

# Time-on-task Impairment of Psychomotor Vigilance Is Affected by Mild Skin Warming and Changes With Aging and Insomnia

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**Study Objectives:** To investigate the effect of mild manipulations of core and skin temperature on psychomotor vigilance (PVT) in young adults, elderly, and elderly insomniacs.

**Design:** 432 PVTs were obtained during a 2-day semi-constant routine protocol, while differentially manipulating core and skin temperatures within a comfortable thermoneutral range.

**Setting:** Sleep laboratory of the Netherlands Institute for Neuroscience.

**Patients or Participants:** Groups of 8 sex-matched young adults (27.0±2.4 years, mean±s.e.m.), elderly (65.8±2.8 years), and insomniacs (59.1±1.9 years).

**Measurements and Results:** During the 7-minute PVTs, response speed typically declined with increasing time-on-task. Proximal skin warming by only ±0.6°C accelerated this decline by 67% ( $P = 0.05$ ) in young adults and by 50% ( $P < 0.05$ ) in elderly subjects. In elderly insomniacs, proximal warming slowed down the mean response speed already from the onset of the task (3% level drop,  $P < 0.001$ ). Response speed tended to decrease with age ( $P < 0.10$ ), reaching significance only in elderly insomniacs

( $P < 0.05$ ). Speed decrements occurred mostly towards the end of the time-on-task in young adults; earlier and more gradually in elderly without sleep complaints; and very early and in a pronounced fashion in insomniacs. Interestingly, the worsening by warming followed the time pattern already present within each group.

**Conclusions:** The results are compatible with the hypothesis that the endogenous circadian variation of skin temperature could modulate vigilance regulating brain areas and thus contribute to the circadian rhythm in vigilance. Minute-by-minute PVT analyses revealed effects of age and insomnia not previously disclosed in studies applying time-point aggregation. Our data indicate that “age-related cognitive slowing” may result, in part, from age-related sleep problems.

**Keywords:** Core body temperature, skin temperature, thermoregulation, psychomotor vigilance, sustained attention, aging, insomnia

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## INTRODUCTION

THERE IS A CLOSE RELATIONSHIP BETWEEN THE CIRCADIAN RHYTHM OF CORE BODY TEMPERATURE (CBT) AND THE DAILY VARIATION IN VIGILANCE, AS SHOWN by Kleitman.<sup>1</sup> Vigilance is optimal during the circadian phase of increased CBT.<sup>2-6</sup> Under controlled conditions, the rhythm in CBT results to a large extent from the rhythm in skin blood flow, which determines skin temperature, and the resulting heat transfer gradient from the body to the environment. Skin temperature thus shows a circadian rhythm that is reciprocal to the CBT rhythm, i.e., low during the habitual wake period,<sup>7-9</sup> although a reversal of the proximal skin temperature has been found under specific conditions.<sup>10</sup> We have proposed that these intrinsic changes in both CBT and skin temperature could modulate neuronal activity in vigilance regulating brain areas.<sup>11</sup> A likely brain structure linking vigilance with core body and skin temperature is the preoptic area/anterior hypothalamus (POAH), the major thermoregulatory center of the mammalian brain as well as a key structure in vigilance state control. Both local brain temperature and skin temperature modulate the firing rate of thermosensitive neurons in the POAH and other brain areas involved in vigilance regulation.<sup>11,12</sup>

### Disclosure Statement

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Support for a causal contribution of skin, but not core, temperature to vigilance regulation has been provided by a strictly controlled laboratory study, demonstrating accelerated sleep onset with very subtle warming of the skin in a comfortable and thermoneutral range.<sup>13</sup> The simultaneous and independent induction of changes in core body temperature did not affect sleep propensity. These findings suggest that the previously reported positive phase relation of the circadian rhythm in core body temperature and the circadian rhythm in vigilance<sup>2-6</sup> might also be an indirect reflection of a reciprocal phase relation of the circadian rhythm in skin temperature and the circadian rhythm in vigilance.

A limited number of experimental studies have investigated the effect of skin temperature manipulation on vigilance. These studies manipulated ambient temperature to induce skin temperatures beyond the range of the normal diurnal fluctuations in skin and core body temperature. A recent meta-analysis on the effects of temperature manipulation on task performance indicates an inverted U-shape, not surprisingly demonstrating that both high and low temperatures that activate thermoregulatory responses adversely affect performance.<sup>14</sup> Thus, both heat and cold stress negatively affected sustained vigilance.<sup>15,16</sup> This makes sense from the point of view that the brain needs to readdress its resources from optimal task performance towards thermal stress defense. These findings cannot be generalized to the normal diurnal range of in skin temperature. Consequently, no conclusion can be drawn regarding a causal contribution of the circadian rhythm in skin temperature to the circadian rhythm in vigilance.

The aim of the present study was to investigate whether the induction of changes in skin and core body temperature within the comfortable range of normal diurnal rhythm could causally affect vigilance. Our recently developed experimental set-up<sup>13</sup> allowed us to induce subtle changes in core body temperature

(+ and - 0.1°C) and proximal and distal skin temperature (+ and - 0.3°C) in a balanced protocol. As the dependent variable, we obtained sustained response speed as measured with the psychomotor vigilance task (PVT).<sup>17</sup> We investigated the effect of core body and skin temperature manipulations on psychomotor vigilance not only in healthy young adults, but also in elderly without sleep problems and elderly who complained of poor sleep. Elderly subjects are of particular interest because (1) thermosensitivity decreases with aging<sup>18</sup>; (2) aging slows the response speed during a psychomotor vigilance task<sup>19-22</sup>; (3) elderly are at a higher risk of chronic poor sleep,<sup>23</sup> and acute sleep restriction affects vigilance—although less so in well sleeping elderly subjects than in young adults.<sup>19-22</sup>

## MATERIALS AND METHODS

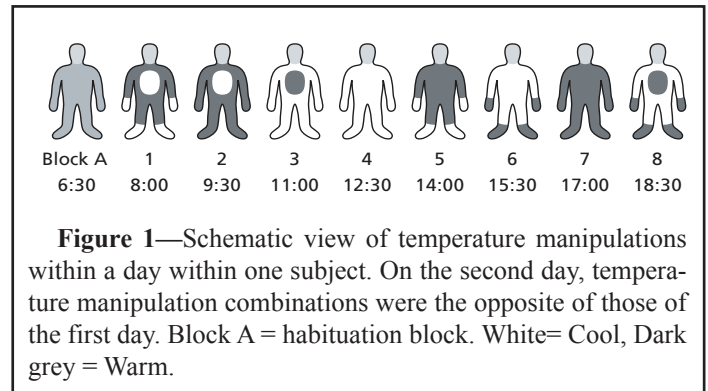
### Subjects

Eight healthy young adults free from sleep complaints (21-39 years old; mean±s.e.m.: 27.0±2.4 years; 4 males), 8 healthy elderly free from sleep complaints (56-80 years old; 65.8 ± 2.8 years; 4 males), and 8 otherwise healthy elderly insomniacs (51-66 years old; 59.1 ± 1.9 years; 4 males) participated with informed consent. The protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam. All participants were free of medication known to affect thermoregulation, sleep or the circadian system, cardiovascular medication, and psychotropic medication. One female used oral contraceptives. Subjective sleep quality and complaints were measured using a Dutch adaptation<sup>24</sup> of the 75-item Sleep Disorders Questionnaire (SDQ)<sup>25</sup> and the Pittsburgh Sleep Quality Index (PSQI).<sup>26</sup> Insomniacs were defined by a PSQI score > 5 and an SDQ-Insomnia score >2.5. None of the subjects scored higher than the cutoff score of 3 on the SDQ subscales Narcolepsy, Apnea, Restless legs, and Psychiatry. In the young adult group, females participated between day 4 and day 12 of the menstrual cycle (midfollicular phase or pseudofollicular phase). All elderly females were postmenopausal.

### Design and Experimental Procedures

One week before the experiment, subjects visited the laboratory for an introductory session and habituation to the procedures. The vigilance task was trained for 3 times to minimize possible subsequent learning effects.<sup>27</sup> Participants were instructed to refrain from caffeine, alcohol, and tobacco for 8 hours before arriving at the sleep laboratory. Subjects were interviewed to verify compliance with the instructions. The night before each of the 2 experimental days, the subjects reported to the sleep laboratory at 22:00, when they were prepared for polysomnography and fitted with a comfortable stretch knit fabric thermosuit for skin temperature manipulation. From midnight until 06:00, lights were turned off and subjects were allowed to sleep. They were awakened at 06:00, so sleep duration was restricted to a maximum of 6 hours.

The experiment consisted of measuring psychomotor vigilance 18 times for each subject over 2 experimental days, while manipulating CBT with food and drinks and skin temperature with a thermosuit. An experimental day started at 06:30 and consisted of a modified constant-routine protocol<sup>28,29</sup> under dim light (<10 Lux) conditions and a fixed body position schedule. Both experimental days consisted of 9 consecutive blocks of 1.5 hours each.



Each block was conducted as follows: The subjects were required to leave the bed and walk 5 meters to use the bathroom if needed. At minute 10 of each block, skin temperature manipulation was started and subjects were seated in a bed in semi-supine position, and were served a snack and a drink to consume in approximately 10 minutes. Subsequently a self-paced computerized neuropsychological task battery was completed. This task battery included assessment of psychomotor vigilance, as described below in detail. At 60 minutes, the bed was set in supine position, the lights switched off, and the participants were asked to try to sleep. Maximum lights-off time was 30 minutes, completing the 90 minutes of each block. Results of the effects of temperature manipulation on sleep latency in healthy young adults have been reported elsewhere,<sup>13</sup> and the results in the elderly are in preparation.

Skin and core body temperature were manipulated differently in every block. During the first block of each day, skin temperatures were kept at an intermediate level. This block served as a habituation period for participants to dissipate sleep inertia and become accustomed to the protocol; this period was omitted from all analyses.

In the remaining 8 blocks, core body temperature, proximal skin temperature, and distal skin temperature were independently manipulated in either a slightly warmer or cooler direction, but within a comfortable, thermoneutral range. This 2x2x2 experimental design (core body temperature warm or cool [CBT+ or CBT-], proximal skin temperature warm or cool [PST+ or PST-], distal skin temperature warm or cool [DST+ or DST-]) brings up 8 possible manipulation combinations that were all tested within a day in every subject (see Figure 1). The sequence of the manipulation combinations was different for each subject, such that every manipulation combination was given once in each of the 8 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 using the same procedure; the only difference was that the temperature manipulation combinations were the opposite of those of the first day to provide a protocol balanced for circadian effects. For example, if the second block of a specific subject on day one consisted of core warming, proximal skin cooling, and distal skin warming, that participant was subjected to core cooling, proximal skin warming, and distal skin cooling during the second block on day 2.

### Temperature Manipulations and Measurement

Temperature manipulations and measurements have been described in detail previously.<sup>13</sup> In brief, core body temperature was

manipulated by means of 200 ml hot (heated to 80°C, served 2 minutes later) or cold (0°C, crushed ice) tea (4.25 Kcal), (Iced Tea Mix [Diet Decaffeinated Lemon], Lipton, Englewood Cliffs, NJ) together with an isocaloric hot or cold snack of the subject's choice (200 Kcal). Skin temperatures ( $T_{sk}$ ) were manipulated using a thermosuit (Coretech Cool Tube Suit, Med-Eng Systems Inc., Ottawa, Canada). 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 water in the bath was 33°C in the cool condition and 37°C in the warm condition, resulting in temperatures of approximately 31°C and 34°C measured at the tubes just before entering the thermosuit.

This range of skin temperature manipulations was chosen to be comfortable and not trigger major thermoregulatory responses. Ingestion of food and drinks to manipulate core body temperature manipulation and skin temperature manipulations were started about 25 minutes before the start of the PVT. Subjects were well habituated to the thermosuit and skin temperature manipulation; during the prior night they had slept in the suit, while being subjected to slow temperature variations within the same range (to be reported elsewhere).

Body temperature was obtained using 8 thermistors (P-8432, ICBT, Tokyo, Japan). Core body temperature ( $T_{re}$ ) was measured using a rectal thermistor. Proximal skin temperature was measured at 3 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 4 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. Average distal skin temperature ( $T_{dist}$ ) and a weighted average for proximal skin temperature ( $T_{prox}$ ) were calculated as described previously.<sup>13</sup> Temperature data were averaged over 20-minute intervals surrounding the PVT assessments and used for further analyses. As a final check, when a single averaged data point differed more than 2 standard deviations from the other 20-minute averages during that day, the nonaveraged data were once more checked for artifacts and corrected or removed when needed.

Vigilance was assessed using a 7-minute version of the Psychomotor Vigilance Task (PVT)<sup>17</sup> that can be regarded as a viable alternative to the standard 10-minute PVT test.<sup>30</sup> During the task, subjects focused on a blank box in the middle of a computer screen. At random intervals, a millisecond counter started to scroll, and subjects had to press a key to stop the counter as quickly as possible. After pressing the key, the counter displayed the achieved reaction time (RT, in milliseconds) for 1 second, providing the subject with feedback on performance. Interstimulus intervals ranged randomly from 2 to 10 seconds, and the task lasted 7 minutes. Response speed, calculated as reciprocal RT ( $RRT = 1000/RT$ ) was averaged per minute. The vigilance measure of interest was the characteristic decline of response speed with increasing time-on-task. This decline was modelled using up to second order regression fits over the subsequent one-minute means, starting at the second minute. The first minute of data was excluded from analyses because many subjects showed unrepresentative long reaction times at the start of the PVT (see Figure 2).

### Statistical Analysis

To determine the effects of skin and core body temperature manipulation on body temperatures and on vigilance, hierarchi-

cal regression analysis was applied (also known as multilevel or random coefficient analysis) using the MLwiN software package (Centre for Multilevel Modelling, Institute of Education, London, UK). The regression takes into account the multileveled interdependency of the data points inherent to the hierarchical structure of the design.<sup>31</sup>

It was first evaluated how core body and skin temperatures ( $T_{re}$ ,  $T_{prox}$ , and  $T_{dist}$ ) were affected by the manipulations. To do so, CBT, PST, and DST were dummy coded as dichotomous predictor variables, with 0 reflecting the cool manipulation and 1 reflecting the warm manipulation. A 3-level regression model was fitted (the sequential 20-minute average temperatures in each block (i), nested within days (j), nested within subjects (k)). 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.

Subsequently, 4-level regression models were applied to PVT response speed: the sequential one-minute averaged response speeds (i), nested within measurements (blocks, (j)), nested within each day (k), nested within subjects (l). The final regression model included the best of linear and nonlinear approximations for the rate of decline in response speed (linear, second order, and square root, i.e., Minutes, Minutes<sup>2</sup>, and  $\sqrt{\text{Minutes}}$ ). Two series of regression analyses were run. The first series evaluated the effect of the dummy coded (factorial) temperature manipulations on response speed and its rate of decline with increasing time-on-task. The second series evaluated the relation of the actual momentary body temperatures to response speed.

In order to account for possible diurnal variation and learning effects, both time of day (Hour) and the number of times the task was performed (Repeats, ranging from 1 to 16) were entered in the models as covariates, up to the second order as needed (Hour, Hour<sup>2</sup>,  $\sqrt{\text{Hour}}$  set at zero on both days for the first block included in the analysis; Repeats, Repeats<sup>2</sup>,  $\sqrt{\text{Repeats}}$ , set at one for the first block included in the analysis on day one). Maximum likelihood was used to estimate the regression coefficients, which were tested for significance with the Wald test. Independent variables were allowed and kept in the model only if their coefficients were significant and if residual error of the model was reduced according the likelihood ratio test. Two-tailed significance levels were set at 0.05.

## RESULTS

### Induced Temperatures

The effects of the temperature manipulations on core body and skin temperatures for all groups are shown in Table 1 and Table 2. Note that the values reflect the temperatures during task performance and therefore differ slightly from the previously reported temperatures after completion of the task, just prior to sleep onset latency determination.<sup>10</sup>

$T_{re}$  was significantly affected by the core body temperature manipulation, with 0.25°C, 0.20°C, and 0.18°C higher  $T_{re}$  in the CBT+ condition, compared with the CBT- condition for young adults, elderly subjects, and elderly insomniacs, respectively.  $T_{re}$  also showed modulation over the time of day, accounting for respectively 20%, 47%, and 37% of the variance. The core body temperature manipulation accounted for another 51%, 32%, and 35% of the residual variance in  $T_{re}$ . The addition of preceding temperature manipulations to test for carryover effects accounted for

**Table 1**—Temperature (°C) means ± s.e.m. by temperature condition for each group

	Core body temperature ( $T_{re}$ )	Proximal skin temperature ( $T_{prox}$ )	Distal skin temperature ( $T_{dist}$ )
<b>Young adults without sleep complaints</b>			
CBT-	36.75±0.03	35.12±0.07	34.75±0.07
CBT+	36.99±0.03	35.07±0.05	35.44±0.08
PST-	36.89±0.03	34.76±0.04	34.98±0.09
PST+	36.85±0.04	35.43±0.04	35.21±0.08
DST-	36.87±0.04	35.08±0.06	34.78±0.08
DST+	36.87±0.03	35.12±0.06	35.42±0.07
<b>Elderly without sleep complaints</b>			
CBT-	36.74±0.05	34.97±0.06	34.78±0.08
CBT+	36.94±0.04	35.09±0.06	35.20±0.08
PST-	36.86±0.05	34.75±0.05	34.90±0.09
PST+	36.82±0.04	35.31±0.05	35.08±0.08
DST-	36.83±0.04	35.01±0.06	34.66±0.08
DST+	36.84±0.05	35.05±0.06	35.32±0.07
<b>Elderly Insomniacs</b>			
CBT-	36.70±0.03	34.98±0.06	34.83±0.07
CBT+	36.87±0.04	35.00±0.06	35.40±0.07
PST-	36.80±0.04	34.71±0.05	35.05±0.08
PST+	36.78±0.04	35.28±0.05	35.18±0.07
DST-	36.80±0.04	34.96±0.06	34.81±0.07
DST+	36.77±0.04	35.02±0.06	35.40±0.06

CBT, core body temperature; PST, proximal skin temperature; DST, distal skin temperature. + and -, Warm and cool, respectively.

**Table 2**—Multilevel estimates of effects (± s.e.m.) of manipulations and time on body temperatures. Regression model:  $T_{ijk} = \beta_{0ijk} + \beta_1 * Hour_{ijk} + \beta_2 * Hour^2_{ijk} + \beta_3 * \sqrt{Hour}_{ijk} + \beta_4 * CBT_{ijk} + \beta_5 * PST_{ijk} + \beta_6 * DST_{ijk}$

	Core body temperature ( $T_{re}$ )	Proximal skin temperature ( $T_{prox}$ )	Distal skin temperature ( $T_{dist}$ )
<b>Young adults without sleep complaints</b>			
Intercept	36.53±0.07 <sup>c</sup>	34.76±0.10 <sup>c</sup>	34.42±0.15 <sup>c</sup>
Hour <sup>2</sup>	-0.002±0.001 <sup>b</sup>		-0.003±0.001 <sup>c</sup>
√Hour	0.14±0.02 <sup>c</sup>		
CBT	0.25±0.02 <sup>c</sup>		0.69±0.05 <sup>c</sup>
PST		0.68±0.03 <sup>c</sup>	0.24±0.05 <sup>c</sup>
DST			0.64±0.05 <sup>c</sup>
<b>Elderly without sleep complaints</b>			
Intercept	36.38±0.10 <sup>c</sup>	34.48±0.10 <sup>c</sup>	34.36±0.16 <sup>c</sup>
√Hour	0.18±0.02 <sup>c</sup>	0.10±0.02 <sup>c</sup>	
CBT	0.20±0.03 <sup>c</sup>	0.12±0.04 <sup>b</sup>	0.42±0.06 <sup>c</sup>
PST		0.56±0.04 <sup>c</sup>	0.17±0.06 <sup>c</sup>
DST			0.67±0.06 <sup>c</sup>
<b>Elderly Insomniacs</b>			
Intercept	36.44±0.08 <sup>c</sup>	34.62±0.10 <sup>c</sup>	34.57±0.12 <sup>c</sup>
Hour		0.02±0.01 <sup>b</sup>	
Hour <sup>2</sup>			-0.002±0.001 <sup>c</sup>
√Hour	0.12±0.01 <sup>c</sup>		
CBT	0.18±0.02 <sup>c</sup>		0.56±0.05 <sup>c</sup>
PST		0.57±0.04 <sup>c</sup>	0.12±0.05 <sup>a</sup>
DST			0.59±0.05 <sup>c</sup>

Estimates of the effects of temperature manipulation and time of day on body temperatures. Core body, proximal skin, and distal skin temperature manipulation (CBT, PST, DST) were included in the model as dichotomous variables, with cool and warm coded as 0 and 1. For  $T_{re}$ ,  $T_{prox}$ , and  $T_{dist}$ , the optimal models are shown, with only the significantly contributing predictors. Hour = Time of day. Significance levels are indicated as <sup>a</sup>P<0.05; <sup>b</sup>P<0.01; <sup>c</sup>P<0.001.

an additional 14%, 24%, and 20% of the variance, respectively.

$T_{prox}$  was significantly affected by the proximal skin temperature manipulation with 0.68°C, 0.56°C, and 0.57°C higher  $T_{prox}$  in the PST+ condition compared with the PST- condition for young adults, elderly subjects, and elderly insomniacs, respectively. Moreover, in elderly subjects,  $T_{prox}$  was significantly affected by the core body temperature manipulation, with 0.12°C higher  $T_{prox}$  in the CBT+ condition compared with the CBT-. In young subjects the proximal temperature manipulation accounted for 78% of the variance. In both elderly groups only,  $T_{prox}$  showed modulation over the time of day, accounting for 8% and 3% of the variance for elderly subjects and elderly insomniacs, respectively. The temperature manipulations accounted for another 65% and 69% of the residual variance in  $T_{prox}$ . The addition of preceding temperature manipulations to test for carryover effects accounted for an additional 1%, 7%, and 1% of the variance, respectively.

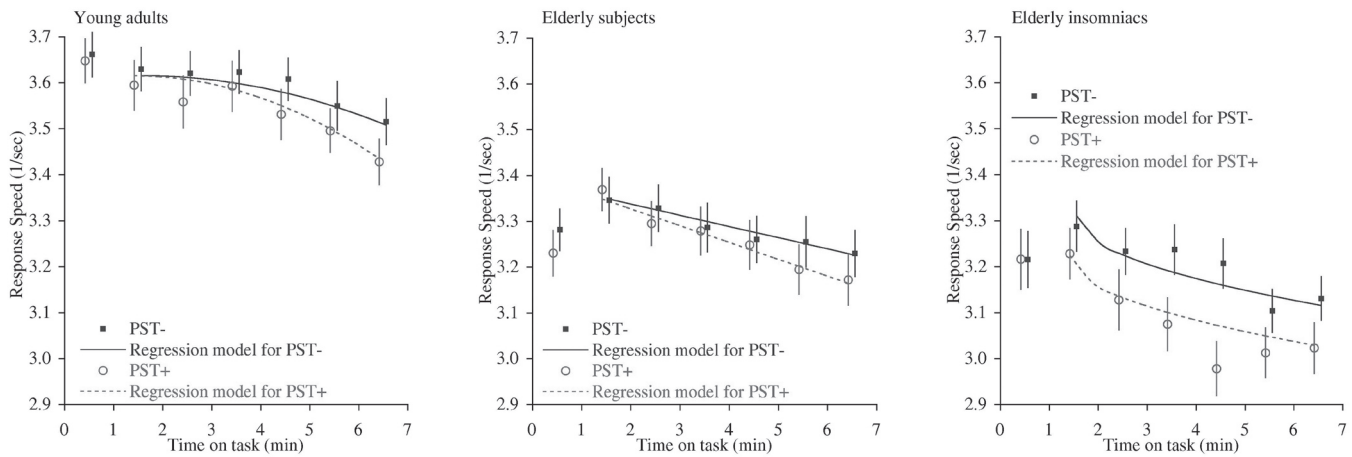
$T_{dist}$  was significantly affected by the distal skin temperature manipulation, with 0.64°C, 0.67°C, and 0.59°C higher  $T_{dist}$  in the DST+ condition compared with the DST- condition for young adults, elderly subjects, and elderly insomniacs, respectively.  $T_{dist}$  was also modulated by proximal skin manipulations (0.24°C, 0.17°C, and 0.12°C higher  $T_{dist}$  in the PST+ condition) and core body temperature manipulation (0.69°C, 0.42°C, and 0.56°C higher  $T_{dist}$  in the CBT+ condition). In the two groups with no sleep complaints,  $T_{dist}$  also showed modulation over the time of day, accounting for 3% of the variance in both groups. The temperature manipulations accounted for another 75%, 75%, and 68% of the residual variance in  $T_{dist}$ . The addition of preceding temperature manipulations to test for carryover effects accounted for an additional 4%, 2%, and 12% of the variance, respectively.

In summary, the manipulations accounted for the major part of the variance in body temperatures, even though some carryover of manipulations in the previous block occurred.  $T_{prox}$  was co-modulated by core body temperature manipulation in the elderly subjects, and  $T_{dist}$  by the core body and distal manipulation in all groups.

### Effect of Temperature Manipulation on Vigilance

The first minute of the PVT performance was characterized by long reaction times in both groups of elderly, suggesting some difficulty initiating the right mind-set for the task (see Figure 2). Analyses were therefore limited to the minutes 2 to 7. There was a typical worsening, i.e., a decline in response speed (RRT), with increasing time-on-task (see Table 3 and Figure 2). Proximal warming accelerated this decline by 67% in young adults (PST x Minute<sup>2</sup>, P = 0.05) and by 50% in the elderly subjects (PST x Minute, P<0.05). In the elderly insomniacs, proximal warming lowered the overall response speed by 3%, independent of time-on-task (PST, P<0.001). There was no significant difference in response speed between the cool and warm core body and distal skin temperature manipulations in any group.

Since the effects of the temperature manipulations were not always restricted to the body sites aimed for, and some carryover effects of previous temperature manipulations occurred, we also



**Figure 2**—Means ( $\pm$  standard error) and regression models of response speed over the 7 subsequent minutes of PVT performance during proximal cooling (closed squares, solid line) and warming (open circles, dashed line) for young adults (left panel), elderly without sleeping problems (middle panel), and elderly insomniacs (right panel). Note the deviating response speed during the first minute in elderly subjects; the first minute was therefore excluded from the analyses. Decline in response speed with increasing time-on-task is evident in all three groups. Note that proximal warming accelerated this decline in young adults and elderly good sleepers, while it lowered response speed as a main effect in elderly insomniacs.

analyzed the relation of the actually measured temperatures  $T_{re}$ ,  $T_{prox}$ , and  $T_{dist}$  (regressor variables) to response speed. In young adults, a higher  $T_{prox}$  was marginally associated with a faster decline in response speed with increasing time-on-task ( $T_{prox} \times \text{Minute}^2$ ,  $P = 0.05$ ). In the elderly insomniacs a higher  $T_{prox}$  also tended to be associated with a lower response speed, but now independent of time-on-task ( $T_{prox}$ ,  $P < 0.10$ ). For these both groups, the model best fitting the data was comparable to the aforementioned models with dichotomous manipulation levels. In the elderly subjects, lower  $T_{re}$  was associated with lower response speed independent of time-on-task ( $T_{re}$ ,  $P < 0.05$ ).

Summarizing the relation between body temperatures and vigilance, proximal skin warming worsens the response speed on a vigilance task. In elderly subjects, a lower rectal temperature is associated with a lower response speed.

### Effect of Age and Insomnia on Vigilance

Between-group comparisons indicated that aging tended to lower the overall response speed ( $P < 0.10$ ), reaching significance only in the elderly insomniacs ( $P < 0.05$ ). The groups also differed in the profile of the decline in response speed with increasing time-on-task. This decline was best approximated quadratically in young adults ( $\text{Minutes}^2$ ,  $P < 0.001$ ), linearly in elderly subjects ( $\text{Minutes}$ ,  $P < 0.001$ ), and by a square root in elderly insomniacs ( $\sqrt{\text{Minutes}}$ ,  $P < 0.001$ ). As evident from Figure 2, these profiles indicate that (1) young subjects perform well initially and begin to do worse halfway through the task; (2) elderly show a linear gradual decline commencing earlier; and (3) elderly insomniacs show their vigilance drop soon after the start of the task.

Elderly subjects and insomniacs also differed from young adults by not showing the modulation of the average response speed by number of repeats that was present in the latter group ( $\sqrt{\text{Repeats}}$ ,  $P < 0.05$ ), indicating a learning effect. Finally, no change in performance in the course of the day (hour) was present in any of the groups.

## DISCUSSION

Psychomotor vigilance is partly determined by the endogenous *SLEEP*, Vol. 30, No. 1, 2007

circadian clock,<sup>2,6</sup> but the mechanisms involved in this circadian modulation are not known. We investigated whether subtle changes in core body and skin temperatures, mimicking those that are naturally occurring during the circadian cycle, could contribute to changes in psychomotor vigilance. In order to prevent cause-and-effect interpretation difficulties inherent to correlations, we chose to experimentally manipulate core body and skin temperatures and observe the effects on PVT performance. Our study is the first of its kind to study relative changes in vigilance under conditions of simultaneously and differentially controlled core body and skin temperatures. In young and elderly subjects without sleep complaints, the decline in response speed with increasing time-on-task became stronger with slight warming of the proximal skin area. In elderly insomniacs, the overall response speed decreased with such subtle proximal skin warming. Since all manipulations induced changes in the temperature range normally seen in everyday life, the circadian modulation of these temperatures could indeed contribute to the circadian modulation in vigilance. During the circadian phase of habitual nocturnal sleep there is a parallel increase in vigilance impairment<sup>32</sup> and average or proximal skin temperature,<sup>7,8</sup> although the proximal skin temperature profile may reverse under colder laboratory conditions,<sup>10</sup> as discussed recently.<sup>9</sup>

A mechanism that may be involved is that skin warming has been shown to increase neuronal activity in the preoptic and anterior hypothalamic area in rodents<sup>12</sup> and humans,<sup>33</sup> comprising areas critically involved in both sleep and arousal regulation. Such a mechanism is also supported by our recent finding that subtle skin warming accelerates sleep onset in young healthy adults, despite being experienced as less comfortable.<sup>13</sup> Our studies provide indirect support for a modulatory role of skin temperature on brain areas involved in the regulation of sleep propensity and vigilance.<sup>11</sup> Drummond and colleagues<sup>34</sup> reported that slower reaction times in the PVT task were associated with greater activity in a “default mode network”<sup>35</sup> that consists of frontal and posterior midline regions. Our findings suggest that the activity in this network is sensitive to skin temperature, possibly indirectly through a signaling pathway from the preoptic and anterior hypothalamic area to this network.

A limitation of the study is that we have not been able to fulfill our aim to completely and independently manipulate core body and distal and proximal skin temperatures. The strongest cross-talk occurred from core body temperature manipulations on distal skin temperature and minor carryover effects from preceding temperature manipulations have been elicited. On the other hand, the combined manipulations accounted for most of the variability observed throughout the day in core body and skin temperatures.

We therefore followed up on the factorial analyses with subsequent analyses investigating the association of actually measured temperatures with response speed. These analyses confirmed that PVT performance is negatively related to proximal temperature, significantly so in young adult subjects, at trend level in elderly insomniacs, but not reaching significance in elderly subjects.

In the elderly good sleepers, a significant association emerged between vigilance performance and rectal temperature. This is compatible with previous reports on a worsening of vigilance during the circadian phase of lowered CBT.<sup>2-6</sup>

We optimized the design in order to exclude systematic errors due to circadian variation, not only by applying both cool and warm conditions to the same subject at the same times of day, but also by stratified randomization in order to have different sequences for all subjects. Thus, there was no fixed sequence that would allow for a systematic error due to possible carryover effects.

The range in *core* temperatures covered throughout our manipulations should have been sufficient to alter vigilance, if vigilance was indeed causally affected by the normal circadian variation in core body temperature. The difference of about 0.2°C on average in  $T_{re}$  we established between the warm and the cool conditions is about half of the reported circadian amplitude in core body temperature (0.44°C) under controlled conditions.<sup>10</sup> The normal diurnal time course of *distal* skin temperature reaches values much lower than we have applied. During everyday life, distal skin temperature reaches temperatures of several degrees below the values measured at the proximal skin.<sup>8,9,36</sup> Also under strictly controlled laboratory conditions, the distal 24-hour minimum, maximum, and 24-hour mean skin temperatures were lower than their proximal equivalents.<sup>10</sup> The averaged induced  $T_{prox}$  and  $T_{dist}$  in our study were however comparable to each other (see Table 1). We may thus have been manipulating distal skin temperature too close to the ceiling of its normal diurnal pattern, hence we cannot exclude that applying distal skin temperature manipulations in a slightly lower range could be at least as effective in modulating vigilance.

In order to investigate whether the changes in subjective thermal comfort and thermal sensation might have contributed to the findings, we post hoc added both variables, that were included in the neuropsychological test battery,<sup>13</sup> to the optimal models. Neither subjective thermal sensation nor thermal comfort was associated with response speed in any of the groups (thermal sensation:  $P = 0.69$ ,  $P = 0.26$ , and  $P = 0.67$  and thermal comfort:  $P = 0.78$ ,  $P = 0.90$ , and  $P = 0.51$  for young adults, elderly without sleeping problems, and elderly insomniacs, respectively). Hence the performance impairment is a direct effect of the change in temperature rather than an effect of the concurrent change in subjective thermal comfort or thermal sensation. We also performed a post hoc analysis to test whether the polysomnographically assessed sleep duration or efficiency during the previous night might have been involved in the group differences in response speed. No sig-

**Table 3**—Multilevel estimates of effects ( $\pm$  s.e.m.) of manipulations, time and repeats on response speed of the PVT

	Young adults without sleep complaints	Elderly without sleep complaints	Elderly Insomniacs
Intercept	3.61 $\pm$ 0.10 <sup>c</sup>	3.35 $\pm$ 0.12 <sup>c</sup>	3.31 $\pm$ 0.13 <sup>c</sup>
$\sqrt{\text{Repeats}(c)}$	0.05 $\pm$ 0.02 <sup>a</sup>		
Minute		-0.025 $\pm$ 0.005 <sup>c</sup>	
Minute <sup>2</sup>	-0.004 $\pm$ 0.001 <sup>c</sup>		
$\sqrt{\text{Minute}}$			-0.087 $\pm$ 0.010 <sup>c</sup>
PST			-0.087 $\pm$ 0.026 <sup>c</sup>
PST x Minute		-0.012 $\pm$ 0.006 <sup>a</sup>	
PST x Minute <sup>2</sup>	-0.003 $\pm$ 0.002 <sup>a</sup>		

Estimates of the effects of temperature manipulation (CBT, PST, DST), Time of Day and Time-on-Task on the PVT Response Speed. Core body, proximal skin, and distal skin temperature manipulations were included in the model as dichotomous variables, with cool and warm dummy coded as 0 and 1, respectively. Shown are the optimal models, including only the significantly contributing predictors. Repeats(c) = the number of times the task was performed (centered), Minute = PVT time-on-task. Significance levels are indicated as <sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.01$ ; <sup>c</sup> $P < 0.001$ .

nificant contribution to response speed could be demonstrated (sleep duration:  $P = 0.41$ , sleep efficiency:  $P = 0.36$ ), indicating that the group differences cannot be attributed to the sleep pattern of the nights directly preceding the vigilance assessment days.

Our data also revealed a number of age-related and insomnia-related changes in performance on the PVT under strictly controlled and balanced conditions. Of note, elderly subjects who were good sleepers responded only marginally less fast than young adults ( $P < 0.10$ ). Only if elderly were poor sleepers, their response speed became significantly worse than that of young adults ( $P < 0.05$ ). Whereas previous studies have also reported PVT response speed slowing with aging,<sup>20,37</sup> our data suggest that a part of the “age-related cognitive slowing” may in fact be due to sleep changes inherent to aging. The fact that only elderly insomniacs showed a robust worsening of PVT response speed supports the possible involvement of what one could call “chronic poor sleep-related cognitive slowing” in “age-related cognitive slowing.” On the other hand, it may be that elderly good sleepers are not representative for the cognitive alterations present in the aged population. Whereas some previous studies on the effects of aging on vigilance may have been biased by selecting well-sleeping elderly only, we purposely included separate groups of well-sleeping and elderly insomniacs, thus allowing us to separate sleep-related changes from changes associated with aging.

The minute-by-minute analyses of the PVT moreover showed notable differences in the time-on-task-related vigilance decline between young adults, elderly, and elderly insomniacs, which could not have been disclosed with the often applied aggregation of time-points.

First, whereas young adults show a slowing of speed only starting halfway the 7 minutes time-on-task, the slowing was linear in elderly subjects and occurred at the beginning of the task in elderly insomniacs. Thus, aging results in an earlier onset and more gradual decline in response speed with increasing time-on-task. Insomnia, on the other hand, results in a near maximal drop in response speed by the third minute, indicating that insomnia spe-

cifically affects the cognitive resource “reserve” that is required to maintain a highly vigilant state for a prolonged period of time. This specific defect associated with insomnia was mirrored also in the effects of proximal warming on the response speed. Whereas the effect of proximal warming developed slowly with increasing time-on-task in young and elderly subjects without sleep complaints, the effect was present at the onset of the task in the elderly insomniacs. It is remarkable that the group differences in the profile of speed decline with increasing time-on-task-related were mirrored in the worsening with mild warming: only late in young adults, gradual in elderly subjects and at onset in elderly insomniacs. The fact that the group differences in the profile of temperature effect were exactly similar to the overall time-on-task effects within the groups provides strong support for the robustness of the group differences in time-on-task effects. Interestingly, the gradual change from (1) a performance decline starting only halfway the task (young adults), to (2) a linear performance decline starting soon after onset of the task (elderly without sleep complaints), to (3) a performance decline that is very pronounced already soon after onset of the task – closely resembles previously reported effects of increasing sleep propensity on time-on-task profiles.<sup>38</sup>

Second, we observed marked group differences in the mean response time within the first minute of the PVT. Whereas the young adults showed the fastest responses during the first minute, the elderly subjects reached their fastest response speed only by the second minute. The data of Kribbs and Dinges<sup>39</sup> also clearly show a delay of the fastest response in adults with obstructive sleep apnea. The initial poor performance indicates that elderly experience some difficulty initiating the right mind-set for the task. The finding is compatible with the fact that aging affects executive functioning in general, and task switching in particular.<sup>40</sup> Our novel finding that this age effect is also present in repeated PVT assessments has consequences for the use and interpretation of its most commonly calculated outcome measures (median RT, mean of the fastest 10% RT, mean of the slowest 10% reciprocal RTs, SD of the RT, and number of lapses [RT > 500 ms]) when comparing different age groups. None of these measures adequately describe the typical decline in response speed with increasing time-on-task, in which we found the most interesting age- and insomnia related changes. We favor the opinion of Kribbs and Dinges<sup>39</sup> that “analysis of the overall mean response often does not truly reflect the entire impairment process and, in fact, may sometimes obscure actual performance impairment.” We advise others to include an examination of time-on-task effects before aggregating data. In age-related studies on such time-on-task effects, the first minute of PVT response data may be excluded.

A further age-related finding of our study is that young subjects showed increase in response speed related to the number of times the task was performed (learning effect), but this modulation was not present in either group of elderly subjects.

In conclusion, our results add to the significance of previous correlational studies<sup>6</sup> on the relation between body temperature and vigilance by now demonstrating for the first time that an experimentally induced subtle increase in skin temperature may in fact *cause* a decrease in vigilance performance. The findings are compatible with the model we have previously put forward, stating that the diurnal modulation of skin temperature should be regarded not only as an output signal of the circadian timing system but also as an input signal modulating vigilance regulating brain

areas.<sup>11</sup> We also demonstrated that a minute-by-minute analysis of the PVT helps to reveal and disentangle age- and insomnia-related changes in vigilance regulation.

A practical implication of our findings is that manipulation of skin temperature may be well suited for improvement of vigilance states, at least in the range of our manipulations. The manipulations appear to have the greatest effect in the subjects whose vigilance state could be expected to be the most compromised, i.e., elderly subjects suffering from chronic poor sleep. Future studies should investigate whether vigilance can be changed if manipulation of skin temperature starts from an unmanipulated endogenous regulated skin temperature. Comparing the time-on-task effects on psychomotor vigilance of subtle skin warming or skin cooling with the time on task effects in a thermal neutral state (i.e. without manipulation) is necessary to assess the feasibility for practical application.

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