Skin temperature and vigilance: from association to application

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Summary, general discussion and future perspectives

CHAPTER 7

General discussion

The core model of sleep-wake regulation consists of a circadian component (the so-called *clock*) and a homeostatic component (the so-called *hourglass*) (Borbély, 1982; Daan et al., 1984; Dijk & Czeisler, 1995). Located in the suprachiasmatic nucleus, the circadian component drives many behavioural rhythms, amongst which is the promotion of sleep and wake during the night and day, respectively (Mistlberger, 2005). The homeostatic component, on the other hand, describes the positive correlation between time awake and sleep pressure, in which adenosine (Porkka-Heiskanen et al., 1997), cytokines (Krueger et al., 2011) and an increase in synaptic density during wakefulness are suggested to play a role (Tononi & Cirelli, 2006). However, although these core components have shown to be highly valuable to understand the regulation and disturbances of sleep and wakefulness, additional modulatory factors need to be considered as well. We have proposed to call these 'sleep permissive' and 'wake promoting' factors, which include posture, environmental light, nutritional status, pain and stress.

A common effect of all these additional factors is that they alter skin flow, and thereby skin temperature, within the thermoneutral range. Skin temperature is influenced by posture (Nakajima et al., 2002; Tikuisis & Ducharme, 1996), environmental light (Cajochen et al., 2005; Van de Werken et al., 2010), anxiety (Lack et al., 2008), nutritional status (Kräuchi et al., 2000), pain (Hampf, 1990; Iannetti et al., 2004; Lei et al., 2008) and stress (Rimm-Kaufman & Kagan, 1996). As reviewed in detail previously (Van Someren, 2000), previous studies suggest that skin temperature has an effect on several brain areas involved in sleep regulation. Therefore, it is possible that the small but significant effect of sleep permissive / wake promoting factors on skin temperature might contribute to their effect on vigilance. As a first step to address this possibility, the present thesis evaluated whether vigilance covaries with spontaneous fluctuations in skin temperature within the thermoneutral range.

Experimental studies have shown that there is a causal link between (experimentally induced) fluctuations in skin temperature, sleep and alertness (Raymann et al., 2005, 2008; Raymann & Van Someren, 2007). The induction of a relatively high skin temperature, yet within the thermoneutral range, resulted in increased sleepiness; slower responses on sustained attention tasks; faster sleep onset; and deeper sleep.

In conclusion, skin temperature manipulation studies support a causal effect of skin temperature on vigilance. However, so far it has not been studied whether *naturally occurring* fluctuations in skin temperature within the thermoneutral zone are similarly associated with vigilance under well-rested and vigilance-challenging conditions.

The present thesis aimed to evaluate whether naturally occurring fluctuations in skin temperature are related to fluctuations in vigilance, and whether such association is still present after sleep deprivation. Furthermore, the thesis addressed brain areas and mechanisms that could be involved in the link between fluctuations in vigilance and skin temperature. Finally, the thesis addressed whether the link can be utilized by adding skin temperature assessment to devices that aim to unobtrusively assess the sleep-wake state from wrist movements, and thus improve the performance of these devices. A number of experiments were designed to evaluate the following hypotheses:

Hypotheses

1. Fluctuations in skin temperature and sustained attention performance are negatively correlated.
2. Sleep deprivation affects skin temperature and its association with vigilance.
3. Fluctuations in skin temperature and electroencephalographic vigilance markers are negatively correlated.
4. Hypothalamic damage affects the coupling between skin temperature and vigilance.
5. Fluctuations in skin temperature and polysomnographically determined sleep are positively correlated; the association can be utilised to improve actigraphic sleep estimates.

Overview of findings

In the **second chapter**, we examined whether fluctuations in skin temperature are associated with those in vigilance level, under conditions similar to everyday-life situations requiring sustained attention. Eight healthy participants participated in a two-day protocol during which vigilance and skin temperature were assessed 4 times per day in a silent dimly-lit, temperature-controlled room. Out of the three measured locations, distal, proximal and intermediate, especially the spontaneous fluctuations in proximal temperature were negatively associated with fluctuations in response speed, and positively with lapse rate on the vigilance task. We therefore concluded that a higher proximal skin temperature was associated with decreased vigilance.

In the **third chapter**, we 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. Eight healthy young adults participated in a repeated-measures constant routine design, in which 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 body (foot-leg), and on the association between fluctuations in performance and 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. Therefore, we 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.

The **fourth chapter** described how fluctuations of skin temperature are associated with changes in the electroencephalographic power spectrum and event related potentials, recorded during a sustained attention task both under well-rested and sleep-deprived conditions, as measured by event related potentials. Simultaneous measurement of activity in the central nervous system (CNS), the autonomous nervous system (ANS), and behavior allowed us to determine if the correlation between skin temperature and lapses in vigilance is not only visible in *behavioral output* associated with vigilance, but if this correlation is reflected by altered *cerebral* activity associated with attention. Correlating event related potentials elicited by stimuli in a reaction task to temperature measured at the ear, we have shown that elevations in skin temperature were correlated to increased P300 latency, indicating decreased vigilance. Furthermore, fluctuations in the skin temperature gradient measured from the earlobe and mastoid were associated with fluctuations in parieto-occipital high beta band (20-40 Hz) power of the pre-stimulus background EEG, but only after sleep deprivation, which indicates fluctuations in compensatory efforts in order to maintain vigilance.

The **fifth chapter** focused on the relationship between skin temperature and sleep onset in subjects with hypothalamic damage. The hypothalamus is crucially involved in the circadian timing of the sleep-wake rhythm, and also accommodates the most important thermoregulatory neuronal network. We have shown before that adults with pituitary insufficiency and history of chiasm compression due to a tumor with suprasellar extension fall asleep later and sleep shorter than those without such history, and presume hypothalamic involvement. To further evaluate the hypothesized hypothalamic involvement in the association between vigilance and thermoregulation, we investigated whether hypothalamic impairment also affects skin temperature and its association with sleep onset. In a case-control study in fifty patients with pituitary insufficiency, thirty-three of which had a history of chiasm compression, ambulatory distal and proximal skin temperatures were assessed continuously for 24 hours. Sleep parameters were assessed via questionnaires. Group differences in mean skin temperature, calculated over the wake and sleep periods separately, and group differences in the strength of association between pre-sleep skin temperature and sleep onset latency were compared. Results showed that patients with a history of chiasm compression had a lower proximal skin temperature during the day (34.1 ± .7 vs. 34.6 ± .7 °C, $p = .045$). Additionally, the typical association between sleep onset latency and pre-sleep distal-to-proximal skin temperature gradient was absent in these patients ($r = -.01$, $p = .96$), while it was unimpaired in those without chiasm compression ($r = -.61$, $p = .02$). Thus, patients with a history of chiasm compression show impaired skin temperature regulation in association with disturbed sleep.

The **sixth chapter** focused on the practical application of the knowledge acquired on the association between skin temperature, sleep and vigilance. Due to its low invasiveness and costs, actigraphy is widely used as an alternative to polysomnography (PSG) to measure sleep wake rhythms in human subjects. However, although actigraphy and PSG correspond relatively well during PSG during sleep (Ancoli-Israel et al., 2003), actigraphy has problems detecting wake during immobility (Pollak et al., 2001). Since skin temperature is closely correlated to vigilance and sleep under so many conditions and in so many populations, it could be a very useful output parameter to easily increase the accuracy of sleep/wake classification. Under normal daily routine conditions, 52 subjects diagnosed with sleep disorders such as OSAS, insomnia, and PLMS, were monitored via ambulatory EEG, actiwatch, and skin temperature sensors. The ratio between congruent actiwatch/PSG scoring was calculated before, and after adaptation of the actiwatch scoring based on temperature data. Results showed on average a lower skin temperature during false sleep classifications than during true sleep classifications. Also, a higher skin temperature was recorded during false wake classifications than during true wake classifications. However, using temperature as additional information in the actigraphy scoring algorithm, did not significantly alter the misclassification of sleep or wake epochs. We propose that the sluggish response of the sensor and/or skin to changes in skin perfusion may have interfered with the possibility to exploit the systematic skin temperature differences. Infrared temperature sensing or even perfusion sensing may be required to improve actigraphic sleep estimates.

Evaluation of hypotheses

Since our results support our initial hypotheses, we can therefore conclude that:

1. Under semi-controlled conditions, naturally occurring high skin temperature is correlated to decreased vigilance.
2. Although skin temperature changes under vigilance-challenging conditions, skin temperature fluctuations are still correlated to changes in vigilance. Furthermore, we have found that sleep deprivation is correlated with a dissociation between the skin temperature gradients of the middle and low section of the body.
3. Skin temperature fluctuations are not only correlated to vigilance fluctuations on a behavioral level, but also to cortical markers of vigilance.
4. In hypothalamic damage, both skin temperature and sleep are dysregulated, as is the relation between skin temperature, skin temperature gradients and sleep onset latency.
5. Skin temperature differs between true and false actigraphic sleep estimates, but faster sensors may be required to exploit this difference to actigraphic sleep estimates.

General conclusion and perspectives

The findings provide support for the notion that naturally occurring fluctuations in skin temperature are related to fluctuations in vigilance. It has been demonstrated in healthy participants that higher proximal skin temperature is associated with lower alertness under well-rested conditions (chapter 2, this thesis). Furthermore, this correlation is still present after a vigilance-challenging occurrence such as an entire night of sleep deprivation (chapter 3). As a first step towards elucidating the brain mechanisms involved in the coupling of infraslow fluctuations in skin temperature and alertness, the present work showed that they also coincide with fluctuations in the latency of an event related potential, the P300 (chapter 4). A practical consequence of this finding is that the sensitivity of ERP studies might increase if skin temperature would be co-registered and included in the statistical analysis as a nuisance variable. A second step towards understanding brain structures involved in the coupling was the demonstration that it is compromised in patients with hypothalamic damage (chapter 5).
Finally, the correlation between naturally occurring skin temperature fluctuations and vigilance was used in an attempt to improve movement-based sleep-wake assessment (chapter 6).

With regard to wake-promoting and sleep-permissive signals to the brain, our results corroborate the earlier findings in thermomanipulation studies, where skin temperature has been shown to have a greater impact on wake and sleep regulation, as well as vigilance regulation, than core temperature does in the thermoneutral range (Raymann et al., 2005; Raymann & Van Someren, 2007). The association between vigilance and body temperature has been studied for a long time, but mostly either focused on core body temperature, or on extreme environmental temperature. Our findings illustrate the use of investigating fluctuations in skin temperature as they occur under thermoneutral conditions. Predominance of skin temperature over core temperature effects on the brain makes sense from a survival perspective. Given the fact that the central part of the body is thermally buffered, it would be a disadvantage if an animal would respond only by the time an environmental thermal challenge has affected core temperature. A predominance of skin temperature effects has also been reported with respect to the disrupting effect of body cooling on performance. For example, Cheung et al. (Cheung et al., 2007) administered vigilance and spatial attention tests while subjects were immersed in a cool water bath and reported that all disruptive effects on performance occurred immediately with skin cooling, while performance did not get any worse with the much slower developing decline in core body temperature. Of note, studies like these differ with respect to the applied temperature range. With all our aforementioned studies on manipulation of sleep and vigilance, temperature was only manipulated within the thermoneutral zone, thus not stressful, neither activating thermoregulatory mechanisms to defend temperature. People neither sleep nor perform well at extreme environmental temperatures, and sleep versus wake-promoting effects may be restricted to a narrow comfortable temperature range, where the optimal temperature for sleep slightly differs from the optimal temperature to e.g. sustain attention. This is schematically shown in Figure 1.

The findings presented in this thesis may have relevance for the field of environmental ergonomics. Because the skin is rather poikilotherm, its manipulation by means of environmental temperature in combination with clothing could make the difference between being alert and being sleepy. This contention is supported by the skin temperature manipulation studies within the thermoneutral zone (Raymann et al., 2005; Raymann & Van Someren, 2007), as well as by the finding that elderly people with and without dementia report less daytime sleepiness if they have a slightly lower skin temperature.

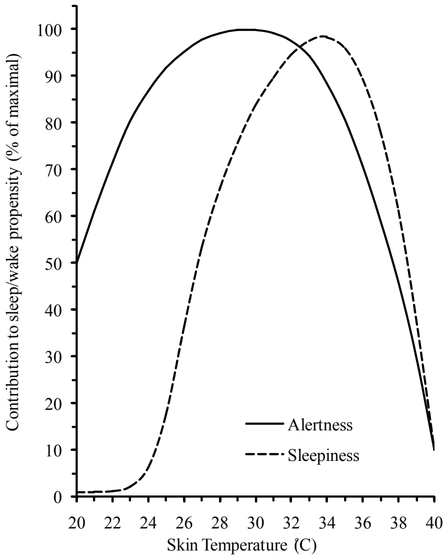

Figure 1 A schematic representation of how we envision skin temperature may affect sleep and wake propensity regulation. Both the capacity to initiate or maintain sleep or to perform/performance on a sustained attention tasks are compromised at low and high temperatures because the brain will prioritize recruitment of its resources to solve a possibly disadvantageous thermal situation. Within a relatively small comfortable thermoneutral zone, there is no need for the brain to activate thermoregulatory defense mechanisms. Within this range, small differences in skin temperature may promote the brain to reach its peaks of vigilance-promoting and sleep-promoting capacities. It requires only the assumption that the temperature at which the peaks reach their maximum differs slightly for vigilance-promoting and sleep-promoting capacities.

Perspectives: towards further insight into vigilance-regulating networks in the human brain

Our studies have shown that naturally occurring skin temperature fluctuations can be regarded as sleep-permissive or wake-promoting factor. However, as previously stated in the introduction, one of the reasons why we hypothesized skin temperature to provide the brain with information on sleep-permissive and wake-promoting conditions, is because it changes with most if not all of them. This provides an exciting new area of investigation, because it is currently unclear what the contribution of other perturbations is on sleep and wake regulation, and to what extent the effects of these perturbations are mediated by the changes in skin temperature they induce, or other mechanisms. For instance, while it is known that skin temperature is influenced by postural changes (Nakajima et al., 2002; Tikuisis & Ducharme, 1996), and that postural changes are able to influence vigilance (Caldwell et al., 2003; Caldwell et al., 2000; Cole, 1989), it is currently not clear in how far posture effects are mediated by the changes in skin temperature postural changes induce. Further possible perturbations to wake-sleep regulation such as light intensity and physical exercise could be studied as well. Ideally, this would involve a multiple-day, repeated measure protocol in which vigilance would be assessed both behaviorally, via reaction time tasks and questionnaires, as well as physiologically, by use of high-density EEG. Parameters such as skin temperature, heart rate and blood pressure could be used as output parameters to assess autonomic responses to perturbations. Perturbations would consist of changes in posture, environmental light, and physical exercise, allowing assessment of their effects on vigilance and skin temperature. To disentangle the effect of temperature changes on vigilance, the previously described perturbations would need to be done in a condition where skin temperature is free to fluctuate autonomously, and a condition wherein skin temperature would be clamped. Clamping of skin temperature is possible by use of a water-perfused suit, which has been used previously (Raymann et al., 2005). Analysis of the resulting multivariate dataset, for instance using multilevel regression, would allow for assessment of the separate effect of each perturbation, which will enhance our insight into the mechanisms of thermoregulation as well as vigilance regulation.

Perspectives: towards practical application of thermoregulation as aid in sleep-wake assessment

Chapter 6 of this thesis accounts of an attempt to use skin temperature measured at the wrist as a relatively low-cost, non-invasive way to increase accuracy of ambulatory sleep-wake assessment. Indeed, on average a lower skin temperature was recorded during false sleep classifications than during true sleep classifications. Also, a higher skin temperature was recorded during false wake classifications than during true wake classifications. However, no relevant improvement to actigraphic sleep estimates could be made, likely because of the sluggish response of the temperature sensor and/or skin temperature to the fluctuations in skin perfusion that are directly reflecting the changes in autonomic output that occur at transitions between the wake and sleep states. The use of skin temperature to improve the accuracy of actigraphic sleep estimates may require a temperature sensor with a shorter time constant, like an infrared sensor, or may even require direct assessment of changes skin perfusion in order to overcome the sluggishness of the resulting changes in skin temperature.

Another recommendation can be done based on the findings in this thesis. The temperature gradient analysis done in chapter 3 have shown that especially the skin temperature gradient measured at the ear and mastoid was the most resilient predictor of vigilance in cases of sleep deprivation. Based on this knowledge, it is therefore not unfeasible that in cases where sleep deprivation is studied in the field, an earpiece would be used, similar to the Bluetooth headsets currently available for mobile phones. Such an earpiece could contain two thermosensors, measuring both the ear as well as the mastoid against a single clock. The previously mentioned disadvantage of post-hoc synchronization with the actigraph on the wrist would either have to be accepted or solved using low-power wireless connection solutions such as Bluetooth v3.

Finally, since we have shown that temperature can be of aid in vigilance assessment, a possibility for online analysis could be of great value for vigilance demanding processes, for instance driving. However, since the range of naturally occurring skin temperature differs between individuals, such an application would preferably entail calibration per individual for increased accuracy. Possible solutions could involve a 24-hour calibration using ambulatory equipment described above, and online analysis using the constantly increasing computational power of mobile devices such as cellphones and tablets.

Overall, this thesis has provided a proof of principle: Naturally occurring skin temperature fluctuations are correlated to vigilance and sleep, in both healthy and patient populations.

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