Skin Temperature, Sleep and Vigilance

Bart Te Lindert¹

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Abstract

A large number of studies showed a close association between the 24-hour rhythms in core body temperature and sleep propensity. More recently, studies have commenced to elucidate an intriguing association of sleep with *skin* temperature as well. The present chapter addresses the association of sleep and alertness with skin temperature. It discusses whether the association could reflect common underlying drivers of both sleep propensity and skin vasodilation; whether it could reflect efferents of sleep-regulating brain circuits to thermoregulatory circuits; and whether skin temperature could provide afferent input to sleep-regulating brain circuits. Sleep regulation and concomitant changes in skin temperature are systematically discussed and suggest three parallel factors: a circadian clock mechanism, a homeostatic hourglass mechanism, and a third set of sleep-permissive and wake-promoting factors that gate the effectiveness of signals from the clock and hourglass in the actual induction of sleep or maintenance of alert wakefulness. The chapter moreover discusses how the association between skin temperature and arousal can change with sleep deprivation and insomnia. Finally it addresses whether the promising laboratory findings on the effects of skin temperature manipulations on vigilance can be applied to improve sleep in everyday life.

Introduction

The previous chapter (by Ronald Szymusiak) discussed the long-known association of sleep with the 24-hour rhythm in core body temperature. A growing number of more recent studies commenced to elucidate an intriguing association of the sleep-wake rhythm with *skin* temperature as well. Like core body temperature, skin temperature shows a diurnal rhythm in synchrony with the rhythm in sleep and wakefulness. In fact, the declining part of the circadian rhythm in core body temperature is mainly determined by an increase skin blood flow. This increase results in a higher skin temperature, which facilitates heat loss to the environment (Kräuchi and Wirz-Justice, 1994).

The present chapter addresses the association of sleep with skin temperature in detail. For a detailed overview of the functional architecture of the thermoregulatory system, see Romanovsky (2007). In general, the association between time-varying sleep and skin temperature can reflect (a combination of) three scenarios: first, changes in both variables are driven by changes in a common underlying third variable; second, changes in sleep drive changes in skin temperature; and third, changes in skin temperature could affect sleep (Figure 1). These three scenarios should be considered when evaluating the association of sleep with skin temperature. Each of the scenarios generates a different prediction for the outcome of experimental studies that manipulate sleep, skin temperature, or both.

The first scenario could occur if the hierarchically most central brain circuits that regulate the diurnal timing of sleep would not only top-down affect downstream sleep-effectuating circuits, but in parallel as well downstream thermoregulatory circuits. The second scenario would mean that sleep-effectuating circuits of the brain would themselves provide direct efferents to thermoregulatory circuits and affect their neuronal activity. And finally, the third scenario could occur if changes in skin temperature - irrespective of whether they are internally or externally generated - would provide afferent input to the brain circuits that regulate sleep and alertness, and affect their neuronal activity.

<Insert Figure 1>

In order to be able to evaluate to what extent each of these three scenarios contributes to the association between sleep and skin temperature, the part "Sleep regulation: clock, hourglass and gates" first provides a concise overview of how sleep propensity and arousal state can be modulated across the 24-hour day by circadian, homeostatic, sleep-permissive and wake-promoting factors. The second part "Phenomenology of clock-, hourglass- and gate-associated changes in skin temperature" will discuss how skin temperature changes in association with changes in these three factors. Subsequently, the third part "The link between

changes in skin temperature and arousal state" systematically discusses the different scenarios of causality between changes in skin temperature and changes in arousal state. This chapter closes with two practical parts. The first addresses whether disrupted sleep involves an altered link between skin temperature and arousal, and the second addresses whether skin temperature manipulations can be applied to improve sleep in practice.

Sleep regulation: clock, hourglass and gates

The ease of sleeping at any particular time of the 24-hr day has been proposed to involve two processes (Borbély, 1982; Daan et al., 1984; Dijk and Czeisler, 1995; Borbély et al., 2016).

The first process is a circadian (circa=about, dies=day) process 'C' that promotes or inhibits sleep in a *clock*-like fashion according to the phase of the ~24 hr cycle (Mistlberger, 2005). The central clock of our brain is located in the hypothalamic suprachiasmatic nucleus (SCN) and drives many physiological and behavioral rhythms including the promotion of sleep during one part of the circadian cycle and wakefulness during the other part. Moreover, molecular clock mechanisms are found in every single cell (see review by Dibner et al., 2010). Temperature can affect central and peripheral clock mechanisms (Dibner et al., 2010; Van Someren, 2003). 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 cyclic changes in environmental temperature as a result of heating up by radiation from the sun and cooling down during its nocturnal absence.

The second process is a homeostatic process 'S' that promotes sleep pressure increasingly according to the accumulated time awake in an *hourglass*-like fashion. While the pressure for sleep increases the longer we are awake, it dissipates during sleep. As soon as we wake up, the process starts over, like turning an hourglass at every transition between sleep and wakefulness (Achermann et al., 1993; Leemburg et al., 2010; Van Someren, 2010; Borbély et al., 2016). The neurobiological mechanisms underlying the hourglass could involve neuronal-activity dependent accumulation of interstitial adenosine (Porkka-Heiskanen et al., 1997), of synaptic density (Tononi and Cirelli, 2014), and of cytokines (Krueger et al., 2011).

Process 'C' and 'S' account for much of the variance in the probability of being asleep or awake at any particular time of day in laboratory conditions, and thus seem *necessary* components for sleep regulation. Less attention has been paid to the question whether these components are also *sufficient* to determine the probability to fall – or stay – asleep (Romeijn et al., 2012a). While this may seem to be the case, laboratory conditions hardly ever resemble the conditions of everyday life. From an evolutionary perspective, it seems necessary for an organism to check whether a few conditions other than appropriate sleep pressure according to 'C' and 'S' have been fulfilled prior to falling asleep. It is not wise to fall asleep in the presence of danger, e.g. of predators, or in the presence of scarce opportunities, like the presence of food that may be gone after a period of napping or sleep. It is likewise not wise to fall asleep in thermoregulatory challenging conditions. Prior to giving in to sleep, one would want to make sure that overheating or undercooling would not occur. This third type of *gate*-like processes has been coined 'sleep-permissive and wake-promoting factors' (Romeijn et al., 2012a).

Phenomenology of clock-, hourglass- and gate-associated changes in skin temperature

Clock

A circadian modulation of skin temperature regulation has been observed in thermally challenging conditions. During the night, humans show less cold-induced peripheral vasoconstriction: this seems to start only if core temperature falls below 36.0°C (Tayefeh et al., 1998; Ozaki et al., 2001). In the early morning, cold-induced vasoconstriction is restored and may even show its diurnal maximal response (Hildebrandt, 1974).

A circadian modulation of skin temperature has also been observed in several studies in

thermal neutral conditions, which do not activate thermoregulatory defense mechanisms like shivering or sweating. Both in laboratory animals and in humans, most of the well-known diurnal rhythm in core body temperature is determined by a diurnal rhythm in skin vasodilation and the consequent skin temperature increase and heat loss, and much less by the diurnal rhythm in heat production (Young and Dawson, 1982; Marotte and Timbal, 1982b; Fuller et al., 1985; Gordon, 1990; Kräuchi and Wirz-Justice, 1994; Refinetti and Menaker, 1992). The circadian modulation of resting state metabolic heat production in young adult humans is only about 17% (Kräuchi and Wirz-Justice, 1994). Under well-controlled laboratory conditions when people are kept awake, the circadian rhythm in distal skin temperature, i.e. the feet, hands and ears, shows a strong amplitude that is out of phase with the rhythm in core temperature: low during the day and high at night (Kräuchi and Wirz-Justice, 1994). Under those conditions, the circadian pattern of proximal skin temperature has a smaller amplitude and varies in phase with core temperature: high during the day and low at night. The profiles are shown in Figure 2.

<Insert Figure 2>

However, when sleep is normally allowed, both proximal and distal temperature reach values that are significantly higher than values seen during wakefulness (Kräuchi et al., 1997a; Marotte and Timbal, 1982a; Marotte and Timbal, 1982b) (Figure 3). It is important to note that the diurnal rhythm in skin temperature is not only a matter of autonomic thermoregulation, but is also strongly supported by behavioral thermoregulation. People use bedding to create a sleeping microclimate of about 34 °C (Vokac and Hjeltne, 1981; Muzet et al., 1984), which is much higher than the usual daytime temperature and even higher than thermoneutrality (± 29 °C). This finding is important because it suggests that behavioral thermoregulation aims at heat preservation during sleep, rather than the heat loss that is suggested by the autonomic regulated increased skin blood flow. It has been noted that increased skin blood flow does not necessarily have to be interpreted as an attempt to lose heat; it could as well serve maintenance of the skin in its role as a primary barrier in host defense (Van Someren, 2006).

<Insert Figure 3>

In summary, animal and human studies suggest increased skin temperature during the phase of the diurnal cycle where most sleep occurs. With respect to the functional neuroanatomy underlying the circadian rhythm in skin temperature, it has been shown that projections of the SCN to the hypothalamic subparaventricular zone mediate the circadian modulation of thermoregulation (Lu et al., 2001). In addition, a multisynaptic projection to the pineal is important for the circadian modulation of skin temperature. Because the SCN output to the pineal is diurnally modulated, melatonin is only secreted during the night. In humans, circulating melatonin results in a very strong peripheral vasodilation. This heat loss-promoting property of melatonin has been estimated to even account for 40% of the amplitude of the circadian rhythm in core temperature. The strong effect of melatonin on skin blood flow may act both through melatonin receptors in the preoptic area / anterior hypothalamus (POAH) and receptors in the vasculature endothelium (Krause and Dubocovich, 1990; Viswanathan et al., 1990; Viswanathan et al., 1993; Urata et al., 1999; Aoki et al., 2006; Aoki et al., 2008).

Hourglass

Many parents have observed red blushing ears and cheeks in their tired toddlers, and have learned to interpret it as a bedtime signal. The observation suggests that sleep propensity increases skin blood flow - and thus skin temperature - in the distal skin areas that are most strongly involved in the regulation of heat loss because of their richness in arteriovenous anastomoses. Another common experience is 'feeling cold' after prolonged sleep deprivation, as if we are indeed losing too much heat. In contrast to how common these observations are,

relatively few experimental studies systematically investigated how an increase in sleep propensity affects skin temperature under comfortable thermoneutral circumstances. Prolonged sleep deprivation studies in rats confirm a progressive decline in core body temperature, which occurs in spite of increased food intake and energy expenditure (Rechtschaffen et al., 2002). Also, it has been reported that sleep-deprived humans are more vulnerable to heat loss during cold thermal challenges (Landis et al., 1998; Opstad and Bahr, 1991; Young et al., 1998; Savourey and Bittel, 1994).

In contrast, the best-controlled experimental study on the effect of sleep deprivation under comfortable thermoneutral circumstances, reported no effect on a heat-loss proxy measure calculated as the whole body distal-to-proximal skin temperature gradient (DPG). The finding suggested no effect of sleep deprivation on the thermoregulatory system (Kräuchi et al., 2006). It has been suggested however that the lack of effect in this study might have to do with keeping the subjects in a semi-supine posture throughout the experiment (Romeijn et al., 2012b). A supine posture is known to facilitate vasodilation in the skin, bringing it near to its maximum and allowing only limited headroom for any further increase. In everyday life, sleep deprived people will rather try to maintain an upright or sitting posture when trying to resist falling asleep. And in such an upright position, thermoregulatory skin blood flow has to compete with baroreceptor-mediated blood flow regulation (Brothers et al., 2010): the orthostatic challenge unloads baroreceptors, resulting in the baroreceptor reflex that regulates blood flow to prevent venous pooling of blood in the lower limbs.

One experimental study therefore evaluated the effect of sleep deprivation on skin temperature, while participants maintained an upright sitting posture (Romeijn et al., 2012b). Sleep deprivation induced an increase in the temperature of the feet. Interestingly, while in well-rested people the natural fluctuations in the distal temperatures of the feet and hands are positively correlated, this association inversed after sleep deprivation. Sleep deprivation thus 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.

In summary, most studies suggest that distal skin temperature can increase with increasing sleep propensity. Insofar as central nervous system accumulation of adenosine is involved in the homeostatic sleep propensity process S (Landolt, 2012; Urry and Landolt, 2015), it is of relevance to note that pharmacological activation of central adenosine receptors can indeed induce vasodilation of skin arterioles and consequently an increase in skin temperature (Proctor et al., 1991). Other than this study there is a scarcity on the functional neuroanatomy of how sleep propensity could result in skin warming.

Sleep-permissive and wake-promoting gates

In real life conditions, the circadian and homeostatically driven propensity for sleep are implemented only when some crucial conditions are met. The most recognizable condition may be that one needs to attain an appropriate posture. If one desires to sleep, most of us succeed much better when lying down (Aeschbach et al., 1994; Nicholson and Stone, 1987) than in an upright posture. Alternatively, 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., 2000; Caldwell et al., 2003; Cole, 1989; Kräuchi et al., 1997b). A supine position can thus be considered a sleep-permissive condition whereas an upright standing posture is wake-promoting condition. Other examples of wake-promoting versus sleep-permissive conditions are, respectively; a brightly lit versus dark environment (Van De Werken et al., 2010); being comfortably warm versus cold (Palca et al., 1986; Sewitch et al., 1986); being safe versus in danger (Halasz, 1998; Charuvastra and Cloitre, 2009); and feeling well versus being in pain (Drewes et al., 1997; Lavigne et al., 2001) or stressed (Akerstedt et al., 2007; Vandekerckhove et al., 2011). All these conditions alter skin temperature. Skin temperature changes with posture (Tikuisis and Ducharme, 1996; Nakajima et al., 2002), with environmental light (Cajochen et al., 2005; Van De Werken et al., 2010), with fear (Lack et al., 2008), with nutritional status (Kräuchi et al., 2000), with pain (Lei et al., 2008; Iannetti et al., 2004; Hampf, 1990) and with stress (Rimm-Kaufman and Kagan, 1996). Interestingly,

wake-promoting conditions have in common that they tend to be associated with *lower* skin temperatures. In contrast, *sleep-permissive* conditions have in common that they tend to be associated with *higher* skin temperature. If the neuronal circuits that implement the clock and hourglass are sensitive to skin temperature, the changes in skin temperature elicited by wake-promoting and sleep-permissive conditions may thus (also) indirectly moderate the efficiency by which the clock and homeostat manage to initiate or maintain sleep or wakefulness.

In conclusion, clock-, hourglass- and gate-associated changes in skin temperature point in the same direction: a higher probability for sleep goes hand in hand with a higher skin temperature. The overview above moreover indicates that an increase in skin temperature is not just a consequence of being asleep. Indeed, controlled studies showed that sleep initiation follows rather than precedes skin warming by increased skin blood flow (Baker et al., 2005; Kräuchi et al., 2005). Finally, it can be questioned whether this increase in skin blood flow and skin temperature should be interpreted as an autonomic thermoregulatory effort to promote heat loss. In fact, sleep-related behaviors suggest the opposite, they are aimed at restricting heat loss. Examples include the insulated warm microclimate by means of warm clothing and bedding in humans, and behaviors like curling up, huddling and cuddling in animals. The next section will address whether activity of sleep-wake regulating neuronal circuits affect skin temperature and can in return be modulated by changes in skin temperature.

The link between changes in skin temperature and arousal state

Parallel changes in sleep propensity and skin temperature?

A parallel between sleep and skin warming has been proposed to reflect the fact that a major brain region driving skin vasodilation, the POAH, is also of key importance in sleep regulation (Van Someren, 2000). Even at the cellular level, there is an overlap: neurons that are sensitive to heat (warm sensitive neurons, WSN) have been shown to also change their firing pattern preceding and during sleep. The association between heat loss and preparedness to sleep may thus in part reflect a common underlying factor, involving POAH neurons with multiple functions: in sleep regulation and in thermoregulation. However, this interpretation cannot account for the finding that sleep impairment in POAH-lesioned animals can be restored by placing them in a warm environment (Szymusiak et al., 1991).

Does sleep alter skin temperature?

Sleep, relative to wakefulness, is associated with a redistribution of heat, from the core, to the periphery of the body (Kräuchi et al., 1999). Hypotheses on the causal relation have focused disproportionately on the effect of sleep on this redistribution and the arousal state. However, the redistribution of heat that coincides with sleep is to a large extent due to a change in body position and occurs even when sleep is not allowed (Van Dongen et al., 1996; Almirall et al., 1993; Beersma and Dijk, 1992). The contribution of sleep to the decline in core temperature can be as small as 10% of the amplitude of the core circadian temperature rhythm (cf. Refinetti and Menaker, 1992). Moreover, the decline in core temperature precedes rather than follows sleep. In rats hypothalamic temperature starts to drop 2 minutes before the transition from wake to sleep (Gao et al., 1995). In humans, the diurnal rhythm in core temperature starts to decline several hours before sleep onset, and starts to increase two to four hours before wake onset (Aschoff, 1970; Geschickter et al., 1966; Reinberg and Smolensky, 1983). Heat loss by skin vasodilation, and thus skin warming, commences about half an hour before sleep (Geschickter et al., 1966). Although skin vasodilation was estimated to be 84% higher during sleep than during wakefulness, 30 to 40% of the increase occurs already at bedtime (Sindrup et al., 1991; Sindrup et al., 1992). Indeed, the ease of falling asleep correlates best with the amount of heat dissipation preceding sleep (Kräuchi et al., 1999), in line with the early idea of Magnussen (1943; 1939) that skin warming by peripheral vasodilation indexes 'Schlafbereitschaft', i.e. the readiness for sleep.

Within sleep, there are some observations that different sleep stages have different thermoregulatory profiles. Systemic low vascular resistance seems most marked during Slow wave sleep (SWS). Rapid Eye Movement (REM) sleep seems best characterized by an impaired homeostatic thermoregulation (Parmeggiani, 1988; Parmeggiani et al., 1999). During REM sleep, increased sympathetic-nerve activity can result in vasoconstriction in the skin. However, during occasional muscle twitches that can occur during REM, this sympathetic output drops sharply and leads to a release of this vasoconstriction (Somers et al., 1993). These opposed phenomena result in a marked fluctuation in systemic vascular resistance during REM sleep (cf. Liguori et al., 2000).

Can skin temperature affect sleep?

If skin warming by peripheral vasodilation indexes preparedness for sleep so well, is it conceivable that activity of thermoreceptors in the skin could feed back to sleep regulating circuits in the brain? This possible relationship was suggested by Roberts and Robinson (1969), but received little attention in experimental studies until about a decade ago. The brain monitors skin temperature by means of cold and warm receptors that convey their information through the thermosensitive afferent pathways (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 including sleep regulation (reviewed in Van Someren, 2000). Support for an effect of skin temperature on sleep and arousal will be discussed more extensively in the next paragraphs.

Skin temperature-sensitive brain areas involved in sleep regulation or expression.

Of the brain areas that are involved in sleep regulation and show sensitivity to changes in skin temperature, the POAH stands out. Animal studies showed that mild skin warming by means of e.g. a water-perfused wrap, induces firing patterns of POAH neurons which resemble those that occur spontaneously during sleep (McGinty and Szymusiak, 1990; Alam et al., 1995; McGinty et al., 2001). Similar congruency was found in the posterior hypothalamic area. Other areas where mild skin warming elicited sleep-like neuronal activity include the cerebral cortex and midbrain reticular formation. Details on the neuroanatomical pathways that could mediate the effect of skin temperature on the regulation of sleep and arousal can be found in a previous review (Van Someren, 2000). The conclusion of the overview was that a mild increase in skin temperature could drive neurons in several brain areas towards more sleep-like firing patterns. Although many of the studies involved animals, activation of a brain area compatible with the POAH by means of thermal manipulation has also been shown in humans (Egan et al., 2005). Not only subcortical effects of mild skin temperature manipulations have been demonstrated in humans. Craig et al. (2000) showed deactivation of the insula with mild skin warming. This is an interesting observation, because the insula represents the cortical area where, if deactivated, the slow waves that are typical for deep sleep show the highest probability of being ignited (Murphy et al., 2009). Based on these and other findings a number of observational and experimental studies were undertaken to evaluate whether a mild increase in skin temperature within the thermoneutral zone might lower the arousal level and promote sleep.

Support for an effect of skin temperature on vigilance in humans

Human observational studies that investigated spontaneous induced fluctuations in skin temperature support an association with vigilance, where the latter has been operationalized as the ability to initiate or maintain sleep or alert wakefulness, or subjective sleepiness. In healthy volunteers, falling asleep is easier if the temperature of the skin or bed is in the higher part of the comfortable thermoneutral range (Kräuchi et al., 1999; Kräuchi et al., 2000; Weysen et al., 2010). The same has been shown for people with cold hands due to Raynaud's disease or vasospastic syndrome (Pache et al., 2001) and people suffering from narcolepsy (Fronczek et al., 2006). When it is undesirable to fall asleep, the maintenance of alert wakefulness and high performance is best during the troughs of normal fluctuations in distal skin temperature (Romeijn and Van Someren, 2011), possibly most reliably predicted by the

temperature of the pinna of the ears (Romeijn et al., 2012b). Both in demented and non-demented elderly people, individuals with a higher daytime skin temperature also report more daytime sleepiness (Most et al., 2012).

In addition to these observational studies, there is stronger, experimental, support for an effect of skin temperature on vigilance. Skin temperature can be manipulated precisely within the comfortable thermoneutral zone using a water-perfused thermosuit. An advantage of the method is that it is possible to perform subtle manipulations that do not affect core body temperature. Using this experimental approach, it has been shown that very mild cooling, especially of the proximal skin area, enhances sustained task performance and the ability to maintain wakefulness (Raymann and Van Someren, 2007; Fronczek et al., 2008b). Very mild skin warming on the other hand promoted sleep onset (Raymann et al., 2005; Raymann and Van Someren, 2008), slow wave sleep and sleep maintenance (Raymann et al., 2008; Fronczek et al., 2008a). Of note, these effects were not secondary to thermal comfort and could even occur in spite of slightly lower thermal comfort in the warmer range of the manipulation (Raymann et al., 2005).

The findings support a causal effect of skin temperature on vigilance. It is important to note that all these studies manipulated temperature only within the thermoneutral zone. The manipulations thus were not stressful, nor activated thermoregulatory defense mechanisms, which would impede both sound sleep and optimal alert performance. Figure 4 schematically shows how the thermoneutral skin temperature range that is optimal sleep may be slightly higher than the skin temperature range that is optimal for alert performance.

<insert Figure 4 >

Does disrupted sleep involve an altered link between skin temperature and arousal?

Sleep deprivation

Few studies addressed whether the link between skin temperature and arousal changes if sleep is disturbed. As has been mentioned above, enforced sleep deprivation affects the coordination between skin blood flow fluctuations of the upper and lower limbs when people are exposed to the orthostatic challenge of an upright posture (Romeijn et al., 2012b). Under these conditions, the inverse skin temperature fluctuations of the hands and feet are no longer predictive of performance on a sustained attention task, like they were when the same people were measured under well-rested conditions. Predictive value for performance was only maintained for the temperature fluctuations of the pinna of the ears, which represent the most upper arteriovenous anastomose-rich skin area of the body. Temperature fluctuations of the pinna of the ears were also associated with fluctuations in electroencephalographic (EEG) power in the beta band - suggestive of increased effort - and with a longer latency of the event related potential P300 peak in response to visual stimuli - suggestive of slower processing (Ramautar et al., 2013). Consequently, the ears may be the most robust sites for skin temperature measurements in practical applications to predict vigilance if the history of sleep debt is unknown.

Insomnia

Other than the name of the disorder suggests, insomnia is very unlike sleep deprivation in many ways. Insomnia is a common burden in the general population (Morin et al., 2006). Insomnia Disorder can be diagnosed if subjective problems with initiating sleep, maintaining sleep or waking up too early occur at least three nights a week, persist for at least three months and are accompanied by at least one form of subjective daytime impairments like fatigue, malaise or difficulties with concentration (American Psychiatric Association, 1994). Insomnia is characterized by fragmented and sometimes short sleep rather than a complete absence of sleep - although it may be experienced like a complete absence of sleep for some. Whereas experimental sleep deprivation of good sleepers induces an increasingly irresistible sleep propensity, people with insomnia have difficulty falling asleep also during daytime. A

similar dissociation was reported in studies that use the sustained attention reaction time paradigm that showed sensitivity for skin temperature manipulation in several of the studies mentioned above: whereas sleep deprivation induces a slowing of reaction times, people with insomnia may even be faster than controls without sleep complaints (Altena et al., 2008). Also in their thermoregulatory profile, insomnia differs from sleep deprivation. While sleep deprivation can make people sensitive to undercooling (Landis et al., 1998), insomnia is rather characterized by a state of generalized arousal including hypermetabolism and elevated core body temperature (Lack et al., 2008).

How does insomnia affect the link between skin temperature and arousal? A comparative study on the effect of mild skin warming and cooling on a sustained attention reaction time task suggests an increased sensitivity in people suffering from insomnia (Raymann and Van Someren, 2007). On the other hand, people suffering from insomnia showed less pronounced effects of mild skin temperature manipulation on sleep onset latency (Raymann et al., 2007; Raymann and Van Someren, 2008) and on the EEG spectral power during sleep (Raymann et al., 2008). Concertedly, these observations suggest that people with insomnia are less likely to profit from the effect of optimal skin temperature on sleep, yet more likely to experience adverse effects of suboptimal warm skin temperature on performance during daytime. The latter is strongly supported by a recent study that used a novel multi-factor survey that systematically addresses subjectively experienced thermoregulation and thermosensitivity: 240 people suffering from insomnia differed most strongly from 240 matched controls with the experienced adverse effect of warming up on fatigue (Van Someren et al., 2016). Also on most other factors queried by this survey, people with insomnia reported to be more sensitive. Interestingly, in strong contrast to the apparent high sensitivity to temperature, people with insomnia are *less* likely to discriminate the comforting effect that a nice thermal stimulus can have (Raymann and Van Someren, 2008), which may reflect a generalized deficiency in comfort sensing (Diaz et al., 2013). The deficiency could involve structural abnormalities in the orbitofrontal cortex, a brain area that is essential for the evaluation of thermal comfort (Kringelbach, 2005; Dunn et al., 2010). Several structural brain imaging studies indicate that people with a low gray matter density in a part of their orbitofrontal cortex are vulnerable to early morning awakening (Stoffers et al., 2012), insomnia (Altena et al., 2010; Winkelman et al., 2013; Joo et al., 2013), fragmented sleep (Lim et al., 2016) and low perceived sleep quality (Chao et al., 2014).

Can temperature manipulations be applied to improve sleep in practice?

A final topic to be addressed in the present chapter is whether it is possible to implement skin temperature manipulations at home in everyday life to improve sleep in normal sleeping conditions. Whereas the well-controlled lab studies applying thermosuits demonstrated proof-of-principle, the translation towards a practical application is not as easy as it may seem. The use of a regular electrical heating blanket for example was shown to actually disrupt sleep (Fletcher et al., 1999). A problem with this approach is that it does not only increase skin temperature but also core body temperature. It is well known that increasing core body temperature is not conducive to sleep. On the contrary, sleep is most easily induced and maintained on the downgoing slope of the 24-hr rhythm in core body temperature. The key question seems if it would be possible to keep skin temperature in the higher range or thermoneutrality, while simultaneously promoting heat loss to cool the core of the body.

A first physiological possibility to attain this goal is to use exercise, a hot bath or sauna in order to raise core body temperature about three hours prior to sleep. These body warming procedures may activate heat dissipation by skin vasodilation and consequently skin warming for several hours. Several studies showed that this procedure can improve sleep onset, but only about two-three hours after discontinuing the body warming, i.e. when core body temperature is back to normal or even lower because skin perfusion continues to be elevated (Horne and Shackell, 1987; Horne and Reid, 1985; Jordan et al., 1990; Bunnell and Horvath, 1985; Bunnell et al., 1988; Di Nisi et al., 1989; Kanda et al., 1999; Dorsey et al., 1996;

Dorsey et al., 1998; Dorsey et al., 1999; Sung and Tochihara, 2000). Unfortunately the restricted interval of increased sleep propensity makes this procedure suitable only to facilitate sleep onset and possibly sleep quality in the first hours of the night. Other approaches seem necessary to improve sleep later on in the night, for example to alleviate the very common complaint of early morning awakening that was amenable to improvement in well-controlled lab studies (Raymann et al., 2008).

A second, artificial, possibility to attain the goal to simultaneously mildly warming the skin while promoting heat loss to cool the core of the body at any time of the night may be possibly by means of a feedback-controlled bed warming system. The bed microclimate temperature that the skin is exposed to strongly determines skin blood flow and consequently the efficiency of dissipating heat from the skin to the microclimate. Studies that slowly warmed the skin showed that there is a critical temperature at which skin blood flow dramatically increases (Barcroft and Edholm, 1943; Fagrell, 1985; Vuksanović et al., 2008) (Figure 5). If it would be possible to maintain skin temperature just marginally above this critical temperature, heat loss to the environment would be promoted without the risk of 'injecting' heat from the environment back into the bloodstream that would occur at higher microclimate temperatures. Such closed loop manipulations may have to be adapted to individual differences in the exact temperature range where the steep increase in skin blood flow occurs. It remains to be evaluate whether such systems are indeed feasible, but it seems worth the effort of trying given the adverse consequences of disturbed sleep (Van Someren et al., 2015) and the unmet need of novel and better ways to improve sleep.

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Legends

Figure 1. Schematic representation of three scenarios on how sleep and skin temperature could interact. From top to bottom, the scheme shows the levels of brain, body, skin and environment. Sleep regulation and thermoregulation are shown as columns side by side. A first scenario is that a common central brain circuit affects both sleep and thermoregulation (1). In a second scenario (2), sleep-regulating brain circuits would project to thermoregulatory circuits. In the third scenario (3), changes in skin temperature - irrespective of whether they are internally or externally generated - would provide afferent input to the brain circuits that regulate sleep and alertness, and affect their neuronal activity. Note that a sleep-consolidating loop may evolve because two behavioral measures that are part of effectuating sleep (taking a supine posture and creating an insulating microclimate) both enhance skin warming.

Figure 2. Smoothed average human temperature curves, as measured under constant routine conditions for core (upper curve), proximal skin (second curve) and distal skin (lower curve) areas. Adapted from Kräuchi et al (1994), who kindly provided the data. The figure has been presented before in (Van Someren, 2006). Note the nocturnal increase in distal skin temperature, but not proximal skin temperature. The latter is in contrast to the habitual nocturnal increase in proximal skin temperature under natural sleeping conditions in a microclimate of 34-36°C, as shown in Figure 3.

Figure 3. Example of the profiles of core body temperature (grey line), mean proximal (thick black line) and mean distal (thin black line) temperature during three days under natural living conditions in a single case. For all temperature curves, outliers surpassing one interquartile distance from the Q25 or Q75 for either level or rate of change were excluded, after which missing data were linearly interpolated. Also shown are the time spent in bed (grey area) and activity level (black columns, arbitrary units from simultaneous actigraphic recording). Note that the marked and simultaneous nocturnal elevation of both proximal and distal temperature during the time in bed never occurs during wakefulness. During the sleep period, proximal and distal skin temperature differ minimally and are both above 35°C. During wakefulness, proximal and distal skin temperature differ most of the time and do not exceed 33°C for any prolonged period of time. Adapted from Van Marken Lichtenbelt et al. (van Marken Lichtenbelt et al., 2006) and presented before in (Van Someren, 2006).

Figure 4. 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 differ slightly for vigilance-promoting and sleep-promoting capacities. From (Romeijn et al., 2012a).

Figure 5. Correlation between skin temperature and resting blood flow velocity (CBV) in one nailfold capillary of a healthy 37-year-old man. Notice the marked increase in CBV occurring at 34 °C. Figure and legend text above are after Fagrell and Intaglietta (1977), who investigated the effect of skin warming on skin blood flow. The figure illustrates that warming the skin to at least 34 °C can dramatically increase skin blood flow and may theoretically improve heat loss to the environment. From (Romeijn et al., 2012a).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5