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## **Skin temperature and vigilance: from association to application**

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# Introduction

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## Introduction

The present thesis focuses on interactions between the neuronal networks of the brain that regulate body temperature and those that regulate sleep and vigilance, as can be measured at the systems level in humans. In order to provide an intuitive idea of the topic one may try to imagine two situations, likely familiar to most researchers and clinicians. The first situation is as follows. Consider a moment of considerable fatigue after a long working day, while there is still that one manuscript that needs to be read and commented on today. What would be the best strategy to promote alertness and finish the job: reading it sitting at one's desk, or rather lying down on the sofa to give in somewhat to the fatigue, and read it semi-supine? The second situation is also familiar to many of us. Imagine flying back home from a demanding conference, eager to catch a nap. How does trying to sleep in a sitting position compare to trying to sleep in a supine position? For most of us, answers to these questions come without even the slightest bit of doubt. If one has to stay awake, chances to do so successfully are better with sitting, and even more so with standing, as compared to lying down (Caldwell et al., 2003; 2000; Cole, 1989; Kräuchi et al., 1997). If one desires to sleep on the other hand, most of us succeed much better when lying down (Aeschbach et al., 1994; Nicholson & Stone, 1987). One's posture apparently strongly affects the ability to fall asleep or maintain vigilance. The present thesis provides indirect support for the possibility that thermoregulatory adaptations associated with postural changes could contribute to the effect of posture on vigilance. Before evaluating this contribution, one may first consider how current models on the regulation of sleep and alertness would account for the well-known effect of posture on vigilance.

*Sleep regulation: are a clock and an hourglass sufficient?*

The core model of sleep-wake regulation consists of a circadian component and a homeostatic component (Borbély, 1982; Daan et al., 1984; Dijk & Czeisler, 1995). The circadian (circa=about, dies=day) component refers to the clock of the brain. The central clock of our brain is located in the hypothalamic suprachiasmatic nucleus (SCN) and drives many physiological and behavioural rhythms including the promotion of sleep during one part of the circadian cycle and wakefulness during the other part (Mistlberger, 2005), in humans respectively night and day. However, circadian processes are not limited to the central circadian pacemaker formed by the SCN. Indeed, molecular clock mechanisms are found in every single cell (reviewed in Dibner et al., 2010). This is not surprising given the fact that the evolution of life on our rotating planet has always occurred in an environment with near-24 hr cycles of light and darkness, and corresponding higher and lower environmental temperatures. Given this origin it is also not surprising that both light and temperature can affect clock mechanisms at the cellular and systems level, as will be touched upon later (Dibner et al., 2010; Van Someren, 2003).

The homeostatic component refers to the hourglass of the brain. The longer we're awake, the stronger the pressure for sleep. While we're asleep, this pressure dissipates, and as soon as we wake up, the process starts all over again, just like turning an hourglass at every transition between sleep and wakefulness (Achermann et al., 1993; Leemburg et al., 2010; Van Someren, 2010). The neurobiological mechanisms underlying the hourglass are not characterized as well as the mechanisms of the clock are. Important roles have been assigned to adenosine (Porkka-Heiskanen et al., 1997), to an increase in synaptic density during wakefulness (Tononi & Cirelli, 2006), and to cytokines (Krueger et al., 2011).

However, even though the clock & hourglass model has brought us very far in understanding the regulation of sleep and wakefulness, they are limited in their own respects. Both components are necessary to understand the maintenance and transitions of states. They model it so well under comfortable, safe and variance-limiting laboratory conditions that we tend to forget that the model may not necessarily be sufficient for a complete understanding of the maintenance and transitions of states, as we will argue below.

### *Sleep-permissive and wake-promoting conditions*

In real life, sleep onset and maintenance also depend on whether some seemingly trivial yet crucial conditions are met. Are we as likely to maintain the state of sleep or wakefulness in a brightly lit versus dark environment (Van De Werken et al., 2010)? And, whatever state the clock and hourglass tells our sleep-regulating systems to implement, how easy are we going to fall asleep, or continue to sleep, in case of acute cold (Palca et al., 1986; Sewitch et al., 1986), heat (Haskell et al., 1981; Okamoto-Mizuno et al., 2005), danger (Charuvastra & Cloitre, 2009; Halasz, 1998), pain (Drewes et al., 1997) (Lavigne et al., 2001) or stress (Akerstedt et al., 2007; Vandekerckhove et al., 2011)? Just like the clock mechanisms are strongly rooted in evolution, so are the sensitivities to sleep-permissive and wake-promoting conditions: the odds for survival would be severely compromised if these were not effective. We plea that insights into the parameters and mechanisms of sleep-permissive and wake-promoting conditions are no less important for our understanding of sleep regulation and sleep disorders than insights into the mechanisms underlying the clock and hourglass are.

The present thesis primarily focuses on one of these conditions: skin temperature. Skin temperature is quite well-suited to provide the brain with information on sleep-permissive and wake-promoting conditions, because it changes with most if not all of them. Because the skin is rather poikilotherm, its temperature changes with environmental heat and cold. It changes also with 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). Its effect on the brain may thus moderate the efficacy by which the clock and homeostat manage to initiate or maintain sleep or wakefulness.

### *Skin temperature*

Skin temperature is influenced by the environment, by behaviour and by several endogenous processes. Skin temperature is influenced by environmental temperature but also depends on endogenous central and autonomic nervous system processes that actively regulate blood flow through the skin (reviewed in Johnson & Kellogg, 2010). Variation in perfusion of the skin with the  $\sim 37^\circ\text{C}$  blood thus results an endogenous modulation of skin temperature. Information on skin temperature, measured with cold and warm receptors and conveyed through thermosensitive afferent pathways, reaches the brain in order to allow for thermoregulation (Hensel, 1973). However, information on skin temperature does not only reach brain areas with a primary involvement in thermoregulation, but also brain areas involved in other functions (reviewed in Van Someren, 2000).

### *Skin temperature and sleep-wake regulation*

Indeed, several neuronal systems that are directly or indirectly involved in sleep-wake-regulation are sensitive to temperature (reviewed in Van Someren, 2003, 2004; Van Someren, 2006). This is not surprising from an evolutionary perspective given that environmental temperature has a long history of affecting sleep-wake behavior. In the evolutionary older ectotherms, the behavioral relationship between temperature and vigilance level is relatively straightforward. Ectotherms require warming up by exposure to the radiation of the sun, in order to become active. On the other hand, endotherms aim to maintain their core body temperature within a small range, which makes the relationship between temperature and vigilance more complex. The most studied organisms, humans and small furred mammals (such as rats, ground squirrels and hamsters) mainly sleep during that part of the day when their core body temperature is low, and are most awake during the part of the day when their core body temperature is high, which resembles the behavior of ectotherms. But unlike ectotherms, their skin temperature is elevated during the sleep period due to an increase in skin blood flow in combination with behaviour that limits heat loss through insulation by creating a warm microclimate, like covering and curling up. This results in an inverse relationship between core and skin temperature in everyday life, while in ectotherms skin and core body temperature covary over time in phase. The question thus becomes more complicated: to what extent are the biological systems that are involved in sleep-wake rhythm regulation differentially affected by the normal variations in core temperature versus skin temperature?

## Chapter 1

As extensively reviewed elsewhere (Van Someren, 2000), several brain areas involved in sleep regulation are differentially sensitive to the local brain temperature which covaries with core temperature, versus skin temperature which shows an inverse relation to core temperature during the 24-hour cycle. An area that plays a key role in both sleep and temperature regulation is the preoptic area and anterior hypothalamus (POAH). Animal studies indicate that both mild local warming of the area using a micro-thermode, as well as mild skin warming using a wrap, induce its neuronal fire patterns to resemble those of sleep and inhibit those associated with wakefulness (Alam et al., 1995; McGinty et al., 2001; McGinty & Szymusiak, 1990). The same was shown in the posterior hypothalamic area. Mild skin warming has also been associated with sleep-like activity in the cerebral cortex and midbrain reticular formation. Local brain warming has furthermore been shown to induce sleep-like firing patterns in the diagonal band but also wake-like firing patterns in the midbrain reticular formation and midline thalamic nuclei. A detailed description of the neuroanatomical pathways involved in the effect of skin temperature on vigilance-regulation is beyond the scope of the present paper, and has been reviewed previously (Van Someren, 2000). Taken together, the effect of a mild increase in brain temperature may differentially drive different brain areas towards either a more sleep-like or a more wake-like firing pattern. The complex relationship between brain temperature and neuronal firing patterns makes an unequivocal sleep-promoting effect of mild increases in brain temperature unlikely. In contrast, the effect of a mild increase in skin temperature in general seemed to drive different brain areas towards more sleep-like firing patterns. If these findings can be translated to a real-life situation, a mild increase in skin temperature might promote sleep.

Next to these general functional anatomy considerations, how would core and skin temperature affect the specific functional anatomy that underlies the hourglass and clock of sleep regulation? Little is known on specific effects of temperature on the incompletely understood regulation of adenosine that is thought to be involved in the homeostatic aspect of sleep regulation. With respect to the much better understood clock-related systems, evidence has accumulated over the last decade to indicate that peripheral oscillators, including those in the brain (e.g. cerebral cortex) can be entrained by ambient temperature cycles (Brown et al., 2002; Buhr et al., 2010; Edery, 2010). On the other hand, such cycles do not appear to affect the intact SCN, the central clock of the brain. The SCN itself becomes sensitive to ambient temperature cycles only if communication between its neurons is restricted, as is the case in early development (Herzog & Huckfeldt, 2003) or can be accomplished with application of tetrodotoxin (Buhr et al., 2010). This is an interesting observation with respect to aging, where communication between SCN neurons is likely to be compromised because of low expression of vasoactive intestinal polypeptide (VIP), an essential factor in electrical synchronization of SCN neurons (Maywood et al., 2006). In humans,

the decrease in VIP occurs in a gender-specific way, i.e. in males mostly (Swaab et al., 1996). Thus, it may be that exogenous temperature cycles have the capacity to enhance sleep-wake rhythms more prominently at high age, where rhythms are most vulnerable and associated with well-being (Carvalho-Bos et al., 2007).

*Support for an effect of skin temperature on vigilance in humans*

What is, in humans, the current observational support for an association between skin temperature and vigilance, operationalized as the ability to initiate or maintain sleep or alert wakefulness? First, constant routine and forced desynchrony studies provide unequivocal observational support that people sleep best while they head towards the trough of their 24-hour core body temperature and perform best around its peak (Wright et al., 2002). Constant routine protocols fix posture, activity, light, behavioural state and food intake over a prolonged period of time. These normally give confounding effects because of coinciding with the transition between wake and sleep or their preferred circadian phase of occurrence. In forced desynchrony protocols, sleep-wake cycles of more (e.g. 28 hrs) or less (e.g. 20 hrs) than 24 hour are implemented. The endogenous biological clock cannot keep pace with these periods, so that, if continued long enough, effects of its near-24-hr rhythms can be deconvolved from the effects of the imposed non-24 hr rhythm. Unfortunately, because skin temperature was usually not measured during these studies, the relative contribution of the inversely related core and skin temperature changes to the variance in vigilance could not be evaluated. A number of studies that specifically investigated spontaneous or indirectly experimentally induced fluctuations in skin temperature however, strongly support an association with vigilance. Healthy people fall asleep more easily if their skin temperature or bed temperature is mildly increased (Kräuchi et al., 1999, 2000; Weysen et al., 2010). The same association was shown for people with a vasospastic syndrome, who have a lower temperature of their hands and tend to have difficulties falling asleep (Pache et al., 2001); and for narcoleptic patients, where skin temperature is correlated to their daytime sleep propensity (Fronczek et al., 2006).

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.

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### Scope of this thesis

Most of the aforementioned studies focused on the relationship between skin temperature and sleep. However, even though sleep and wakefulness are closely related, it does not necessarily need to be the case that what applies for sleep, can be generalized to the wake state. This thesis therefore addresses the association between skin temperature and the level of vigilance during wakefulness. More specifically, this thesis primarily aims 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 addresses brain areas and mechanisms that could be involved in the link between fluctuations in vigilance and skin temperature. Finally, the thesis addresses 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:

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### 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.

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. Examining the correlation between vigilance and thermoregulation would increase our understanding of the brain mechanism of ultradian variation in vigilance level. Furthermore, it would reveal the possible contribution the assessment of spontaneous fluctuations in skin temperature could make in estimating the risk of lapses of vigilance and long reaction times.

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. Understanding the effect of sleep deprivation is not only of academic interest, but also of crucial importance from an applied point of view. We propose that information on skin temperature fluctuations could be of aid 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.

The fourth and fifth chapter aim to contribute to understanding the brain mechanisms involved in the relationship between skin temperature and vigilance. The **fourth chapter** describes 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 behaviour allowed us to determine if the correlation between skin temperature and lapses in vigilance is not only visible in behavioural output associated with vigilance, but if this correlation is mediated through altered cerebral activity associated with attention.

The **fifth chapter** will focus 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.

## Chapter 1

The **sixth chapter** will focus on the practical application of the knowledge acquired on the association between skin temperature, sleep and vigilance. 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. 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 has been found to be closely related to sleep onset (Kräuchi et al., 1999; Lack & Gradisar, 2002), we therefore examined if the addition of skin temperature measurements to actigraphy can improve sleep and wake detection.

The **seventh chapter** will offer a summary of the findings so far, and will reflect on the mechanisms behind the correlation of skin temperature, sleep and vigilance. This chapter also includes a discussion on how our findings can be practically implemented, and suggest directions for future research.

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