–166, 2001.
30. Kräuchi K, Cajochen C, Werth E, and Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol* 278: R741–R748, 2000.
31. Kräuchi K, Cajochen C, Werth E, and Wirz-Justice A. Warm feet promote the rapid onset of sleep. *Nature* 401: 36–37, 1999.
32. Kräuchi K, Cajochen C, and Wirz-Justice A. Circadian and homeostatic regulation of core body temperature and alertness in humans: what is the role of melatonin? In: *Circadian Clocks and Entrainment*, edited by Honma K and Honma S. Sapporo: Hokkaido Univ. Press, 1998, p. 131–146.
33. Kräuchi K, Cajochen C, and Wirz-Justice A. Thermophysiological aspects of the three-process-model of sleepiness regulation. *Clin Sports Med* 24: 287–300, 2005.
34. Kräuchi K, Cajochen C, and Wirz-Justice A. Waking up properly: is there a role of thermoregulation in sleep inertia? *J Sleep Res* 13: 121–127, 2004.
35. Kräuchi K, Knoblauch V, Renz C, Müller T, Wirz-Justice A, and Cajochen C. Thermoregulatory changes at lights off dependent on circadian phase but not on sleep pressure or sleep. *J Sleep Res* 11, Suppl 1: 128, 2002.
36. Kräuchi K and Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *Am J Physiol Regul Integr Comp Physiol* 267: R819–R829, 1994.
37. Lack L and Gradisar M. Acute finger temperature changes preceding sleep onsets over a 45-h period. *J Sleep Res* 11: 275–282, 2002.
38. Lack L and Lushington K. The rhythms of human sleep propensity and core body temperature. *J Sleep Res* 5: 1–11, 1996.
39. Lavie P. Melatonin: role in gating nocturnal rise in sleep propensity. *J Biol Rhythms* 12: 657–665, 1997.
40. McGinty D and Szymusiak R. Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. *Trends Neurosci* 13: 480–487, 1990.
41. Mills JN, Minors DS, and Waterhouse JM. Adaptation to abrupt time shifts of the oscillator(s) controlling human circadian rhythms. *J Physiol* 285: 455–470, 1978.
42. Münch M, Knoblauch V, Blatter K, Schröder C, Schnitzler C, Kräuchi K, Wirz-Justice A, and Cajochen C. Age-related attenuation of the evening circadian arousal signal in humans. *Neurobiol Aging* In press.
43. Sewitch DE. Slow wave sleep deficiency insomnia: a problem in thermoregulation at sleep onset. *Psychophysiology* 24: 200–215, 1987.
44. Sewitch DE, Kittrell EMW, Kupfer DJ, and Reynolds CF. Body temperature and sleep architecture in response to a mild cold stress in women. *Physiol Behav* 36: 951–957, 1986.
45. Sindrup JH, Kastrup J, Jorgensen B, Bülow J, and Lassen NA. Nocturnal variations in subcutaneous blood flow rate in lower leg of normal human subjects. *Am J Physiol Heart Circ Physiol* 260: H480–H485, 1991.
46. Torsvall L and Åkerstedt T. A diurnal type scale. Construction, consistency and validation in shift work. *Scand J Work Environ Health* 6: 283–290, 1980.
47. Van Someren EJW. Sleep propensity is modulated by circadian and behavior-induced changes in cutaneous temperature. *J Therm Biol* 29: 437–444, 2004.
48. Weber JM, Schwander JC, Unger I, and Meier D. A ultrasensitive RIA for the determination of melatonin in human saliva: comparison with serum levels. *Sleep Res* 26: A112–A113, 1997.
49. Zepelin H. Mammalian sleep. In: *Principles and Practice of Sleep Medicine*, edited by Kryger MH, Roth T, and Dement WC. Philadelphia, PA: Saunders, 2000, p. 82–92.
50. Zulley J and Wever R. Interaction between the sleep-wake cycle and the rhythm of rectal temperature. In: *Vertebrate Circadian Systems*, edited by Aschoff J, Daan S, and Groos G. Berlin: Springer Verlag, 1982, p. 253–261.
51. Zulley J, Wever R, and Aschoff J. The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflügers Arch* 391: 314–318, 1981.