Hypocretin deficiency : neuronal loss and functional consequences

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Manipulation of Core Body and Skin Temperature improves Sleepiness and Maintenance of Wakefulness in Narcolepsy

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Manipulation of Core Body and Skin Temperature improves Vigilance and Maintenance of Wakefulness in Narcolepsy

Objective | Impaired vigilance and sleepiness are two major daily complaints of patients with narcolepsy. We previously showed their sleepiness to be correlated to an abnormally regulated skin temperature, i.e. an increased distal skin relative to proximal skin temperature. Our goal was to investigate a possible causal contribution of skin temperature disturbances to impairments in the ability to maintain vigilance and wakefulness in narcolepsy.

Methods | In a modified constant routine protocol, the Psychomotor Vigilance Task (PVT) and the Maintenance of Wakefulness Test (MWT) were repeatedly assessed. Meanwhile, skin and core body temperatures were mildly manipulated within the thermoneutral range of the normal diurnal rhythm using a thermosuit and hot or cold food and drinks.

Patients | Eight patients (5 males) diagnosed with narcolepsy with cataplexy according to the ICSD-2 criteria (mean age ± SD: 28.6 ± 6.4, range 18-35 years).

Results | Compared to core cooling, core warming attenuated the typical decline in PVT response speed with increasing time-on-task by 25% (P = 0.02). Compared to distal skin warming, distal skin cooling increased the time that the patients were able to maintain wakefulness by 24% (distal warming: 1.88 min. vs. distal warming: 2.34 min.; P < 0.01).

Conclusion | Core body and skin temperatures causally affect vigilance and sleepiness in narcolepsy. This could lead to future practical applications.

Introduction

Narcolepsy is a syndrome characterized by excessive daytime sleepiness (EDS) and cataplexy.[1] Although sleepiness in narcolepsy is generally described as inadvertently falling asleep, a perhaps equally important aspect of it is impaired performance in the waking state due to disturbed vigilance.[2,3]

In healthy controls, both sleepiness and vigilance show a relationship with core body temperature and skin temperature. When core body temperature is high during daytime, skin temperature is relatively low, a combination that is correlated to optimal vigilance.[4-9] In contrast, core body temperature is low at night time, when skin temperature is

relatively high, and this combination is correlated to optimal sleep.[4-9] Skin temperature thus shows a circadian rhythm that is the inverse to the core body temperature rhythm.[10] Furthermore, a relatively high temperature of the distal skin (hands and feet) compared to the temperature of the proximal skin has been shown to be related to the process of falling asleep: a higher distal-to-proximal gradient (DPG) promotes sleep onset.[11] A causal contribution of core body temperature and skin temperature to vigilance and sleepiness has been shown to exist in healthy subjects, in whom mild warming of the proximal skin leads to an accelerated decline in vigilance and to an earlier onset of sleep.[12,13] It has been proposed that changes in both core body temperature and skin temperature modulate neuronal activity of thermosensitive neurons in brain areas that regulate vigilance and sleepiness.[14]

In a previous study, we reported an altered pattern of skin-temperature regulation in narcolepsy.[15] Narcoleptic subjects showed a combination of higher distal skin temperatures and lower proximal skin temperatures, which in healthy subjects is associated with the process of falling asleep.[11] We suggested that this pattern may in fact contribute to sleepiness.[15]

In this paper, we investigate whether direct manipulations of core body and skin temperature induce corresponding changes in the degree of sleepiness and vigilance in narcolepsy. We measured vigilance and the ability to maintain wakefulness in narcoleptic subjects while subtly manipulating skin and core body temperature within the thermoneutral range of the normal diurnal rhythm in a modified constant routine protocol.

Materials and Methods

Subjects
Eight narcoleptic subjects (5 males, 18-35 years of age; mean ± SD: 28.6 ± 6.4 years) participated with informed consent. All suffered from excessive daytime sleepiness (EDS) and typical cataplexy according to the ICSD-2 criteria for narcolepsy with cataplexy.[16] The protocol was approved by the local Medical Ethics Committee. All subjects were free of medication, except for one female subject using oral contraceptives. Females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase). Females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase). Subjects were excluded when they suffered from conditions that could influence their peripheral vascular bed, such as the metabolic syndrome, diabetes mellitus, thyroid function disorder, and cardiovascular pathological conditions.

Design
A previously described design was used,[12] that consisted of a modified constant routine protocol[17,18] over 2 experimental days during which vigilance was measured using the Psychomotor Vigilance Task (PVT) and sleepiness was measured using the maintenance of wakefulness test (MWT). Meanwhile, proximal and distal skin temperature were
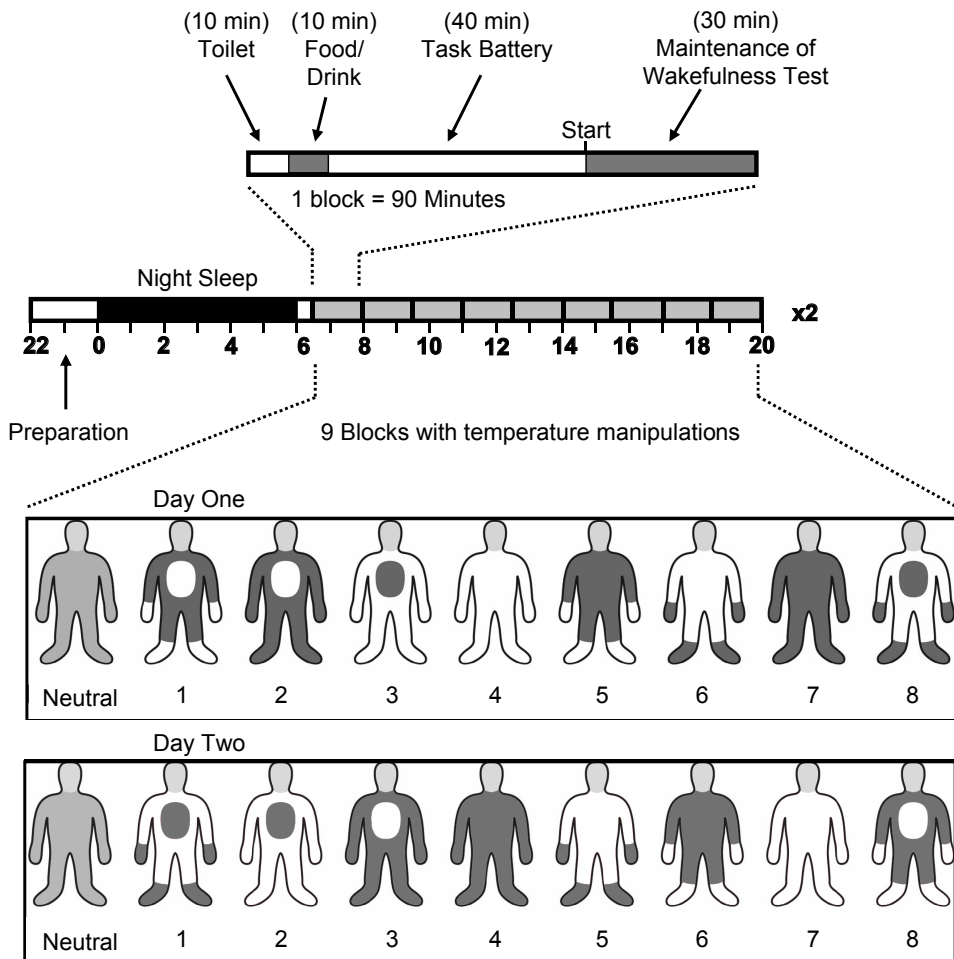
Figure 10.1 | Study Design

This figure shows a schematic overview of the two experimental days. Each day, subjects entered the lab at 22.00 hrs and were prepared for temperature manipulation and sleep registration. After six hours of night sleep, a modified constant routine protocol was started with nine identical 90 minute blocks. During each block, subjects walked to the toilet (10 min), consumed hot or cold food and drinks (10 min), performed tests on a computerized task battery (including PVT, 40 min) and underwent a MWT (40 min). Core body, proximal and distal skin manipulation occurred during every block. Manipulation patterns are shown in the human outlines with white representing cooling and dark grey representing warming. On the second day, the protocol was identical, but temperature manipulations were exactly the opposite of day one.

subtly manipulated using a thermosuit, while core body temperature was manipulated using hot or cold food and drinks (see Figure 10.1).

Constant routine protocol

Subjects first visited the sleep laboratory to get familiar with the test environment and to practise the PVT. One week later, the actual experiment was performed. Subjects

refrained from caffeine, alcohol and tobacco for 8 hours before reporting at the sleep laboratory at 22:00 hr, where they were prepared for polysomnography and fitted with the thermosuit. At midnight, lights were turned off and subjects were allowed to sleep until 06:00 hr. The experiment started at 06:30 hr under dim-light conditions (10 lux) with a fixed body position (semi-supine) and consisted of 9 consecutive blocks with durations of 1.5 hours each (described below). At the end of the first day subjects went home and returned to the laboratory the next evening for a repeated assessment according to the same procedure, but with a different temperature manipulation scheme (see Figure 10.1).

Block Design.
Each block was similar: It started by having the subjects get out of bed and walk 5 meters, using the bathroom if needed. Ten minutes after the start of each block skin temperature manipulation was started and subjects were served a snack and a drink to consume in approximately 10 minutes. Subsequently a self-paced computerized neuropsychological task battery was completed, including the PVT (see below) and assessment of thermal comfort and temperature sensation, with the use of 100-mm visual analogue scales ranging from uncomfortable to comfortable and from cool to warm. During these tests a researcher was present to keep subjects awake if necessary. After 60 minutes the researcher left the room and subjects were asked to remain awake while lying quietly.[19] If sleep was attained (see the sleep scoring subsection)[20] subjects were awakened and kept awake for the remaining part of the MWT time of 30 minutes.

Table 1. Estimates of the effects of temperature manipulation (in gray) and time of day on core and skin temperatures during the PVT and 5 minutes before start of sleep latency test.

	Core Body Temperature (T_{re})			Proximal Skin Temperature (T_{prox})			Distal Skin Temperature (T_{dist})		
PVT - Temperature during test									
Intercept	36.47	±	0.14	34.74	±	0.15	35.11	±	0.11
Hour^2		n.s.			n.s.		-0.004	±	0.001
$\sqrt{Hour}$	0.08	±	0.01 ***		n.s.			n.s.	
CBT:+/-	0.14	±	0.02 ***	0.21	±	0.05 ***	0.56	±	0.06
PST:+/-		n.s.		0.50	±	0.05 ***	0.22	±	0.06
DST:+/-		n.s.		0.14	±	0.05 **	0.45	±	0.06
MWT - Temperature 5 minutes before start of sleep latency test									
Intercept	36.46	±	0.14	34.78	±	0.15	35.12	±	0.10
Hour	0.05	±	0.01 ***		n.s.			n.s.	
Hour^2	-0.003	±	0.001 ***		n.s.		-0.005	±	0.001
CBT:+/-	0.10	±	0.02 ***	0.15	±	0.04 ***	0.36	±	0.06
PST:+/-		n.s.		0.62	±	0.04 ***	0.32	±	0.06
DST:+/-		n.s.		0.15	±	0.04 ***	0.57	±	0.06

Intercepts represent means. Values are ± standard error. Significance levels are indicated as *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Temperature Manipulation Sequence

Skin and core body temperature were manipulated differentially in every block according to a method described before.[12] In short, the 2x2x2 design consisted of three body sites of manipulation: core body (CB), proximal skin (PS), distal skin (DS). At each, temperature could be increased or decreased (T+ and T-), resulting in eight 8 combinations (CBT+,CBT-,PST+,PST-,DST+,DST-). All eight were tested in one day (Figure 10.1). The sequence differed between subjects in order to balance the protocol such that over all subjects, every manipulation combination was given once in each of the 8 blocks and every transition from one to any other combination occurred no more than once for each time of day. To balance for circadian effects, the second experimental day temperature manipulation combinations were the inverse of those of the first day (for example: day 1, block 1, CBT+, PST-, DST-; day 2, block 1, CBT-, PST+, DST+, Figure 10.1).

Temperature Manipulation method

Core body temperature was manipulated by means of 200 ml hot (heated to 80ºC, served 2 minutes later) or cold (0ºC, crushed ice) diet decaffeinated tea 4.25 Kcal, Diet Decaffeinated Iced Tea Mix, Lipton, Englewood Cliffs, USA) together with a hot or cold snack at subjects' choice (200 Kcal). Skin temperature was manipulated using a full-body thermosuit (Coretech Cool tube suit, Med-Eng Systems Inc., Ottawa, Canada) connected to two computer-controlled circulation thermostat baths (K6KP, Lauda, Lauda-Köningshofen, Germany). During the first 20 min of each block, the water in the thermostat baths changed to the desired temperature, while the bath temperature was kept constant for the remaining 70 min of the block. The water in the tubes was ~31°C and ~34°C just before entering the thermosuit. This range of skin temperature was chosen to avoid major thermoregulatory responses.

Body Temperature Recordings

Core body temperature was measured using a rectal thermistor. Proximal skin temperature was measured at three places: right on the middle of the frontal aspect of the tigh, abdomen (1 cm above the navel), and the right infraclavicular area. Distal skin temperature was measured at four points: thenar eminence of the left and right hand and medial plantar aspect of the left and right foot. Temperature was measured using thermistors (P-8432, ICBT, Tokyo, Japan) and digitally recorded at 1 Hz (Embla A10 and Somnologica software, Flaga, Reykjavik, Iceland). An automated procedure was applied to remove occasional artefacts and to calculate average distal and proximal skin temperature by a weighted average as described before.[12] Temperature data were averaged over 20 minute intervals surrounding the PVT assessments and over the 5 min before the start of the sleep latency test (Figure 10.1).

Sleep scoring

Polysomnographic sleep recordings were performed according to standard procedures.[20] Sleep onset was determined online during the experiment according to standard criteria, defined as three consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep.[19] Sleep-onset latency was defined as the time between the start of

Table 2 Estimates of the effects of temperature manipulation on temperature sensation and thermal comfort.

	Subjective Measures					
	Temperature Sensation			Thermal Comfort		
Intercept	64.27	± 4.34		47.24	± 2.62	
CBT:+/-	11.31	± 2.81	***	-15.00	± 3.62	***
PST:+/-	14.95	± 2.80	***	-13.50	± 3.62	***
DST:+/-		n.s.			n.s.	

Values are means ± standard error. 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). Significance levels are indicated as *P < 0.05, **P < 0.01, ***P < 0.001.

the MWT and sleep onset. If the subject did not sleep during the 30 min, sleep-onset latency was scored as 30 min. One data point could not be included in the analysis due to loss of EEG data.

Vigilance

Vigilance was assessed using a seven minute version of the psychomotor vigilance test (PVT).[21,22] Subjects focused on a blank rectangle in the middle of a computer screen. At random intervals (2-10 sec.), a reaction time counter started, shown as the number of milliseconds since start, in the rectangle. Subjects had to press a key to stop it as quickly as possible. The obtained reaction time (RT) count was shown for 1 second, providing performance feedback. Because the distribution of reaction times deviates from normality, PVT results are as a standard reported as response speed, i.e. reciprocal RT (RRT=1000/RT), In order to quantify the typical performance decline with increasing time-on-task response speed averages were calculated per minute. The vigilance measure of interest was the decline of response speed with increasing time-on-task.

Statistical analyses

To determine the effects of skin and core temperature manipulations on actual measured temperatures (core body, proximal skin, and distal skin) and on PVT performance and subjective comfort, hierarchical regression analysis was applied using MLwiN software (Centre for Multilevel Modelling, Institute of Education, London, UK). Because the frequency distribution of sleep-onset latencies was skewed, longitudinal Poisson regression analysis was used to determine the effects of skin and core temperature manipulations and induced temperatures on MWT sleep onset latency. The hierarchical regression 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.[23] 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, thermal comfort, time-on-task decline of PVT response speed, and sleep-onset latency as dependent variables; and body temperature manipulations as
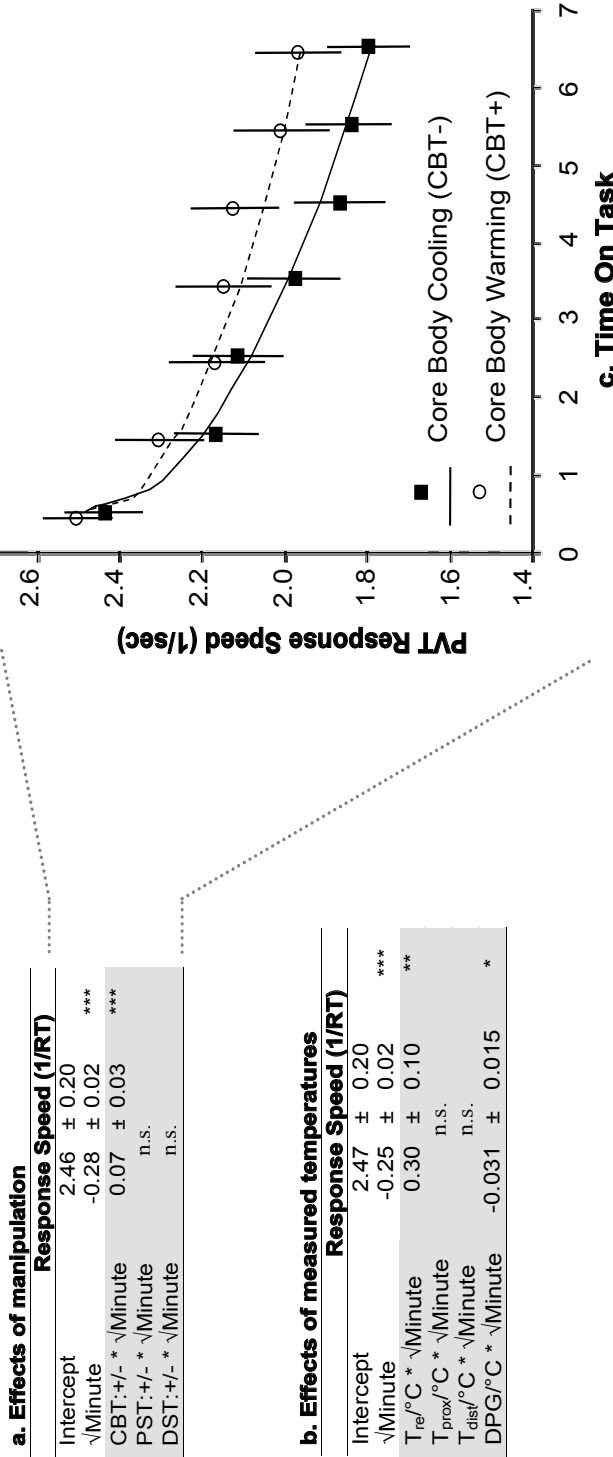
a. Effects of manipulation

	Response Speed (1/RT)		
Intercept √Minute	2.46 ± 0.20 -0.28 ± 0.02		***
CBT:+/- * √Minute	0.07 ± 0.03		***
PST:+/- * √Minute	n.s.		
DST:+/- * √Minute	n.s.		

b. Effects of measured temperatures

	Response Speed (1/RT)		
Intercept √Minute	2.47 ± 0.20 -0.25 ± 0.02		***
T_{re}/°C * √Minute	0.30 ± 0.10		**
T_{prox}/°C * √Minute	n.s.		
T_{dist}/°C * √Minute	n.s.		
DPG/°C * √Minute	-0.031 ± 0.015		*

Legend:
- ■ Core Body Cooling (CBT-) ———
- ○ Core Body Warming (CBT+) - - - -

c. Time On Task (x-axis, 0–7)

PVT Response Speed (1/sec) (y-axis, 1.4–2.6)

Figure 10.2 | Effects on Vigilance

Estimates of the effects of temperature manipulation and time on task on PVT response speed (a), estimates of the effects of actual measured temperatures and time on task on PVT response speed (b) and regression model of response speed over the seven subsequent minutes of PVT performance in the core warming (CBT+, open circles) and core cooling (CBT-, solid squares) conditions (c). Intercepts represent overall means. Values are means ± standard error. Significance levels are indicated as *:p<0.05, **:p<0.01, ***:p<0.001. Narcoleptic subjects show a low response speed and a time on task effect with a fast decline already during the first minutes. The response speed improves during the core body warming condition.

centred dichotomous predictor variables (with -0.5 reflecting the cool manipulation level and 0.5 reflecting the warm manipulation level, for ease of interpretation of the intercept, now showing the overall average). For the longitudinal Poisson regression analysis, all independent variables were centred at the within-subject single-day level.
A second series of analyses was performed, now not evaluating the manipulation conditions but rather how the actually measured core body, proximal and distal skin temperatures, and the distal-to-proximal gradient (DPG) predicted the time-on-task decline of PVT response speed and MWT sleep-onset latency.

Time (hour, hour2 and √hour; defined as the number of hours since the start of the first included PVT or MWT within each day, starting with 0 at 09:00) was allowed in the models for induced temperatures to account for possible diurnal variations in core and skin temperature.[24] For all regression analyses, we calculated the full model, with all temperature manipulation variables and covariates in the model and subsequently stepwise removed nonsignificant terms to obtain optimal models, containing only the significant contributions. Maximum likelihood was used to estimate the regression coefficients, which were tested for significance with the Wald test.[23] In order to obtain the optimal linear models, additional terms were allowed in the regression equation only if their coefficients were significant and only if their inclusion improved the regression model according to the likelihood ratio test. In order to obtain the optimal Poisson regression models, additional terms were allowed in the regression equation only if their coefficients were significant and if the residual error of the model was reduced.

The following regression models were used: [1] effects of manipulation on measured temperature: $T_{ijk} = \beta_{0ijk} + \beta_1 \times Hour_{ijk} + \beta_2 \times Hour^2_{ijk} + \beta_3 \times \sqrt{Hour}_{ijk} + \beta_4 \times CBT_{ijk} + \beta_5 \times PST_{ijk} + \beta_6 \times DST_{ijk}$ (Subscripts indicate i^{th} observation on day j for subject k); [2] effects of manipulation on PVT response speed: $PVT_{ijkl} = \beta_{0ijkl} + \beta_1 \times CBT_{ijkl} + \beta_2 \times PST_{ijkl} + \beta_3 \times DST_{ijkl} + \beta_4 \times \sqrt{Minute}_{ijkl}$ (Subscripts indicate i^{th} minute during the jth PVT on day k for subject l); [3] relation of measured temperatures on PVT response speed: $PVT_{ijk} = \beta_{0ijkl} + \beta_1 \times Tre_{ijkl} + \beta_2 \times Tprox_{ijkl} + \beta_3 \times Tdist_{ijkl} + \beta_4 \times \sqrt{Minute}_{ijkl}$ (Subscripts indicate i^{th} minute during the jth PVT on day k for subject l); [4] effects of manipulation on sleep latency: $ln(latency) = \beta_{0ijk} + \beta_1 \times CBT_{ijk} + \beta_2 \times PST_{ijk} + \beta_3 \times DST_{ijk} + \beta_4 \times Hour^2_{ijk}$ (Subscripts indicate i^{th} observation on day j for subject k); [5] effects of measured temperatures on sleep latency: $ln(latency)_{ijk} = \beta_{0ijk} + \beta_1 \times Tre_{ijk} + \beta_2 \times Tprox_{ijk} + \beta3 \times Tdist_{ijk} + \beta_4 \times Hour^2_{ijk}$ $(+ \beta_5 \times DPG_{ijk})$ (Subscripts indicate i^{th} observation on day j for subject k); [6] effects of manipulation on temperature sensation and comfort: $Outcome\text{-}variable_{ijk} = \beta_{0ijk} + \beta_1 \times CBT_{ijk} + \beta_2 \times PST_{ijk} + \beta_3 \times DST_{ijk} + \beta_4 \times Hour^2_{ijk}$. In the tables the optimal models are shown, with only the significant contributing factors. Note that the values in the tables represent the effect coefficients as estimated from the Poisson regression analysis: in order to transform these coefficients to the number of 30-sec epochs, one should calculate e to the power of the regression equation. Transformation to minutes subsequently takes a division by two. In the results section, sleep latencies have thus been transformed and are reported in minutes. Two-tailed significance levels were set at 0.05.

a. Effects of manipulation

	Sleep Latency (min)		
	mean	confidence interval	
Intercept	2.10	1.52 – 2.90	
Hour^2	0.50	0.50 – 0.50	***
CBT:+/-	n.s.		
PST:+/-	n.s.		
DST:+/-	-0.40	0.34 – 0.47	**

b. Effects of measured temperatures

	Sleep Latency (min) (factorial model)			Sleep Latency (min) (DPG model)		
	mean	confidence interval		mean	confidence interval	
Intercept	2.10	1.52 – 2-91		2.10	1.52 – 2-91	
Hour^2	0.50	0.50 – 0.50	***	0.50	0.50 – 0.50	***
T_{re}/°C	n.s.					
T_{prox}/°C	n.s.					
T_{dist}/°C	-0.40	0.34 – 0.48	**			
DPG/°C				-0.40	0.33 – 0.49	*

c. Distal Manipulation

Figure 10.3 | **Effects on Maintenance of Wakefulness**

Estimates of the effects of temperature manipulation and time of day on sleep latency (a), estimates of the effects of measured temperatures and time of day on sleep latency (b) and the means (± 95% Confidence Interval) of sleep latency in the distal cooling (left bar) and distal warming (right bar) conditions (c). Intercepts represent overall means. Values in tables are means ± standard error. Significance levels are indicated as *:p<0.05, **:p<0.01, ***:p<0.001. Narcoleptic subjects were characterized by very short sleep latencies. Sleep latency was longer in the distal skin cooling condition as compared to the distal skin warming condition (**p < 0.02).
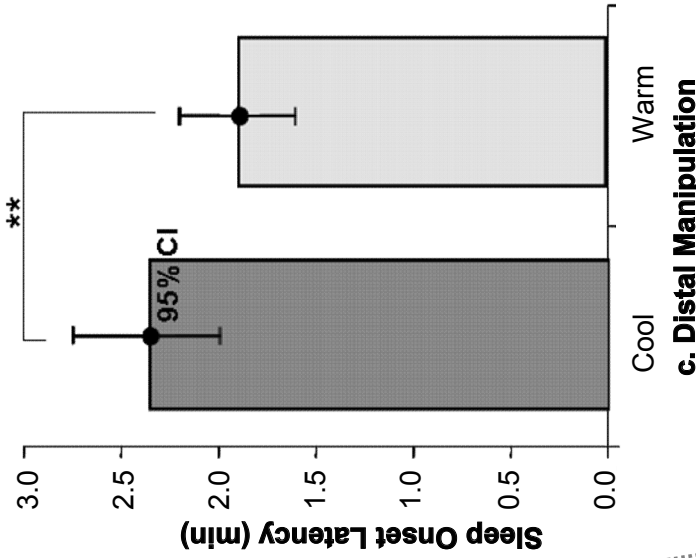
Results

Effects of manipulation on temperature and comfort
The effects of the manipulations on core body and skin temperatures during the PVT and before the start of the MWT are shown in Table 1. Core body and distal skin temperature were significantly modified by time of day ($p < 0.001$), accounting for 10-25% of variance during the PVT and the MWT.

The core body temperature manipulation was the sole factor influencing core body temperature during the PVT and the MWT (effect size: 0.10 - 0.12 ºC, $p < 0.001$) and accounted for 29% of the variance during the PVT and 17% of the variance during the MWT.

Proximal and distal skin temperatures during the PVT and the MWT were mainly affected by their respective skin temperature manipulation (effect size: 0.45 – 0.62 ºC, $p < 0.001$), but also to a lesser extend by core body temperature and by the other skin temperature manipulation (effect size: 0.14 – 0.56 ºC, $p < 0.001$). The temperature manipulations accounted for 60% of the variance during the PVT and the MWT.

The effects of the manipulations on thermal comfort and temperature sensation, measured before the MWT are shown in Table 2. In summary, the warm conditions were experienced as less comfortable and warmer than the cool conditions. Comfort was significantly lower when the core body and proximal skin were warmed ($p < 0.001$), with a trend for warming of the distal skin ($p = 0.06$). The highest comfort was achieved when cooling was induced at all three sites. Temperature was perceived as higher in the core body and proximal skin warming condition ($p < 0.001$). Subjects did not perceive the distal skin warming condition as a significantly warmer condition than the distal skin cooling condition ($p = 0.26$).

Effect of temperature manipulation on psychomotor vigilance
The overall average RRT of narcoleptic subjects was 2.46 ± 0.20 sec^{-1}. There was a typical worsening, i.e. a decline in response speed, with increasing time-on-task (see Figure 10.2). This decline was best approximated by a square root function of time-on-task ($\sqrt{\text{Minutes}}$, $p < 0.001$). As evident from Figure 10.2, these profiles indicate that vigilance declined quickly after starting the task. As compared to core body cooling, core body warming attenuated this decline by 25% (CBT x $\sqrt{\text{Minute}}$, $p = 0.02$), while effects induced by proximal or distal skin temperature manipulations were not significant ($p > 0.20$).

Regressing PVT on the actually induced temperatures showed essentially the same effects: a higher core body temperature was associated with an *attenuated* decline in response speed over the time-on-task (T_{re} x $\sqrt{\text{Minute}}$, $p = 0.004$). Moreover, a higher DPG was associated with an *accelerated* decline in response speed (DPG x Minute, $p = 0.04$).

Effect of temperature manipulation on maintenance of wakefulness
Figure 10.3 shows the effects of the temperature manipulations on maintenance of wakefulness as derived from the regression analysis. Overall average sleep latency was 2.10 min (95% Confidence Interval CI: 1.52 - 2.90). Sleep onset latency was significantly modulated by time (hour^2) and the distal skin manipulation, with an estimated shorter latency (1.88 min; CI: 1.60 – 2.21) in the DST+ condition compared to a longer latency (2.34 min; CI: 1.99 – 2.75) in the DST- condition (p < 0.01, Figure 10.3). Cooling the distal skin thus meant that subject remained awake for 24% longer as when the distal skin was warmed. Sleep latency was not significantly affected by core and proximal manipulations (all p > 0.20).

Regressing MWT on the actually measured temperatures resulted in significance for the same variables: sleep onset latency was significantly modulated by time (hour2) and by distal skin temperature. The regression coefficients, transformed to minutes (Figure 10.3ab), can be interpreted as follows: patients could stay awake for 1.89 (CI: 1.60 – 2.24) minutes when distal skin temperature was 0.5 ˚C higher than the average distal skin temperature, as compared to 2.34 (CI: 1.97 – 2.77) minutes when distal skin temperature was 0.5 ˚C lower than the average distal skin temperature (p < 0.01, Figure 10.3c). One degree of decrease in distal skin temperature thus increased the time patients succeeded to maintain wakefulness by 24%. Sleep latency was not significantly related to core and proximal temperatures (all p > 0.31).

Discussion

We investigated whether subtle manipulations of core body and skin temperatures within the natural range of the diurnal cycle, affected vigilance and sleepiness in narcolepsy.

Firstly, patients were better able to maintain vigilance when core body temperature was increased than when it was lowered. In short, vigilance in narcolepsy can be altered simply by altering the temperature of food and drinks. Secondly, the ability to maintain wakefulness was better when distal skin temperature was lowered than when it was increased. We were thus able to influence the process of falling asleep in narcoleptic subjects by gently cooling or warming their hands and feet. The acceleration of sleep onset by distal skin warming occurred in spite of the fact that warming was perceived as slightly less comfortable.

Our data furthermore showed a number of narcolepsy-related aspects on PVT-performance and maintenance of wakefulness under strictly controlled and balanced conditions. In agreement with previous investigations,[2] narcoleptic subjects showed a very poor average PVT response speed, not only compared to matched controls, but also compared to elderly and elderly insomniacs previously submitted to the same protocol.[13] Although untreated narcolepsy is already characterized by a very short MWT sleep latency (around 6 minutes),[19] in our constant routine protocol all patients had great difficulties remaining awake for longer than 3 minutes. These shorter MWT values relative to previous reports may be due to the restricted time allowed for sleep during

the night prior to the investigation (6 hours) and continuous low-light, stimulus-free, semi-supine circumstances, known to promote falling asleep.[25] The more remarkable it is that even under these high sleep pressure inducing conditions, distal skin cooling significantly increased sleep latency with 24%.

Note that in this study, sleep-onset was defined as 3 consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep. This differs from the definition of 16 sec of stage 1 (or deeper) sleep that is commonly used in the clinical setting. In our study design, sleep scoring was performed online and subjects had to be woken up immediately after the onset of sleep. For this purpose, we had to be absolutely sure of sleep onset, and therefore used the three 30-s epoch criterion. To compare results with other studies, the exact definition of sleep onset needs to be taken into account. However, using the clinical definition of sleep onset would not have changed the outcome of this study, since there was no occasion when a subject showed an epoch of wake after the occurrence of stage 1 sleep.

It is known that the clinical efficacy of commonly used stimulants, such as modafinil, is not adequately revealed by its small effects on sleep latency as measured in the MWT.[26] Although the definition of sleep onset may have differed between studies, the changes in sleep latency in our study are comparable to those seen with modafinil. Temperature manipulations may thus have a more significant clinical effect.

We initiated this study based upon our previous findings that narcoleptic subjects have an increased distal relative to proximal skin temperature (distal-to-proximal gradient, DPG) that was related to an increased sleepiness.[15] In that previous study, we did not measure core body temperature. Other studies have reported conflicting results regarding core body temperature. Therefore, we compared the T_{core} measured in this study in narcoleptic subjects, with the earlier published T_{core} measured in healthy controls that underwent the same protocol and matched on age and gender.[12] core body temperature was lower in narcolepsy than in controls (T_{re}: narcolepsy 36.47 ± 0.14°C; controls, 36.88 ± 0.06°C; p = 0.01 (Z-test)). A partial normalization of the low core body temperature in the core warming condition may have been involved in its positive effects on PVT performance. This interpretation is supported by the positive relation between core body temperature and vigilance we previously found in elderly subjects in an identical protocol [13] and by previous work showing a correlation between the circadian modulation of vigilance and of core body temperature.[5-9] The effects of distal skin warming and cooling on maintenance of wakefulness in narcoleptic subjects are in line with our earlier findings of an abnormally increased distal skin temperature that correlated with the ease of falling asleep in narcolepsy.[15]

In previous studies of our group, both young and elderly subjects without sleep problems and insomniac elderly showed worsening of PVT performance and shorter sleep latencies with proximal skin warming.[12,13] Given the repeatability of the proximal warming results over the 3 groups in those previous studies, the more remarkable it is that narcoleptic subjects do not show sensitivity of vigilance performance and sleepiness to proximal warming. It is not unlikely that this difference with healthy controls—and

with elderly subjects reported previously—is related to the markedly lower core and proximal temperature of narcoleptic subjects in combination with a higher distal skin temperature, even under the strictly controlled conditions of the present experiment and found previously under less controlled circumstances.[15]

Of note, the present study differs from previous work e.g.[24,27,28] in that *mild* manipulations within the thermoneutral zone were applied. Since such manipulations induced only changes within the temperature range normally covered during everyday life, the circadian modulation of these temperatures could contribute to the circadian modulation in vigilance and sleepiness.

In conclusion, our results demonstrate a modulatory role for body temperature in the regulation of vigilance and maintenance of wakefulness in narcolepsy. Experimentally induced subtle changes in core body and skin temperature *caused* changes in vigilance and the ability to maintain wakefulness. A practical implication of our findings is that temperature manipulations may be of value in the management of vigilance and sleepiness problems in narcolepsy. An ultimate practical application could for example be clothing with integrated measurement and regulation of skin temperature. For the time being, the advice may be to utilise a warm drink or meal in combination with cooling of the extremities to aid their fight against vigilance impairment and daytime sleepiness.

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