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Cutaneous warming promotes sleep onset

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Raymann, Roy J. E. M., Dick F. Swaab, and Eus J. W. Van Someren. Cutaneous warming promotes sleep onset. *Am J Physiol Regul Integr Comp Physiol* 288: R1589–R1597, 2005. First published January 27, 2005; doi:10.1152/ajpregu.00492.2004.—Sleep occurs in close relation to changes in body temperature. Both the monophasic sleep period in humans and the polyphasic sleep periods in rodents tend to be initiated when core body temperature is declining. This decline is mainly due to an increase in skin blood flow and consequently skin warming and heat loss. We have proposed that these intrinsically occurring changes in core and skin temperatures could modulate neuronal activity in sleep-regulating brain areas (Van Someren EJW, *Chronobiol Int* 17: 313–54, 2000). We here provide results compatible with this hypothesis. We obtained 144 sleep-onset latencies while directly manipulating core and skin temperatures within the comfortable range in eight healthy subjects under controlled conditions. The induction of a proximal skin temperature difference of only $0.78 \pm 0.03^\circ\text{C}$ (mean \pm SE) around a mean of $35.13 \pm 0.11^\circ\text{C}$ changed sleep-onset latency by 26%, i.e., by 3.09 minutes [95% confidence interval (CI), 1.91 to 4.28] around a mean of 11.85 min (CI, 9.74 to 14.41), with faster sleep onsets when the proximal skin was warmed. The reduction in sleep-onset latency occurred despite a small but significant decrease in subjective comfort during proximal skin warming. The induction of changes in core temperature ($\delta = 0.20 \pm 0.02^\circ\text{C}$) and distal skin temperature ($\delta = 0.74 \pm 0.05^\circ\text{C}$) were ineffective. Previous studies have demonstrated correlations between skin temperature and sleep-onset latency. Also, sleep disruption by ambient temperatures that activate thermoregulatory defense mechanisms has been shown. The present study is the first to experimentally demonstrate a causal contribution to sleep-onset latency of skin temperature manipulations within the normal nocturnal fluctuation range. Circadian and sleep-appetitive behavior-induced variations in skin temperature might act as an input signal to sleep-regulating systems.

sleep electroencephalogram; body and skin temperatures; thermoregulation; sleep-onset latency; circadian rhythms

HUMAN SLEEP AND BODY TEMPERATURE both show a day-night rhythm that appears to be strongly coupled. Habitual sleep onset tends to closely follow the timing of the maximal rate of decline in core body temperature (26, 38). In experimental protocols that disentangle the rhythms by imposing ultrashort (28, 30, 32, 43) or very long (15) sleep-wake cycles while core body temperature maintains its circadian rhythm, the ability to initiate and maintain sleep is maximal during the phase of lowered core body temperature. If sleep is prohibited, as during the so-called constant routine protocols, a circadian rhythm in body temperature is still present (30). These findings demonstrate that the daily decline in core body temperature is not merely the result of sleep. Moreover, the possibility exists that the neuronal mechanisms underlying the circadian modulation

of sleep propensity and those underlying the circadian modulation of core body temperature share a common component. It may even be proposed that the thermoregulatory state of the body could affect sleep-regulating systems.

Animal experiments indeed have shown that sleep onset and a decline in core body temperature can be induced by a single common stimulus, i.e., local warming of the preoptic anterior hypothalamus (POAH) (35, 36). This structure is considered the thermointegrative center of the mammalian brain and plays a key role in arousal-state regulation and is thus involved in the induction of both heat loss and sleep. It has moreover been demonstrated that about two-thirds of the POAH neurons that spontaneously change their firing rate during sleep show a similar change in firing rate in response to experimental local warming (1). A similar thermosensitivity in relation to sleep has been demonstrated in the diagonal band (2). It might thus be argued that sleep is facilitated when brain temperature exceeds a threshold level (35).

Despite the robustness of the experimental induction of sleep by local POAH warming, it is highly unlikely that the elevation in brain temperature occurring daily under control of the circadian timing system is causally involved in the circadian modulation of sleep propensity. On the contrary, sleep onset tends to occur on the declining part of the core body temperature rhythm, and the major sleep period ends on its rising part. Thus a circadian-modulated input to sleep-related POAH neurons other than local temperature should be postulated if we presume their involvement in the coupling between sleep and temperature rhythms. In fact, this input signal should direct POAH neurons toward their sleep-type firing patterns despite local temperature favoring wake-type firing patterns. Putative signals include adenosine and prostaglandin D₂, which were found to excite sleep-active neurons (36, 45). We have in addition suggested skin temperature as a candidate to provide such a signal to sleep-related neurons (48) because the majority of neurons sensitive to local brain temperature also receive input originating from the skin thermoreceptors (6). Thus skin temperature may modulate thermosensitive neurons in the POAH and other brain structures involved in arousal-state regulation. It is important to note that this hypothesis goes further than stating that vasodilatation and sleep onset merely coincide because increased activity of a subset of POAH warm-sensitive neurons has the dual effect of promoting sleep and inducing vasodilatation. The hypothesis explicitly states that skin warming, resulting from this vasodilatation or otherwise induced, will cause enhanced activity of sleep-inducing warm-sensitive neurons.

The potential role of skin temperature in sleep, already recognized by Magnussen in 1939 (33), has been almost totally

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neglected. Only at the end of the past century have studies on the relation between skin temperature and sleep reemerged. Kräuchi and colleagues (23, 24) showed that the degree of heat loss at the skin of the hands and feet was the best physiological predictor for a fast sleep onset and that, during the phase of lowered core body temperature, rate of heat loss is elevated. In studies on the close relationship between sleep regulation and body temperature, the circadian rhythm in skin temperature has received much less attention than the circadian rhythm in core body temperature. Under constant conditions, with subjects kept supine in a thermoneutral environment without food or drinks, the mean skin temperature is elevated during the night and low throughout the day, thus showing a rhythm inverse to that of core body temperature (34). In everyday life, this day-night difference is even amplified by the nocturnal increase in skin temperature associated with the postural change from upright or sitting to a supine position (25, 46), the use of bedding to create a microclimate of 34–36°C (19, 39, 51), and the relaxation associated with the preparedness to sleep signaled by lights off (27). Because skin warming due to these changes occurs before sleep onset, it might affect the process of falling asleep. In animal studies, afferents conveying information about skin temperature have been shown to modulate the firing rate of thermosensitive neurons in the POAH at least as strong as local brain temperature does, and, in cases of simultaneous and differential local brain and skin temperature manipulations, the response of POAH neurons is dominated by skin temperature (7).

Indirect support for our hypothesis, that sleep onset might be modulated by small changes in skin temperature, was given by Kräuchi and colleagues (23, 24) who reported a strong negative correlation between the increase in especially distal skin temperature before lights out and sleep-onset latency. However, this finding could also be interpreted as indicative of a common mechanism promoting both an increase in skin temperature and sleep onset. We here report the first experimental support for the hypothesis that sleep-onset latency might be modulated by small changes in skin temperature in humans. In previous reports, sleep was disrupted by skin temperature being manipulated toward uncomfortably high or low levels. In this study, however, we applied only minute changes in skin temperature within the range covered by the nocturnal skin temperature under thermoneutral conditions.

MATERIALS AND METHODS

Participants. Eight healthy volunteers (21–39 yr old; mean \pm SE: 27.00 \pm 2.41 yr, 4 men) participated with informed consent. All participants were free of medications known to affect sleep or the circadian system, cardiovascular medication, and psychotropic medication, except for one female that used oral contraceptives. None of the subjects reported sleep complaints, and their subjective sleep quality was rated as being good. The scores on the insomnia scale of the 75-item Dutch Sleep Disorders Questionnaire (44) were significantly below the cut-off score of 3 (insomnia; 1.76 \pm 0.10, $P < 0.001$), and the scores on the Pittsburgh Sleep Quality Index (8) were significantly below the cut-off score of 6 (4.00 \pm 0.46, $P < 0.005$). The women participated between *day 4* and *day 12* of the menstrual cycle (midfollicular phase). The protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam.

Design and procedure. Participants were instructed to keep a regular sleep-wake pattern by minimizing variability in bedtime and

wake-up time in the 2 wk before the experiment, which was screened with a sleep diary (31) and with actigraphy (Actiwatch, Cambridge Neuro-Technology, Cambridge, UK). One week before the experiment, subjects visited the sleep laboratory for an introductory session and were habituated to the procedures. Participants were instructed to refrain from caffeine, alcohol, and tobacco for 8 h before arriving at the sleep laboratory. In brief, the experiment consisted of determining 18 sleep-onset latencies for each subject over 2 experimental days while core temperature was manipulated with food and drinks and skin temperature was manipulated with a thermosuit. The night before, and then each experimental day, subjects reported to the sleep laboratory at 2200. Compliance to the instructions was verified by questioning. They were prepared for polysomnography and fitted with a comfortable stretch knit fabric thermosuit for skin temperature manipulation. From midnight until 0600, lights were turned off and subjects were allowed to sleep. At 0600, subjects were awakened. The experiment started at 0630 and consisted of a modified constant-routine protocol (14, 37) under dim-light conditions (< 10 Lux) and a fixed body position schedule. Both experimental days consisted of nine consecutive blocks with a duration of 1.5 h each. Each block consisted of the following procedures. It started by requiring the subjects to leave the bed and walk 5 m to use the bathroom if needed. After 10 min, they returned to bed, were put in semi-supine position, and were served a snack and a drink to consume in ~ 10 min. Next, a self-paced computerized neuropsychological task battery was given, which took ~ 35 min to complete. This battery included assessment of thermal comfort and temperature sensation with the use of 100-mm visual analog scales ranging from uncomfortable to comfortable and from cool to warm, respectively. At 60 min, the bed was set in a supine position, the lights were switched off, and the participants were asked to try to sleep. Sleep onset was determined online [Multiple Sleep Latency Test (MSLT)] (11, 12), and subjects were awakened directly after sleep-onset determination (see below). When awakened, subjects stayed in bed in a supine position with the light turned on (< 10 Lux), and they had to stay awake. The maximum time allowed to fall asleep was 30 min, finishing up the 1.5 h of a block. Skin and core temperatures were manipulated differently in every block. During the first block, skin temperatures were kept at an intermediate temperature. This block served as an adaptation period for participants to wake up and get used to the protocol. In the remaining eight blocks, core body temperature, proximal skin temperature, and distal skin temperature were independently manipulated in either a slightly warmer or cooler direction, but within the comfortable and thermoneutral range. This $2 \times 2 \times 2$ experimental design [core body temperature warm or cool (CBT+ or CBT-), proximal skin temperature warm or cool (PST+ or PST-), and distal skin temperature warm or cool (DST+ or DST-)] allows for eight possible manipulation combinations, which were all tested within 1 day in every subject (see Fig. 1). The sequence of the manipulation combinations was different for each subject such that, over all subjects, every manipulation combination was given once in each of the eight blocks, and every transition from one to any other combination occurred only once. At the end of the first day, subjects went home and returned to the laboratory the next evening for a repeated assessment according to

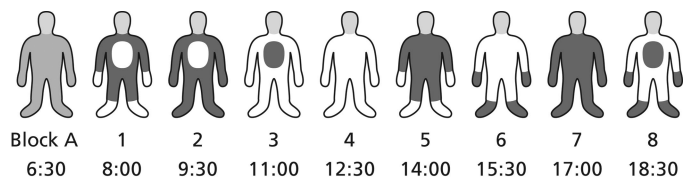


Fig. 1. Schematic view of temperature manipulations within 1 day within 1 subject. On the 2nd day, temperature manipulation combinations were the opposite of those of the 1st day to provide a protocol balanced for circadian effects. Block A, habituation block. White represents cool; dark gray represents warm.

the same procedure, with the only difference being the temperature manipulation combinations opposite to those of the first day, thus providing a protocol balanced for circadian effects. For example, if the second block of a specific subject on *day 1* consisted of core warming, proximal skin cooling, and distal skin warming, that participant was subjected to core cooling, proximal warming, and distal skin cooling during the second block on *day 2*.

Temperature manipulations and measurement. Core body temperature was manipulated by means of 200-ml hot (heated to 80°C, served 2 min later) or cold (0°C, crushed ice) diet (4.25 kcal), decaffeinated tea [iced tea mix (diet decaffeinated lemon), Lipton, Englewood Cliffs, NJ] together with an isocaloric hot or cold snack chosen by the subject (200 kcal). Ingestion of food and drinks to manipulate core body temperature was started 50 min before lights off because it has been shown, at least for core body cooling, that the core body temperature after intake of crushed ice is maximally decreased a time lag of ~50 min, whereas the distal vasoconstriction induced by the intake of crushed ice has to a large extent, although not fully, subsided by that time (27). Skin temperature was manipulated with the use of a thermosuit (Coretech Cool tube suit, Med-Eng Systems, Ottawa, Canada). The suit provided a full torso, arms, hands, and lower body coverage, with a snug-fit design for maximum contact, thus allowing optimal temperature manipulation and optimal comfort and range of motion. It was connected to two computer-controlled bath-circulation thermostats (K6KP, Lauda, Lauda-Köningshofen, Germany), one for distal and one for proximal skin temperature manipulation. The thermosuit trousers and long-sleeve shirt induced the proximal skin temperature manipulation, whereas the distal skin temperature manipulation was provided by the socks and the hand gloves of the thermosuit. We programmed the sequence of the temperature manipulations using Wintherm software (Lauda). During the first 20 min of each block, the water in the thermostat baths changed to the desired temperature with a programmed ramp of $\pm 0.2^\circ\text{C}/\text{min}$. For the remaining 70 min of the block, the bath temperature was kept constant. The water in the bath was 33°C in the cool condition and 37°C in the warm condition, resulting in temperatures of ~31°C and 34°C measured at the tubes just before entering the thermosuit. Water circulated from and to the thermostat baths via isolated connecting tubes through the network of microtubes inside the thermosuit. The range of skin temperature manipulations was chosen so as not to differentially trigger major thermoregulatory responses. Subjects were habituated to the diurnal skin manipulation by application of similar nocturnal thermosuit manipulations (alternating periods of 15 or 30 min of 33°C and 37°C water bath temperature, with ramps in between lasting 15 min). Manipulation temperatures were measured in the bath with a built-in PT100 element; on the connection-tube just before entering the thermo-suit; and on connection-tube just after departing the thermo-suit (the latter locations with PT100 element RTD-3-3105, Omega) and were recorded and stored on PC once a minute using the Wintherm software. The recordings of the manipulation temperature data were visually checked for possible artifacts. Occasional erroneous recordings characterized by abrupt steep changes ($>0.3^\circ\text{C}/\text{min}$) in connection-tube temperature within the time window of interest were removed and linearly interpolated when feasible. Body temperature was obtained using eight thermistors (P-8432, ICBT, Tokyo, Japan). We measured core body temperature using a rectal thermistor, which was self-inserted by subjects 13 cm into the rectum. Proximal skin temperature was measured at three places: right mid thigh on the musculus rectus femoris, abdomen (1 cm above the navel), and the right infraclavicular area. Distal skin temperature was measured at four points: thenar area at the palmar sites of the left and right hand and medial metatarsal area at the plantar sites of the left and right foot. The skin thermistors were attached to the skin with thermal probe covers (no. 090-2764, ConMed, Utica, NY) that reflect ambient heat and ensure a more accurate recording. Temperature was digitally recorded at 1 Hz (Embla A10 and Somnologica software, Flaga, Reykjavik, Iceland).

Body temperature data were downsampled to 0.1 Hz. Based on visual inspection of the data, an automated procedure was applied to remove occasional artifacts, defined for core body temperature as outside the 35.5–38°C range and for skin temperature as outside the 32–37°C range. In addition, visually obvious artifacts [abrupt steep changes in skin temperature ($>0.3^\circ\text{C}/\text{min}$) or core body temperature ($>0.1^\circ\text{C}/\text{min}$)] were removed and linearly interpolated when feasible. Average distal skin temperature was calculated as the average temperature of averages measured from both feet and from both hands. A weighted average was calculated for proximal skin temperature ($0.383 \times \text{mid thigh} + 0.293 \times \text{infraclavicular} + 0.324 \times \text{abdomen}$) according to a modification of the method used by Kräuchi et al. (22), who, in contrast to our protocol, also included forehead temperature. Temperature data averaged over the 5 min before lights off were used for further analyses. As a final check, when a single averaged data point differed more than ± 2 SD from the other 5-min averages during a particular day, the nonaveraged data were checked again for artifacts and corrected or removed when needed.

Sleep. Polysomnographic sleep recordings consisted of electroencephalography (EEG), electromyography, and electrooculography. EEG was derived from two bipolar leads FpzCz and PzOz (50) with the E-net and Hydrodot system (Physiometrix, Billerica, MA). Submental electromyography and horizontal electrooculography from the outer canthi were recorded with disposable Ag/AgCl electrodes (type 4203 Meditrac, Graphic Controls, Buffalo, NY). All polysomnographic signals were digitally recorded at 200 Hz using the Embla A10 recorder and Somnologica software (both from Flaga).

Sleep onset was determined online during the experiment according to standard criteria (41), with sleep onset defined as three consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep (12). Online sleep stage determination was aided by the use of spectral views of the EEG signal, which facilitated the observation of disappearance of the alpha (8–12 Hz) peak, dominance of the proportion of the theta (4–8 Hz) peak over the proportion of alpha activity, or the clear appearance of spindle (12–15 Hz) peaks. MSLT, and sleep recordings were once more visually scored offline by two independent scorers blind to the manipulations, and in case of scoring differences, consensus was reached. Sleep-onset latency was defined as the time between lights off and sleep onset. If the subject did not sleep during the 30 min, sleep-onset latency was scored as 30 min.

Statistical analyses. To determine the effects of skin and core temperature manipulations on core body, proximal skin, and distal skin temperatures and on subjective comfort, hierarchical linear modeling (i.e., random coefficient analysis) was applied using the MLwiN software (Centre for Multilevel Modelling, Institute of Education, London, UK). Because the frequency distribution of sleep-onset latencies may be slightly skewed, longitudinal Poisson regression analysis, also referred to as longitudinal log-linear regression analysis, was used to determine the effects of skin and core temperature manipulations and induced temperatures on sleep onset latency. Both analyses take into account the interdependency of the data points inherent to the hierarchical structure of the design, in our case the sequential sleep-onset observations, *i*, that were nested within days, *j*, once more nested within subjects, *k* (47). The first block of both days (the habituation block) was omitted from analyses. Analyses were run with induced body temperatures (core body, proximal skin, and distal skin), subjective comfort, and sleep-onset latency as dependent variables, and body temperature manipulations as dichotomous predictor variables, with 0 reflecting the cool manipulation and 1 reflecting the warm manipulation. The effects on sleep-onset latency were also (post hoc) analyzed with the actual induced core body, proximal skin, and distal skin temperatures as predictor variables. Additional models were run to test for carryover effects of the temperature manipulations, by adding temperature manipulations of the preceding block (pCBT, pPST, and pDST) to the regression models.

A number of variables that might account for variance in the dependent variables were also allowed in the model. More specifi-



cally, time (hour; defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900) was allowed in the models for induced temperatures to account for possible diurnal variations in core and skin temperature (26). Both time and the number of repeats trying to fall asleep (repeats; defined as the number of times allowed to fall asleep since *day 1*, starting with 1) were entered in the models for sleep-onset latency to account for possible diurnal variations in sleep-onset latency and for a possible decrease of sleep-onset latency with practice (13, 29). Because these effects are likely to be nonlinear, their square-root and squared values were allowed in the model in addition to their possible linear contribution. For the longitudinal Poisson regression analysis, all independent variables were centered at the within-day level, except for repeats, which was centered at the within-subject level over the 2 days. For all regression analyses, we report both the full model, with all temperature manipulation variables and covariates in the model, and the optimal model, containing only the significant contributions.

Maximum likelihood was used to estimate the regression coefficients, which were tested for significance with the Wald test (52). For the optimal linear models, additional terms were allowed in the model only if their coefficients were significant and only if the model improved according to the likelihood ratio test of the models. For the longitudinal Poisson regression analysis, additional terms were allowed in the model only if their coefficients were significant and if the residual error of the model was reduced. Two-tailed significance levels were set at 0.05.

RESULTS

Induced body temperatures. The observed mean sleep-onset latencies and temperatures per temperature condition are shown in Table 1. The observed mean temperatures and SEs per day and time of day are displayed in Table 2. Table 3 shows the effects of temperature manipulations on core and skin temperatures, as derived from the regression analyses. Figure 2, *middle*, provides an example of measured temperatures in a representative subject throughout the 2 experimental days.

The overall average core body temperature during the 5 min before lights off was $36.88 \pm 0.06^\circ\text{C}$ (mean \pm SE). Core body temperature was modulated by time (hour, $\sqrt{\text{hour}}$) and affected significantly by the core temperature manipulation, with a $0.20 \pm 0.02^\circ\text{C}$ higher core body temperature in the CBT+ condition compared with the CBT- condition. Entering time (hour, $\sqrt{\text{hour}}$) into the model accounted for 21% of the variance, whereas the addition of the core body temperature manipulation accounted for another 44% of the residual variance in core body temperature. The addition of preceding temperature manipulations, to test for carryover effects, revealed a positive contribution of pPST ($0.11 \pm 0.02^\circ\text{C}$) that accounted for an additional 16% of the variance.

Table 1. Sleep-onset latency and temperature by temperature condition

Manipulation	Sleep Onset Latency, min	Core Body Temperature, $^\circ\text{C}$	Proximal Skin Temperature, $^\circ\text{C}$	Distal Skin Temperature, $^\circ\text{C}$
CBT-	12.16 ± 0.88	36.78 ± 0.03	35.15 ± 0.07	34.92 ± 0.09
CBT+	11.52 ± 0.97	36.97 ± 0.03	35.11 ± 0.06	35.36 ± 0.09
PST-	13.44 ± 1.05	36.88 ± 0.03	34.74 ± 0.05	34.95 ± 0.10
PST+	10.25 ± 0.73	36.87 ± 0.03	35.52 ± 0.05	35.33 ± 0.08
DST-	11.96 ± 0.93	36.88 ± 0.03	35.08 ± 0.07	34.77 ± 0.09
DST+	11.73 ± 0.92	36.88 ± 0.03	35.17 ± 0.07	35.51 ± 0.07

Values are means \pm SE. CBT, core body temperature; PST, proximal skin temperature; DST, distal skin temperature. + and -, Warm and cool, respectively.

Table 2. Sleep-onset latency and temperature by day and time of day

Time	Sleep Onset Latency, min	Core Body Temperature, $^\circ\text{C}$	Proximal Skin Temperature, $^\circ\text{C}$	Distal Skin Temperature, $^\circ\text{C}$
<i>Day 1</i>	13.20 ± 1.04	36.85 ± 0.04	35.15 ± 0.07	35.17 ± 0.09
09:00	13.44 ± 3.04	36.69 ± 0.08	35.19 ± 0.21	35.21 ± 0.20
10:30	12.94 ± 2.55	36.83 ± 0.08	35.16 ± 0.19	35.07 ± 0.29
12:00	11.00 ± 2.91	36.90 ± 0.11	35.21 ± 0.25	35.46 ± 0.18
13:30	12.56 ± 2.02	36.88 ± 0.12	35.12 ± 0.22	35.24 ± 0.16
15:00	12.81 ± 3.70	36.91 ± 0.10	35.12 ± 0.19	35.29 ± 0.19
16:30	11.81 ± 2.95	36.83 ± 0.10	35.03 ± 0.22	34.99 ± 0.22
18:00	12.56 ± 3.12	36.85 ± 0.16	35.17 ± 0.16	35.01 ± 0.38
19:30	18.44 ± 3.50	36.95 ± 0.13	35.17 ± 0.14	35.12 ± 0.31
<i>Day 2</i>	10.49 ± 0.75	36.89 ± 0.03	35.11 ± 0.07	35.11 ± 0.09
09:00	7.81 ± 1.16	36.66 ± 0.08	34.97 ± 0.19	35.26 ± 0.20
10:30	8.94 ± 1.60	36.79 ± 0.08	35.05 ± 0.24	35.29 ± 0.24
12:00	8.25 ± 1.61	36.86 ± 0.05	35.13 ± 0.13	35.21 ± 0.27
13:30	9.00 ± 1.72	36.97 ± 0.05	35.08 ± 0.16	35.15 ± 0.32
15:00	8.56 ± 2.01	36.96 ± 0.05	35.12 ± 0.20	35.18 ± 0.26
16:30	11.13 ± 1.75	36.99 ± 0.08	35.14 ± 0.15	34.97 ± 0.42
18:00	11.13 ± 2.26	36.94 ± 0.07	35.18 ± 0.24	35.01 ± 0.18
19:30	19.13 ± 2.35	37.00 ± 0.06	35.20 ± 0.25	34.78 ± 0.18

Values are means \pm SE.

The overall average proximal skin temperature during the 5 min before lights off was $35.13 \pm 0.11^\circ\text{C}$. Proximal temperature was not only affected by the proximal skin temperature manipulation but also, albeit very modestly, by distal skin temperature manipulation. Proximal temperature was $0.78 \pm 0.03^\circ\text{C}$ higher in the PST+ condition compared with the PST- condition and $0.09 \pm 0.03^\circ\text{C}$ higher in the DST+ condition compared with the DST- condition. The manipulations accounted for 82% of the variance in proximal temperature.

The overall average distal skin temperature during the 5 min before lights off was $35.14 \pm 0.15^\circ\text{C}$. Distal temperature was modulated by time of day (hour²) and significantly affected by all temperature manipulations. Distal temperature was $0.74 \pm 0.05^\circ\text{C}$ higher in the DST+ condition compared with the DST- condition, $0.38 \pm 0.05^\circ\text{C}$ higher in a PST+ compared with the PST- condition, and $0.44 \pm 0.05^\circ\text{C}$ higher in a CBT+ compared with the CBT- condition. Entering time into the model accounted for 4% of the variance and adding the manipulations accounted for another 73% of the residual variance in distal temperature. The addition of preceding temperature manipulations, to test for carryover effects, revealed a positive contribution of pPST ($0.17 \pm 0.06^\circ\text{C}$) that accounted for an additional 2% of the variance.

Summarizing, the manipulations accounted for a high proportion of the variance in skin and core temperature but were not fully successful in independently controlling the core body, distal, and proximal skin temperatures. Moreover, a carryover effect was present in that the previous proximal manipulations slightly affected distal and core temperature.

Temperature perception. The effect of the temperature manipulations on temperature sensation and thermal comfort is shown in Table 4. The overall average rating of thermal comfort before lights off was 59.1 ± 2.3 . When all conditions were cool (CBT-, PST-, and DST-), thermal comfort was rated close to maximal (81.5 ± 3.3 on the 100-mm scale ranging from 0 = uncomfortable to 100 = comfortable). Thermal comfort was slightly but significantly lower in the CBT+, PST+, and DST+ conditions (-20.2 ± 2.8 for CBT+, -18.6 ± 2.8 for PST+, and -5.9 ± 2.8 for DST+).

Table 3. Estimates of the effects of temperature manipulation and time of sleep initiation on core and skin temperatures

	Core Body Temperature		Proximal Skin Temperature		Distal Skin Temperature	
	Full model	Optimal model	Full model	Optimal model	Full model	Optimal model
Intercept	36.57 ± 0.07‡	36.57 ± 0.07‡	34.66 ± 0.12‡	34.69 ± 0.11‡	34.44 ± 0.17‡	34.48 ± 0.16‡
Hour	-0.02 ± 0.04	-0.03 ± 0.01†	-0.07 ± 0.07		-0.01 ± 0.10	
Hour ²	0.00 ± 0.00		0.00 ± 0.00		0.00 ± 0.01	-0.003 ± 0.001†
√Hour	0.16 ± 0.07*	0.18 ± 0.04‡	0.12 ± 0.12		0.04 ± 0.19	
CBT	0.20 ± 0.02†	0.20 ± 0.02‡	-0.04 ± 0.03		0.44 ± 0.05‡	0.44 ± 0.05‡
PST	0.00 ± 0.02		0.78 ± 0.03‡	0.78 ± 0.03‡	0.38 ± 0.05‡	0.38 ± 0.05‡
DST	0.02 ± 0.02		0.09 ± 0.03†	0.09 ± 0.03†	0.74 ± 0.05‡	0.74 ± 0.05‡

Values are means ± SE. Regression model was as follows: $T_{ijk} = \beta_{0ijk} + \beta_1 \times \text{hour}_{ijk} + \beta_2 \times \text{hour}_{ijk}^2 + \beta_3 \times \sqrt{\text{hour}_{ijk}} + \beta_4 \times \text{CBT}_{ijk} + \beta_5 \times \text{PST}_{ijk} + \beta_6 \times \text{DST}_{ijk}$ (see text; subscripts indicate *i*th observation on day *j* for subject *k*). Core body and proximal skin and distal skin temperature manipulations were included in the model as dichotomous variables, with cool and warm coded as 0 and 1. Hour (time), defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900. Full model data show all predictors, whereas optimal model data show only significantly contributing predictors. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

The overall average rating of temperature sensation before lights off was 62.4 ± 1.8 . When all conditions were cool (CBT-, PST-, and DST-), the temperature sensation was neutral (47.66 ± 2.27 on the 100-mm scale, ranging from 0 = cool to 100 = warm). Temperature was perceived as significantly higher in the CBT+, PST+, and DST+ conditions (12.03 ± 1.62 for CBT+, 13.19 ± 1.62 for PST+, and 4.19 ± 1.62 for DST+).

In summary, the warm conditions were experienced as less comfortable and warmer than the cool conditions.

Sleep-onset latency. The effects of the temperature manipulations on sleep onset latency are shown in Table 1 and Table 5, with the temperature manipulations as dichotomous predictor variables. The observed mean sleep-onset latencies and SEs per day and time of day are displayed at Table 2. Figure 2, bottom, provides an example of measured sleep-onset latencies in a representative subject throughout the 2 experimental days.

The overall average sleep-onset latency was 11.85 min [95% confidence interval (CI) 9.73 to 14.41]. Sleep-onset latency was significantly modulated by time (hour²) and affected by the number of sleep-onset repeats (√repeats) and the proximal skin temperature manipulation. Sleep-onset latency was 3.09 min (CI 1.91 to 4.28) shorter in the PST+ compared with the PST- condition. Sleep-onset latency was not altered by core or distal skin temperature manipulations. The addition of preceding temperature manipulations did not decrease the residual error of the regression model, indicating a lack of significant carryover effects. Figure 3 gives a graphical representation of the model best fitting the data of all subjects.

Because the temperature manipulations did not completely independently control core, proximal, and distal temperatures but did account for most of the variances in these temperatures, we did a post hoc analysis entering the actually induced temperatures into the model rather than the dichotomous ma-

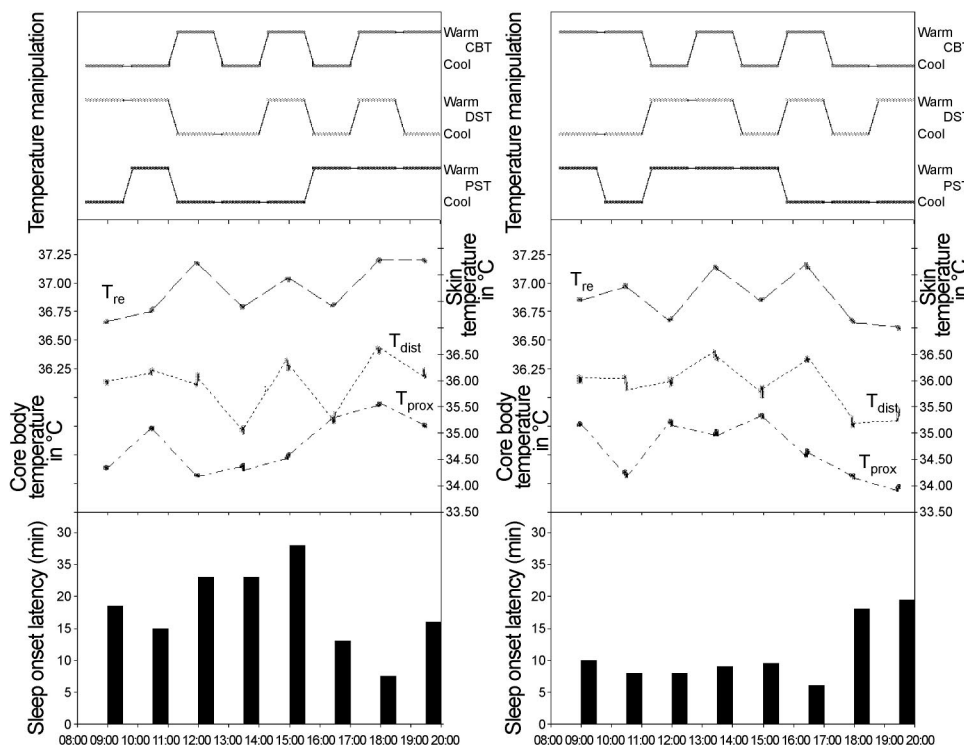


Fig. 2. Examples of manipulations and measurements in a representative subject throughout the 2 experimental days. Top: temperature manipulation combinations. CBT, core body temperature manipulation; DST, distal skin temperature manipulation; PST, proximal skin temperature manipulation. Middle: measured body temperatures over 5 min before lights off, connected by lines for clarity. Left axes show core body temperature (T_{re}); right axes show proximal (T_{prox}) and distal (T_{dist}) temperatures. Bottom: measured sleep-onset latencies. For this specific subject, if dichotomized, only 2 of 16 observations (day 2, at 10:30 and 16:30) fail to match the general consistent pattern of shorter latencies being restricted to occur during the warm proximal condition.

Table 4. Estimates of the effects of temperature manipulation, on temperature sensation and thermal comfort

	Temperature Sensation	Thermal Comfort
Intercept	47.66 ± 2.27‡	81.49 ± 3.29‡
CBT	12.03 ± 1.62‡	-20.21 ± 2.77‡
PST	13.19 ± 1.62‡	-18.60 ± 2.77‡
DST	4.19 ± 1.62†	-5.91 ± 2.77*

Values are means ± SE. Regression model was as follows: $Y_{ijk} = \beta_{0ijk} + \beta_1 \times CBT_{ijk} + \beta_2 \times PST_{ijk} + \beta_3 \times DST_{ijk}$. Temperature sensation was measured on a visual analog scale ranging from 0 (cool) to 100 (warm), with 50 reflecting thermoneutral. Thermal comfort was measured on a visual analog scale ranging from 0 (uncomfortable) to 100 (comfortable). * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

nipulation levels (see Table 6). The model best fitting the data turned out to contain the same variables as the aforementioned model with dichotomous manipulation levels. A 1°C increase in proximal skin temperature shortens sleep-onset latency by 2.68 min (CI of 1.34–4.03). The effects on sleep-onset latency of time of day and the number of times allowed to fall asleep are highly comparable to the effects in the dichotomous model. Sleep-onset latency was not significantly related to the induced changes in core or distal skin temperature.

In summary, sleep-onset latencies increase with time over the day but decrease by “practice” and proximal skin warming.

DISCUSSION

The present study investigated whether sleep-onset latency is affected by manipulation of core body and skin temperatures within the range of their normal circadian fluctuations under strictly controlled conditions. This study is the first of its kind to experimentally manipulate core and skin temperatures independently with the aim of modifying sleep-onset latency. We show that the process of falling asleep is accelerated by warming of the proximal skin within the temperature range normally covered during everyday life under comfortable conditions. This effect occurred despite this warming being perceived by subjects as slightly less comfortable.

Table 5. Estimates of the effects of temperature manipulation, time, and number of repeats on sleep-onset latency

	Full Model	Optimal Model
Intercept	2.44 ± 0.09‡	2.44 ± 0.09‡
Hour ²	0.008 ± 0.001‡	0.007 ± 0.001‡
Repeats	-0.05 ± 0.02*	-0.05 ± 0.02†
CBT	-0.09 ± 0.05	
PST	-0.27 ± 0.05‡	-0.27 ± 0.05‡
DST	-0.02 ± 0.02	

Values are means ± SE. Regression model was as follows: $\ln(SOL_{ijk}) = \beta_{0ijk} + \beta_1 \times \text{hour}_{ijk}^2 + \beta_2 \times \text{repeats}_{ijk} + \beta_3 \times CBT_{ijk} + \beta_4 \times PST_{ijk} + \beta_5 \times DST_{ijk}$ (see text; subscripts indicate the *i*th observation on *day j* for subject *k*). Core body temperature and proximal skin and distal skin temperature manipulations were included in the model as dichotomous variables, with cool and warm coded as -0.5 and +0.5. SOL, sleep-onset latency. Hour (time), defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900. Repeats, defined as the number of times allowed to fall asleep since *day one*, starting with 1. All independent variables were centered at the within-day level, except for ‘Repeats’, which was centered at the within-subject level over the two days. Covariates without significant contributions in the model are not shown. Full model data show all predictors, whereas optimal model data show only significantly contributing predictors. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

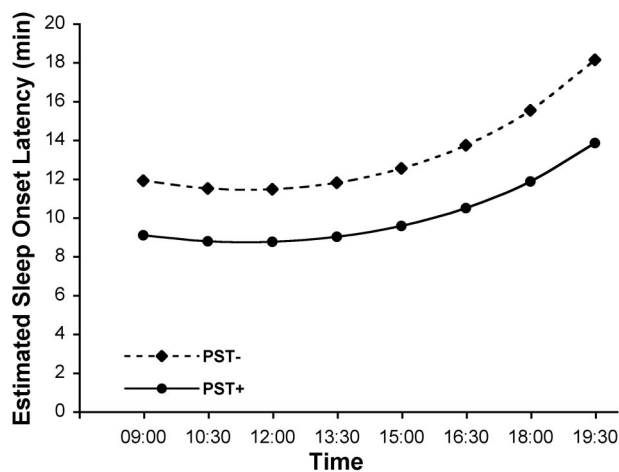


Fig. 3. Graphical representation of the effect of PST manipulation in the model best fitting the data of all subjects: $\ln(SOL_{ijk}) = 2.44 + 0.007 \times \text{hour}^2 - 0.05 \times \text{repeats} - 0.27 \times \text{PST}$ (where SOL is sleep-onset latency) (see Table 5, right columns, and text). Estimated sleep onset latency is thus given by $e^{2.44+0.007 \times \text{hour}^2 - 0.05 \times \text{repeats} - 0.27 \times \text{PST}}$. Sleep onset latency data are given in minutes, and PST is coded -0.5 for the cool proximal skin manipulation and +0.5 for the warm proximal skin manipulation (centered dummy coding). ‘Repeats’ was defined as the number of times allowed to fall asleep since *day 1*, starting with 1 and centered within subject. ‘Hour’ was defined as the number of hours since the start of the first multiple sleep latency test within each day, starting with 0 at 0900 and was centered within subject within day. For this figure, giving an impression of SOLs obtained on the two experimental days, the average over two days of the centered values of Repeats were used in the model.

Before we discuss the possible interpretations and implications of our findings, the restrictions of the present study deserve attention. First, we have not been able to fulfill our aim to independently manipulate core body and distal and proximal skin temperatures. Although these areas were primarily and most strongly affected by their respective manipulations, thermoregulatory responses affecting other areas or carryover effects from preceding proximal skin temperature manipulations seem to have been elicited. Core temperature manipulations induced not only changes in core body temperature but also affected distal skin temperature. Proximal skin temperature

Table 6. Estimates of the effects of actual core and skin temperatures, time, and repeats on sleep-onset latency

	Full Model	Optimal Model
Intercept	2.44 ± 0.09‡	2.45 ± 0.09‡
Hour ²	0.007 ± 0.001‡	0.008 ± 0.001‡
Repeats	-0.05 ± 0.02*	-0.05 ± 0.02‡
Core body temperature	0.000 ± 0.000	
Proximal temperature	-0.19 ± 0.07†	-0.23 ± 0.06‡
Distal temperature	-0.07 ± 0.05	

Values are means ± SE. Regression model was as follows: $\ln(SOL_{ijk}) = \beta_{0ijk} + \beta_1 \times \text{hour}_{ijk}^2 + \beta_2 \times \text{repeats}_{ijk} + \beta_3 \times \text{core temperature}_{ijk} + \beta_4 \times \text{proximal temperature}_{ijk} + \beta_5 \times \text{distal temperature}_{ijk}$. Sleep onset latency was regressed on actual core and skin temperatures (see text; subscripts indicate the *i*th observation on *day j* for subject *k*). SOL, sleep-onset latency. Hour (time), defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900. Repeats, defined as the number of times allowed to fall asleep since *day one*, starting with 1. All independent variables were centered at the within day level, except for ‘Repeats’, which was centered at the within-subject level over the two days. Covariates without significant contributions in the model are not shown. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

manipulations affected primarily proximal skin temperature but also distal and to a lesser extent affected core and distal temperatures in the next block. Distal skin temperature manipulations affected primarily distal but also proximal skin temperatures. We optimized the design to prevent systematic errors due to circadian variation, not only by applying both cool and warm conditions to the same subject at the same time of day but also by stratified randomization to have different sequences for all subjects. Thus there was also no fixed sequence allowing possible carryover effects to introduce a systematic error. Despite these limitations, the momentary manipulations did account for most of the variability in core and skin temperatures, and a post hoc analysis regressing sleep-onset latencies on the induced temperatures rather than on the manipulation levels provided essentially the same results, i.e., a reduction of sleep-onset latency associated with a warmer proximal skin.

A second restraint is that one should be cautious with extrapolation of the findings to temperature ranges and times of the day that were not covered in the present experiment. Both animal and human studies have demonstrated disturbed sleep with thermal manipulations that activate heat or cold stress mechanisms (20, 40). Thus, beyond the physiological range that we applied, a further increase in skin temperature is likely to disturb sleep-onset mechanisms rather than facilitate it at some point. On the other hand, the normal diurnal time course of distal skin temperature reaches values much lower than we have applied. During everyday life, diurnal distal skin temperature easily reaches temperatures of several degrees below the diurnal values measured at the proximal skin (53). Also, under strictly controlled laboratory conditions, the distal 24-h minimum and maximum and the 24-h mean skin temperatures were lower than their proximal equivalents (26). The averaged induced proximal and distal skin temperatures in our study were however comparable to each other (see Table 2). Thus we may have manipulated the distal skin temperature too close to the ceiling of its normal diurnal pattern, not leaving the range optimal for sleep onset. Whereas the small proximal skin temperature manipulations that we applied were sufficient to affect sleep-onset latency, we cannot exclude that applying distal skin temperature manipulations in a slightly lower range would be at least as adequate in affecting sleep-onset latency. In fact, increases in distal skin temperature relative to the proximal skin temperature (the distal-to-proximal gradient) have previously been shown to be correlated to sleep-onset latency (23). With respect to the gradient findings, it should be noted that all manipulation blocks where distal and proximal temperatures were both warm or both cool resemble the gradient condition found to be correlated to sleep-onset latency by Kräuchi et al. (23).

Third, the dichotomous nature of our manipulation is such that the terms “warm” and “cool” can be interpreted only as relative to each other. Theoretically, sleep-onset latency might either be increased in the cool condition or decreased in the warm condition. Several arguments favor the interpretation in terms of the warm condition promoting sleep onset rather than the cool condition delaying sleep onset. First, the cool rather than the warm condition was subjectively experienced as being most comfortable, with the highest score on the visual analog scales on comfort. The cool condition was also subjectively experienced as most thermoneutral, with values nearest to 50 on the visual analog scale ranging from cool (0) to warm (100). Yet, sleep-onset latency was shorter in the warm (subjectively

less thermoneutral and slightly less comfortable) condition. Second, although sleep-onset latencies differ strongly from laboratory to laboratory and from clinic to clinic, the average sleep-onset latency that we obtained in the warm proximal skin temperature condition [10.25 ± 0.73 (SE) min] tends to be lower than that reported in the majority of studies in healthy adults (e.g., Refs. 10, 13, 17, 54, 55). Third, even in the cool condition, the induced average proximal skin temperature (34.7°C) was slightly higher than the average minimum proximal skin temperature (33.8°C) reported in the primary controlled study on circadian modulation of skin temperature under laboratory conditions (26).

A related issue is that it is presently not known to what extent the induced skin temperatures of $\sim 35.1^{\circ}\text{C}$ are representative of the temperatures that occur in everyday life when preparing for sleep. In an experimental setting, somewhat lower average proximal and distal skin temperatures (34.5°C) were reported to occur when subjects prepared for sleep after lights off (27). On the other hand, earlier studies under more natural sleeping conditions, measured skin temperatures of $35\text{--}36^{\circ}\text{C}$ during sleep and bed temperature microclimates of $34\text{--}36^{\circ}\text{C}$ (19, 39, 51). Although none of the previously performed studies is of a sample size large enough to provide normative data on the range of skin temperatures under habitual waking and sleeping conditions, these examples at least suggest that the proximal skin temperature was manipulated within or close to the subject's habitual nocturnal range. In fact, it is likely that the temperature that we applied resembles more closely the natural environmental temperature during sleep than the microclimate temperature in, for example, the studies of Kräuchi et al. (24, 26), who provided subjects only with a light bed cover in an ambient temperature of 22°C . Their experimental setup may have reflected the habitual daytime environmental temperature but may not have allowed the subjects to attain their natural nocturnal microclimate temperature of $34\text{--}36^{\circ}\text{C}$. In both rodents and humans, the self-selected ambient temperature is higher during the lower part of the core body temperature cycle (reviewed in Ref. 49).

As to core temperatures, we are confident that the range in core temperatures that was induced by our manipulations should be sufficient to alter sleep-onset latencies if they were indeed dependent on core body temperature, as has been proposed previously (5, 9, 38). The difference of 0.20°C in core body temperature that we established between the warm and the cool condition is about one-half of the reported circadian amplitude in core body temperature (0.44°C) under controlled conditions (26). In humans, the onset to the major sleep period tends to closely follow the timing of the maximal rate of decline in core body temperature, halfway from its peak to its trough (26, 38). In rats, which show a polyphasic sleep pattern and more ultradian fluctuations in core temperature, sleep onset similarly tends to occur near the maximal rate of decline of these fluctuations (16). It consequently has been proposed that a declining core body temperature might be involved in promoting sleep onset (9, 38).

Whereas our data do not support this idea that core temperature itself is involved in promoting sleep onset, they do support the notion that the heat loss mechanisms underlying this drop in core temperature are involved. The circadian rhythm in core body temperature is to a large extent due to variations in heat loss (26): a circadian-regulated nocturnal increase in skin blood flow, resulting in increased skin tem-

perature, promotes heat transfer from the body to the environment. Although our observations have been limited to the human sleep EEG, they are compatible with the idea that, rather than changes in core temperature, the associated warming of the skin could provide a signal to sleep-regulating areas in the brain. This contention is supported by early animal studies of Boulant and Bignall (7), who demonstrated that the activity of the thermosensitive neurons in the POAH is modulated predominantly by skin temperature if local brain temperature and skin temperature are manipulated simultaneously and differentially. Skin warming has moreover been shown to promote sleep-type firing patterns in other brain areas involved in the regulation or expression of sleep (reviewed in Ref. 48). In humans, an increase in (distal) skin blood flow and consequently skin temperature starts at ~2000 and induces a maximum plateau of skin temperature at between 2300 and 0700 (3, 4, 34). We have previously suggested that, in response to this change in skin temperature, a subpopulation of sleep-related warm-sensitive neurons increases firing rate, thus promoting sleep. This idea can at present only receive indirect support in humans, since the presently available neuroimaging tools do not yet provide the possibility for ultrahigh-resolution imaging of changes induced by slowly changing thermal stimuli.

Our findings may at first be difficult to reconcile with the inverse circadian rhythms of sleep propensity and proximal temperature under constant routine conditions (26). If anything, the evening decline in proximal skin temperature that has been shown to occur under constant routine conditions would be predicted, according to our findings, to inhibit the onset of sleep. However, this inhibition would take only as long as the subject has not appropriately prepared for safe sleep by taking a supine position in a relatively warm microclimate due to bedding and relaxing to allow sleep to occur. Only if these conditions have been met, proximal skin temperature will strongly increase after lights off, at least if subjects know that they are allowed to fall asleep. Proximal skin temperature then stays higher than presleep levels throughout most of the night, in contrast to its further decline if sleep is not allowed (27). If safe sleeping conditions have not yet been established, the low proximal temperature might be of functional importance to support wakefulness when the time awake is usually long and sleep pressure is high. When safe sleeping conditions have been established, its fast increase may promote sleep onset. This tentative idea should be verified by investigating whether sleep-onset latency is related to the steepness of the increase in proximal skin temperature that occurs between lights off and sleep onset. Some caution in interpreting the inverse relation of the circadian rhythms in sleep propensity and proximal temperature is furthermore warranted, given the fact that this relation has been established under constant routing conditions in a “daytime” environmental temperature (26). As we noted above, the preferred nocturnal temperature may differ from what has been applied in constant routine studies. The diurnal rhythm in proximal skin temperature under natural living conditions has to our knowledge not been studied in detail and may differ from the unmasked rhythm obtained in a constant routine protocol.

We have previously suggested that the proposed signaling of skin temperature to sleep-related brain areas may have a functional role: a warm skin is most likely to occur if the sleep-appetitive behaviors of lying down and covering up are

fulfilled, and it is thus safe for the organism to fall asleep (48). A question of considerable interest is whether skin temperature is also involved in the maintenance and depth of sleep.

Our findings may have implications for sleep-onset latency in everyday life. Warming the proximal skin resulted in a 26% decrease in sleep-onset latency, which approximates the order of magnitude that can be obtained with hypnotic compounds. In healthy subjects, daytime administration of melatonin, Temazepam, and Zopiclone induced reductions of at most 3–7 min (18, 21, 42). Hence, warming of the skin either by promotion of peripheral heat loss or by subtle and feedback-controlled warming of the skin within the thermoneutral range might provide a means to improve sleep onset in people who have trouble falling asleep in the beginning of the night or after nocturnal or early morning awakening. Such nonpharmacological treatment is likely to lack the adverse effects that characterize chronic use of hypnotics. Although we are not aware of comprehensive studies on the effects on sleep onset of the many pharmaceuticals that induce vasodilatation, some studies at least suggest that vasodilatation is correlated with the ease of sleep onset. For example, the rate of heat loss induced by melatonin and Temazepam is correlated with their effect on sleep-onset latency (18, 24).

In conclusion, our results add to the significance of previous studies demonstrating a correlation between skin temperature changes and sleep-onset latency by showing for the first time that an experimentally induced subtle increase in skin temperature may in fact cause a decrease in sleep-onset latency. The findings are compatible with the model that our group has previously put forward (48), in which it was shown that the diurnal modulation of skin temperature is possibly not only an output signal of the circadian timing system but may also act as an input signal to sleep-regulating brain areas.

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