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

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Context: 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., increased distal skin temperature compared with proximal skin temperature.

Objective: 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.

Design: 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.

Setting: Tertiary narcolepsy referral center in a university hospital

Patients or Other Participants: 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).

Intervention(s): None

Main Outcome Measure(s): MWT sleep latency and PVT response speed.

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).

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

Keywords: Hypocretin, orexin, core body temperature, skin temperature, thermoregulation, sleep latency, psychomotor vigilance task, vigilance, sustained attention, maintenance of wakefulness.

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suffered from excessive daytime sleepiness (EDS) and typical cataplexy according to the ICSD-2 criteria for narcolepsy with cataplexy. 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). 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, that consisted of a modified constant routine protocol 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 subtly manipulated using a thermosuit, while core body temperature was manipulated using hot or cold food and drinks (see Figure 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, 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. The experiment started at 06:30 under dim-light conditions.

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*Figure 1—Study Design. This figure shows a schematic overview of the two experimental days. Each day, subjects entered the lab at 22:00 and were prepared for temperature manipulation and sleep registration. After 6 hours of night sleep, a modified constant routine protocol was started with 9 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 (30 min). Core body and 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.*
ections (10 lux) with a fixed body position (semisupine) 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 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 min. 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 min, the researcher left the room and subjects were asked to remain awake while lying quietly. If sleep was attained (see the sleep scoring subsection) subjects were awakened and kept awake for the remaining part of the MWT time of 30 min.

**Temperature Manipulation**

**Manipulation Sequence**

Skin and core body temperature were manipulated differentially in every block according to a method described before. In short, the 2x2x2 design consisted of 3 body sites of manipulation: core body (CB), proximal skin (PS), and distal skin (DS). At each temperature, core body temperature could be increased or decreased (T+ and T-), resulting in 8 combinations (CB+T+, CB-T+, PST+, PST-, DST+, DST-). All 8 were tested in one day (Figure 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, CB+T+, PST-, DST-; day 2, block 1, CB-, PST+, DST+, figure 1).

**Manipulation Method**

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 decaffeinated tea (4.25 Kcal, Diet Decaffeinated Iced Tea Mix, Lipton, Englewood Cliffs, USA) together with a hot or cold snack of 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 thermometer. Proximal skin temperature was measured at 3 places: right on the middle of the frontal aspect of the thigh, 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 artifacts and to calculate average distal and proximal skin temperature by a weighted average as described before. Temperature data were averaged over 20-min intervals surrounding the PVT assessments and over the 5 min before the start of the sleep latency test (Figure 1).

**Sleep Scoring**

Polysomnographic sleep recordings were performed according to standard procedures. Sleep onset was determined online during the experiment according to standard criteria, defined as 3 consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep. Sleep-onset latency was defined as the time between the start of 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 7-min version of the psychomotor vigilance test (PVT). 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 msec 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 normal, 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 min. 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...
Table 1—Estimates of the Effects of Temperature Manipulation and Time of Day on Core and Skin Temperatures During the PVT and 5 Minutes Before Start of Sleep Latency Test

<table>
<thead>
<tr>
<th>Time (hour, hour(^2))</th>
<th>Core Body Temperature ((T_{rc}))</th>
<th>Proximal Skin Temperature ((T_{prox}))</th>
<th>Distal Skin Temperature ((T_{dist}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>36.47 ± 0.14</td>
<td>34.74 ± 0.15</td>
<td>35.11 ± 0.11</td>
</tr>
<tr>
<td>(\sqrt{\text{Hour}})</td>
<td>n.s.</td>
<td>n.s.</td>
<td>-0.004 ± 0.001***</td>
</tr>
<tr>
<td>(\text{CBT}:+/-)</td>
<td>0.14 ± 0.02***</td>
<td>0.21 ± 0.05***</td>
<td>0.56 ± 0.06***</td>
</tr>
<tr>
<td>(\text{PST}:+/-)</td>
<td>n.s.</td>
<td>0.50 ± 0.05***</td>
<td>0.22 ± 0.06***</td>
</tr>
<tr>
<td>(\text{DST}:+/-)</td>
<td>n.s.</td>
<td>0.14 ± 0.05**</td>
<td>0.45 ± 0.06**</td>
</tr>
</tbody>
</table>

MWT - Temperature 5 minutes before start of sleep latency test

| Intercept                | 36.46 ± 0.14                      | 34.78 ± 0.15                          | 35.12 ± 0.10                         |
| \(\sqrt{\text{Hour}}\)  | 0.05 ± 0.01***                    | n.s.                                  | n.s.                                 |
| \(\text{CBT}:+/-\)      | -0.003 ± 0.001***                 | 0.15 ± 0.04***                        | 0.36 ± 0.06**                        |
| \(\text{PST}:+/-\)      | 0.10 ± 0.02***                    | 0.62 ± 0.04***                        | 0.32 ± 0.06**                        |
| \(\text{DST}:+/-\)      | 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.

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. 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 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, hour\(^2\)) and \(\sqrt{\text{hour}}\); 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. 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. In order to obtain the optimal linear 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: \(T_{ijkl} = \beta_{0ijkl} + \beta_1 x CBT_{ijkl} + \beta_2 x PST_{ijkl} + \beta_3 x DST_{ijkl} + \beta_4 x \sqrt{\text{Minute}_{ijkl}}\) (Subscripts indicate \(i\)th observation on day \(j\) for subject \(k\)); [2] effects of manipulation on PVT response speed: \(\text{PVT}_{ijkl} = \beta_{0ijkl} + \beta_1 x CBT_{ijkl} + \beta_2 x PST_{ijkl} + \beta_3 x DST_{ijkl} + \beta_4 x \sqrt{\text{Minute}_{ijkl}}\) (Subscripts indicate \(i\)th minute during the jth PVT on day \(k\) for subject \(l\)); [3] relation of measured temperatures on PVT response speed: \(\text{PVT}_{ijkl} = \beta_{0ijkl} + \beta_1 x \text{MWT}_{ijkl} + \beta_2 x \text{PVT}_{ijkl} + \beta_3 x \text{DST}_{ijkl} + \beta_4 x \sqrt{\text{Minute}_{ijkl}}\) (Subscripts indicate \(i\)th observation on day \(j\) for subject \(k\)); [4] effects of manipulation on sleep latency: \(\ln(\text{latency}) = \beta_{0ijkl} + \beta_1 x \text{CBT}_{ijkl} + \beta_2 x \text{PST}_{ijkl} + \beta_3 x \text{DST}_{ijkl} + \beta_4 x \sqrt{\text{Minute}_{ijkl}}\) (Subscripts indicate \(i\)th observation on day \(j\) for subject \(k\)); [5] effects of measured temperatures on sleep latency: \(\ln(\text{latency})_ijkl = \beta_{0ijkl} + \beta_1 x \text{MWT}_{ijkl} + \beta_2 x \text{PVT}_{ijkl} + \beta_3 x \text{DST}_{ijkl} + \beta_4 x \sqrt{\text{Minute}_{ijkl}} + \beta_5 x \text{DPG}_{ijkl}\) (Subscripts indicate \(i\)th observation on day \(j\) for subject \(k\)); [6] effects of manipulation on temperature sensation and comfort: \(\text{Outcome-variable}_{ijkl} = \beta_{0ijkl} + \beta_1 x \text{CBT}_{ijkl} + \beta_2 x \text{PST}_{ijkl} + \beta_3 x \text{DST}_{ijkl} + \beta_4 x \text{DPG}_{ijkl}\) (Subscripts indicate \(i\)th observation on day \(j\) for subject \(k\)). 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.

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...
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 2). This decline was best approximated by a square root function of time-on-task (√Minutes, P < 0.001). As evident from figure 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 √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 Psychomotor Vigilance

shown in Table 1. Core body and distal skin temperature were significantly modified by time of day (P < 0.001), accounting for 10% to 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°C, 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°C, 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°C, 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 3 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).

Figure 2—Psychomotor Vigilance Task. 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 7 subsequent min 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.

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

<table>
<thead>
<tr>
<th>Subjective Measures</th>
<th>Temperature Sensation</th>
<th>Thermal Comfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>64.27 ± 4.34</td>
<td>47.24 ± 2.62</td>
</tr>
<tr>
<td>CBT:+/-</td>
<td>11.31 ± 2.81***</td>
<td>-15.00 ± 3.62***</td>
</tr>
<tr>
<td>PST:+/-</td>
<td>14.95 ± 2.80***</td>
<td>-13.50 ± 3.62***</td>
</tr>
<tr>
<td>DST:+/-</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

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.
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.


First, 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. Second, 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, narcoleptic subjects showed a very poor average PVT response speed, not only compared with matched controls, but also compared with elderly good sleepers and elderly insomniacs previously submitted to the same protocol. Although untreated narcolepsy is already characterized by a very short MWT sleep latency (around 6 min), our constant routine protocol all patients had great difficulties remaining awake for longer than 3 min. 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 h) and continuous low-light, stimulus-free, semisupine circumstances, known to promote falling asleep. The more remarkable it is that even under these high sleep pressure inducing conditions, distal skin cooling significantly increased sleep latency by 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 one 30-s epoch.
och 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.\textsuperscript{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.\textsuperscript{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 $T_{\text{core}}$ measured in this study in narcoleptic subjects, with the earlier published $T_{\text{core}}$ measured in healthy controls that underwent the same protocol and matched on age and gender.\textsuperscript{12} Core body temperature was lower in narcolepsy than in controls ($T_{\text{nc}}$: 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\textsuperscript{13} and by previous work showing a correlation between the circadian modulation of vigilance and core body temperature.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{15}

Of note, the present study differs from previous work\textsuperscript{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 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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