Cold hands, warm feet: sleep deprivation disrupts thermoregulation and its association with vigilance

Based on:

Abstract

Vigilance is affected by induced and spontaneous skin temperature fluctuations. Whereas sleep deprivation strongly affects vigilance, no previous study examined in detail its effect on human skin temperature fluctuations and their association with vigilance. Eight healthy young adults (5 males, 22.0 ± 1.8 (mean ± SD) years of age participated individually in a repeated-measures constant routine design, wherein skin temperatures were assessed continuously from 14 locations while performance was assessed using a reaction time task, including eyes-open video monitoring, performed five times a day for two days, following a normal sleep or sleep deprivation night. Mixed-effect regression models were used to evaluate the effect of sleep deprivation on skin temperature gradients of the upper (ear-mastoid), middle (hand-arm) and lower (foot-leg) body, and on the association between fluctuations in performance and in temperature gradients. Sleep deprivation induced a marked dissociation of thermoregulatory skin temperature gradients, indicative of attenuated heat loss from the hands co-occurring with enhanced heat loss from the feet. Sleep deprivation moreover attenuated the association between fluctuations in performance and temperature gradients; the association was best preserved for the upper body gradient.

We therefore concluded that sleep deprivation disrupts coordination of fluctuations in thermoregulatory skin temperature gradients. The dissociation of middle and lower body temperature gradients may therefore be evaluated as a marker for sleep debt, and the upper body gradient as possible aid in vigilance assessment when sleep debt is unknown. Importantly, our findings suggest that sleep deprivation affects the coordination between skin blood flow fluctuations and the baroreceptor-mediated cardiovascular regulation that prevents venous pooling of blood in the lower limbs when there is the orthostatic challenge of an upright posture.
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Introduction

It has long been known that sleep and thermoregulation are closely related. This association has traditionally been studied mostly for the association of sleep or alertness with core body temperature (Everson et al., 1989; Wright et al., 2002). During the last decade, several studies have suggested this association to be at least in part secondary to an association of sleep and alertness with heat loss, the major determinant of core body temperature (Kräuchi et al., 1999, 2000). A primary determinant of heat loss is skin blood flow. Increased perfusion warms the skin, facilitating convection of heat from the core of the body to the environment. In support of a contribution of skin temperature to the regulation of sleep and alertness, several studies have shown that sleep and sustained attention, also referred to as vigilance, are affected by both spontaneous fluctuations and induced changes in skin temperature (Fronczek et al., 2008; Kräuchi et al., 1999; Raymann et al., 2005; Raymann & Van Someren, 2007; Romeijn & Van Someren, 2011). Measurable fluctuations in skin temperature occur at multiple timescales. Very weak fluctuations with a periodicity starting at about half a minute can be measured in laboratory settings, and fluctuations in the range of several minutes and hours, as well as a clear 24-hour rhythm are more prominent, with changes of up to several degrees (Kräuchi & Wirz-Justice, 1994; Podtaev et al., 2008; Van Someren, 2006). It has been suggested that vigilance is most strongly associated especially with the temperature gradient between distal skin areas relative to more proximal skin areas (Kräuchi et al., 1999, 2000), although some studies failed to find an advantage of the gradient over mere proximal or distal skin temperatures (Fronczek et al., 2006; Romeijn & Van Someren, 2011).

Whereas vigilance is also the cognitive domain that is most sensitive to sleep deprivation (Lim & Dinges, 2010), it is not known how sleep deprivation affects the different skin temperature gradients that can be measured over the human body while maintaining an upright posture as we normally do when trying to keep awake after sleep deprivation. One study investigated the effect of sleep deprivation on an integrated whole body distal to proximal skin temperature gradient in subjects maintaining a semi-supine position, finding no effect of sleep deprivation on the thermoregulatory system (Kräuchi et al., 2006). These findings can unfortunately not easily be generalized to everyday life situations. Sleep deprived people who try to stay awake normally experience the orthostatic challenge of being in an upright position, which results in baroreceptor unloading and the ensuing baroreceptor reflex that regulates blood flow to prevent venous pooling of blood in the lower limbs. In real life situations, thermoregulatory skin blood flow thus has to compete with this baroreceptor reflex blood flow regulation (Brothers et al., 2010). It thus remains to be investigated how sleep deprivation affects the profile of skin temperature if one maintains the upright posture, as is most common for operational control, like car driving. Neither is it known whether the previously reported association of skin temperature with
vigilance is preserved after sleep deprivation. These questions are of considerable interest in order to improve our understanding of thermoregulatory response after sleep deprivation. Subjectively, many of us have experienced ‘feeling cold’ after sleep deprivation. Indeed, one of the hallmarks of prolonged sleep deprivation in rats is a progressive decline in core body temperature in spite of increased food intake and energy expenditure (Rechtschaffen et al., 2002). Also, sleep-deprived humans are more vulnerable to heat loss both at cold and comfortable temperatures (Landis et al., 1998; Opstad & Bahr, 1991; Savourey & Bittel, 1994; Young et al., 1998). The questions are furthermore not only of academic interest, but also of crucial importance from an applied point of view if – as has been proposed – information on skin temperature fluctuations is to be used in systems that aim to monitor and possibly warn or intervene with an increasing risk of a drop in vigilance level. Such systems should work equally well under conditions of normal sleep as well as after sleep deprivation. We therefore here set out to obtain a detailed view on the effect of sleep deprivation on the profile of human skin temperature gradients over the body, as well as on their association with sustained attention.

**Methods**

All procedures complied with the declaration of Helsinki and medical ethical approval was obtained from the medical ethical committee of the VU University medical center.

**Participants**

Eight healthy volunteers (20-26 years of age; mean ± SD: 22 ± 1.8 years, 5 males, 3 females) completed the study; an additional subject was excluded because of uncertainty on compliance to sleep deprivation (see below). According to a brief questionnaire, subjects were in good health and had no presence or history of neurological or psychiatric disease, neither of drug abuse. None of the participants had sleep-related problems, as indicated by any the following questionnaires: The Athens Insomnia Scale (AIS, Soldatos et al., 2000), the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989), the Dutch version of the Sleep Diagnosis Questionnaire (Douglass et al., 1994; Sweere et al., 1998), and the Epworth Sleepiness Scale (ESS, Johns, 1991). All participants were right-handed and had a body mass index between 18.7 and 24.9 (mean ± SD: 22.0 ± 1.8).
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Experimental Procedure

The experimental procedure is detailed schematically in figure 1. It consisted of a modified constant routine protocol over 2 days during which temperatures were measured continuously and vigilance was measured five times at 90 minute intervals using an adaptation of the Psychomotor Vigilance Task (PVT, Dinges & Powell, 1985) called the Brief Stimulus Reaction Task (BSRT, Romeijn & Van Someren, 2011) which will be described in more detail later. The two days were separated by 4.3 ± 1.6 days in between (mean ± standard error). Females participated in the follicular phase (between day 4 and 12) of their menstrual cycle, both days in the same follicular phase.

One week prior to the first experimental day, participants visited the laboratory for an introductory session to explain the procedure and to practice the BSRT. Participants were asked to keep a regular sleep/wake pattern for the week prior to the first laboratory day, logged both objectively with actigraphy (Actiwatch, Cambridge Neuro-Technology, Cambridge, UK) as well as subjective report using a sleep diary.

On the evening prior to each of the two experimental days, participants were visited at home. Between 17.00 hr and 21.00 hr temperature sensors were fitted. On one occasion, participants were allowed a normal night of sleep at home, which will be referred to as the normal sleep (NS) condition. On the other occasion, referred to as the sleep deprivation (SD) condition, participants had to stay up all night. The order of conditions was counterbalanced over subjects. In both conditions, exercise, alcohol, caffeine, nicotine and other stimulant consumption were not allowed from 20.00 hr onward, as was eating from 04.00 hr onward. Compliance was verified by interview the next morning. Successful completion of total sleep deprivation was verified using actigraphy; actigraphic sleep estimates were obtained using the Sleep Analysis software of Cambridge Neuro-Technology (Cambridge, UK). Actigraphy is highly sensitive to the detection of naps, overestimating rather than underestimating sleep (Kanady et al., 2011). We excluded one participant of whom actigraphy suggested the possibility of having slept, as indicated by inactivity for 10 minutes or more (Lotjonen et al., 2003), leaving the 8 participants who completed the study as detailed above.

The following morning participants reported to the laboratory at 08.30 hr. To ensure safety while commuting from home to the laboratory after sleep deprivation, they used public transport for all traveling. To exclude confounders relating to traveling, such as environmental temperature, physical activity and posture history, subjects were asked to stay seated for 90 minutes after arrival to the lab. At 10.00 hr, the first of five assessment blocks started. During the entire day, participants were seated in a comfortable chair in a dimly-lit room (<15 lux measured in the eye gaze direction).

The procedure followed in each of the ten blocks (five on each day) was as follows. In the first ten minutes, e.g. from 10.00 hr to 10.10 hr, participants were allowed to use the restroom. In order to keep the history of postural changes and
Figure 1 Overview of the experimental protocol Eight participants were measured in a modified constant routine protocol over 2 experimental days. Counterbalanced across subjects, participants underwent a night of normal sleep or total sleep deprivation on the night prior to each experimental day. Vigilance was measured 5 times per day (block 1-5) at regular intervals using the Brief Stimulus Reaction Task (BSRT, Romeijn & Van Someren 2011). Each of the five daily blocks was identical, and consisted of the following procedures: Restroom break, isocaloric meal and drink (300 kcal per block), and rest period comprised the first half hour of each block, after which a computerized task battery was started. In each block subjects performed the BSRT sustained attention task. Output measures were reaction speed and lapses, defined as lack of responses, including responses slower than the 10th percentile calculated on the well rested day.

physical movement identical across blocks, participants were obligated to get out their chair and walk 5 meters to the restroom, regardless of their need to use the facilities at that time. In the next 10 minutes, e.g. from 10.10 to 10.20 hr, a snack of 230 kcal was served together with 70 kcal worth of low-caloric Ice tea (decaffeinated lemon ice tea mix, Lipton, Englewood Cliffs, NJ, USA), resulting in a total energy intake of 300 kcal per block. Both the snack and the tea were offered at room temperature. The following 10 minutes (e.g. from 10.20 hr to 10.30 hr) allowed for reading literature of personal choice.
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After the end of the reading period, e.g. at 10.30 hr, an audio cue signaled the start of assessments. After 5 minutes of alpha attenuation task, sustained attention was measured as of e.g. 10.35 for 20 minutes continuously using a 120-stimulus Brief-Stimulus Reaction Task (BSRT). During task completion, video monitoring (iView Red, SensoMotoric Instruments (SMI), Teltow, Germany) was used to continuously track eye gaze direction and whether eyes were open at the time a stimulus was given.

Temperature Assessment Material
Temperatures were continuously measured from 14 locations on the skin (see below), completed by one core temperature measurement recorded rectally. Where skin areas were sufficiently large, multiple iButtons (type DS1922L, MAXIM-IC, Sunnyvale, CA, USA) were affixed. The use of multiple sensors to assess a single skin area may improve its robustness by accounting for spatial heterogeneity (Wardell et al., 1994). iButtons were set to acquire temperature samples at 30 second intervals with a resolution of 0.0625°C. The method has previously been validated and described in detail (Van Marken Lichtenbelt et al., 2006). For skin surfaces that were too small to measure comfortably with iButtons (see below), as well as for rectal temperature measurement, thermistors (P-8432, ICBT, Tokyo, Japan) connected to a HOBO u12-06 data logger (Onset Computer Corporation, Massachusetts, USA) were used and sampled at 30 second intervals with a resolution of 0.03°C.

Measurement and calculation of skin temperature averages and gradients
The gradient between the skin temperatures of an extremity and a more proximal area of a limb provides a reliable estimate of thermoregulatory autonomic nervous system activity if the more distal area is richer in arteriovenous anastomoses (AVA’s) than a nearby more proximal area (Rubinstein & Sessler, 1990). Arteriovenous anastomoses are capillary beds which, when opened, induce a strong increase in heat exchange between the skin and environment and therefore play a crucial role in temperature regulation. They are abundant in the skin of the ears, hands and feet (see e.g. Blankfield, 2006). A gradient could thus be calculated for each of these three distal areas with a corresponding nearby skin area where AVA’s are absent or less abundant, respectively the head, arm and leg. Gradients have also been calculated between the average temperature of multiple different extremities (hands and feet) and multiple more proximal limb areas or even the trunk (Kräuchi et al., 2000). This averaging procedure presumes a strong covariation between different distal areas and between different proximal areas. The validity of this assumption however remains to be demonstrated under normal well-rested circumstances, let alone when subjects are sleep deprived. We therefore calculated three separate gradients, for the upper, middle and lower part of the body, as described below. The first, upper body, distal to proximal gradient \( (D_{\text{up}}) \) was calculated between sensors attached to the AVA-rich earlobe and the nearby mastoid skin area. The second, middle body, distal to
proximal gradient (DPG\textsubscript{mid}) was calculated between the AVA-rich hand (average of four sensors, attached to the ventral side of the tip of the middle finger, the dorsal and ventral side of the base of the middle finger and the palmar side of the hand) and the arm (average of two sensors, dorsally attached to the upper arm at the level of the apex of the deltoid muscle and to the lower arm at the level of the wrist). The third, lower body, distal to proximal gradient (DPG\textsubscript{low}) was calculated between the AVA-rich foot (average of two sensors, attached to the plantar side at the level of the instep and to the dorsal side of the big toe) and the leg (average of two sensors, attached to the upper leg at the medial side of the calf and to the lower leg at the mid-level of the calf). Although not the focus of interest of the present study, we also assessed core temperature using a rectal sensor as well as trunk skin temperature using two sensors attached to the infraclavicular area on the chest and above the navel.

\textit{Vigilance Assessment}

Vigilance was assessed using an adaptation of the Psychomotor Vigilance Task (PVT, Dingess & Powell, 1985) called the Brief Stimulus Reaction Task (BSRT), which has been described in more detail before (Romeijn & Van Someren, 2011). In brief, participants were required to press the spacebar of a keyboard with their dominant hand as quickly as possible as soon as they saw a briefly (25ms) displayed ‘minus sign (−)’ stimulus presented in-between a fixation ‘plus sign (+)’ at interstimulus intervals varying quasi-randomly between 4-14 s. After each stimulus, participants were given a fixed interval of 1000 ms to respond, after which the next interstimulus interval commenced. Each BSRT assessment consisted of 120 stimuli, thus lasting 20 minutes. Due to the brief duration of each stimulus, as well as its low contrast and image change, the task is highly reliant on top down attentional processes, like the PVT. We specifically chose to use the BSRT because it yields longer reaction times and more lapses, as we demonstrated before (Romeijn & Van Someren, 2011). Lapses were defined as omissions and reaction times (RTs) exceeding the 90th percentile of the distribution (Santhi et al., 2007) of all recorded RTs on the day following normal sleep.

In order to obtain a normal distribution for the recorded responses, the inverse of reaction times was taken, denoted as ‘speed’ (s\textsuperscript{-1}). Given the importance of discriminating lapses that occur with eyes open, eyes closed or looking away from the target area at the screen (Anderson et al., 2010), video monitoring (IView Red, SensoMotoric Instruments (SMI), Teltow, Germany) was used to continuously track eye gaze direction and whether eyes were open and gaze was directed to the target area at the time a stimulus was given. The eye movie was sampled at a rate of 25 frames per second. Based on pupil diameter and circumference, an automated algorithm scored each frame as either eyes open or closed, after which the data was downsampled to 30 second intervals.
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Data analysis
All analyses were restricted to the behavioral responses, and corresponding last measured temperature readouts, belonging only to those stimuli that were presented during video monitoring-confirmed eyes open and proper gaze angle. This resulted in a variable number of missing values for those reaction times (or lapses) and corresponding last measured temperature readouts. On average 14±4% (mean ± standard error) of the data points for a subject were discarded because they were recorded during eyes closed or diverted, inattentive gaze. In order to appropriately account for the variable number of missing values, mixed effect regression models were used for all analysis (MLwiN, Centre for Multilevel Modeling, University of Bristol, Bristol, UK). This approach also accounts for the four-level hierarchical dependency of data points, i.e. temperature and performance values are nested within five blocks, which are in turn nested within two days, again nested within eight participants (Petkova & Teresi, 2002; Twisk, 2003). Regression coefficients (e.g. the effect of temperature on performance or the effect of sleep deprivation on temperature or performance) were considered significant if the z-distributed ratio of its estimate over its standard error exceeded a value of 1.96, corresponding to a two-sided p-value less than 0.05 (Petkova & Teresi, 2002; Twisk, 2003).

Effect of sleep deprivation on temperature gradients and performance
MLwiN was used to obtain missing-cases-weighted average temperature gradients and reaction speed, as well as their standard errors, both for the normal sleep condition and for the sleep deprivation condition. The effect of sleep deprivation on temperature gradients and reaction speed was tested by including sleep deprivation as a dummy in linear regression analyses. The same approach, but now with logistic regression, was used to estimate effect of sleep deprivation on the probability of lapses.

Effect of sleep deprivation on the association between temperature gradients and performance
Linear and nonlinear regression analyses were likewise used to obtain missing-cases-weighted average predictive effects of fluctuations in temperature gradients on fluctuations in reaction speed and the probability of lapses. These effect estimates integrate the temperature and vigilance fluctuations that normally occur continuously (Romeijn & Van Someren, 2011; Van Marken Lichtenbelt et al., 2006), both within and between blocks. Estimates were obtained for the normal sleep condition separately, for the sleep deprivation condition separately, and for the integral dataset. These three analyses provide the predictive value of skin temperature gradients to estimate vigilance in situations of respectively normal sleep, sleep deprivation, and an unknown sleep history. Regression analyses on the integral dataset were moreover used to formally test whether the predictive effect of temperature gradients on performance changed significantly with sleep deprivation.
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Results

**Actigraphic verification of sleep deprivation compliance**

Actigraphic recordings were inspected closely to verify compliance with the sleep deprivation protocol. To do so, three cumulative distributions of immobility bout durations were obtained for each participant: (1) the period between lights out and final awakening during the night preceding the NS condition; (2) the corresponding nocturnal period during the SD condition and (3) a corresponding 12-hr earlier daytime period on the day prior to the NS condition. For each period, the cumulative distributions of immobility bout duration were averaged over subjects and plotted (Figure 2). Due to inclusion criteria (one participant was excluded from analyses), no immobility bout lasting more than 10 minutes occurred during the sleep deprivation night, while during the normal night, 75% of all immobility time occurs in bouts lasted longer than 10 minutes. The profile of immobility bout durations during the sleep deprivation night closely resembles the profile seen during a normal wake day, where only limited (7%) of the immobility time occurs in bouts lasting longer than 10 minutes. The immobility profiles indicate good compliance with the sleep deprivation protocol in all included participant.

**Effect of sleep deprivation on temperature gradients and performance**

Table 1 summarizes the effects of sleep deprivation on skin temperature gradients. Sleep deprivation did not significantly alter DPG\textsubscript{up}, which was \(-3.91\pm0.17 ^\circ C\) after a normal night’s sleep and \(-4.09\pm0.33 ^\circ C\) after sleep deprivation (p=0.51). Figure 3 shows the effects of sleep deprivation on DPG\textsubscript{mid} and DPG\textsubscript{low}. Sleep deprivation lowered DPG\textsubscript{mid} from \(-0.86\pm0.76 ^\circ C\) after a normal night’s sleep to \(-1.59\pm0.79 ^\circ C\) after sleep deprivation (p=0.03). In marked contrast, sleep deprivation increased DPG\textsubscript{low} from \(-4.29\pm0.96 ^\circ C\) after a normal night’s sleep to \(-3.41\pm1.15 ^\circ C\) after sleep deprivation (p=0.04).
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Table 1 The effect of sleep deprivation on temperature gradients.

<table>
<thead>
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<th></th>
<th>Normal Sleep</th>
<th>Sleep Deprived</th>
<th>Effect of Sleep Deprivation</th>
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<tr>
<td></td>
<td>mean (°C)</td>
<td>se (°C)</td>
<td>mean (°C)</td>
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<tr>
<td>$D_{PG_{up}}$</td>
<td>-3.91</td>
<td>0.17</td>
<td>-4.09</td>
</tr>
<tr>
<td>$D_{PG_{mid}}$</td>
<td>-0.86</td>
<td>0.76</td>
<td>-1.59</td>
</tr>
<tr>
<td>$D_{PG_{low}}$</td>
<td>-4.29</td>
<td>0.96</td>
<td>-3.41</td>
</tr>
<tr>
<td>$D_{PG_{mid}}$\mid$D_{PG_{low}}$</td>
<td>3.44</td>
<td>0.64</td>
<td>1.82</td>
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</table>

Temperature gradients (°C) of the upper ($D_{PG_{up}}$: ear-mastoid), the middle ($D_{PG_{mid}}$: hand-arm) and lower body ($D_{PG_{low}}$: foot-leg), as well as the difference between $D_{PG_{mid}}$-$D_{PG_{low}}$, under well rested conditions and sleep deprived conditions, and the effect of sleep deprivation.

Figure 2 Actigraphic verification of sleep deprivation. Cumulative distribution of immobility bout duration during the sleep deprivation night (solid black line), during a normal wake day (dotted black line) and during a night of normal sleep (grey line). The horizontal axis shows the range of immobility bout durations observed (max 99.5 minutes, axis stopped at 60 minutes). The vertical axis shows the average percentage of immobility time occurring in bouts that last longer than the corresponding Immobility Bout Duration denoted at the horizontal axis. Due to inclusion criteria, no immobility bout lasting more than 10 minutes occurred during the sleep deprivation night, while during a normal night, 75% of all immobility time occurs in bouts lasted longer than 10 minutes. The profile of immobility bout durations during the sleep deprivation night closely resembles the profile seen during a normal wake day, where only limited (7%) of the immobility time occurs in bouts lasting longer than 10 minutes.
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To determine whether $DpG_{\text{mid}}$ and $DpG_{\text{low}}$ fluctuated in synchrony, linear regression analyses were used to estimate how changes $DpG_{\text{mid}}$ were associated with changes in $DpG_{\text{low}}$ after normal sleep and after sleep deprivation. After normal sleep, increases in $DpG_{\text{mid}}$ coincided with increases in $DpG_{\text{low}}$ ($\beta=0.29\pm0.04$, $p=9\times10^{-13}$), as to be expected for effective thermoregulation. After sleep deprivation however, increases in $DpG_{\text{mid}}$ coincided with decreases in $DpG_{\text{low}}$ ($\beta=-0.23\pm0.03$, $p=5\times10^{-15}$), indicating that fluctuations occurred in anti-phase. The effect of sleep deprivation on the predictive value of $DpG_{\text{low}}$ for $DpG_{\text{mid}}$ was highly significant ($\beta=-0.47\pm0.05$, $z=-8.74$, $p=0$).

Concerning performance, sleep deprivation significantly ($p=9\times10^{-6}$) decreased reaction speed, which was $2.40\pm0.10$ s$^{-1}$ after a normal night’s sleep and $2.29\pm0.12$ s$^{-1}$ after sleep deprivation.

Sleep deprivation significantly ($p=3\times10^{-15}$) increased the number of lapses, which had a probability of 0.21 (95% CI: 0.16-0.27) after normal sleep and 0.49 (95% CI: 0.39-0.59) after sleep deprivation.

**Effect of sleep deprivation on the association between fluctuations in temperature gradients and performance speed**

As shown in figure 4 and table 2a and 2b, fluctuations in $DpG_{\text{up}}$ predicted fluctuations in performance speed. Figure 4 provides an integrated example of the fluctuations in skin temperature and reaction speed that occur on the time scales of hours to seconds, as well as their association. Speed dropped by $0.147\pm0.027$ S$^{-1}$ per °C increase in $DpG_{\text{up}}$ ($p=5\times10^{-4}$) after a normal night’s sleep and by $0.093\pm0.024$ S$^{-1}$ per °C increase in $DpG_{\text{up}}$ ($p=0.001$) after sleep deprivation. $DpG_{\text{up}}$ fluctuations thus predicted performance speed fluctuations only nonsignificantly ($p=0.08$) less well after sleep deprivation. Ignoring information on sleep history, an increase in $DpG_{\text{up}}$ still strongly predicted a drop in performance speed by $0.104\pm0.017$ S$^{-1}$ per °C ($p=9\times10^{-10}$). Note that we use the word ‘prediction’ in its statistical connotation throughout the manuscript, indicating an effect of a regressor on the outcome measure of interest, without inferring mechanistic causality.

Fluctuations in $DpG_{\text{mid}}$ predicted fluctuations in performance speed only after a normal night’s sleep. Speed dropped by $0.046\pm0.008$ S$^{-1}$ per °C increase in $DpG_{\text{mid}}$ ($p=9\times10^{-10}$) after a normal night’s sleep and by a nonsignificant $0.014\pm0.015$ S$^{-1}$ per °C increase in $DpG_{\text{mid}}$ ($p=0.35$) after sleep deprivation. $DpG_{\text{mid}}$ fluctuations thus predicted performance speed significantly worse after sleep deprivation ($p=0.008$). Ignoring information on sleep history, an increase in $DpG_{\text{mid}}$ still strongly predicted a drop in performance speed by $0.039\pm0.007$ S$^{-1}$ per °C ($p=3\times10^{-8}$).

Fluctuations in $DpG_{\text{low}}$ did not significantly predict fluctuations in performance speed, neither after a normal night’s sleep ($p=0.82$), nor after sleep deprivation ($p=0.48$).
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Effect of sleep deprivation on the association between fluctuations in temperature gradients and lapses.

As can be seen in table 3a and 3b, fluctuations in \( \Delta P_{G_{up}} \) predicted fluctuations in lapse probability. The odds ratio was 1.55 (95% CI: 1.07-2.25) per °C increase in \( \Delta P_{G_{up}} \) (\( p=0.02 \)) after a normal night’s sleep and 2.16 (95% CI: 1.59-2.93) per °C increase in \( \Delta P_{G_{up}} \) (\( p=7*10^{-7} \)) after sleep deprivation. The enhancement of predictive value after sleep deprivation was not significant (\( p=0.30 \)). Ignoring information on sleep history, an increase in \( \Delta P_{G_{up}} \) still strongly predicted a rise in risk probability with an odds ratio of 1.84 (95% CI: 1.47-2.31) per °C (\( p=1*10^{-7} \)).

Fluctuations in \( \Delta P_{G_{mid}} \) predicted fluctuations in lapse probability only after a normal night’s sleep. The odds ratio was 1.31 (95% CI: 1.17-1.46) per °C increase in \( \Delta P_{G_{mid}} \) (\( p=1*10^{-6} \)) after a normal night’s sleep and a nonsignificant 1.12 (95% CI: 0.94-1.33) per °C increase in \( \Delta P_{G_{mid}} \) (\( p=0.20 \)) after sleep deprivation. \( \Delta P_{G_{mid}} \) fluctuations predicted lapse probability significantly worse after sleep deprivation (\( p=0.03 \)). Ignoring information on sleep history, an increase in \( \Delta P_{G_{mid}} \) still strongly predicted a rise in lapse probability with an odds ratio of 1.24 (95% CI: 1.12-1.36) per °C (\( p=2*10^{-5} \)).

Fluctuations in \( \Delta P_{G_{low}} \) significantly predicted fluctuations in lapse probability only after a normal night’s sleep. The odds ratio was 1.19 (95% CI: 1.01-1.39) per °C increase in \( \Delta P_{G_{low}} \) (\( p=0.03 \)) after a normal night’s sleep and a nonsignificant 1.12 (95% CI: 0.95-1.32) per °C increase in \( \Delta P_{G_{low}} \) (\( p=0.19 \)) after sleep deprivation. The attenuation of the predictive value of \( \Delta P_{G_{low}} \) due to sleep deprivation was not significant (\( p=0.54 \)). Ignoring information on sleep history, an increase in \( \Delta P_{G_{low}} \) predicted a rise in lapse probability with an odds ratio of 1.19 (95% CI: 1.06-1.33) per °C (\( p=3*10^{-3} \)).

Figure 3 Effect of sleep deprivation on local temperature gradients
Mean ± standard error of the mean of the distal-to-proximal gradients measured at the hand vs. the arm (\( \Delta P_{G_{up}} \)) and the foot vs. the leg (\( \Delta P_{G_{low}} \)) after a night of normal sleep and sleep deprivation. The decrease of \( \Delta P_{G_{mid}} \) after sleep deprivation and the increase of \( \Delta P_{G_{low}} \) were both significant.
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Figure 4 Examples of associated DPG\textsubscript{up} and reaction speed fluctuations. Upper panel: Mean $\pm$ standard error of DPG\textsubscript{up} (black line) and reaction speed (grey line) fluctuations for the five assessment blocks after normal sleep (NS, left part) and after sleep deprivation (SD, right part) in a single subject. Note that all plots use an inverse scale, from maximal to minimal, for the DPG\textsubscript{up} axis, in order to better visualize its association with reaction speed. Also, in all plots, closed markers indicate data obtained after normal sleep, open markers indicate data points obtained after sleep deprivation. The inset scatterplot shows the association between the block averages, with regression lines for data obtained after normal sleep (black line), after sleep deprivation (broken line), as well as the overall regression line for the combination of these data (grey line).

Lower panels: Examples of the association between DPG\textsubscript{up} (black line) and reaction speed (grey markers and line) fluctuations within a block, taken from different subjects. For graphing purposes only, but not applied in any analysis, a 2.5 minute smoothing window is applied to generate the curves. The inset scatterplots show the association between the individual reaction speed and temperature gradient data points. Use of markers, scales and lines as in the upper panel.
### Table 2a Temperature gradients as predictors of reaction speed under well rested conditions and sleep deprived conditions.

<table>
<thead>
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<th>Normal Sleep</th>
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<th>Sleep Deprived</th>
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</table>

Temperature gradients of the upper ($D_{PG_{up}}$: ear-mastoid), the middle ($D_{PG_{mid}}$: hand-arm) and lower body ($D_{PG_{low}}$: foot-leg) as predictors of reaction speed under well rested and sleep deprived conditions ($s^{-1}/^\circ C$).

### Table 2b Temperature gradients as predictors of reaction speed if sleep history is unknown

<table>
<thead>
<tr>
<th></th>
<th>Unknown Sleep History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>effect</td>
</tr>
<tr>
<td>$D_{PG_{up}}$</td>
<td>-0.104</td>
</tr>
<tr>
<td>$D_{PG_{mid}}$</td>
<td>-0.039</td>
</tr>
<tr>
<td>$D_{PG_{low}}$</td>
<td>-0.012</td>
</tr>
</tbody>
</table>

Temperature gradients of the upper ($D_{PG_{up}}$: ear-mastoid), the middle ($D_{PG_{mid}}$: hand-arm) and lower body ($D_{PG_{low}}$: foot-leg) as predictors of reaction speed if sleep history is unknown ($s^{-1}/^\circ C$).
Table 3a Temperature gradients as predictors of lapse probability under well rested conditions and sleep deprived conditions.

<table>
<thead>
<tr>
<th></th>
<th>Normal Sleep</th>
<th>Sleep Deprived</th>
<th>Between condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O.R.</td>
<td>95% C.I.</td>
<td>z</td>
</tr>
<tr>
<td>DPG&lt;sub&gt;up&lt;/sub&gt;</td>
<td>1.55</td>
<td>1.07-2.25</td>
<td>2.33</td>
</tr>
<tr>
<td>DPG&lt;sub&gt;mid&lt;/sub&gt;</td>
<td>1.31</td>
<td>1.17-1.46</td>
<td>4.82</td>
</tr>
<tr>
<td>DPG&lt;sub&gt;low&lt;/sub&gt;</td>
<td>1.19</td>
<td>1.01-1.39</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Temperature gradients of the upper (DPG<sub>up</sub>; ear-mastoid), the middle (DPG<sub>mid</sub>; hand-arm) and lower body (DPG<sub>low</sub>; foot-leg) as predictors of lapse probability under well rested and sleep deprived conditions. O.R.: Odds ratio; 95% C.I.: 95% Confidence Interval.

Table 3b Temperature gradients as predictors of lapse probability if sleep history is unknown.

<table>
<thead>
<tr>
<th></th>
<th>Unknown Sleep History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O.R.</td>
</tr>
<tr>
<td>DPG&lt;sub&gt;up&lt;/sub&gt;</td>
<td>1.84</td>
</tr>
<tr>
<td>DPG&lt;sub&gt;mid&lt;/sub&gt;</td>
<td>1.24</td>
</tr>
<tr>
<td>DPG&lt;sub&gt;low&lt;/sub&gt;</td>
<td>1.19</td>
</tr>
</tbody>
</table>

Temperature gradients of the upper (DPG<sub>up</sub>; ear-mastoid), the middle (DPG<sub>mid</sub>; hand-arm) and lower body (DPG<sub>low</sub>; foot-leg) as predictors of lapse probability if sleep history is unknown. O.R.: Odds ratio; 95% C.I.: 95% Confidence Interval.
Chapter 3

Post-hoc analyses
A number of ancillary post-hoc analyses were performed in order to improve the interpretability of the findings as well as to distill methodological recommendations for further fundamental and applied research.
As a first ancillary analysis, we further investigated the surprising opposed effect of sleep deprivation on the three different DPG's we measured. While DPG_{up} did not change significantly, DPG_{mid} decreased, and DPG_{low} increased. We therefore investigated whether this discrepancy between DPG's might be an even better thermoregulatory marker to discriminate someone's sleep history than any of the DPG's per se. To do so, the difference between DPG_{mid} and DPG_{low} was calculated. Indeed, sleep deprivation affected this difference more than it affected any other change in the temperature profile (1.61±0.38 °C, p=3*10^{-3}).

In conclusion, activation of heat loss from the feet in the presence of activation of heat preservation from the hands may thus be a most characteristic skin temperature profile signature of being sleep deprived.

Another set of ancillary analyses was performed to rule out the possibility that systematic parallel effects of time of day on temperature gradients and performance might be present and could have introduced spurious associations. Linear and nonlinear time of day effects were evaluated by adding time and time^2 (i.e. 2nd order) in the regression models. Of the three gradients, only DPG_{low} changed with time of day, as indicated by a significant linear term (p=2*10^{-3}) and a nonsignificant 2nd order term (p=0.07). However, since neither lapses nor speed showed significant time of day effects (0.15<p<0.40), the systematic changes of DPG_{low} over the time of day were unlikely to have induced spurious associations due to parallel time-of-day changes of temperature and performance. Formal testing of the robustness of the predictive value of temperature for performance by inclusion of the linear and second order terms representing time of day in the regression equations, confirmed absence of any spurious associations: addition of time hardly changed the predictive effect sizes and their significance.

Finally, for completeness, we evaluated the effects of sleep deprivation on core body temperature as well as the association of fluctuations of performance with those in core body temperature. Core body temperature did not differ between the normal sleep (37.38±0.08) and sleep deprived (37.37±0.10 °C) conditions (p=0.92). There was no main effect of core temperature on performance speed (0.03±0.08 S^{-1} per °C, p=0.68), neither a core temperature by sleep condition interaction effect (-0.03±0.09 S^{-1} per °C, p=0.74). There was no main effect of core temperature on lapse probability (odds ratio 1.22 per °C, 95% CI: 0.54-2.77, p=0.64, neither a core temperature by sleep condition interaction effect (odds ratio 3.71 per °C, 95% CI: 0.56-24.54, p=0.17). Of note, whereas these findings rule out the possibility that our skin temperature findings were secondary to core body temperature associations with vigilance they should not be interpreted as a evidence against such association, because the present protocol was tuned to the detection of faster fluctuations, that do not normally occur at rest in core body temperature.
Discussion

In this study we set out to uncover how sleep deprivation affects the different skin temperature gradients that can be measured over the human body, as well as their association with sustained attention, under conditions of the upright seated posture that we normally maintain trying to keep awake after sleep deprivation.

Our first main finding was that sleep deprivation induces a dissociation between skin temperature gradients. Sleep deprivation induces an overall enhanced heat loss activation as measured from the foot-to-leg gradient, while it attenuates heat loss activation as measured from the hand-to-arm gradient. The larger negative hand-to-arm gradient suggests an augmented sympathetic tone resulting in vasoconstriction of the hand, whereas the less negative, closer to zero foot-to-leg gradient indicates an attenuated sympathetic tone, resulting in a release from vasoconstriction of the feet.

Most amazingly, this dissociation was even present for the fluctuations occurring within a day. While the changes in distal-to-proximal temperature gradients that reflect fluctuations in thermoregulatory heat loss normally occur in synchrony (Stoner et al., 1991), sleep deprivation caused them to fluctuate in antiphase. Sleep deprivation thus disrupts coordinated sympathetic control of skin blood flow of the hands and feet. Activation of heat loss from the feet in the presence of activation of heat preservation from the hands may thus be a most characteristic skin temperature profile signature of being sleep deprived.

The present findings differ from earlier reports of the effect of sleep deprivation on either foot temperature (Holmes et al., 2002) or on the average temperature of hands and feet (Kräuchi & Wirz-Justice, 1994). The essential difference of the present study is that participants were measured in a constant upright seated position, in order to allow for extrapolation to everyday life situations where sleep deprived people try to stay awake and maintain optimal operational control by keeping an upright rather than the supine posture subjects had to maintain in previous studies (Holmes et al., 2002; Kräuchi & Wirz-Justice, 1994). The marked discrepancy between the previous work on thermoregulation in a supine position and our present findings in an upright seated position actually help to pinpoint, as a likely candidate for the critical underlying mechanism involved, the competition between thermoregulation and the regulation of blood pressure. If people change from a supine to an upright position, an orthostatic challenge is induced and vasoconstriction of the lower part of the body is required to maintain blood flow in the upper part of the body within acceptable limits. This is accomplished by an increase in sympathetic tone. In sleep deprived people in an upright position, but not in a supine position, the necessity of this increase has to compete with the tendency for a decrease in sympathetic tone innervating the vascular bed that has been reported after sleep deprivation (Kato et al., 2000;
Ogawa et al., 2003). Our findings suggest that insufficient vasoconstriction may cause some venous pooling in the legs and the associated increase in DPG, and thereby some insufficiency in the perfusion of upper parts of the body including the arms, in turn resulting in a relative decrease in DPG. The proposed mechanism would also account for the intriguing finding of anticorrelated fluctuations in the hand-to-arm and foot-to-leg gradients. Our findings indicate that it is important to consider body posture and if possible manipulate them in fundamental studies on thermoregulation and vigilance after sleep deprivation. For practical generalizability to everyday life situations, a sitting position seems more appropriate.

Our second main finding is that sleep history affects the predictive value of skin temperature gradients to estimate vigilance. The gradient measured between ear and mastoid however remained most robustly valuable for this purpose, significantly predicting reaction speed and lapse probability irrespective of whether subjects experienced normal sleep, were sleep deprived, or in case sleep history is unknown. The use of video monitoring allowed us to strictly detect lapses that occurred while subjects actually looked at the target area while discarding no responses in association with eye closure or looking away from the target area (Anderson et al., 2010). In spite of this strict criterion, on average 86±4% (mean ± standard error) of the data points for a subject were valid. Given the large number of data points (2 days x 5 blocks x 120 = 1200 stimuli for each subject), the loss of 14% of the data hardly affected the statistical power of the present study, while the procedure enhances the interpretability of the results. Accordingly, lapses here reported indicate a failure of the brain to timely process the stimuli, not lapses resulting from being distracted, blinking, or closing the eyes, which are inevitable in a tediously monotonous task that is fully dependent on top-down attention for 20 minutes.

Some limitations of the present study need to be addressed. First, overnight sleep deprivation was implemented at home, unsupervised. Ideally, sleep deprivation should be supervised continuously and include polysomnography. Only such a protocol would allow quantification of actual amount of time spent asleep, including microsleeps. However, our use of actigraphy with a sensitive sleep detection threshold, makes it very likely that the participants spent the night fully awake; the one subject where actigraphy suggested a period of more than ten minutes of continued inactivity was excluded (Lotjonen et al., 2003). The profile of immobility bout durations during the sleep deprivation night closely resembled the profile seen during a normal wake day, while it is known that actigraphy is highly sensitive to the detection of naps and overestimates rather than underestimates sleep (Kanady et al., 2011). Close examination of the actigraphic recordings moreover suggested that all participants refrained from exercise, as requested. Our study cannot however fully ascertain abstinence of caffeine and other stimulants and had to trust on subjective confirmation.
Cold hands, warm feet

The statistical power of the protocol should be discussed as well. As demonstrated by the findings, our protocol was extremely well powered to statistically detect even very subtle within-subjects associations and effects, because of the availability of a maximum of 9600 pairs of data points (2 days × 5 blocks × 120 stimuli × 8 participants). It should however be considered that our protocol may have missed small effects of sleep deprivation on skin temperature and its association with performance that are less general to all people, but could occur in some. Larger studies including considerably more than eight participants would be required if one would also be interested in the effects and associations that are less generalizable to all.

Possible limitations of the adapted constant routine protocol should be discussed as well. Theoretically, skin temperature might respond to the scheduled intake of food and drinks as well as the brief physical activity and postural change associated with restroom visits. As is habitual for constant routine protocols, food and fluids were given in small amounts with equal and low caloric values (Kräuchi et al., 1997; Kräuchi et al., 2002). Previous studies on the effect of meals on skin temperature usually evaluated the effect of meals containing at least five times the calories of our combined food and fluid intake. Even then they frequently failed to find systematic effects on skin temperature (Harada et al., 1998; Shlygin et al., 1999; Westerterp-Plantenga et al., 1990), rendering systematic effects of the low calorie intake in our study unlikely. For the scheduled visits to the restroom, which was part of the lab space with equal environmental light and temperature, participants got up, walked 5 meters, sat down again for ten minutes, got up, walked back to the research chair and sat down again. This procedure thus twice required approximately 5 seconds of being upright and walking. The associated short lasting postural changes are unlikely to affect skin temperature during the later vigilance assessment: whereas changes between supine and upright postures affect skin temperature considerably (Kräuchi et al., 1997; Tikuisis & Ducharme, 1996), the mean skin temperatures of the two upright postures of sitting and standing are equal (Tikuisis & Ducharme, 1996). The associated physical activity of twice ~5 seconds is equally unlikely to affect skin temperature during the later vigilance assessment; first, the activity required is marginal both in duration and intensity and second, the effect of physical activity on skin temperature shows an inverted u profile, slowly increasing to peak after a lag of ~10 minutes, to subsequently decline again (Van Marken Lichtenbelt et al., 2006). No effect can be expected at the onset of the vigilance task, which is 35 minutes after moving to the restroom and 25 minutes after moving back to the lab room. In summary, systematic effects of calorie intake and changes in posture and activity are unlikely. Although other procedures, like the use of blood lines, catheters and bed pans may be applied, they may induce stress and affect skin temperature accordingly. Future studies may consider random sampling in the natural environment using a combination of ambulatory physiological and environmental monitoring and PDA-based experience sampling and performance assessment.
To our knowledge, this is the first time the gradient between ear and mastoid was used in a study on the association between thermoregulation and vigilance. Further research on applicability of this novel finding seems warranted. Given the recent advances in micro-electronics it should not be too difficult to incorporate sensors to measure ear and mastoid temperatures in devices like hearing aids and Bluetooth headsets, and evaluate whether they may aid in vigilance assessment, for example during car driving.

In conclusion, the present study showed that sleep deprivation disturbs coordinated thermoregulatory responses between the lower and middle part of the body. The specific thermoregulatory profile of sleep-deprived people is marked by a relatively increase in heat loss from the lower limbs, a relative decrease of heat loss from the upper limbs, and anticorrelated fluctuations between these two. Future studies should further evaluate how sleep deprivation affects competitive needs for thermoregulation and blood pressure regulation. The findings moreover warrant further research on the possibility that the gradient between ear and mastoid temperature may be of value to aid vigilance estimates under both well-rested and sleep-deprived conditions.

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Cold hands, warm feet

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