Roy Raymann

Mild skin warming, a non-pharmacological way to modulate sleep and vigilance

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Mild skin warming, a non-pharmacological way to modulate sleep and vigilance

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Roy Joan Eli Marie Raymann

geboren te Venlo

promotoren: prof.dr. E.J.W. van Someren

prof.dr. D.F.Swaab

FESTINA LENTE CAUTA FAC OMNIA MENTE

"Haast je langzaam, doe alles met je verstand."

Wapenspreuk gemeente Venlo

Contents

INTRODUCTION

Chapter 1

Sleep, vigilance and thermosensitivity

Nico Romeijn
Roy J.E.M. Raymann
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Bart te Lindert
Wisse P. van der Meijden
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Co-authored with Nico Romeijn and Eus van Someren, based on a part of Pflügers Archiv - European Journal of Physiology 2012(463), p. 169–176.

Summary

The regulation of sleep and wakefulness is well-modeled with two underlying processes: a circadian and a homeostatic one. So far the parameters and mechanisms of additional sleep-permissive and wake-promoting conditions have been largely overlooked. The present thesis focuses on one of these conditions: the effect of skin temperature on the onset and maintenance of sleep, and daytime vigilance. 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. Skin temperature changes with environmental heat and cold, but also with posture, environmental light, danger, nutritional status, pain and stress. Its effect on the brain may thus moderate the efficacy by which the clock and homeostat manage to initiate or maintain sleep or wakefulness. This introductory chapter provides a brief overview of the neuroanatomical pathways and physiological mechanisms by which skin temperature could affect the regulation of sleep and vigilance and outlines the contents of the thesis.

Introduction

In order to provide an intuitive idea on the focus of the present thesis on sleep, vigilance and thermosensitivity one may try to imagine two situations, likely familiar to most researchers and clinicians reading this thesis. 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[9,10,13,29]. If one desires to sleep on the other hand, most of us succeed much better when lying down[1,39]. Although most sleep researchers agree with these answers, are they supported by current models on the regulation of sleep and alertness?

Sleep regulation: are a clock and an hourglass sufficient?

As reviewed many times before[5,14,16], the core model of sleep-wake regulation consists of a circadian component and a homeostatic component. 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 behavioral rhythms including the rhythm in sleep and wakefulness. In humans, this central clock promotes sleep during the night and wakefulness during the 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[15]. 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.

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. 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[43], to an increase in synaptic density during wakefulness[50], and to cytokines[30].

Back to our question: how does the consensus model of sleep regulation account for the quite familiar experience that it is easier to stay awake in an upright position and easier to fall asleep in a supine position? Does this simple change of posture phase-shift our clock? Does it tilt the hourglass? Does it affect these processes at all? The answer seems to be a definitive no. The clock & hourglass model has brought us very far in understanding the regulation of sleep and wakefulness. 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, like having attained an appropriate posture. Being in a supine position is being in a *sleep-permissive condition*. Being upright is being in a *wake-promoting condition*[1,9,10,13,29,39]. Posture is just one of several examples of permissive and promoting conditions. Are we as likely to maintain the state of sleep or wakefulness in a brightly lit versus dark environment?[52] And, whatever state the clock and hourglass tells our sleep-regulating systems to implement, are we going to fall asleep in case of acute cold[42,47], heat[22,40], danger[12,20], pain[17,32] or stress[2,51]? 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 focuses on one of these conditions: the effect of skin temperature on the onset and maintenance of sleep, and vigilance. Skin temperature is quite well-suited to provide the brain with information on sleep-permissive and wake-promoting conditions, because skin temperature changes with most sleep-permissive and wake-promoting conditions, if not all of them. Because the skin is rather *poikilotherm* (poikilio = varied or irregular, therm = temperature), its temperature changes with environmental heat and cold[4]. It changes also with posture[38,49], environmental light[8,52], anxiety[31], food intake[46], pain[21,25,33] and stress[44]. 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 modulated by environmental and endogenous processes. The human skin is under the influence of environmental temperature. In addition, skin temperature depends on endogenous central and autonomic nervous system processes that actively regulate blood flow through the skin[26]. Variation in perfusion of the skin with the ~37˚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[23]. 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[54].

Skin temperature and sleep-wake regulation

Indeed, several neuronal systems that are directly or indirectly involved in sleep-wake-regulation are sensitive to temperature[55,56,57]. 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* (ecto =outside, therm = temperature), 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* (endo =inside, therm = temperature), 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 behavior 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?

As extensively reviewed elsewhere[54], 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 of the 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[3,35,36]. 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. 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 seems 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[6,7,18]. 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[24] or can be accomplished with application of tetrodotoxin[7]. 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[34]. In humans, the decrease in VIP occurs in a gender-specific way, i.e. in males mostly[48]. Thus, it may be that temperature cycles have the capacity to enhance sleep-wake rhythms more prominently at high age, where rest-activity rhythms are most vulnerable and strongly associated with well-being[11]. It is therefore of considerable interest to review in detail the mechanisms and functional implications of age-

related changes in thermoreception and temperature regulation and their circadian modulation. We do so extensively in Chapter 2, which has been published in Ageing Research Reviews 2002(1), p. 721-778.

Support for an effect of skin temperature on vigilance in humans

What is, in humans, the *observational* support for an association between skin temperature and vigilance, operationalized as the ability to initiate or maintain sleep or alert wakefulness? On *anecdotal* level we mention the sleep promoting effect of the warmth of the sun, when lying on the beach, the red earlobes of young children getting tired, the use of the fan and air conditioner in the car to stay alert when driving during a hot summer day, or the warm rosy feeling after being deprived from sleep.

On *scientific* level 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[59]. Constant routine protocols fix posture, activity, light, behavioral state, and food intake over a prolonged period of time in order to minimize the confounding effects of the aforementioned conditions on wake and sleep and/or circadian phase. In forced desynchrony protocols, sleep–wake cycles of more (e.g., 28 h) or less (e.g., 20 h) than 24 h are implemented. Since the endogenous biological clock cannot keep pace with these long or short periods, the effects of its near-24-h rhythms can be disentangled from the effects of the imposed non-24-h rhythm. Unfortunately, because skin temperature has usually not been 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 higher[27,28,58]. 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[41]; and for narcoleptic patients, where skin temperature is correlated to their daytime sleep propensity[19]. With respect to the ability to maintain alert wakefulness, healthy people perform better during the troughs of their normal daytime skin temperature fluctuations[45]. Findings in both healthy elderly people and demented elderly people also indicate more complaints on daytime sleepiness in those who have elevated daytime skin temperature[37].

These correlational studies can be interpreted as merely indicating that skin temperature reflects an underlying process of vigilance regulation. But what is the actual *experimental* support for a

causal contribution of skin temperature to vigilance regulation in humans? At the onset of the series of studies presented in this thesis, such support was lacking. Of course, several studies had shown that extremely low or high temperatures impede both sleep and sustained attention, which are of secondary interest when survival is at stake. In case of extremely low or high temperatures, the organism should address all its resources for behavioral and autonomic thermoregulation. However, no previous human studies measured sleep and sustained attention while selectively and systematically manipulating skin temperature within the thermoneutral range - where a thermoregulatory response is not necessary.

In short, literature shows that not only the observed drop in core body temperature, but also the increase in skin temperature might play a sleep permissive role. Temperature sensed at skin level serves as input to the sleep regulating brain areas. Mild skin warming, within the thermoneutral range, should be able to induce a sleep permissive state and as such facilitate sleep. To test to what extent skin and core body temperature affect sleep, we manipulated both skin temperature and core body temperature simultaneously within the thermoneutral range in young health adults. Next to that, we applied the same interventions in 2 patient groups that have both altered thermoregulation and sleep complaints. It is known that thermoregulation in elderly is compromised (see Chapter 2) and it recently has been shown that daytime skin temperature regulation is altered in narcoleptic patients[19]. In these patient groups we aimed at improving both sleep and vigilance by changing using mild skin warming.
It has been shown that the firing rate of warm sensitive neurons involved in sleep- or arousal-regulation is primarily dependent of the skin temperature and only secondary to the core body temperature. When the skin is cold, the firing rate stayed low, no matter how the brain temperature changed, whereas the firing rate increased when the skin was warmed only slightly[54]. Based on this observation, we expect skin temperature manipulations to be more effective than core body temperature manipulations in changing sleep propensity. Since the density of the thermoreceptors in the distal skin areas (i.e. hands and feet) is rather large as compared to density of the thermoreceptors in the proximal skin area (i.e. legs, trunk and arms) and a habitual increase in distal skin temperature can be observed during sleep (onset)[54], we expect mild distal skin warming to be more effective as compared to proximal.

The work presented in this thesis focuses on the effects of mild manipulations of skin temperature on sleep onset (Chapters 3, 4 and 5), on daytime vigilance (Chapter 6 and 7), and on sleep depth and maintenance (Chapter 8 and 9). A first experiment applied home-applicable distal skin temperature manipulation in order to evaluate to what extent simple and more local skin tem-

perature manipulation approaches might be of value to improve sleep onset in everyday life in young and older healthy adults as well as in elderly people suffering from insomnia (Chapter 3). Using a water-perfused thermosuit – during wakefulness in combination with hot and cold food and drinks (to manipulate core body temperature) - a well-controlled experimental set-up was designed that allowed for simultaneous and relatively independent manipulation of the temperatures of the core, of the distal skin areas, and of the proximal skin areas. We studied the effects in younger (Chapters 4, 6 and 8) and older healthy adults as well as in elderly people suffering from subjective sleep complaints (Chapters 5, 6 and 8). Subsequently, we studied the effects of the manipulations in narcolepsy, a patient group in which skin temperature is correlated to daytime sleep propensity[19] (Chapters 7 and 8). In order to facilitate field studies into skin temperature and its association with sleep and vigilance in health and disease, we meanwhile validated a miniature temperature logger for use in human physiology (not represented in a chapter)[53].

Concertedly, the studies addressed the following hypotheses:

1. Within the thermoneutral range, mild skin warming promotes sleep onset (1a) and sleep depth (1b) and impedes sustained attention (1c).
2. Skin temperature manipulations yield stronger effects than core body temperature manipulations.
3. Distal skin temperature manipulations yield stronger effects than proximal skin temperature manipulations.
4. Skin temperature manipulations yield stronger effects the more sleep is compromised, i.e. small effects in young people without sleep complaints, medium effects in elderly people without sleep complaints and strong effects in elderly people suffering from chronic insomnia and patients diagnosed with narcolepsy.

Following the literature review of Chapter 2 and the experimental studies of Chapter 3 to Chapter 9, Chapter 10 provides a general discussion summarizing findings and revisiting the hypotheses.

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Chapter 2

Circadian and age-related modulation of thermo-reception and temperature regulation: mechanisms and functional implications

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Summary

At older ages, the circadian rhythm of body temperature shows a decreased amplitude, an advanced phase, and decreased stability. The present review evaluates to what extent these changes may result from age-related deficiencies at several levels of the thermoregulatory system, including thermo-reception, thermogenesis and conservation, heat loss, and central regulation. Whereas some changes are related to the aging process per se, others appear to be secondary to other factors, for which the risk increases with aging, notably a decreased level of fitness and physical activity.

Moreover, functional implications of the body temperature rhythm are discussed. For example, the relation between circadian rhythm and thermoregulation has hardly been investigated, while evidence showed that sleep quality is dependent on both aspects. It is proposed that the circadian rhythm in temperature in homeotherms should not be regarded as a leftover of ectothermy in early evolution, but appears to be of functional significance for physiology from the level of molecules to cognition. A new view on the functional significance of the circadian rhythm in peripheral vasodilation and the consequent out-of-phase rhythms in skin and core temperature is presented. It is unlikely that the strong, daily occurring, peripheral vasodilation primarily represents heat loss in response to a lowering of set point, since behavioral measures are simultaneously taken in order to prevent heat loss. Several indications rather point towards a supportive role in immunological host defense mechanisms. Given the functional significance of the temperature rhythm, research should focus on the feasibility and effectiveness of methods that can in principle be applied in order to enhance the weakened circadian temperature rhythm in the elderly.

1. Introduction

Evolution has taken place in an environment where the rotation and orbit of the earth and moon resulted in continuing cyclic variations of light and temperature, now known as days, months and seasons. The present review focuses on age-related changes in temperature cycles in humans, who despite being homeothermic have not abandoned the cyclic variation. On the contrary, the cyclic variation in body temperature is internalized, generated actively and appears to be of importance to our well-being. Whereas Claude Bernard's homeostatic principle has for quite some time been the leading paradigm, it has become evident only during the last decennia, that rhythmic variations in human functions are the rule rather than the exception. It seems appropriate, therefore, to discuss age-related changes in thermoregulation and thermoreception from a rhythmic perspective.

The circadian rhythm in core temperature is the result of circadian rhythms in heat production and heat loss. Core temperature is maximal in the late afternoon and reaches its minimum in the early morning. Mean skin temperature on the other hand is increased during the decline in core temperature. Deviations from the temperature range allowed by the circadian clock at a certain time of day have two main sources: internally generated heat resulting from physical activity and environmental heat or cold transferred through clothing. These changes need to be sensed, processed and counteracted if necessary. Thus, the thermoregulatory system can be conceptualized as containing three parts: thermosensitive afferent pathways, neuronal integration and control systems, and descending effector pathways altering heat gain or loss. The functional anatomy and physiological mechanisms of these compartments, including alterations due to circadian modulation and aging, will be covered in Section 2 (thermoreception), Section 3 (thermogenesis, heat gain and heat retention), Section 4 (heat loss and reduction of heat gain), Section 5 (central thermoregulatory control). Section 6 summarizes age-related changes in the circadian modulation of body temperature. Section 7 shows that the daily temperature cycle is not merely an evolutionary leftover, but has important functional implications. The increased vulnerability to deviations from the normal limits of this cycle at older ages has consequences for physical and mental functioning and health. Therefore, it is of importance to investigate factors that promote thermoregulation and the temperature rhythm amplitude, and these are discussed in Section 8.

A rather artificial but still important discrimination can be made concerning primary and secondary age-related changes. Primary age-related alterations are those that are present even in the very fit and healthy elderly, or after correction for such secondary alterations. Secondary age-related changes are those that cannot be attributed to aging per se, but to factors for which elderly are at a higher 'risk'. Examples are: a sedentary lifestyle, a lower fitness level and a variety of diseases. The discrimination is somewhat artificial since chronic diseases and disabilities affect

more than 60% of those over 75 years of age[118], and can in many aspects be considered as age related.

Of necessity, a review can cover only a limited range of topics. For thermoreception, innocuous, but not nocuous thermal stimuli are discussed. The discussion on the regulatory and effector stages is also limited to the 'healthy' range, excluding, e.g. hypothermia, the fever response[294] and hot flashes[138,139]. It needs to be mentioned that much of the basic knowledge on thermoreception and thermoregulation has been derived from the first and still excellent monograph on this topic by Hensel[175]. The terminology and definitions used in this review are according to glossary of terms for thermal physiology[193].

2. Thermoreception

Deviations from the limits on core and skin temperature accepted by the circadian timing system at a certain time of the day need to be sensed and reported to integrating and controller systems in order to allow for adequate regulatory measures. This sensing is referred to as thermoreception, which may or may not be associated with an actual subjective conscious experience of warmth, cold or thermal (dis)comfort. For example, the sensations versus metabolic responses induced by cooling may be highly divergent[34]. Another example is the strong effect of the circadian rhythm in temperature on sleep that goes without awareness. Moreover, not all thermosensitive structures are also involved in controlling temperature, or relaying information to controlling structures. In the brain, for example, there are abundant thermosensitive neurons that apparently are *not* involved in the regulatory control of temperature. Not until recently, a function has been proposed for their presence: they may be involved in the coupling of arousal states, i.e. sleep and wakefulness, to the circadian modulation of core and skin temperature[399].

Temperature sensitive structures are present in the skin, deep body and central nervous system (CNS). The *sensation* of warm and cold mainly depends on the activity of cutaneous thermoreceptors, the physiological thermoregulatory *responses* mainly depend on core temperature, and the emotional experience of thermal *comfort* or discomfort depends on the total thermoregulatory state, including the input from core and skin thermoreceptors[54,175].

2.1. Anatomy and physiology of skin thermoreception

The thermosensitivity of the *skin* is determined by the cutaneous nerve endings—mostly without clear corpuscles—of neurons located in the dorsal root ganglia. The firing rate of the afferent fibers responds not only to *changes* of the temperature of the skin but is also determined by the *static* temperature of the skin. Skin thermoreceptors also play a major role in informing us about the wetness of the skin, since we have no humidity sensors in the skin. Sudden cooling is in cer-

tain circumstance identified as a wet skin. Cold receptors are located at a depth of ±0.16 mm at the endings of thin myelinated Aδ fibers, and increase their firing rate with a decreasing or static low temperature. Warm receptors are located at a depth of ±0.45 mm at the endings of the slower unmyelinated C fibers and increase their firing rate with increasing or static elevated temperature. Cold receptors outnumber warm receptors by a factor 3–10 in most areas of the body[160]. Small skin temperature changes within the limits of 30–40°C have profound effects since they induce simultaneous and opposite changes in the most sensitive range of both cold and warm receptors. A schematic overview of the range of temperature that affects thermoreceptive fibers is shown in Fig. 1.

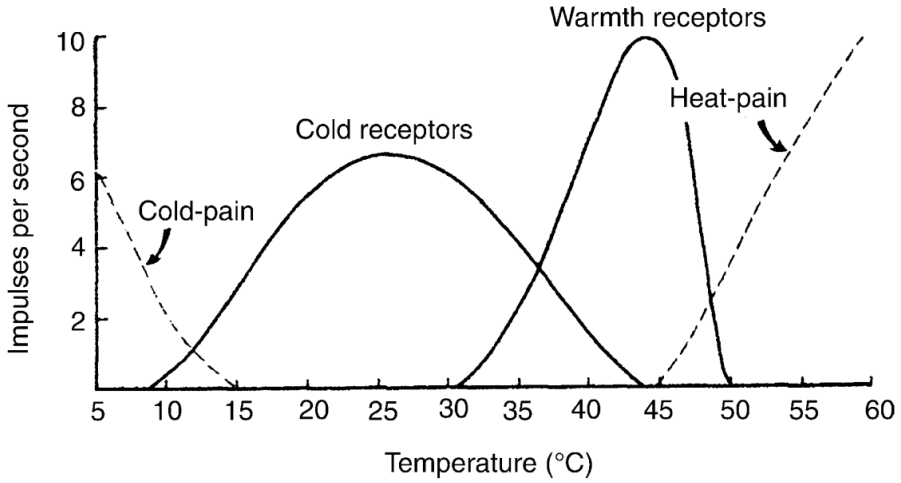

Fig. 1. Discharge frequency of fibers transmitting cold-pain, cold, warmth and heat-pain, plotted against the temperature applied to the skin. Adapted from Guyton[160], with permission.

Skin temperature changes activate not only specific thermoreceptors, but also tactile receptors[352]. Skin areas at several sites of the body differ in their sensitivity to thermal stimuli. As in animals, the nose and lips are the most sensitive areas in man[174,175].

The thermosensitive fibers ascending from the skin reach the *spinal cord* via the dorsal root ganglion, and terminate on second-order neurons in lamina I of the dorsal horn. From the dorsal horn, the thermosensitive afferents are projected mainly via the contralateral anterolateral spinothalamic tract, but projections via the ipsilateral dorsolateral spinocervical tract have also been demonstrated[175].Thermosensitive nerve endings in the face, originating in the trigeminal ganglion cells, innervate second-order neurons in the trigeminal nucleus in the *medulla oblongata*. Ascending secondary fibers join the spinal ascending fibers to terminate on third-order neurons in the ventrobasal *thalamic* relay nuclei, which project to the somatosensory cerebral *cortex*. Ascending

secondary fibers are also relayed to the midbrain raphe nuclei, the reticular formation, and the hypothalamus[57,58,59,75].

Thermoreceptive information originating in the skin *converges* while ascending, and also *diverges* to several brain areas. The amount of convergence strongly depends on the skin area where the thermal information occurs. When thermal stimuli are applied to multiple discrete skin areas the evoked signals may be summed up, e.g. as is the case when cooling two hands. In other combinations of sites, saturation may occur, e.g. the evoked signal does not augment when the forehead is cooled in addition to cooling of a hand. Another factor determining the response to thermal stimuli is the baseline or 'adapting' temperature of the skin. A warm skin can detect even a small increase in temperature, whereas the detection of cooling needs quite a large decrease in temperature. At low baseline levels, the reverse is true[60,162,213]. In fact, cortical somatosensory evoked potentials can only be demonstrated with warm stimuli applied to a skin with a baseline temperature of at least 35°C[70].

There is a topographic *cerebral representation* of the temperatures of different areas of the skin. During stereotactic brain surgery, thermal sensations can be evoked by microstimulation of the posteroinferior and cutaneous core regions of the ventrocaudal thalamic nucleus[235] and the postcentral gyrus of the cerebral cortex[111]. Cortical lesions in humans impair thermosensitivity[2]. The 'thermal' representation of skin areas in the brain differs markedly from the actual surface size represented, much like the out-of-proportion 'homunculus' representing tactile sensations[314]. The face and extremities are disproportionally represented in the brain, and indeed the fingers and lips are very sensitive to mild warming[155,264]. Thermal stimulation of a small area on the extremities or face elicits activity in 10 times the number of thalamic neurons as compared to the number of neurons responding to thermal stimulation of the same surface area on the trunk[258]. A similarly 'distorted' cortical representation was confirmed in studies using warm and cool stimuli and measuring blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI)[36] and evoked potentials[70]. Meh and Denislic recently demonstrated that the amplitude of such evoked potentials is indeed correlated with the subjective thermal sensation[265]. Already in 1937, Hardy estimated that merely the hands and forearms "form an area which is nearly as sensitive as the whole body surface"[165].

2.2. Anatomy and physiology of deep body thermoreception

Thermosensitivity is not limited to the skin, but is also present in the *deep body*, although the anatomy and physiology are much less understood. Equivocal results have been reported concerning the presence of thermoreceptors in the *vasculature* and muscles in some early studies[175]. At least in the cat, carotid baroreceptors and chemoreceptors are sensitive to the temperature of

the blood. Moreover, thermosensitivity has been reported for vascular areas that play an important role in heat loss, as the ear pinna. A *local* thermosensitive effect has been demonstrated by Vanhoutte and Shepherd[398]. The temperature of the perfusing blood modulates the response of the peripheral vasculature to sympathetic input. Thus, a given amount of sympathetic input to the vasculature may induce strong vasoconstriction when the blood temperature is low (as in the early morning) or attenuated vasoconstriction when the core temperature is high (as in the afternoon).

The presence of cold and warm receptors has been demonstrated in the knee *joint* of dogs and cats[428], but we are not aware of such studies in humans.

Intra-abdominal temperature may affect thermoregulatory centers via the splanchnic nerve[175], and sensitivity to intragastric cooling has also been demonstrated in humans[290]. Primary vagal afferents convey information of thermosensitive nerve endings from most internal organs via the cervical and thoracic branches to neurons in the Nucleus of the Solitary Tact[39]. The system appears able to signal constant levels of temperature, since non-adapting responses were recorded.

2.3. Anatomy and physiology of central nervous system thermoreception

Thermosensitive neurons have been demonstrated at all levels of the neural axis, from the spinal cord to the cerebral cortex[45,175,399]. Thermosensitive neurons are defined as neurons whose evoked or spontaneous firing rate depends on local and/or peripheral (cutaneous) temperature. It is of note that this change in activity exceeds by far the normal temperature-dependence that is present in all biochemical processes. Most chemical reactions speed up about 2–3-fold for every 10°C increase in temperature[115]. This increase is known as the 'Q10': the ratio of biochemical activity levels at temperatures 10°C apart. Eisenman and coworkers[117] have proposed to reserve the term 'thermosensitive' for neurons with a Q10 of greater than 2 at a physiological temperature range, i.e. not limited to occur only with extremely low or high temperature. For example, a Q10 of about 8 has been found in many neurons in the cat sensorimotor cortex[26]. Another criterion for warm-sensitivity is an increase in firing rate of at least 0.8 impulses/°C warming[46].

Neurons that increase their firing rate with warming are called 'warm-sensitive neurons' (WSN), and neurons that increase their firing rate with cooling are called 'cold-sensitive neurons' (CSN). An example is shown in Fig. 2.

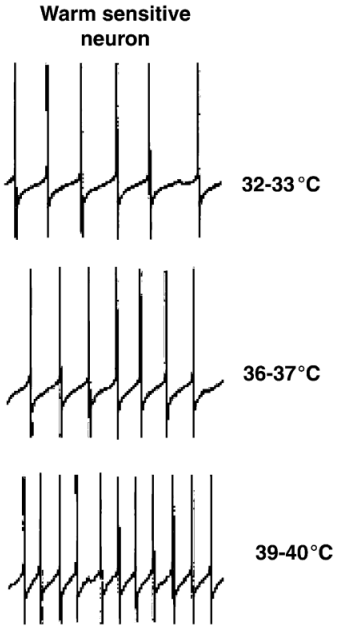

Fig. 2. Effect of local temperature changes on the firing rate of a warm-sensitive neuron recorded in an SCN tissue slice. From the upper to lower panel, the peak-trough vertical axes cover ±120, 115 and 100 mV, respectively. The vertical axes cover ±600 ms. Adapted from Burgoon and Boulant[55], with permission.

Generally, WSNs account for about 30% of the neurons in thermosensitive brain structures. Most of them retain their thermosensitivity even when their synaptic input is experimentally blocked[47,92,249]. The principal cellular physiological determinant that discriminates WSNs from temperature insensitive neurons is a marked thermosensitivity of the rate of depolarization of the prepotential[45]. CSNs account for about 5–10% of the neurons in these structures, and their thermosensitivity usually disappears during synaptic blockade, suggesting that their sensitivity is not intrinsic but due to synaptic inhibition from adjacent warm-sensitive neurons, and 'cold-sensitivity' may be regarded a misnomer[45,47,249]. A detailed account of their representation in the brain can be found in Van Someren[399]. In short, thermosensitive neurons have been demonstrated in the midbrain reticular formation including the raphe nuclei and locus coeruleus; in hypothalamic areas including the posterior hypothalamus (PH), preoptic area and anterior hypothalamus (POAH); in parts of the basal forebrain including the horizontal limb of the diagonal band of Broca (DBB); in thalamic nuclei including the ventrobasal complex and midline reuniens and the reticular nuclei; and in parts of the cerebral cortex including, but not limited to, the somatosensory cortex. Arteries of considerable size are located in close vicinity to thermosensitive neurons, so that blood temperature and brain temperature are closely coupled.

There is considerable *integration* of thermal signals at all levels of the neural axis[175,399]. For example, about two-thirds of the thermosensitive neurons in the POAH also respond to thermal stimulation of the spinal cord and skin. When the skin temperature is high, the POAH neuron's firing rate is high, relatively independent of changes in local brain temperature, indicating the predominant impact of skin temperature on POAH WSNs[48]. At a lower level of the neuraxis, thermosensitive neurons in the midbrain reticular formation are sensitive to ascending thermal information originating in the skin, but not to thermal stimulation of the POAH. Almost all thermosensitive neurons in the spinal cord also respond to thermal stimulation of the skin, whereas thermoinsensitive neurons in the spinal cord do not respond to skin temperature changes. These findings indicate a hierarchical organization of thermoreception.

2.4. Circadian modulation of thermoreception

Surprisingly little is known about the circadian modulation of thermosensitivity. Most studies on this topic have investigated the circadian modulation of the threshold or gain of a thermoregulatory response, and do not specifically untangle whether the modulation concerns the thermoreception, integration and control, or thermoregulatory part of the system. These studies will be discussed later in this review, categorized according to the response investigated. Only a few studies have been reported that are relevant to circadian modulation of thermoreception and did not use a thermoregulatory response as primary outcome variable.

At the cellular level, the thermosensitivity of the POAH is modulated by sleep, when less neurons show thermosensitivity[153]. Some cells do, however, not show any circadian modulation in sensitivity[328]. In a slice preparation, neurons in the rat suprachiasmatic nucleus similarly show decreased thermosensitivity during the projected sleep (light) period[94].

At the subjective phenomenological level, the perceived coldness of a strong cold stimulus applied to the skin is maximal in the afternoon[120] and attenuated during the night and early morning, possibly due to a relatively high level of peripheral perfusion with warm blood[212,302]. On the other hand, the ability to perceive small differences in skin temperature does not show any diurnal variation[74,371].

2.5. Age-related changes in thermoreception

In contrast to the extensive number of studies on the effect of aging on the sensory perception of vision, hearing, touch, taste and smelling[41,351] the number of studies on the effect on thermal senses is quite limited. The free nerve endings associated with thermal sensations appear to remain intact in elderly humans, in contrast to the decreasing number of specific encapsulated skin receptors subserving the sense of touch, e.g. the Meissner and Pacinian corpuscles[283]. In addition,

the conduction velocity and number of the smaller diameter afferents subserving thermal sensations (Aδ and C) appear to remain intact at advanced age, in contrast to the large diameter afferents[344,405]. The neocortical primary sensory areas also remain relatively intact in aging[51,327].

Still, *thermal perception* is attenuated. After some equivocal findings in early studies in small groups and 'young' elderly[213], Meh and Denislic[264] determined normal values for subjective warm and cold sensations at several skin regions in a large group (n = 150) of subjects aged 10–73 years. As shown in Fig. 3, they found a marked decrease in perceptive sensitivity, especially in the distal parts, confirming previous studies reporting an age-related loss of thermosensitivity for warm stimuli but not cold stimuli, and especially at the feet[30,38,214]. Others in fact did find a 50% decrease in "cold spots" in the elderly[288]. Heft and coworkers[174] applied fast cool and warm stimuli to a limited (0.8 cm^2) area of the face (upper lip and chin) and found a modest elevation of sensory thresholds as well as decrease in above-threshold discrimination ability with aging. Fowler and colleagues[134] found an increased facial warm but not cold sensitivity threshold, contrary to Becser et al.[30], who found the strongest increase in facial cold threshold, a smaller increase in facial warm threshold, and furthermore no change in thresholds at the hands. Kenshalo[214] noted that elderly mainly show a decreased sensitivity to warm—not cold—stimuli applied to the plantar side of the feet but not to other locations. It should be noted that the between-subject thermosensitivity variability also increased with age, indicating diminished sensitivity in some, but intact sensitivity in other elderly subjects. Furthermore, these laboratory measurements are all based on warming or cooling small individual sites, and do not take into account the fact that skin sites have different spatial summation properties, as discussed previously.

Concerning *secondary* age-related thermoreceptive changes, diabetes, for which elderly are at risk, is associated with increased thermal sensibility thresholds[199]. The feet appear to be rather sensitive to a loss of sensibility for thermal stimuli not only in healthy elderly: a marked loss was also found in diabetics without symptoms or signs of a clinical neuropathy[199]. The increase in thermal thresholds are consistent with elevated thresholds for other modalities[174]. Also here, the glabrous skin of the palm and sole are the areas in which the strongest loss of tactile sensitivity with aging is present[213].

To the best of our knowledge, no thermosensitivity studies have been performed in *Alzheimer's disease* (AD) patients. However, for the other modalities, the conduction velocities of the primary afferent nerves are preserved[358] and the patients show normal sensitivity to pain and vibratory stimulation[188]. Also at a higher level of the neuraxis, the neocortical primary somatosensory areas are relatively intact in AD[17,42], possibly because of the high degree of protective myelination[49]. Taken together, the changes in peripheral afferent nerves in AD are quite similar to those observed in healthy aging.

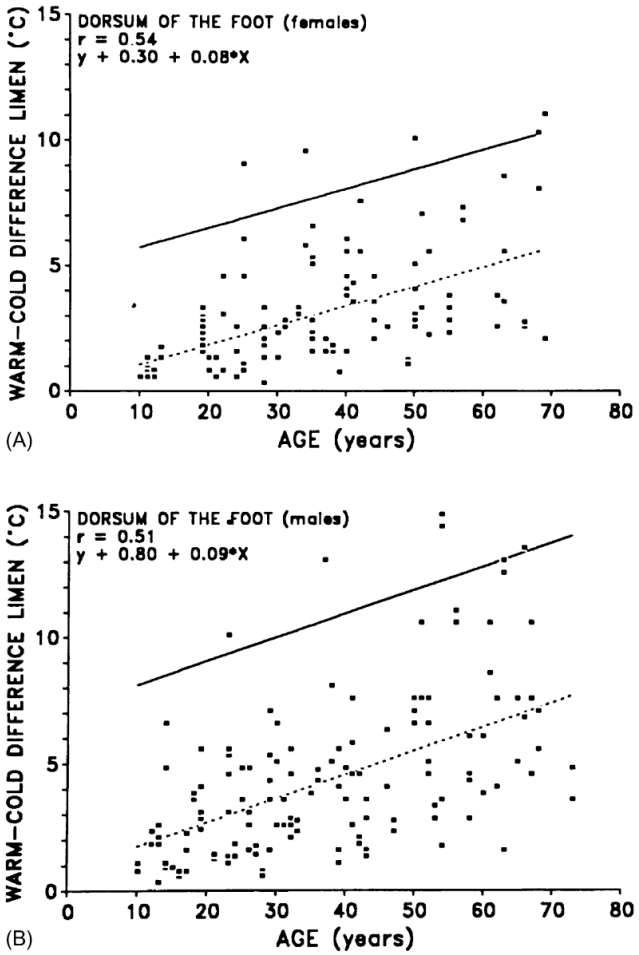

Fig. 3. The interval of temperatures applied to the skin necessary to elicit a temperature sensation (limen) increases with age. Results of temperature sensitivity assessed at the dorsum of the foot in 67 women aged 10–69 years (A) and 83 men aged 10–73 years (B). Regression equations clearly indicate that the unresponsive range increases with aging. Adapted from Meh and Denislic[264], with permission.

The question arises why the threshold for temperature increases with age, if the thermosensitive nerve endings, ascending fibers and primary cortical projection areas appear to remain intact. A hypothetical explanation might be that properties of the skin important for thermal conductivity, e.g. the density of collagen fibers and elastic tissue, change during the course of life[25,77,174]. Another possibility is that the reduced vascular supply to skin tissues is involved: it has been demonstrated in monkey that the functionality of cold receptors is highly dependent on oxygen supply[189]. A further possibility is that whereas the anatomical substrate for the ascending information is preserved at old age, its transmissive properties have declined. It may, for example, be that

changes in the ion content of cells and intercellular space affect threshold for synaptic transmission.

Subjective *comfort* is dependent on, but not equal to thermal sensation. Sensations rely mainly on skin thermoreceptors and occur fast, whereas comfort is a slower process depending on integration of skin and internal thermoreceptors as well as the sensations resulting from thermoregulatory actions. In spite of common belief, the comfortable temperature *average* does not change with aging. When exposed to cold with access to a lever that turns on heating, old rats show an equal amount of behavioral thermoregulation in comparison to young rats[194]. Elderly humans in similar situations show a much less precise operation of thermoregulatory instruments as compared to young subjects. They, thus, tolerate larger *deviations* from this average before discomfort is felt and action is undertaken[78,79,137,201,391], indicating a decreased subjective thermal perception.

In summary, the results indicate a loss of thermal perception in the absence of macroscopic neuroanatomical changes, especially for cold stimuli applied at the lower extremities. Structural changes in the skin may be involved.

3. Thermogenesis, heat gain and heat retention

When a deviation from the allowed circadian temperature range is reported, controller systems need to initiate countermeasures aimed at either both gain and preservation of heat, or loss of heat. Section 3 discusses the mechanisms associated with the obligatory (Section 3.1) and facultative (Section 3.2) generation of heat, as well as measures in order to promote the gain of heat from the environment and the retention of body heat (Section 3.3).

Thermogenesis, i.e. the production of heat is present in *obligatory* as well as *facultative* ways[195]. Obligatory thermogenesis refers to the heat produced in association with cellular metabolic processes that are a part of life itself, as well as to heat generated during behavior not per se aimed at heat gain but inevitable for the fulfillment of other vital purposes. These processes continuously generate heat. When the organism cools down in spite of this obligatory heat production, e.g. in a cold environment, *facultative* thermogenesis occurs. Facultative thermogenesis can be subdivided into (1) voluntary increased physical activity, (2) shivering thermogenesis, and (3) humoral thermogenesis. Humoral thermogenesis has again been subdivided into (3.a) the 'classical' non-shivering thermogenesis (NST), i.e. the sympathetic, norepinephrine (NE) induced mitochondrial heat production in brown adipose tissue (BAT) and (3.b) hormonal thermogenesis, associated with epinephrine, glucagon, thyroid, growth hormone (GH), and adrenocorticotropic hormone (ACTH). Another subdivision of thermogenesis often made is *behavioral* versus *autonomic* thermogenesis. Both occur in obligatory and facultative ways.

In addition to these heat-generating mechanisms, the animal has several ways to *gain and preserve* heat. In humans, the ability to preserve heat relies to a large extent on *behavioral* thermoregulation[247], which is also the primary thermoregulatory mechanism in most rodents[381]. Examples include creating a microclimate by means of warm clothing and bedding, the intake of hot drinks, seeking a sunny, warm, dry, wind-sheltered environment and positional measures like curling up, huddling and cuddling. The major human *autonomic* response is constriction of the peripheral vasculature of the skin in order to prevent heat exchange from the warm blood, via the skin, to the cool environment. Whereas in furred animals pilo-erection is another important autonomic way of preventing heat loss, it is of little importance in human cold defense.

The body temperature of older animals drops further after exposure to cold and takes longer to recover[161,241]. Similarly, elderly humans are less able to maintain body core temperature when exposed to cold, and core temperature may be lowered by as much as 1°C[213]. Frail elderly at home and in nursing homes are even at an increased risk of hypothermia, as reviewed in a number of papers that include advice for diagnosis, prevention and treatment[25,64,425]. The mechanisms for the generation, gain and preservation of heat, as well as their circadian and age-related modulations will be discussed in the following sections.

3.1. Obligatory thermogenesis

3.1.1. Basal metabolic rate

Humans are homeotherms, i.e. even at rest the metabolic rate is so high that it provides a continuous internal source of heating, accounting for about 60–75% of the total daily energy expenditure[315]. Aschoff and Wever estimated the relative thermogenic contribution of several parts of the body at rest as follows: skin and muscles 18%, brain 16%, lungs, heart, kidneys and other internal organs 56%, with a prominent involvement of the liver[21]. During physical activity, as will be discussed later in Section 3.2 (facultative thermogenesis), heat generation in muscles is the most important source of heat generation. The basal metabolic rate (BMR) augmented with the heat generated by physical activity and digestion of food is referred to as the total energy expenditure (TEE). Catecholamines and sympathomimetic agents like ephedrine, caffeine and theophylline increase the resting metabolic rate in humans[195,196].

Circadian modulation: BMR is modulated by sleep and a circadian rhythm. BMR during sleep is slightly lower than during wakefulness at complete rest[160,266]. Early reports did not find a circadian variation in the awake resting BMR[270,441], but Kräuchi and Wirz-Justice demonstrated, in an optimally controlled study, a clear peak just before noon[218].

Age-related changes: In BMR, age-related changes may be different in rats and humans. The BMR of old rats is slightly higher than that of young rats, but still old rats have lower body temperature,

indicating decreased heat conservation[234]. Human aging studies indicate that BMR declines. Poehlman et al. report a curvilinear decline with age, significantly decreasing after the age of about 50 years[317]. McDonald and Horwitz mentioned a 1–2% per decade decline of oxygen consumption after the age of 30 years[262]. Elia and coworkers found that the *total* energy expenditure declines per decade by 0.69 MJ per day for men and by 0.43 MJ per day for women[118.] The BMR decline accounts for 44% of this decrease. The decline in BMR is strongly related to the relative loss of fat-free, heat producing tissue[317,208] and to the decrease in fitness level present in many elderly[315]. Increased plasma norepinephrine (NE) concentrations, likely to increase the BMR, are found in highly fit, physically active but not in sedentary elderly[315]. Fitness is not only associated with an increased daytime metabolic rate, but also with a lower nocturnal sleeping metabolic rate, thus, promoting a circadian amplitude[266,420]. A decreased BMR is likely to underlie the age-related decrease in core temperature[130], which is more pronounced in male elderly[133]. The findings on age-related changes of the resting temperature of the skin are equivocal: both increased[227] and decreased[130] finger temperature have been reported. A few studies have been reported on the BMR in Alzheimer's disease. The daily energy expenditure in AD patients is comparable to the energy expenditure of non-demented elderly, and appropriate for their metabolic size[105,318].

In summary, the diurnal variation in BMR contributes to the circadian rhythm in core temperature, and this contribution is less in the elderly, in part and reversibly secondary to a decreased fitness level.

3.1.2. Diet-induced thermogenesis

The increased metabolic demand of digesting food is associated with an increase in core temperature of about 0.01 °C per 159 kcal of food[218], or about 10–18% of the food energy content[270,384]. Whereas carbohydrates and fat in food induce only a 4% increase of the metabolic rate for a brief period of about 1 hour, protein ingestion may induce an increase of up to 30%, lasting for several hours. The resulting increase in core temperature may in turn induce an increased peripheral skin blood flow (skBF) and temperature[178]. Fasting lowers both core and skin temperature[221].

Circadian modulation: There is a clear circadian rhythm in food intake in humans, which is high during the day, and generally absent during the night. A circadian rhythm in the thermic effect of food may be present, in that the same food elicits most thermogenesis in the morning, less in the afternoon, and even less at night[337].

Age-related changes: The intake of food slightly decreases with age[315,118]. Allison et al. demonstrated that hospitalized elderly leave about 40% of the presented food untouched, and that the ensuing malnutrition is associated with a loss of thermoregulation[9]. Some studies indicate that the *thermic effect of food* is reduced in elderly, possibly as a consequence of an attenuated sym-

pathetic increase following meal ingestion[262]. Other studies found no effect of age[118]. The variability in results may be related to a secondary effect of aging, since the thermic effect of food is decreased in subjects with a high percentage body fat and a low level of fitness and spontaneous physical activity[316,384,424].

In summary, the diurnal patterns of food intake and the thermic effect of food contribute to the daytime increase in temperature, and this contribution may be attenuated especially in non-lean, unfit elderly.

3.1.3. Baseline physical activity and posture

Even minimal, obligatory physical activity is associated with heat production from muscular activity. As compared to conditions of continuous sleep and bed rest, changes in core temperature have been noted due to (1) mere wakefulness, (2) an upright posture, and (3) the activity level. Being *awake* rather than asleep, but still in a supine posture and without any activity elevates core temperature by 0.06–0.31°C[28,246,397]. If awake, changing the body *posture* from supine to upright increases the core temperature by 0.1–0.5°C, whereas the mean skin temperature drops by about 5°C[271,389,397]. Even a change from supine to semi-supine (10°) increases core temperature[4]. The effect of standing is stronger than the effect of sitting. Considering the additional temperature increase due to essential *activity*, Levine and colleagues estimated the energy expenditure for standing and walking as compared to sitting to increase by 11 and 106%, respectively[236]. There is an ISO norm (no. 8996) on the relation between metabolism and several activities. It should be noted that all these findings concern short-term laboratory findings and that prolonged bed rest for several days, as may occur in frail, ill elderly, is on the contrary associated with an increase in core temperature, likely due to dehydration[4].

Circadian modulation: The rise in core temperature due to merely being awake rather than asleep is maximal near the endogenous circadian temperature peak in the afternoon[422]. The fact that people assume a supine posture during the night and are upright during the day also contributes to the day–night rhythm core temperature. The temperature increase due to essential activity is of relevance only during the day, although sleep–wake controlled laboratory studies have shown that the amount of activity-induced temperature rise is in fact limited near the endogenous circadian temperature maximum in the afternoon[7,414]. In normal situations, all three factors interact, and comparing laboratory bed rest and natural home activity, Gander and coworkers found the daytime core temperature rhythm peak to be increased by on average 0.16°C[145].

Age-related changes: The sedentary lifestyle of many elderly lowers heat production[77]. Elia et al. estimated that 46% of the age-related decline in total energy expenditure is due to decreased physical activity[118]. Gander et al. found no age differences in the daytime temperature increase due to natural home activity as compared to laboratory bed rest[145]. On the contrary, Monk and

Buysse reported that in fact the reduced baseline physical activity level is a major factor in the decreased diurnal circadian rhythm in temperature[280].

In summary, the diurnal patterns of wakefulness, posture and activity contribute to the daytime increase in temperature, and this contribution is attenuated especially in sedentary elderly. This will keep the daytime temperature lower and, thus, contribute to the age-related attenuation of the amplitude of the diurnal temperature rhythm.

3.2. Facultative thermogenesis

When exposed to a cold environment, core temperature drops unless action is undertaken. The actions listed later have in common that their thermogenic effect is elicited only if the body cools below a critical *threshold*, and that below this threshold the intensity of the action may increase with further cooling. The increase per unit of cooling is often referred to as the sensitivity, but in order to prevent confusion we will adhere to the term gain.

3.2.1. High-level physical activity (sports, fitness training)

Metabolic heat production increases with the level of voluntary physical activity. The temperature increase resulting from a certain amount of exercise is not a function of the absolute intensity of that exercise, but of its VO_2 requirement as a percentage of one's individual VO_2max , i.e. fitness level[27], where VO_2 functionally represents the amount of oxygen that can be removed from circulating blood and used by the working tissues during a specified exercise and period, and VO_2max the maximum hereof.

Circadian modulation: The circadian rhythm in metabolic rate (oxygen consumption) in rodents may to a large extent be due to increased activity[381]. High levels of physical activity are limited to the wake period and, thus, contribute to the circadian modulation of core temperature. The *amount* of exercise-induced hyperthermia and the consequent 'overshooting' post exercise hypothermia depends on the time of day the exercise takes place. Hyperthermia during exercise is limited with exercise timed near the peak of temperature[278,414]. The post exercise hypothermia duration is long following exercise at 8:00 h in the morning, moderate following exercise at 16:00 h in the afternoon, and absent following nocturnal exercise[278].

Age-related changes: Not only during rest, but also during moderate physical activity, the core temperature of elderly remains lower, and this finding cannot be attributed to a secondary age-related reduced fitness level[130].

In summary, the diurnal patterns of voluntary high activity levels contribute to the daytime increase in temperature, and this contribution is attenuated even in fit elderly.

3.2.2. Shivering thermogenesis

Shivering thermogenesis is the production of heat by skeletal muscle tremor. Shivering is more dependent on core than on skin temperature: the ratio of how core and skin temperature changes affect shivering is about 4:1[54]. Shivering can increase the metabolic rate up to a factor 5, and is in addition to peripheral vasoconstriction (discussed later) a second major autonomous cold protective response in humans[31,247,434].

Circadian modulation: No circadian modulation of the shivering response was found when measured in the morning and afternoon only[67]. However, when the full 24 h cycle is examined, the shivering response to hypothermia is impaired during the early sleep period, and maximal in the early morning[176,268]. The modulation of thermoregulatory responses by sleep states has been reviewed by Parmeggiani[311]. In brief, a smaller deviation is necessary for the initiation of the shivering response during quiet sleep, but larger deviations are tolerated during paradoxical sleep.

Age-related changes: Elderly shiver less[78.379], due to a lower core temperature threshold to be reached before shivering starts[136]. Moreover, the muscle mass is smaller[432] and muscles contract at a lower level than is the case in young subjects[77]. The decline may be prominent in elderly males but absent in elderly females[411,434].

In summary, although shivering is not involved in the generation of a diurnal temperature rhythm under thermoneutral conditions, the attenuation of shivering especially in male elderly may cause a lower daytime temperature level during exposure to cold.

3.2.3. Humoral thermogenesis I: 'classical neuronal' non-shivering thermogenesis

Non-shivering thermogenesis (NST) is defined as "heat production due to metabolic energy transformation by processes that do not involve contraction of skeletal muscles"[193], which in rodents mainly involves burning of brown adipose tissue (BAT), triggered by sympathetic activity. BAT-related NST plays a significant role mainly in small mammals, but is negligible in humans[77]. In rats, norepinephrine (NE) release from the sympathetic nervous system is sensed by β3-adrenergic receptors on BAT and induces the expression of mitochondrial uncoupling proteins (UCP). Heat can be produced by uncoupling the metabolic chain from oxidative phosphorylation in the inner membranes of mitochondria[185]. Also in humans NST is activated with body cooling well before the onset of shivering. However, thermogenesis is mainly mediated by β1 and β2 receptors, and only a small amount of BAT is present, so other mechanisms must be involved. At least three candidate mechanisms are available: (1) NE-induced thermogenesis mediated by β1 and β2 receptors in skeletal muscle, (2) white adipose tissue producing heat in response to adrenaline, probably via β3 receptors, and (3) BAT appearance following cold-adaptation. Although UCP1—important in rodents—is hardly detected in humans tissues, a homologue, UCP2, is widely distributed, and another homologue, UCP3 is present in skeletal muscles[140,195,196].

Circadian modulation: In rat pups at rest, BAT thermogenesis is more active during the peak of the endogenous circadian temperature rhythm than during the minimum, or trough[330]. On the other hand, when exposed to cold at different times of the day, no circadian modulation of not further specified metabolic heat production response could be found in mice[381].

Age-related changes: Although senescent rats are undoubtedly more likely to develop hypothermia with cold exposure as compared to young rats, there is no evidence of a reduction in non-shivering thermogenesis in aged mice. The sympathetic outflow to BAT is in fact similar or higher, and the concentration of UCP in BAT mitochondria is unrelated to age[262,347,348,379]. Alternative explanations for the age-related loss of cold defense may be (1) non-UCP-related decrease of BAT functionality, (2) impaired heat conservation or (3) impaired non-BAT mediated thermogenesis. Also in elderly humans, the cold-induced increase in metabolic rate is attenuated, which does not appear to be secondary to a decreased fitness level[130,361].

In summary, the importance of BAT thermogenesis is negligible in adult and elderly humans. In rodents, circadian modulation of BAT thermogenesis is equivocal, and the age-related decrease in cold defense could not be related to altered BAT innervation or UCP induction.

3.2.4. Humoral thermogenesis II: 'non-classical' non-shivering thermogenesis

The humoral response to a cold environment is not limited to an increased sympathetic (NE) output inducing UCP in BAT. First, sympathetic liberation of norepinephrine and epinephrine from the adrenal medulla into the blood stream induces glycogenolysis in muscle and liver cells. Furthermore, *thyroxine* enhances the metabolic rate of most cellular chemical reactions. A complete absence can reduce the metabolic rate by ±50%, whereas extreme activation may increase it by ±100%. However, atrophy and hypertrophy of the thyroid are slow processes, and not involved in acute metabolic responses to cold. The mechanisms involved in the thyroxine regulation have been reviewed by Arancibia et al.[16]. Skin cooling elicits thyrotropin-releasing hormone (TRH) production in the raphe nuclei, which relays this information by a serotonergic projection to the hypothalamic paraven- tricular nucleus (PVN). The PVN synthesizes TRH[158] and secretes it in the portal blood, which in turn induces the pituitary to release thyroid stimulating hormone (TSH) in the blood stream. A secondary effect of increased plasma TSH is the upregulation of UCP3 mRNA[196]. Other humoral factors increas- ing the metabolic rate include testosterone, growth hormone, glucagon, insulin, ACTH and dehydroepiandrosterone (DHEA)[195,232].

Circadian modulation: Since the secretion of most if not all mentioned humoral factors is modulated by sleep and/or a circadian rhythm, the thermogenesis associated with them is likely. However, the relative factual contribution of such modulations to the circadian rhythm in temperature has not been unraveled.

Age-related changes: The levels of most humoral factors change with aging. Examples are the strongly reduced secretion of growth hormone during sleep, and the decrease of DHEA by about 2% per year[406]. Moreover, the circadian rhythm in DHEA, showing lower levels in the evening, almost disappears in elderly subjects[95,406]. A not strictly age related but 'secondary' effect is the increased vulnerability to a decreased thyroid function, which increases the risk of hypothermia[77].
In summary, although most humoral factors with thermogenic properties show circadian and age-related modulations, their significance for the circadian rhythm in body temperature and changes with aging remain to be unraveled.

3.2.5. Heat generation in the brain?

Although the human brain accounts for only 2% of the body mass, it uses about 20% of the oxygen needed to break down glucose for energy supply[323] and is more than six times larger than the average brain size of a typical mammal of the same body weight[152]. There are some brain-specific thermoregulatory topics that justify a separate discussion of its thermogenesis and dissipation of heat. It has often been stated that the brain is vulnerable to damage by low or high temperatures, and that special physiological measures should be taken in order to keep the brain temperature within close limits. The validity of this statement is arguable, since there is little reason to suppose that other organs tolerate larger deviations, and in case of fever brain temperature frequently exceeds body temperature[256].
The metabolic heat produced by the brain is dissipated by the circulating blood, of which the arterial temperature is 0.2–0.5°C lower than the brain temperature[256]. It has been argued that the temperature of the brain depends to a large extent on the temperature of the circulation of the rest of the body, since changes in neuronal activity level contribute little to the temperature variation[10]. There is considerable argument about the existence of selective brain cooling (SBC) in humans[256]. Selective brain cooling involves a mechanism of cooling arterial blood by counter-current air-cooled returning venous blood in the carotid rete. Rats and humans have no carotid rete, although there may be some cooling where the middle carotid passes the sinus cavernous. One of the major arguments put forward in support for the existence of SBC in humans, monkeys and rats is the fact that a ventro-dorsal temperature gradient is present, leaving the dorsal cortex significantly cooler than the base of the brain[10,172,185,267].
However, recent findings suggest that local differences in heat *generation* may account for these results as well. Heat production is often regarded only as a side-product of cellular metabolic processes. However, cellular activity appears to be only a minor factor in neural thermogenesis, suggesting that an active process should be present as well. Horvath et al. recently demonstrated that such an active process is present in the brain, much like it is present in BAT[185]. The mitochondrial uncoupling protein UCP2 as well as its mRNA was demonstrated in neurons and their pro-

jecting axons and axon terminals, mainly in and around the hypothalamus but not in the hippocampus, cortex and thalamic relay nuclei. Horvath et al. suggested that heat produced by the presynaptic axon terminals may modulate pre- and postsynaptic events[185]. Thus, local temperature changes could modulate signaling pathways. Indeed, the temperature of the brain areas where axon terminals containing UCP2 are present were warmer than the areas whiteout UCP2-containing axon terminals. Moreover, cells found to be activated by cold exposure, as indicated by c-*fos* expression, may in fact be modulated by a UCP2 mechanism, since they were abundantly innervated by UCP2-containing axon terminals.

Szelényi has proposed another possible mechanism for the brain thermogenesis that can be seen during acute cold exposure[374]. In the brain, the number of glial cells outnumber the number of neurons by a factor 10, and it is highly unlikely that their function is limited to 'gluing' neurons together. Szelényi proposes that one of the functions of the most abundant astroglia may be to produce heat by glycogenolysis in response to increased intracellular norepinephrine levels, and possibly other substances like adenosine, histamine and vasoactive intestinal polypeptide.

Circadian modulation: Cats show attenuated SBC during paradoxical sleep[23,313]. On the other hand, in pigs and springbok, the magnitude of selective brain cooling is greatest during rest and sleep[143,277]. The species differ in the circadian modulation of SBC: in pigs SBC is relatively high at low body temperatures, but in steenbok at high body temperature.

Age-related changes: We are not aware of studies investigating age-related changes in brain temperature regulation. Szelényi noted that the hypothetical heat-generating astroglia mechanism might be of special importance at high age, when hypothermia is likely to occur, but the relative weight of glia cells is increased, possibly preventing the brain of elderly from becoming as cold as the rest of their body[374].

In summary, the novelty of the ideas about specific brain thermogenesis and selective brain cooling in humans accounts for the lack of studies on circadian and age-related modulation in such rather hypothetical but possibly relevant processes.

3.3. Gain and retention of heat

3.3.1. Behavioral measures for heat gain and retention

Humans have only limited autonomic possibilities to prevent hypothermia in a cold environment. Therefore, behavioral measures are the primary responses and of utmost importance. Examples are the creation and application of clothing, bedding, shelter and heating systems. In contrast to most autonomous thermoregulatory responses, behavioral thermoregulation is not postponed until a drop in core temperature occurs, and is primarily modulated by changes in mean skin temperature[71,85,154].

Circadian modulation: An obvious but little recognized circadian modulation of a behavioral measure is the creation, by means of bedding, of a nocturnal sleeping microclimate of ±34°C[289,409], which is much higher than the usual daytime temperature and even thermoneutrality ±29°C[247]. This finding is suggestive of behavioral thermoregulatory measures aimed at heat preservation during sleep.

Age-related changes: The bed microclimate created by elderly is not different from that of young adults[298]. On the other hand, during daytime, elderly regulate their indoor ambient temperature less precisely and tolerate larger deviations from the comfortable average before action is undertaken[78,79,201,391]. This cannot be attributed to a reduced mobility, since simple hand movements sufficed to change ambient temperature in some experiments.

In summary, whereas the nocturnal ambient microclimate does not change with aging, the poor behavioral response to cool environment during the day contributes to a lower and more variable daytime body temperature and, thus, to the age-related attenuated amplitude and decreased stability of the diurnal temperature rhythm.

3.3.2. Capacitive and insulative properties of the body

The body can be seen as a reservoir including heat producing cells, isolated from the environment by the skin and subcutaneous tissue, with a prominent role for the poor thermoconductive subcutaneous fat. During cold exposure, subcutaneous fat thickness is negatively associated with skin temperature and, thus, heat loss[130,432]. There is some evidence that repeated cold exposure of the skin increases local subcutaneous fat deposit and, thus, enhances thermal insulation and heat retention[191]. Although pilo-erection does occur in humans exposed to cold, it is of no functional significance, in contrast to the effectiveness in furred animals.

Circadian modulation: The body constitution may change, but too slow for circadian modulation to occur. The modulation of thermoregulatory responses by sleep states in animals has been reviewed by Parmeggiani[311]. In brief, during quiet sleep even a small deviation from the set point is sufficient for the initiation of pilo-erection, while on the contrary larger deviations are tolerated during paradoxical sleep.

Age-related changes: The proportion of heat producing cells decreases with age, and the decrease in total body water content results in a lower thermal buffering capacity due to a decrease in the heat reservoir[25,77]. Furthermore, a loss of insulating subcutaneous tissue is present[333]. On the other hand, heat loss would be expected to be less in the elderly due to their increased body fat and smaller body surface area relative to mass[432], but this does not appear to play a prominent role[133]. In AD, total body fat mass was found to be comparable[318], or lower[150] as compared to age-matched controls. Fat-free mass was reported to be lower[332] or higher[365] in AD patients. Thus, the results in AD are highly equivocal and inconclusive.

In summary, the decreased 'heat reservoir' and insulating subcutaneous tissue makes the aged body more vulnerable to deviations from the set point and may be involved in the age-related decreased stability of the diurnal temperature rhythm. It is conceivable that the limited heat reservoir may be involved in the fact that elderly reach their nocturnal temperature minimum earlier in the morning[113,282].

3.3.3. Autonomic heat retention by peripheral vasoconstriction

One of the major physiological adjustments in response to cold exposure is peripheral vasoconstriction, which restricts heat transfer from the internal organs to the skin and from the skin to the environment. Peripheral vasoconstriction is more dependent on core than on skin temperature: the ratio of how changes in core and skin temperature contribute is estimated between 30:1 and 4:1[54,71,85,154]. The sympathetic part of the autonomic nervous system is by far the most important branch involved in regulation of cutaneous vasoconstriction. The involvement of the parasympathetic branch in circulatory regulation is limited to the modulation of heart rate. Most sympathetic outflow is associated with vasoconstriction, although a few vasodilatory fibers exist as well, projecting to muscles rather than the skin. During cold stress, NE is released from sympathetic nerve endings. Sympathetic NE stimulation of the vessel wall can induce vasoconstriction via receptors or vasodilation via β receptors: the skin of the extremities mainly contains α2 receptors and, thus, shows strong vasoconstriction[136,204]. In contrast, there is poor vasoconstrictive capacity in the face, resulting in poorly attenuated heat loss from this site during cold exposure[247].

When exposed to severe cold for a prolonged period the vasoconstriction of the hands is periodically interrupted by periods of cold-induced vasodilation (CIVD). The cyclic process is known as the 'hunting reaction' and was first described by Lewis[237]. CIVD is especially prominent in fingers, lips, cheeks, nose, elbows, which are parts of the body that are rich in arteriovenous anastomoses (AVAs).

When exposed to cold, stress or exercise, increased sympathetic output to the *adrenal medulla* induces it to release more adrenalin as well as some norepinephrine into the blood stream. As mentioned previously, norepinephrine is a strong vasoconstrictive agent, as is epinephrine to a lesser extent. Other powerful vasoconstrictive agents are angiotensin, acting on all arterioles, and vasopressin[160].

Circadian modulation: When exposed to cold at different times of the day, mice show less cutaneous vasoconstriction in the afternoon[381]. On the contrary, in humans, cold-induced peripheral vasoconstriction is attenuated during the night and occurs only if core temperature falls below a threshold of 36.0°C[302,386]. This indicates that optimal vasoconstriction is linked to the preferred activity period: during the night in the nocturnal mice and during the day in the diurnal humans. Cold-induced vasoconstriction in humans is maximal during the early morning[176]. The hunting

reaction also shows a circadian modulation, i.e. it is most pronounced in the afternoon[217], likely associated with the peak in core temperature[85]. As is the case for pilo-erection in response to cold, vasoconstriction is also modulated by sleep states. During quiet sleep even a small deviation from the set point is sufficient for the initiation of vasoconstriction, while on the contrary larger deviations are tolerated during paradoxical sleep[311].

Age-related changes: Under thermoneutral ambient conditions the skin temperature at the extremities is lower in the elderly[324], which is indicative of enhanced baseline vasoconstriction. However, during cold exposure both in laboratory and outdoor situations, elderly show an attenuated efficiency in diverting blood from the skin to help conserve body heat and consequently the skin remains relatively warm[25,78,201,215,297,391]. This age-related change is likely to be the most important factor involved in poor cold defense[133]. The loss of vasoconstrictive cold defense may be prominent in male elderly and absent in females[432,434]. Also during the night, vasoconstriction of the fingers in response to facial cooling is attenuated in the elderly[197]. In contrast to their attenuated constriction, elderly were more easily awakened by the facial cooling stimuli, indicating that the problem is related to decreased constrictive capacity rather than a loss of thermoreceptive sensibility. The age-related loss of vasoconstriction is present at both the threshold, gain and maximum level. Frank et al. demonstrated that the threshold for cold-induced vasoconstriction lies at a lower core temperature at high age, and that the maximal vasoconstriction is reduced, likely associated with a decrease in evoked NE release[137]. On the other hand, when exposed to cold for a more prolonged period the difference between young and elderly may disappear[432], making an age-related decrease in the maximal constriction equivocal. The mechanism underlying the decreased cold-induced vasoconstriction is most likely an increased arterial wall stiffness. A decrease in the smooth muscle -adrenergic receptor has also been demonstrated, which is, however, compensated by an increased sympathetic nervous system activity, leaving the net result unchanged[133]. The hunting reaction weakens with advancing age[366,430]. The findings concerning the rate of rewarming of the fingers after discontinuation of the cold stimulus are equivocal: both faster[227] and slower[324] rates have been reported to occur in the elderly.

In summary, the delayed and slower evolving vasoconstrictive response to a cool environment will contribute to a lower and more variable body temperature, most likely during the daytime and, thus, to the age-related attenuated amplitude and decreased stability of the diurnal temperature rhythm.

4. Heat loss and reduction of heat gain

When an animal is exposed to ambient heat and/or involved in rigorous physical activity it should limit its heat production and promote the radiation, conduction, convection and evaporation of

heat from the body to the environment. *Radiation* is the emission of heat through infrared electro-magnetic waves. *Conduction* is the transmission of heat to other objects and air by direct contact. *Convection* aids conduction if the warm air rises up and away from the body or is promoted by air movement (wind). *Evaporation* of water from the skin and lungs also continuously draws heat from the body, further increasing when sweating occurs. Behavioral and autonomic changes are involved in the accomplishment of heat loss in order to prevent unacceptable elevated body temperature. Behavioral measures include the intake of fluids to prevent dehydration; decreasing the level of physical activity; and seeking a cool, shady, windy environment. In addition, autonomic measures are taken. Passive heating results in a decrease of the sympathetic outflow to the periphery, while active heating (exercise) first increases the sympathetic outflow to the periphery, inducing vasoconstriction, until eventually the rise in core temperature attenuates the outflow. Both are associated with sweating.

4.1. Peripheral blood flow

An increase in core or skin temperature induces peripheral vasodilation. Cutaneous vasodilation results in increased skin blood flow (SkBF), which serves three heat-loss enhancing mechanisms. First, heat is convected from the internal organs and working muscles to the skin. Second, the resulting increase in skin temperature promotes dry heat loss by convection and radiation to the (cooler) environment. Third, the increase in skin temperature also elevates the skin-to-ambient vapor pressure gradient which promotes sweat evaporation. At neutral (24–25°C) ambient temperatures at rest, with a core temperature of about 37°C and a skin temperature of about 34°C, the human core temperature is mainly regulated by alterations in skin blood flow, rather than by changes in metabolism or evaporative heat loss[52]. In this zone, sympathetic innervation regulates skin blood flow between 2 and 6 ml blood/(min 100 ml skin). If heat loss is needed, the total perfusion of the skin with warm blood may increase from ±0.2–0.5 to 7–8 l/min, resulting in an up to eight-fold increase in the transfer of heat from the core to the skin[160]. Such elevated skin blood flow can take as much as half of the cardiac output and requires a redistribution of blood flow from other circulations, the splanchnic and renal circulations in particular[207].

In the extremities, the increase in skin blood flow is to a large extent due to the opening of arteriovenous anastomoses (AVAs), which are shunts between the arteries and the venous plexus. The presence of AVAs is limited to the extremities, i.e. the palmar/plantar but not dorsal side of hand and foot as well as the nail bed, elbow, lips, cheeks, ears and nose. They are more numerous in the more distal parts, i.e. maximal in the fingertips[85]. AVAs are sympathetically innervated, and both cholinergic and noradrenergic terminals have been found, as well as α-adrenoreceptors[85].

AVAs are fully dependent on this innervation and do not respond significantly to changes in local skin temperature[220].

At rest and in thermoneutrality skin blood flow is controlled by the sympathetic vasoconstrictor system. During warming of the skin, not only a release of the tonic adrenergic vasoconstrictor tone but rather an active vasodilator system is activated, accounting for up to 80–95% of the elevated peripheral blood flow[52]. The neurotransmission mechanism of active vasodilation is not fully understood, and may be related to sympathetic sudomotor activity, although acetylcholine is not implicated[204]. It has also been suggested that parasympathetic cholinergic innervation of the vessels induces a sequence of steps leading to nitric oxide release which relaxes the vascular smooth muscles[261]. However, no parasympathetic nerves are found in the skin or muscles[85]. The involvement of the sympathetic nervous system in the active vasodilatory system was demonstrated in microneurography studies. Skin sympathetic nerve activity associated with vasodilation was found in the peroneal nerve innervating the hairy part of the feet, but not in the tibial nerve innervating the plantar glabrous skin[253]. Active vasodilation indeed occurs in the back of fingers and hands[200]. Minson et al. recently demonstrated that active vasodilation consists of at least two components: an early axon reflex followed by a more sustained endothelial nitric oxide induced vasodilation[274].

For vasomotor control, three different regions can be distinguished (1) the extremities, (2) the trunk and proximal limbs, and (3) the face[175]. Modulation of the sympathetic constriction is strongly present in the extremities. Active vasodilation may play a more prominent role on the trunk and proximal limbs. On the forehead there is little vasoconstrictive response to cooling, but a vasodilation in response to warming does occur.

With local warming of a skin area, maximal skin blood flow occurs at 42°C[387]. On the other hand, if all the ambient temperature surrounding the skin would exceed 37°C, vasodilation transfer of heat from the environment to the body instead of heat loss would occur, and in order to prevent this, 'heat induced vasoconstriction' occurs in such occasions [85,292].

In addition to strictly thermoregulatory agents, tissue damage and inflammation are associated with agents including bradykinin, histamine and prostaglandin that promote vasodilation and, thus, local heat loss[160]. The vasomotor tone is furthermore modulated by ion concentrations. Vasodilation is furthermore promoted by high ionic concentrations of potassium, magnesium, sodium, hydrogen, acetate and citrate, whereas vasoconstriction is promoted by elevated plasma calcium ion concentrations.

Circadian modulation of peripheral blood flow: At resting conditions, heat loss due to a release of peripheral vasoconstriction shows a circadian rhythm[66,82,142,176,218,334,362], which is the major factor that induces the circadian rhythm in core body temperature. In humans, an increase in distal skin blood flow starts just after 20:00 h and induces a maximum plateau of skin temperature of approximately 33.5°C between 23:00 and 7:00 h[18,19,218,257]. Some studies suggest a more limited noc-

turnal time interval of increased peripheral blood flow. Shaw et al. found lower basal forearm blood flow at 20:00 h as compared to 8:00 and 2:00 h[354]. The induction of endothelium dependent, nitric oxide mediated vasodilation by means of acetylcholine and N-monomethyl-l-arginine was similarly attenuated 20:00 h as compared to 8:00 and 2:00 h. Panza et al. found a higher basal skin blood flow and dilatory response to sympathetic blockade at 7:00 h as compared to 14:00 and 21:00 h[309]. After the nocturnal peak, skin temperature slowly decreases again to a level of approximately 32.2°C. On top of the *circadian* rhythm in vasodilation, the occurrence of *sleep* induces a further vasodilation[219]. A decrease in skin sympathetic nerve activity associated with the vasoconstrictive tone occurs in sleep stages 1 and 2[378]. In animals, a smaller increase in core temperature is sufficient for the initiation of vasodilation during quiet sleep as compared to the increase necessary during wakefulness[311]. On the contrary, larger deviations are tolerated during paradoxical sleep[311]. Melatonin, secreted only at night by the pineal gland also induces a strong peripheral vasodilation in humans. This heat-loss promoting property of melatonin may account for ±40% of the amplitude of the circadian rhythm in core temperature under resting conditions[62].
Both the adrenergic vasoconstrictor system and the non-adrenergic active vasodilator system are involved in the diurnal variation in the cutaneous circulatory response to *passive heat stress*[13,15]. The evening shift towards a higher threshold of core temperature before vasodilation commences is dependent on the active vasodilator system. But, once vasodilation has started after reaching this threshold, the change in cutaneous vasodilation per degree of further increase in core temperature, i.e. the gain, is also higher in the evening as compared to the morning. This appears to be due to a decreased sympathetic noradrenergic vasoconstrictor system activity. The possibility of circadian modulation of postsynaptic receptors is unlikely. The finally reached maximal skin blood flow does not show a circadian modulation. After discontinuation of the passive heat stress, it takes subjects much longer to return to their baseline core temperature in the morning[295].
During *exercise heat stress* the *threshold* for skin vasodilation is lower in the early morning than in the afternoon: vasodilation commences at a relatively low core temperature at night and in the early morning but only at a relatively high core temperature from noon till the evening[367,368,419]. The *gain* of peripheral blood flow, i.e. the increase in blood flow per degree of further increase in core temperature, was minimal at 4:00 h and maximal at 24:00 h, i.e. at midnight every degree increase in core temperature is related to a much stronger increase in vasodilation[368]. The latter finding was not confirmed in another study[12]. Aldemir et al. found a faster increase of forearm blood flow during exercise at 18:00 h as compared to 8:00 h, while the post exercise return to baseline was faster in the morning[7]. This extended morning vasodilation may be involved in the 'overshooting' post exercise hypothermia which, if occurring, is most prolonged following exercise in the morning[278].

Especially in the AVA-rich extremities, skin blood flow, and consequently skin temperature, show a *spontaneous oscillation* with a frequency of ±1 cycle/min. This frequency is lower the more skin temperature deviates from 32°C. Furthermore, there is a circadian modulation of the frequency, showing a maximum in the morning and a trough before bedtime[146,357].

Age-related changes in peripheral blood flow: Kenney and colleagues have investigated age-related changes in the ability to dissipate heat in detail by assessing the response of SkBF to three challenges: (1) passive whole body heating, (2) exercise-induced body heating, and (3) local skin heating. Elderly showed a lower SkBF at a given core temperature in all three experimental conditions. An example is shown in Fig. 4. Especially over the age of 60 years, there is a diminished cutaneous vasodilatory response at any given core temperature[179,206,209,210,272,273].

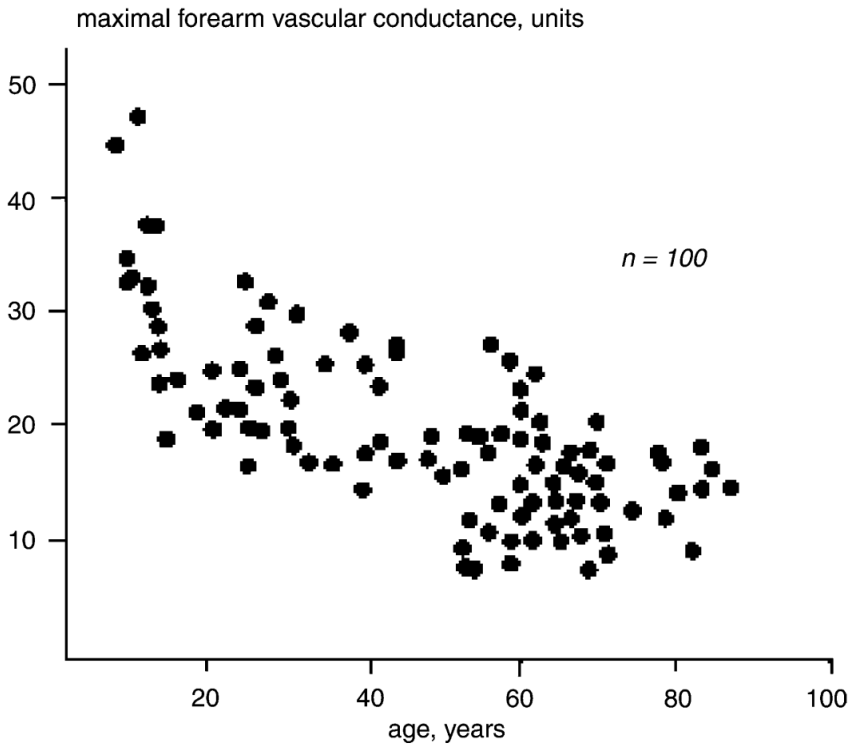

Fig. 4. Prolonged heating of the skin at 42°C elicits maximal skin blood flow in the heated area. The skin temperature of the left forearm was uniformly clamped at 42°C by spraying a fine mist of water over the surface. Maximal forearm skin vascular conductance is shown as a function of age in 100 healthy subjects ranging in age from 5 to 85 years. Each filled circle represents the maximal vascular conductance for an individual subject. Maximal forearm skin conductance (minimal resistance) decreases fairly linearly across this large age span. Adapted from Kenney[207], based on data from Martin et al.[259], with permission.

At high age, the *threshold* for vasodilation with heating is increased[77] which is secondary to poor fitness: no increase in threshold is found when fit elderly are compared to fit young subjects[207]. Indeed, regular aerobic exercise in the long-term results in a lower core temperature threshold needed to induce the onset of vasodilation[179,388]. Changes in the active vasodilator system are involved in the decreased threshold. The *gain*, i.e. the slope of blood flow increase versus core or skin temperature increase, decreases with age[207,391]. The *maximal* SkBF declines linearly by a factor 3 between the ages of 5 and 85 years and can only partly be attributed to changes in fitness level[170,207,259,338]. Although fitness increases maximal skin blood flow in young subjects, it does not so in the elderly[179]. The heat-loss promoting effect of exogenous melatonin is also attenuated in older individuals[63,244], especially in those who have a reduction in the maximal heat induced peripheral vasodilation[149].

Concerning the *mechanisms* of the age-related reduction in vasodilatory capacity, Nadel et al. argued for peripheral rather than central hypothalamic changes[291]. Since both systemic as well as local skin blocking of noradrenergic transmission do not improve the age-related decrease in vasodilation, the involvement of increased sympathetic (NE) vasoconstrictor tone is unlikely, and rather a diminished sensitivity of the active vasodilator system seems to occur[211]. Other factors that may be involved are structural changes in the cutaneous vasculature that limit vessel wall expansion and vascular supply to skin tissue[77,205,206,207]. Indeed, degeneration of the microcirculatory vasculature in the skin was noted in postmortem studies in elderly subjects[283].

Evans et al. suggested that thermally-induced cutaneous blood flow is reduced in older persons at nutritive capillary sites, but not at AVA-rich sites[125]. Other factors involved in the reduced peripheral blood flow are limitations in cardiac output and less redistribution of the circulation from the splanchnic and renal flows to the skin[179,273]. Altered fitness levels may play some role in the latter: whereas increased fitness in young subjects results in increased cardiac output and a greater redistribution of flow from the splanchnic and renal circulation to support SkBF, fitness in the elderly improves only cardiac output, not redistribution[179]. In addition to fitness two other *secondary* age-related factors may be involved in decreased vasodilation. First, dehydration, which often occurs in the elderly, lowers SkBF[169,210]. Second, much like exercise, regular exposure to high as well as low ambient temperature, i.e. heat or cold acclimation, results in a lower threshold of core temperature needed to induce the onset of increased SkBF[175] and elderly in homes for the elderly may seldom experience such exposure.

In summary, the circadian variation in peripheral vasodilation and in the consequent dry heat loss and enhancement of evaporative heat loss is a major factor determining the core body temperature rhythm. Although a low fitness level accounts for a higher threshold of core temperature to be reached before vasodilation commences, it cannot fully account for the age-related decrease in gain and maximal skin blood flow. This decrease will show most prominently during the night,

when peripheral vasodilation is high, and result in an attenuated fall in core temperature, thus, reducing its circadian amplitude. The rhythm will furthermore be more susceptible to fluctuations induced by heat exposure.

4.2. Evaporative heat loss

Increases in core or skin temperature enhance evaporative heat loss, which is more dependent on core than on skin temperature: the ratio of how changes in core and skin temperature contribute has been estimated between 20:1 and 6:1[54]. Repeated heat exposure reduces the threshold for sweating. Unlike most animals, evaporative respiratory heat loss is of little importance in humans, and sweating is the principal evaporative mechanism addressed during exercise and in hot environments. Sweat glands are innervated by the cholinergic, so-called 'sudomotor' sympathetic fibers, i.e. other fibers than those involved in regulating the skin vasomotor tone[239,253]. Sympathetic sudomotor innervation of the hairy skin is activated during heat stress, whereas the sudomotor innervation of the distal glabrous skin is mainly activated during psychogenic stress. In heat-acclimatized subjects, up to 2 l sweat/h can be produced, which allows for the removal of 10 times the basal rate of heat production[160].

Circadian modulation: The *resting sweating rate* is maximal during the evening and night[186,431]. Sudomotor sympathetic nerve activation associated with increased sweating is enhanced during slow wave sleep[296]. The core temperature *threshold* to be reached before sweating occurs also depends on the time of the day. During both *passive and exercise heat stress*, sweating commences at a relatively low core temperature at night and in the early morning but only at a relatively high core temperature in the afternoon[14,368,390,419]. The gain, i.e. the slope of sweating increase versus core temperature increase does not show a circadian modulation. Tayefeh et al. recently confirmed the circadian modulation of threshold and showed that at 3:00 h, sweating occurs on average already when core temperature exceeds 36.6°C, while at 20:00 h, a core temperature of 37.1°C should be reached before sweating occurs[386]. As has been discussed previously for other thermoregulatory responses, evaporative heat loss is also modulated by sleep states[311]. During quiet sleep even a small deviation from the set point is sufficient for the initiation of thermal tachypnea and panting, while during paradoxical sleep large deviations are tolerated without initiating these thermoregulatory responses.

Age-related changes: Elderly have an attenuated sudomotor response, i.e. the sweating response to thermal stimulation is markedly decreased, and the maximal capacity as well as the threshold are increased[77,175]. However, this finding may be secondary to poor fitness. Havenith et al. applied multiple regression analyses on predictors of poor responses to heat stress and demonstrated that low levels of fitness and physical activity account for most of the attenuated sweating re-

sponse[170]. Intact sweating capacity in fit elderly men and women has been demonstrated indeed in other studies[192,308,435]. In one study, fitness level could not account for decreased sweating in elderly women[11], which was suggested to be a result of a lower sweat gland response to stimulation or a structural alteration in the glands or surrounding tissue. No age-related difference in the density of heat activated sweat glands was found[11]. A secondary factor often occurring in aging and negatively affecting the sweating response is dehydration[169].

In summary, elderly show no decrease in sweating, except when fitness is low, which may be the case in many elderly. This decrease will show most prominently during the night, when the sweating rate is high due to circadian and sleep modulation. The age-related loss of slow wave sleep is predicted to further contribute to the decrease. Decreased nocturnal evaporative heat loss will attenuate the nocturnal fall in core temperature. However, the contribution of nocturnal evaporation to the decline in core temperature is less prominent than the contribution of nocturnal vasodilation also because bedding reduces convection of humidity from the body. The circadian temperature rhythm will furthermore be more susceptible to fluctuations induced by heat exposure.

5. Central thermoregulatory control

5.1. Thermoregulatory control

The preoptic and anterior hypothalamic area (POAH) is considered the major site integrating central and peripheral thermosensitive inputs as well as coordinating thermoregulatory outputs. In animal studies, warming of the POAH elicits autonomous heat-loss responses including vasodilation, polypnoea, salivation and sweating as well as behavioral responses like moving to a cooler place and postural changes that increase heat loss[45,175]. POAH cooling can elicit behavioral heat retention responses, cutaneous vasoconstriction and heat production by shivering or non-shivering thermogenesis. Despite the importance of the POAH, the concept of a single or dual integrating control center in the hypothalamus has been abandoned, and it is clear that thermoregulation is hierarchically controlled at several levels of the neuraxis[342]. Spinal reflexes for example, although also modulated by higher centers, are sufficient for the phenomenon that warming of a single hand or foot causes vasodilation in the other. Thermoregulatory responses can, thus, be selectively elicited and suppressed[16]. For example, POAH lesions may affect autonomous reflexes but leave behavioral thermoregulation intact, since the latter are also under control of the posterior hypothalamus. Moreover, the network is involved in, and interacts with, non-thermoregulatory functions[269]. The representation of thermosensitive cells and ascending projections throughout the neuraxis have already been discussed in detail in Section 2, so the present

section will focus on general thermoregulatory output control centers, whereas Section 5.2 will discuss the circadian output control center.

Although the POAH can be considered to represent the highest level of thermoreceptive and thermoregulatory integration, many other brain areas are thermosensitive and can induce thermoregulatory responses. In fact, any autonomous integrated thermoregulatory response can be evoked by appropriate stimulation at the level of the spinal cord. Structures of importance for thermoregulatory control include, in an ascending sequence: the peripheral sympathetic pathways, the spinal cord, parts of the brainstem reticular formation, the preoptic-anterior and preoptic-posterior hypothalamic nuclei, the ventrobasal and intralaminar thalamic nuclei and the somatosensory cortex.

A typical characteristic of the network is that several centers can modulate ascending, descending and reflex transmission[16]. For example, whereas the nucleus raphe magnus has traditionally been regarded a thermo-afferent relay, recent studies suggest that it rather modulates thermoregulatory efferents originating upstream, in the hypothalamus[37]. Indeed, inhibition of medullary raphe neurons with muscimol reduces distal vasoconstriction[43] and results in a drop in core temperature[293]. Another example is that hypocretin projections from the perifornical hypothalamic area to laminae I and II of the superficial dorsal horn of the spinal cord may be involved in inhibition of ascending and reflective nociceptive and thermosensitive information[156.] The strength of vasomotor reflexes induced by local skin temperature changes is indeed modulated by the higher regulatory centers.

A notable property of the thermoregulatory network is that whereas the cold receptors by far outnumber the warm receptors in the skin and deep body[160]—suggesting a predominant function in cold defense—the number of cold-sensitive neurons in the brain are much less than the number of warm-sensitive neurons[399], suggesting a predominant function in heat defense.

With the exception of vasomotor control, which is continuously active in the thermoneutral range, homeotherms including humans rely primarily on behavioral thermoregulation, and only secondarily on autonomic thermoregulation. The anatomical sites involved in the two types of regulation may differ. For example, it has been demonstrated that stimulation of the posterior hypothalamus mainly elicits thermoregulatory behavior, whereas stimulation of the POAH may in addition elicit autonomic thermoregulation[175].

For the control of vasomotor tone, efferents from the POAH project via the medial forebrain bundle to the vasoconstrictor area of (C-1) the rostral ventrolateral medulla[148,284,360]. From this area, a distinct population of sympathetic noradrenergic premotor neurons project to the spinal cord where they excite the sympathetic vasoconstrictor neurons that give rise to the non-myelinated innervation of the skin blood vessels. Even at rest, there is a continuous slow firing of these neurons, inducing a permanent partial constriction called the vasomotor tone. The vasomotor center

receives input not only from the hypothalamus, but also from several cortical areas, the amygdala, the septum and hippocampus[160].

The vasoconstrictor area neurons are not involved in the innervation of brown adipose tissue, for which the sympathetic premotor neurons in the rostral raphe pallidus may be responsible[284].

The primary motor center for shivering is located in the dorsomedial portion of the posterior hypothalamus. It receives inhibitory input from the POAH and excitatory input from skin and spinal cord thermoreceptors[160,382]. The output itself is not rhythmic: the muscle oscillation is probably related to a muscle spindle stretch reflex.

The shivering pathway originates in the posterior hypothalamus, and runs caudally through the midbrain tegmentum and pons, close to the rubrospinal tracts, to the cerebrospinal and reticulospinal tracts (α and γ motoneurons).

Age-related changes in central thermoregulatory control: There is a surprising lack of studies that specifically addressed age-related changes in the brain areas involved in thermoregulation. At the macroscopic whole brain level it has been shown that, in comparison to young rats, aged rats show a decreased or altered temperature response to intracerebroventricular administration of prostaglandin E2, norepinephrine, serotonin, dopamine, and carbachol[131]. In the POAH area, most aging studies addressed the sexual dimorphic nucleus, which is, however, thought to be primarily related to sexual behavior rather than thermoregulation[181]. One study in old female rats showed a decreased number of neurons in the anterior hypothalamic area[187], which would predict an attenuated thermoregulatory capacity. The hypothalamic paraventricular nucleus, of major importance for hypothalamic regulation of the autonomous nervous system stays intact in the course of aging[181], and so does the vasopressin and oxytocin innervation of the parabrachial nucleus in AD patients. The innervation of this autonomic relay center is most probably originating in the PVN[402]. In the C-1 medullary vasomotor center of AD patients, a reduction in the size of neurons was found, without amyloid deposits and only marginal tau-immunoreactivity[56].

In summary, there is only marginal information about age-related changes in the neural substrate of thermoregulatory control, and it is at present not known to what extent these findings are indeed relevant for age-related changes in thermoregulatory control. An important exception is the studies on the hypothalamic suprachiasmatic nuclei (SCN), the biological clock of the brain responsible for the circadian modulation of not only temperature but virtually all physiological processes, as will be discussed later.

5.2. Central control of the circadian rhythm in temperature

The circadian rhythm in body temperature is controlled by the SCN, representing the biological clock of the brain. The SCN consist of two small (±0.25 mm^2 ; ±10.000 vasopressin neurons each)

nuclei located at the bottom of the anterior hypothalamus just above the optic chiasm and separated by the third ventricle.

It is not known in detail at present by which specific *projections* the SCN drives areas involved in thermoregulation. Projections of relevance for thermoregulatory control include those to the POAH[263,415], to the pineal gland and to the paraventricular nucleus (PVN), a key structure in the hypothalamic output regulating the autonomic nervous system. The presence of the SCN projections to the POAH and the PVN have been confirmed in the human hypothalamus[86,87]. However, POAH lesions do not affect the period and even amplify the amplitude in the circadian body temperature rhythm[343,375]. Furthermore, a recent retrograde tracing study on the rat brain structures responsible for sympathetic outflow to the tail artery—of major importance for vasodilatory heat loss—failed to find labeling in the SCN, although many of the major hypothalamic SCN-projection sites (PVN, DMH, VMH, POAH) were labeled[360]. Tracing of the SCN may have been missed because these nuclei were labeled not before 7 days after injecting the retrograde tracer, and no observations were made after 7 days. A projection to the melatonin-producing pineal contributes to the circadian regulation of temperature. Under control of the SCN, melatonin is secreted only during the night, and in human induces a strong peripheral vasodilation. This heat-loss promoting property of melatonin may account for ±40% of the amplitude of the circadian rhythm in core temperature under resting conditions[62].

It should be noted, however, that the nocturnal increase in heat loss commences already before melatonin starts to increase[220]. Melatonin may act both through POAH melatonin receptors[224] and receptors in the vasculature[61]. The role of the SCN in the circadian modulation of activity and posture[116] also has consequences for metabolic heat production and heat loss, respectively due to increased peripheral blood flow and, thus, the core temperature.

As described already, under strict resting conditions the circadian rhythm in core temperature is only to a small extent the result of changes in heat production, which is maximal just before noon[218]. In such conditions, but probably not under normal activity conditions, the diurnal variation in dry heat loss, with a peak plateau during the night, is the major determinant of the circadian rhythm in core temperature[82,142,176,218,334]. This suggests a major role of the SCN in vasomotor control, the primary factor in heat loss.

By what *control mechanism* does the SCN effectuate the circadian rhythm in temperature? Hensel argued that the circadian rhythm could only be accomplished by modulation of a set point, since the temperature rhythm is present in the thermoneutral range where thermoregulatory control actions are near zero[175]. However, we would like to stress that in fact countermeasures are taken in order to *limit* heat loss when the biological clock promotes peripheral vasodilation, which argues against a set point induced change, in which case behavioral thermoregulation would also be aimed at heat loss. For example, gerbils show increased autonomic thermogenesis and behavioral

heat gain during the trough of their temperature rhythm[331], and rats self-select a higher ambient temperature during the time of day when their core temperature is declining[50]. The same is true for humans: although the changes in body position promote peripheral vasodilation, the creation of an insulative microclimate far above thermoneutrality is indicative of thermoregulatory behavior aimed at *limiting* the heat loss. In fact, humans sleep best at 34°C, the habitual microclimate, which is just slightly above the thermoneutral range (28–33°C[133]) and any activation of cold defense disturbs sleep[168,312.] These and other observations[399] argue against the paradigm that a major function of sleep would, with respect to thermoregulation, would be heat loss due to a lower set point, rather that vasodilation is promoted in spite of a set point that does not favor it. This indicates that the circadian modulated increase in peripheral vasodilation and sweating most likely serve a function other than heat loss. A new view on this question will be presented in Section 7.

6. The circadian temperature rhythm in aging and dementia

It was more than a century ago reported that the circadian *amplitude* of human body temperature declines from childhood to senescence by about 50%[417]. This finding has been replicated in many studies, with percentages ranging from 13 to 40%[83,102,113,252,393,408,418]. At least in rats there is a marked inter-individual variability in the amplitude reduction, ranging from strong to absent[238]. This variability may underlie the absence of an amplitude reduction in very healthy elderly[282]. Not only the amplitude, but also the *mean level* of temperature may decrease with age[364]. Changes in the intrinsic free-running period have been reported, but remain equivocal[84,252,418]. On the other hand, many studies have confirmed an advanced phase[83,113] and it appears that especially the early morning rising phase of the rectal rhythm is advanced[113,282].

The relative contribution of the age-related changes in thermoregulation discussed in the present paper to the changes in the circadian rhythm in temperature is at present far from clear, although a major involvement of the decreased vasodilatory capacity is a priori likely.

At a central level, the number of SCN neurons expressing the peptide vasopressin (VP) and mRNA declines at old age, and even more so in AD[243,373]. Vasopressin is strongly implicated in the clock output that is of importance for the regulation of both the level and rhythm of temperature. VP-deficient Brattleboro rats may maintain a temperature rhythm under light–dark cycles, but in the absence of these Zeitgeber, i.e. cues with a circadian timing, the temperature rhythm is lost and temperature is low and irregular[423].

Another change at the central level, the age-associated decrease in *acetylcholine* synthesis[147,359], may also be of importance. Rats treated with a cholinergic neurotoxin show a phase advance and decreased amplitude, but no change in period[122], strikingly similar to the findings in normal aging.

The SCN receives strong cholinergic input from the nucleus basalis magnocellularis[40]. Both nicotinic and muscarinic receptors are present in the SCN, which decrease in number with increasing age[396].

Corticosteroid levels are increased during aging and do not reach the low nocturnal levels observed in young adults[132,394]. Elevated glucocorticoid levels suppress vasopressin synthesis in the SCN[242], and since vasopressin reflects the output strength of the SCN, may thus be involved in an attenuated circadian temperature amplitude. A peripheral action of cortisol is to increase catecholamine synthesis in sympathetic ganglia[16]. Thus, elevated nocturnal cortisol levels may contribute to the attenuated loss of sympathetic vasoconstriction, and the consequent reduction in heat loss and core temperature decline during the night. The nocturnal temperature minimum in elderly indeed remains up to 0.3–0.4°C higher than the minimum in young adults[418], especially in poor sleeping elderly[245].

The age-related increase in the risk of hypothermia may even be worse in *dementia*[173]. A case report also suggested a possible link between the progression of AD and progressive loss of cold defense[99]. However, some studies suggest that the age-related decrease in circadian temperature *amplitude* does not occur in AD patients, which is surprising given their poor sleep–wake rhythms and the considerable evidence for a reduced circadian temperature amplitude with normal aging[393]. Prinz et al. found no differences in amplitude and phase as compared to healthy elderly and confirmed this finding in a larger sample[321,322]. The former study may, however, have been biased since nocturnal rectal assessments were only available in compliant subjects, and low amplitudes occur mainly in very agitated male AD patients[410]. Mishima et al. demonstrated intact temperature amplitudes in AD patients, and a loss of amplitude only in multi-infarct dementia[275]. However, no neuropathological confirmation of this diagnosis was available, and postmortem AD neuropathology is often seen in dementia clinically diagnosed as 'vascular'. The expression of a relatively strong temperature amplitude in AD is also supported by an animal model. Grafting genetically transformed cells that over express β/A4 amyloid into the SCN of adult rats induces a disrupted circadian activity pattern, whereas the body temperature regained a circadian amplitude relatively fast[385]. Concerning the phase of the temperature rhythm, a delayed maximum is found in most patients, and especially in the agitated ones[410]. This phase delay was confirmed by Harper et al., who moreover once more found an intact amplitude[167]. A late temperature minimum was also found in end-stage demented elderly (Van Someren et al., unpublished results). We propose that the degeneration of cholinergic neurons that characterizes AD may contribute to this delay, since cholinergic projections to the SCN, as discussed previously, exert a phase advancing effect[151].

The interpretation of the increase or lack of change in amplitude in demented elderly is difficult, and several factors may be involved. First, if the thermoregulatory capacity is decreased, this may in certain circumstances result in a body temperature that is allowed to oscillate uncontrolled

within a wider temperature range[77], as is the case in POAH lesioned animals[343,375]. Indeed, increased within subject temperature cycle variability has been reported in old rats[238] and AD patients[321,299], especially in agitated subjects[410] and male subjects[322]. Alzheimer patients furthermore show an unpredictable and variable temperature response to serotonin agonists, which in healthy subjects invariably elevates core temperature[233]. This loss of stability may also be related to a reduced vasopressin production in the SCN: in the vasopressin-deficient Brattleboro rats, temperature homeostasis is poor and over responsive to disturbances induced, e.g. by handling[423].

Possible confounding factors may be the use of cholinesterase inhibitors and neuroleptics in AD. Cholinesterase inhibitors as prescribed to patients suffering from AD induce dose-dependent hypothermia in rats[110], monkeys[339] and humans[254]. The anticholinesterases may exert their hypothermic action through the POAH, which receives cholinergic projections from the brain stem[72], but also by acting on the PVN[376,377]. Neuroleptics may increase the body temperature especially in warm environments, but occasionally also induce hypothermia, dependent on individual disposition and dose[73,251]. It is, thus, likely that the prescription of neuroleptics affects the circadian rhythm in body temperature, with an outcome that depends furthermore on the time(s) of intake.

In summary, the results suggest a delayed phase and a strong but highly variable amplitude in elderly suffering from AD, quite the opposite of the advanced phase and flat amplitude associated with normal aging. The increased variability may be a stronger hallmark of dementia related circadian changes than changes in the amplitude per se[401]. Indeed, a study in progress suggests that under constant routine conditions, the amplitude in AD patients is as reduced as in healthy elderly controls[166]. Neuroleptics and cholinesterase inhibitors affect the circadian rhythm in core body temperature.

7. Functional implications of body temperature and the temperature rhythm

Ambient temperature cycles have been of pivotal importance in the very origin of proteins and, thus, the evolution of life itself[286]. It is, therefore, a priori likely that temperature cycles, even if they are internalized as in homeotherms, have functional implications. Indeed, this notion is supported by demonstrations that temperature modulates a variety of physiological and behavioral functions ranging from glucocorticoid receptor binding[439] to complex executive cognitive functions as assessed using the Tower of London task (Van Someren and Raymann, unpublished observations). The present paragraph discusses some recent findings on how body temperature cycles affect daytime and nocturnal functions relevant for human aging.

At the *cellular* level, there is evidence that repeated mild heat stress is able to prevent the onset of various age-related changes during cellular aging in vitro[404]. Human skin fibroblasts in culture

show less of the characteristics of aging cells when they are exposed repeatedly to mild (41°C) warming[325]. Thus, although speculative, it may well be that temperature cycles promote cell integrity.

At the organismic level, there is evidence that a proper circadian temperature rhythm is essential for optimal *homeostatic thermoregulation*. Squirrel monkeys put in a constantly lit environment without circadian time cues lose their circadian temperature rhythm and as a consequence show an attenuated cold defense, indicating that an intact circadian temperature rhythm is required for adequate thermoregulation[141].

Sleep onset and maintenance is modulated by the SCN-induced peripheral skin vasodilation at the end of the day[222,395,399]. Indeed, limitations in the peripheral vasodilatory capacity have devastating effects on sleep, as has been reviewed by Van Someren[399], and recently been confirmed for patients suffering from the vasospastic syndrome[303] and insomnia[245]. Moreover, the timing of the early morning decrease in peripheral vasodilation and heat loss, and consequently the increase in core temperature, is strongly involved in the ability to maintain sleep in the later part of the night[83]. It is difficult to maintain sound sleep once the core temperature is rising, and this difficulty is more pronounced in the elderly[101,112]. Concerning the mechanism by which circadian alterations in core and skin temperature affect sleep, a model has been proposed which stresses the importance of input from thermoreceptors to sleep-related brain structures[399].

Nocturnal temperature may also be involved in the sleep-disturbing increased nocturesis in elderly. Cooling promotes diuresis[171]. Dewald et al. showed that this is likely due to thermosensitive neurons in the hypothalamic PVN[96]. Warming induced an increased firing rate in neurons showing burst discharge, which is characteristic for vasopressinergic neurons. Indeed, plasma AVP concentration in man is increased during heat exposure[353], thus, attenuating diuresis.

Although the major changes in thermoregulation herald rather than follow the transition from wakefulness to sleep, a slight vasoconstriction remains if one is kept awake, even supine in a dark environment, as compared to being asleep. Without sleep, the extremities show a circadian modulated increase in skin blood flow, but full vasodilation is obtained only when sleep is allowed. The proximal part of the skin in fact shows decreased nocturnal vasodilation if one is kept awake, and full vasodilation only if sleep is allowed[219]. Thus, the extremities lead in peripheral vasodilation due to a circadian modulation, and this vasodilation is enhanced at the extremities and spreads out to include the proximal skin areas when sleep is allowed. This strong whole body skin vasodilation of necessity requires a redistribution of the blood flow, attenuating the flow to skeletal muscles and other peripheral organs[80,176] and the brain[255].

An important question, raised in Section 5, is what the purpose of this strong nocturnal perfusion of the skin—requiring a reduced perfusion of vital organs including the brain— might be if it does not primarily serve thermoregulation. We would like to put forward that this increased skin blood

flow is an important part of the previously proposed function of sleep in immunological *host defense*[225]. More specifically, we propose that the increased nocturnal skin blood flow may crucially support the role of the skin as the major barrier and first line of defense against environmental micro-organisms. Leukocytes, whether coming from the lymph vessels, bone marrow or spleen, need transport by blood to reach the parts where they are needed. The strong sleep-associated increase in skin blood flow will, thus, routinely give leukocytes optimal access to this important first defense area, much like the primary response of increased vasodilation and plasma extravasation elicited by irritation or injury of the skin (68). Human sleep is indeed associated with a reduced number of monocytes, natural killer cells and lymphocytes circulating in the blood stream[44,279]. This is indicative of an enhanced redistribution of lymphocytes into extravascular tissues to allow them to perform their functions at the sites that need it most[32,97,98,301]. The migration from the interstitial space to the lymphatic system is however low, since it was demonstrated in both humans and sheep that the efferent lymph output is reduced during night-time rest and sleep[100,124]. Collectively, these findings are indicative of an increase in lymphocytes in skin tissue during sleep.

An increase in regional blood flow is associated with an increase in the amount of fluid leaking out from the capillaries into the interstitial fluid[100]. Consequently, increased nocturnal skin blood flow furthermore enhances the distribution and interstitial flow of endogenous antimicrobial peptides, like cathelicidin and α- and β-defensins in the skin[33,144,163,164]. Especially during sleep, β-defensin 3 may be increased in the human skin because it is upregulated by TNF-α[164], and plasma TNF-α is elevated in association with high power in the slow-wave band of the sleep electroencephalogram[90]. The TNF-α increase during sleep could, however, not be demonstrated in other studies[44,157,320].

The warm skin that results from the combination of increased peripheral blood flow and insulative bedding will strongly enhance capillary permeability and lymph flow[124,300]. In addition, in humans, the nocturnal strong warming of the skin will also contribute to the already upregulated sweating rate during the night. This increased sweating is hardly effective in heat loss because bedding prevents convection, and may once more rather serve host defense, since sweat glands secrete the endogenous antibiotic peptide dermcidin[350].

The nocturnally secreted pineal hormone melatonin supports furthermore nocturnal host defense in humans in several aspects. First, melatonin strongly enhances peripheral blood flow in humans. Second, melatonin increases salivary immunoglobulin A (IgA) concentration, which plays an important role as a first line of defense against bacterial and viral antigens on mucosal surfaces and upper respiratory tract infections[310]. Indeed, inadequate sleep is associated with an increased risk of oral[184] and respiratory[89] infection. With respect to these findings, it is conceivable that the already increased risk of infection in elderly[412] is worsened by their reduced melatonin release as

well as the attenuated vasodilatory effect sorted by melatonin. Recent findings suggest that daytime bright light treatment may have important clinical consequences, because it increases nocturnal melatonin as well as salivary IgA in both young and aged subjects[276,310].

The strongest nocturnal vasodilation takes place in skin of the extremities, which most prominently interact with the environment and are, thus, in need of a strong defense mechanism. It is striking that the first degenerative symptoms of long-term sleep deprivation in rats are ulcerative and hyperkeratotic lesions at the very skin area that normally shows the most dramatic diurnal and sleep-related variation in vasodilation: the tail and plantar surfaces of the paws[127,329], suggesting that these areas indeed suffer most from a lack of full sleep-related vasodilation. The lesions improve within days with recovery sleep[129]. A systemic but not fully successful effort for additional vasodilation in order to make up for the lack of sleep-related vasodilation is one of the hallmarks of such long-term sleep deprivation and accounts for the decrease in core temperature in spite of a strong increase in energy expenditure[437], which is also seen in sleep-deprived humans[346]. This continuous strive to vasodilate during sleep deprivation testifies of the relevance of the cyclic full vasodilation of the skin occurring daily under normal sleeping conditions. Indeed, long-term sleep deprivation in rats results in a breakdown in host defense with blood infection[126]. In addition, live bacteria were found in the lymph nodes[128]. The importance of these findings has been questioned since they do not readily account for *all* symptoms induced by sleep deprivation[35]. On the other hand, it would be highly unlikely that sleep would serve a *single* function, and that symptoms other than those related to collapsing host defense are a priori likely. Under normal, non-deprived conditions, microbial infection and cytokines promote sleep[226] and, thus, skin blood flow, which is in support of our suggestion of a prominent role of the circadian and sleep-related increase in skin blood flow in host defense.

In summary, the strong cutaneous vasodilation associated with the preferred sleeping period in the circadian cycle is not likely serving heat loss due to a lowering of the set point. Several observations support our hypothesis that it may be of importance in host defense.

Circadian cycles in core temperature are paralleled by cycles in *cognitive performance*[281,427]. This might indicate that both processes are under the control of a similar output of the circadian timing system, or alternatively that temperature changes directly affect performance. Strong evidence for either of the possibilities is not presently available.

Although some have suggested that cognitive functioning is rather insensitive to cooling[10], there is considerable evidence for the contrary. Cooling may shift the speed-error trade-off in task performance towards more errors[119,121]. Hoffman[180] and Palinkas[305] reviewed human psychological performance in cold environments and these overviews clearly indicate decrements in manual performance due to changes in tactile sensitivity, dexterity, strength and motor speed. The relation between vigilance and environmental temperature appears to follow an inverted U-shaped

curve, with lowered vigilance both at higher and lower temperatures than the optimal range of 27–32°C. Simple reaction times hardly suffer from cold exposure, whereas more complex reaction time tests do markedly. Other complex tasks, addressing memorizing, recall or complex cognitive functions are also performed poor in cold environments. It is of interest that such tasks are strongly dependent on the prefrontal cortex, and that the majority of neurons in the sulcal part of the prefrontal cortex show thermosensitivity in rats[355].

Lowering of the *core* temperature by 1°C induces a 6–7% reduction of *cerebral blood flow*[335]. Such a reduction in cerebral blood is associated with a significantly worse cognitive performance[123], and is for example in AD related to the severity of dementia and survival[349]. Robinson et al. have described a parallel progressive decline of cognitive performance and core temperature over time in AD[335]. Collins suggested this to represent seasonal variation which is, however, unlikely given the variable time intervals of the patients[76]. An untested hypothesis even suggested that hypothermia, which frequently occurs in the elderly, may alter protease activity and, thus, contribute to the formation of β-amyloid deposits, which are associated with AD[182,183]. Cerebral blood flow is not only sensitive to changes in core temperature, but also to changes in *skin* temperature. During application of a cold pack to the thigh, frontal oxygen saturation decreased, and showed an overshooting increase after removal. During application of a warm pack, frontal oxygen saturation showed an increase with a less marked undershooting decrease after removal. The middle cerebral artery blood flow increased with cool packs and decreased with warm packs[103]. Mild warm stimuli applied to the hand increased cerebral blood flow, most markedly at the left temporal region[340].

Vigilance, as measured by the critical fusion frequency (CFF), increases with passive whole body *warming*[1]. When subjects are instructed to respond with a microswitch press when they become aware of tones presented during the night, increasingly stronger tones are necessary while the core temperature declines, and less loud tones once core temperature starts increasing in the early morning: the curves throughout the night are mirrored[229]. On the other hand, CFF, subjective scales and electroencephalographic parameters also indicate increased vigilance with the application of brief *cold* stimuli to the face and neck[104,230], suggesting a differential effect of skin and core temperature. Temperature suppression after melatonin intake is associated with decreased alertness and performance efficiency[91], which appear to be mediated by the changes in temperature rather than by increased melatonin levels per se[426]. Kräuchi and colleagues demonstrated that decreased alertness is strongly related to distal vasodilation[223].

The findings concerning temperature effects on *learning* are equivocal. Andersen and colleagues found spatial learning to be resistant to temperature changes. In their studies, the acquisition, consolidation and retrieval phases of spatial learning in the Morris water maze, an often used experimental setup for memory testing, were not apparently affected by cooling[10,285,307]. Howev-

er, many other studies in rat have demonstrated that hypothermia may indeed disrupt learning and memory[161,177,198,241,250], including spatial learning[326]. Since the body temperature of older animals drops further after exposure to cold and takes longer to recover, age-related findings on the Morris water maze should be interpreted with caution. Indeed, the enhanced body temperature drop in old rats accounted for a part of the 'age-related' decline in memory and could be restored by rewarming the older rats[241]. Hamm found no age differences in the degree of hypothermia-induced amnesia on a passive avoidance task when taking account for temperature levels[161]. Thus, the age-related increased sensitivity to learning deficits with hypothermia may in some experimental paradigms be accounted for by the decreased cold defense and, hence, lower induced temperatures.

Electrophysiological findings at the *cellular* level surprisingly indicated a strong modulation of hippocampal potentials in the same experiments that demonstrated resistance of spatial learning to cooling[10,285]. During cooling, synaptic potentials get considerably slower and smaller, while action-potentials and after-potentials are in fact somewhat enhanced.

Electrophysiological findings at the *cortical* level support the idea that cognitive functioning is modulated by temperature. In humans, whole body cooling increased the latencies of visual, auditory and somatosensory evoked potentials[248] and attenuated the amplitude of middle latency auditory evoked potentials (MLAEP), but not the amplitude of visual evoked potentials[336]. These findings should be taken into account when assessing the effect of age on evoked potentials, especially since the elderly are vulnerable to hypothermia. In contrast to whole body cooling, skin cooling by application of brief cold stimuli to the face and neck in healthy elderly decreased VEP P300 latencies, whereas warm stimuli increased the latencies[104]. Cold stimuli also elevated the amplitudes. Since a short latency and high amplitude P300 is indicative for increased vigilance, the results suggest a positive correlation between skin temperature and drowsiness, and once more the opposite relation for core temperature.

In summary, the majority of studies indicate that a warm core and a cool skin promote optimal cognitive functioning.

8. Factors promoting thermoregulation & the temperature rhythm amplitude

Given the functional implications of the circadian rhythm in core temperature, it is of practical importance to investigate which factors might be used to support this rhythm in elderly. Several suggestions are given as follows.

There is considerable evidence that the amplitude of the circadian rhythm in core temperature flattens in the absence of *Zeitgeber*. Also the average temperature can decrease considerably when the subject is deprived of circadian clues[77].

Light: The major circadian Zeitgeber is environmental *light*. Core temperature increases with light exposure during the night. At least in Syrian hamsters, the increase is strongly dependent on the circadian phase of application[363]. Light during the habitual night (active period) increased temperature, whereas light during the habitual day did not. The temperature increase could not be attributed to increased physical activity. Humans similarly respond to light during their habitual dark period[24]. The nocturnal light induced increase in core temperature can be antagonized by suppletion of melatonin, which is suppressed by bright light[220,370].

Light during the day has been reported to be ineffective also in humans[24]. However, in other studies, light applied in a thermoneutral to warm environment increased the vasodilatory gain and had the opposite effect of lowering tympanic temperature[5,6]. An artificial increase in daylight furthermore has the delayed effect of increasing the *nocturnal* release of melatonin, which promotes heat loss and the decline of core temperature[276].

It is not presently known whether light similarly affects core temperature in elderly as it does in young subjects. An attenuation is likely, since aging is associated with a decreased immediate early gene expression in the SCN in response to light stimuli[22,372]. Moreover, the age-related loss of vasopressin synthesis in the SCN most likely will attenuate the effectuated output. In addition, the age-related decrease in acetylcholine synthesis may attenuate the effect of light. Sight increases the ACh concentration in the SCN[287]. Cholinergic agonists are capable of mimicking the effects of light[436] and it has been presumed that ACh concentrations in the SCN may increase through retinal projections to basal forebrain cholinergic neurons[433]. However, such connections have not been observed by postmortem tracing of optic nerve projections in the human brain[88].

Melatonin: As mentioned already and confirmed in many studies, suppletion of melatonin promotes heat loss may be used to promote the nocturnal fall in core temperature[399]. The hypothermic action of exogenously administered melatonin is dose-dependent[345]. Zhdanova et al. in fact warned for the possibility of nocturnal hypothermia after a pharmacological dose of melatonin at bedtime when given to elderly insomniacs[438]. Melatonin is under control of the SCN, and might alter heat dissipation centrally through receptors in the POAH[224] and SCN itself, as well as peripherally through receptors in the vasculature[61]. Melatonin increases the peripheral blood flow in human, thus, lowering core temperature, while in rat it has the opposite effect which is compatible with the finding that peripheral blood flow during the night, when melatonin secretion is maximal, is increased in a diurnal species like humans, but decreased in the nocturnal rats. Cagnacci et al. demonstrated that in elderly not only the nocturnal production of melatonin is compromised, but also the hypothermic effect of melatonin[63]. It is likely that this attenuated vasodila-

tory response to melatonin in elderly is due to peripheral rather than central changes, since at least in rats the expression of melatonin receptors in the SCN remains relatively constant with age, whereas on the other hand, a dramatic loss in receptors was found in the arteries[228].

Heat and cold exposure: By definition, the temperature rhythm of heterothermic organisms can also be entrained to environmental temperature rhythms, and this has indeed been demonstrated in bacteria, fungi, insects and vertebrates[304,440]. Several studies indicate that this entrainability is not lost in homeothermic mammals[20,135,240,306,319,392]. A circadian 'memory' has furthermore been demonstrated for the thermoregulatory response to heat and cold exposure. Rats exposed to heat or cold at a fixed time of day for several days show at discontinuation of this daily treatment a drop in temperature during the time of day they were previously exposed[341,356]. It is not known whether such mechanism is present in humans. However, the human temperature rhythm is definitely sensitive to changes in ambient temperature. Humans living in strict isolation show a free-running period that is slightly longer than 24 h. When the ambient temperature could be regulated to be 23°C during wakefulness and 17°C during sleep, the period length increased by about 0.4 hour[421]. Repeated morning lukewarm baths of 37°C do not affect the temperature rhythm in young healthy subjects[159]. Dorsey et al. compared such lukewarm baths with warm baths (40°C) and showed that enforcing an increase in body temperature in the early evening by taking a warm bath 1.5–2 h before bedtime resulted in an average delay of 1.5 h in the nocturnal rectal temperature minimum of elderly female insomniacs[106,107,108]. The length of the delay was correlated with the increase in sleep efficiency. Several other studies confirm changes in the circadian temperature curve and sleep due to active and passive heating[399].

Regular exposure to more extreme high as well as low ambient temperatures, i.e. heat or cold acclimation, results in a lower threshold of core temperature needed to induce the onset of increased skin blood flow during heat exposure[175,192]. It may be hypothesized that this finding is in part due to the trophic influence that regular sympathetic activation is known to exert on the vasodilatory endothelial function of the conduit arteries, but probably not on the microcirculation[8,69,202,203,429].

Exercise: As indicated previously in the present review, some of the age-related changes in thermoregulation are reversible since they result from a low fitness level. Increasing the fitness level by means of regular exercise will enhance the vasodilatory capacity, the sweating response, the diurnal rhythm in basal metabolic rate. In healthy adults, long-term fitness-training affects daytime and night-time metabolic rate in an opposed way: whereas the daytime metabolic rate increases, the night-time metabolic rate decreases[266,420]. Of course, exercise also acutely affects core temperature. During exercise, core temperature increases. Following exercise the rectal temperature starts to fall and decreases even below the level otherwise present at that time of day[278]. This pattern may be applied in insomniac elderly by timing exercise in the late afternoon in

order to enhance the nocturnal sleep-promoting heat loss[399,400]. A higher activity level furthermore contributes to the diurnal amplitude of thermogenesis.

There is some evidence that exercise training increases cold tolerance in humans[109]. However, neither in young nor in old rats does exercise training increase UCP mRNA in the resting state[347]. UCP mRNA has not been evaluated during cold stress.

Other: Elderly are at an increased risk of electrolyte imbalance[29,369], which affects thermoregulation both at a central and peripheral level[403]. These conditions are reversible by proper nutrition and hydration.

Estrogen replacement therapy (ERT) in postmenopausal women lowers the baseline core temperature and the threshold of core temperature to induce the onset of increased skin blood flow, but only when exercising in the heat. It does not affect skin blood flow during passive whole body or local skin heating. A central hypothalamic rather than a vascular mechanism is likely to be involved[53,383].

Application of sheetings of silicone or polyurethane to parts of the skin for several weeks can increase skin blood flow by about 6%, and resting skin temperature by about 4°C[216].

Biofeedback has been used with success to enhance the vasodilatory capacity of the extremities[65,190], also in elderly[3], and in some cases with the secondary effect of improved sleep[93,407,413.]

Transcutaneous electrical nerve stimulation (TENS) can be applied to induce an acute increase in skin blood flow and temperature[81], but it is not known whether repeated treatment could induce long-lasting improvement in skin blood flow.

In mice, the age-related decline in cold defense could be restored to the level of young animals after 15 brief daily sessions of intracranial (hypothalamic) electrical (self) stimulation[380], which is suggestive for plasticity of central thermoregulatory control areas.

Although dysregulation of body temperature might be predicted to contribute to age-related increases in susceptibility to disease, individuals with lower body temperatures throughout adult life may have increased disease resistance and increased lifespans. The strongest support for the latter statement comes from studies of caloric restriction, a dietary manipulation that increases the lifespan of all mammals studied to date[416]. Caloric restriction also improves insulin sensitivity and reduces incidence of various age-related diseases including cardiovascular disease, type 2 diabetes, cancers and neurodegenerative disorders[260]. Caloric restriction consistently lowers body temperature in rodents[114] and primates including humans[231]. Reduced body temperatures may contribute to the anti-aging effects of caloric restriction by reducing cellular metabolism and oxyradical production.

9. General conclusion

The vulnerability of disturbances in the circadian temperature rhythm at old age may result from deficiencies at several levels: thermoreception, thermogenesis and conservation, heat loss, and central regulation. More research is needed in order to evaluate the relative contribution of the range of age-related changes to the decreased amplitude, advanced phase, and increased variability of the circadian rhythm in temperature. The circadian rhythm in temperature in homeotherms should not be regarded as a leftover of ectothermy in early evolution, but appears to be of functional significance for physiology from the molecular to the cognitive level. A new view on the functional significance of the circadian rhythm in peripheral vasodilation was presented. It is unlikely that this phenomenon primarily represents heat loss in response to a lowering of set point, since behavioral measures are taken to prevent heat loss. Several indications rather point towards a prominent function in host defense. Given the functional significance of the temperature rhythm, additional research should evaluate the feasibility and effectiveness of methods that can in principle be applied in order to enhance the weakened circadian temperature rhythm in the elderly.

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PROMOTING SLEEP ONSET

Chapter 3

Skin temperature and sleep-onset latency: changes with age and insomnia

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Summary

Throughout the 24-hour day, the occurrence of sleep and wakefulness are closely related to changes in body temperatures. Changes in skin temperature may causally affect the ability to initiate and maintain sleep. First, we briefly summarize a previously proposed neurobiological mechanism that couples skin temperature to sleep propensity. Next we review previous findings on the relation between skin temperature and sleep onset latency, indicating that sleep propensity can be enhanced by warming the skin to the level that normally occurs prior to – and during – sleep. Finally, we present new data indicating age- and insomnia- related changes in the sleep onset latency response to foot warming, and evaluate whether different methods of foot warming could provide an applicable strategy to address sleep complaints. Foot temperature manipulations included footbaths before sleep onset (*1*), and heatable bed socks applied either before (*2*) or after lights-off (*3*). In adults, sleep onset latency was accelerated by warm and neutral bed socks after lights-off and correlated to the increase in foot temperature. This increase was attenuated in elderly subjects. In elderly subjects without sleep difficulties, sleep onset could be accelerated with neutral bed socks after lights-off and a warm footbath prior to lights-off. In elderly insomniacs, none of the treatments accelerated sleep onset. We illustrated that elderly subjects show an attenuated increase in foot temperature after lights-off and lose the relationship between pre-sleep heat loss activation and sleep latency. The sensitivity of sleep propensity to foot warming changes with age and is attenuated in age-related insomnia.

1. Introduction

Both sleep initiation and termination are temporally related to the circadian rhythm of core body temperature (CBT) and skin temperature. The habitual sleep period coincides with the diurnal phase of lowered CBT and the rise of CBT heralds the end of the sleep period. Habitual sleep onset coincides with the maximal rate of decline in CBT[30,38]. This decline is to a large extent caused by increased skin blood flow, and consequently skin warming and heat loss. Moreover, the habitual sleep period coincides with the diurnal phase of increased skin temperature. A functional link between skin temperature and sleep has been suggested by Kräuchi and colleagues[27,28]. In a series of controlled laboratory studies, they showed that the gradient between the skin temperature of the hands and feet and the proximal skin temperature was highly correlated with subsequent sleep onset latency. A key question is whether this correlation merely results from a single underlying sleep propensity increase that first shows in autonomous measures like skin vasodilation and only later in the central nervous system, as measured by the sleep-electroencephalogram (EEG). An alternative hypothesis[51] proposed that changes in skin temperature causally affect the ability to initiate and maintain sleep. The neurobiological mechanism proposed to underlie this causal relation is as follows.

1.1. Neurobiology and behavior

It has been shown that a subpopulation of warm-sensitive neurons (WSNs) in the preoptic area and anterior hypothalamus (POAH) spontaneously increases its firing rate at sleep onset. Experimental local warming of the POAH induces a similar increase in firing rate and facilitates sleep[1,36,37]. Consequently, it has been proposed that sleep would be facilitated when brain temperature exceeds a threshold level[36]. However, this proposition is in opposition to the chronobiological perspective – namely, that sleep propensity is actually minimal during the phase of high CBT. We proposed the warm sensitive neurons involved in sleep regulation to be sensitive to skin temperature as well. The circadian phase of elevated skin temperature coincides with the period of maximal sleep propensity, and animal studies show that the activity of a high percentage of locally warm sensitive neurons is strongly modulated by thermoafferent projections to the POAH originating in the skin[2]. Afferents conveying information about skin temperature modulate the firing rate of thermosensitive neurons in the POAH at least as strong as does local brain temperature. In case of simultaneous differential local brain temperature and skin temperature manipulations, the latter dominate the POAH response[2,3]. In addition, a recent human neuroimaging study demonstrated hypothalamic activation with warming of the skin[15]. Thus, the changes induced by direct local CBT warming and leading to sleep-related alterations in firing rate – changes that can

be observed in experimental conditions - may well be induced by warming of the skin under more natural conditions.

The behaviors that occur while preparing for sleep strongly favor an increase in skin temperature. The postural change from upright or sitting to a supine position[29,47], the use of bedding to create a microclimate of 34°C to 36°C [19,39,55], and the relaxation associated with the preparedness to sleep that is signaled by lights off[31] - all promote an increase in skin temperature. Since warming of the skin due to these changes occurs already before sleep onset, it could affect the process of falling asleep.

1.2. More evidence for a modulatory role of circadian changes in skin temperature

Several studies have shown that temperatures of the skin and, more specifically, temperatures of the skin of the extremities (i.e. hands and feet) increase prior to sleep onset. The potential role of skin temperature in sleep onset, was already recognized by Magnussen in 1939[35]. He reported that peripheral vasodilation and hence an increase in peripheral skin temperature indicated "Schlafbereitschaft" or "sleep preparedness". Also, Kleitman reported on an increase in toe temperature before sleep onset[26]. Brown confirmed the elevation of toe temperature around sleep onset, and suggested that it was related to the onset of the first period of slow-wave sleep rather than to sleep onset[4]. Van den Heuvel and colleagues also reported on increased peripheral temperatures in the hand and foot prior to and after habitual sleep onset[49]. Kräuchi and colleagues showed that the degree of heat loss at the skin of the hands and feet relative to the proximal part of the body (distal to proximal gradient, or DPG) was the best physiological predictor of a fast sleep onset under strictly controlled experimental conditions[27,28]. Fronczek et al. demonstrated that the DPG was increased in relation to the very short sleep-onset latencies of narcoleptic subjects, and that the association between skin temperature and sleep onset latency was even stronger for proximal and distal skin temperature per se than for their difference[18]. Lack and Gradisar focused on finger temperature on a finer timescale and showed a rapid increase prior to the onset of sleep[33]. In another study, Gradisar and Lack concluded that the rise in finger temperature before sleep onset drives the decline in core body temperature, which in turn is related to sleep onset[20]. Recently, we showed that in a natural setting both distal and proximal skin temperature strongly increase around habitual bed times[50].

1.3. Thermal Manipulations

In addition to the observational, correlational studies on diurnal changes in skin temperatures in relation to sleep onset, several studies have investigated the effect of manipulating body temper-

ature on sleep onset latency, by applying warm baths, warm blankets or water-perfused suits. Horne and colleagues showed in young adults that whole-body warming in the early afternoon induced sleepiness both during and following the warm baths, and decreased sleep onset latency[21,22]. Other studies of bathing have demonstrated shorter sleep onset latencies following passive body heating in the evening, but not after heating in the morning, and it has been suggested that the drop in core body temperature following heating of the body underlies these findings[5,10]. Sung and Tochihara showed that immersion of the body or the feet and lower legs only in a hot water bath before bedtime affected core temperature only marginally, but did result in a elevated skin temperature during the first part of the night and improved sleep-onset latency[45].

Other studies have applied passive body heating in elderly subjects. Kanda and colleagues reported an increase in ease of falling asleep for both young and elderly subjects after taking a hot bath in the evening[25]. Dorsey and colleagues showed that taking a hot bath 1.5 h to 2 h before bedtime resulted in a significant increase in SWS, but did not report on sleep onset[11,12,13].

It has been suggested that the mechanism by means of which passive heating of the body affects sleep is that warming promotes a subsequent steep fall in core body temperature, mimicking the decrease in CBT seen in the hours preceding habitual bedtime[5,12,13,21,22,24,25,45]. We have subsequently proposed that it is not so much the steep decrease in core body temperature but rather the underlying heat-loss activation that increases skin blood flow, and thereby skin temperature and heat loss, that is causally involved in the increase in sleep propensity. Of the aforementioned studies, only the study of Sung and Tochihara included both polysomnography and skin temperature measurements[45]. Of note, in this study, the sleep-promoting effects subsided as soon as a pre-sleep hot footbath-induced increase in skin temperature had normalized after two hours of sleep.

Two studies explored the effects of sleeping with an electric blanket. Fletcher and colleagues found no effects on core body temperature in the first three hours of sleep, but did not report on sleep onset or skin temperature[16]. Okamoto-Mizuno and co-workers showed an elevated foot temperature and bed microclimate temperature when using an electric blanket, but did not find an effect on sleep onset[40].

Using a thermo-suit for more controlled skin temperature manipulations, we showed reduced sleep onset latencies with subtle warming of the proximal skin in the comfortable and thermoneutral range[41]. Distal manipulation was not effective, possibly due to the very small range of the manipulated temperature.

In summary, temperatures of the skin and, more specifically, temperatures of the skin of the extremities (i.e. hands and feet) increase prior to sleep onset. The speed of sleep onset is related to onset of sleep. Direct or indirect warming of the skin prior to onset of sleep speeds up sleep onset and might be a useful treatment for subjects with sleep-onset difficulties.

1.4. New Studies

Recent data from our group give some clues regarding the possibilities of thermal manipulation as a tool for improvement of sleep onset. In this study we explored the effects on sleep onset latency of home-applicable temperature treatments that affect only skin, not core body, temperature. Both timing and temperature of the foot warming are of crucial importance. A foot temperature manipulation that is too warm might induce arousal during sleep initiation, whereas the effect of a manipulation prior to sleep that is too mild might not last until the start of the lights-off period. In short, we examined the effectiveness of both warm and thermoneutral footbaths prior to lights off, and of wearing warm socks prior to and during lights off, in young adults and elderly subjects with no difficulties in getting to sleep and in elderly subjects with difficulties in getting to sleep. Since decreased sleep quality (shorter sleep duration, slower sleep onsets, early awakenings and fragmented sleep)[17,32] in the elderly may be determined in part by age-related changes in thermoregulation (i.e. decreased amplitude and decreased stability), the treatments might be suitable for ameliorating these age-related effects.

We hypothesized that warming the foot will decrease sleep-onset latency. We addressed the following three questions. First, is sleep-onset latency modulated by distal skin temperature manipulation over a somewhat wider range than we applied previously? Second, does the distal skin temperature, *prior* to sleep onset, correlate with sleep-onset latency[27,28] - crucial for a fast subsequent initiation of sleep, or is the distal skin temperature *during* the period from lights-off to sleep onset the crucial factor? Third, to what extend are the effects of distal skin manipulations on sleep onset still effective in elderly, who in general show attenuated thermoreception and peripheral blood flow?[53]. With the possible application of such treatments in mind, we chose to conduct the distal temperature manipulation with home-applicable treatments, both in young and elderly subjects. Since poor sleep is a frequent complaint in the elderly[52] we included both elderly subjects who slept well and those who slept poorly.

2. Materials & Methods

2.1. Subjects

Eight healthy young adults free from sleep complaints (21-39 years old; mean ± s.e.m.: 27.00 ± 2.41 years, 4 males), eight healthy elderly subjects free from sleep complaints (56-80 years old; mean ± SD: 65.75 ± 7.91 years, 4 males) and eight elderly subjects with sleep complaints but otherwise healthy (51-66 years old; 59.13 ± 5.41 years, 4 males) participated with informed consent. All participants were free of medication known to affect sleep or the circadian system, cardiovascular medication or psychotropic medication. One female adult used oral contraceptives. Subjec-

tive sleep quality and complaints were measured using the 75-item Sleep Disorders Questionnaire (SDQ) a Dutch adaptation[46] of the SDQ[14] and the Pittsburgh Sleep Quality Index (PSQI)[6]. Poor sleepers were defined by a SDQ-Insomnia score > 2.5, a PSQI > 5 and a score <= 3 on the SDQ subscales narcolepsy, apnea, restless legs and psychiatry. The adult females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase) and all elderly females were postmenopausal. The protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam.

2.2. Procedures

The participants were instructed to keep a regular as possible sleep-wake pattern by minimizing variability in bedtime and wake-up time in the two weeks prior to the experiment, which was verified with a sleep diary[34] and with actigraphy (Actiwatch, Cambridge NeuroTechnology Ltd., Cambridge, UK). One week before the experiment, participants visited the sleep laboratory for an introductory session and became habituated to the bedroom and the equipment. Participants were instructed to refrain from caffeine, alcohol and tobacco for 8 hours before arriving at the sleep laboratory and were questioned about compliance with this instruction. In brief, the experiment consisted of determining 6 sleep-onset latencies on a single day for each subject while manipulating foot skin temperature with home-applicable methods. The subjects reported to the sleep laboratory at 08:30 hours where they were prepared for polysomnography. Ambient room temperature was kept at approximately 21˚C. The subjects wore their habitual nightclothes, and they were covered by a sheet and a blanket during lights-off. The experiment started at 09:30 h and consisted of 6 consecutive blocks with durations of 1.5 hours each. As shown in Figure 1, each block consisted of the following strictly standardized procedures: It started at 0:00 (block- time) by setting the bed in semi-supine position and requiring the subjects to leave the bed, wear a bathrobe and slippers and sit behind a desk. At 0:10 they were served a drink (200 ml decaffeinated tea; 4.25 kcal, 17.8 kJ; Iced Tea Mix, Diet Decaffeinated Lemon, Lipton, Englewood Cliffs, USA) and an isocaloric snack of the subject's choice (200 kcal, 837.2 kJ) at room-temperature, to be consumed in approximately 10 minutes. Also at 00:10, in 4 of the 6 conditions, foot temperature was manipulated for 30 minutes by applying warm (42˚C) or neutral (32˚C) footbaths (FBPRE), or by means of non-heated or heated bed socks (SOCKPRE). At 00:20 a self-paced computerized neurobehavioral task battery was started, taking around 20 minutes to complete. This battery included assessment of subjective thermal comfort using a 100 mm visual analogue scale (VAS) ranging from uncomfortable to comfortable. At 00:50, the subjects were required to leave the desk and to use the bathroom if needed and returned to bed. At 01:00 in the two remaining of the 6 conditions temperature was manipulated for 30 minutes by applying non-heated or

heated bed socks during the lights-off period in bed (SOCKBED). For all condition at 01:00, the bed was set in supine position, the lights switched off and the participants were asked to try to sleep. Sleep onset was determined online (Multiple Sleep Latency Test, MSLT)[7,8] and subjects were awakened directly after sleep onset determination (see below). When woken up, subjects were kept awake in bed in the supine position, and with the light turned on (<10 Lux). The maximum time allowed for falling asleep was 30 minutes, thus completing the 1.5 hour of a block.

Within the sequence of the manipulations, the thermoneutral and warm levels of each condition (FBPRE, SOCKPRE, SOCK) were paired. All conditions and their two levels were optimally counterbalanced over subjects within each group.

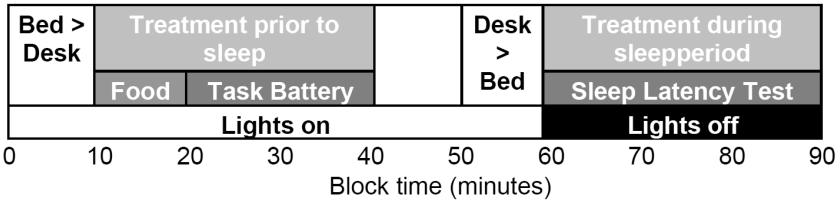

Fig. 1. Schematic view of the experimental design within a block. At 00:10, in 4 of the 6 conditions, foot temperature was manipulated for 30 minutes by applying warm (42˚C) or neutral (32˚C) footbaths (FBPRE), or by means of non-heated or heated bed socks (SOCKPRE). At 00:60 in the two remaining of the 6 conditions temperature was manipulated for 30 minutes by applying non-heated or heated bed socks during the lights-off period in bed (SOCKBED).

2.3. Temperature Manipulations and Measurement

Foot temperature was manipulated by means of a footbath (Philips, HP5225/B, Eindhoven, The Netherlands) and Hot Socks (Nature's Choice, Prinsenbeek, The Netherlands). The loose-fitting bed socks have a removable filling at the sole part of the sock. The filling contains grains and can be heated using a microwave oven. When applying the warm footbath, the bath was filled with 2.8 liter water of 42˚C and the heating of the footbath was turned on. When using the thermoneutral footbath, the bath was filled with 2.8 liter water of 32˚C and the heating of the footbath was turned off. When using the warm bed socks, the 2 fillings were heated for 90 seconds at 620 Watts using a microwave oven. This resulted in a temperature of the sole of the sock of approximately 66˚C, gradually declining to 43˚C in 30 minutes. When applying the thermoneutral bed socks, the fillings were not heated and were at room temperature.

Body temperature was obtained using 3 thermistors (P-8432, ICBT, Tokyo, Japan). Core body temperature (T_{re}) was measured using a rectal thermistor that was self-inserted 13 cm into the rectum. Foot temperature (T_{foot}) was measured at the medial metatarsal area at the plantar sites of the left and right foot. The skin thermistors were attached to the skin with thermal probe covers

(ref 090-2764, ConMed Corporation, Utica, USA) that reflect ambient heat. Temperature was digitally recorded at 1 Hz (Embla A10 and Somnologica software, Flaga hf, Reykjavik, Iceland) and sampled offline at 0.1 Hz. Based on visual inspection of the data, an automated procedure was applied to remove occasional artefacts, defined for core body temperature as outside the range 35.5°C-38°C. In addition, visually obvious artefacts (abrupt steep changes in skin temperature, >0.3°C/min, or in core body temperature, >0.1°C/min, outside the time-window of the foot-temperature manipulation) were removed and omitted from analyses. The average temperature of both feet was used for subsequent analyses.

2.4. Sleep

Polysomnographic sleep recordings consisted of electroencephalography (EEG), electromyography (EMG) and electro-oculography (EOG). The EEG was derived from two bipolar leads FpzCz and PzOz[54] with the E-net and Hydrodot system (Physiometrix Inc., Billerica USA). Submental EMG and horizontal EOG from the outer canthi were recorded using disposable Ag/AgCl electrodes (type 4203 Meditrace, Graphic Controls Corporation, Buffalo 11 USA). All PSG signals were digitally recorded at 200 Hz using the Embla A10 recorder and Somnologica software (both Flaga hf, Reykjavik, Iceland). Sleep onset was determined online during the experiment according to standard criteria[42], with sleep onset defined as three consecutive 30-s epochs of Stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep[8].Online determination of sleep stage was aided by the use of spectral views of the EEG signal, facilitating the observation of disappearance of the alpha (8-12 Hz) peak, dominance of the proportion of theta (4-8 Hz) over the proportion of alpha activity, or the clear appearance of spindle (12-15 Hz) peaks. Recordings of MSLT were visually scored offline by two independent scorers blind to the manipulations and, in case of differences, consensus was reached. Sleep onset latency (SOL) was defined as the time between lights-off and the sleep onset. If the subject did not sleep during the 30 minutes, sleep onset latency was scored as 30 minutes.

2.5. Statistical Analysis

All temperature measures were first averaged into 30-second bins. Mean foot and mean core body temperature were then calculated over block-time 00:20-00:40 ($T_{\text{-pre}}$) and block-time 01:00 until sleep onset ($T_{\text{-bed}}$) for statistical analyses. Additionally the linear rate of change (ROC, in 1˚C/min) in the interval lights-off (blocktime: 01:00) until sleep onset was calculated. For graphical purposes all temperature data were once again averaged in 5-min bins.

To determine the effects the passive cutaneous warming treatment on body temperatures and sleep onset latency, hierarchical regression modeling (i.e. random coefficient analysis) was ap-

plied (MLwiN software, Centre for Multilevel Modelling, Institute of Education, London, UK). This method takes into account the interdependency of the data points inherent to the hierarchical structure of the design, in our case the sequential sleep onset observations i that were nested within subjects j[23]. It moreover allows for varying numbers of missing data within a case.

Since the frequency distribution of SOLs was slightly skewed, a log transformation was applied.

For the 3 groups (young adults free from sleep complaints, elderly free from sleep complaints and elderly with sleep complaints) 5 separate analyses were run with either SOL, $T_{re\text{-}pre}$, $T_{foot\text{-}pre}$, $T_{re\text{-}bed}$ and $T_{foot\text{-}bed}$ as the dependent variable and the treatments as dummy coded predictors. The unwarmed bed socks pre-sleep was selected as reference condition (hereafter referred to as baseline), since it mostly resembles the situation before going to bed in daily living. In the subsequent analyses for sleep-onset latency the actual measured temperatures and temperature changes ($T_{re\text{-}pre}$, $T_{foot\text{-}pre}$, $T_{re\text{-}bed}$ and $T_{foot\text{-}bed}$ and $ROCT_{foot\text{-}bed}$) were entered in the equation.

Time of day (Hour) was entered in the models as covariate, and up to the third order and the square root ($Hour^2$, $Hour^3$, √Hour), as needed, to account for possible diurnal variation in SOL[9]. Maximum likelihood was used to estimate the regression coefficients, which were tested for significance with the Wald test[56]. Additional temperature-related and time-related independent variables were allowed in the model only if their coefficients were significant and if residual error of the model was reduced according to the likelihood ratio test[48]. Finally, the overall mean $ROCT_{foot\text{-}bed}$ was determined for the group of young subjects and the group of all elderly subjects *in the treatments without warming* during the lights-off period, by the intercept of equation for the null-model (i.e. the model without independent variables) for the $ROCT_{foot\text{-}bed}$ of each group. Two-tailed significance levels were set at 0.05.

3. Results

3.1. Induced temperatures

For each group the average core body and foot temperatures per treatment are displayed in Figure 2 and Table 1. Tables 2 shows the regression model effect sizes of treatment and time on foot and core body temperature.

Foot temperature (T_{foot}) was significantly higher during the warm SOCKPRE and FBPRE manipulations as compared to the baseline condition in all the three groups and the effects lasted, albeit less strongly, during the lights-off period. Likewise the warm SOCKBED manipulation induced a significantly higher T_{foot} during the lights-off period for all the three groups. Moreover, the neutral FBPRE condition lowered $T_{foot\text{-}bed}$ in the elderly free from sleep complaints.

Rectal temperature (T_{re}) was significantly lower during the warm FBPRE manipulation as compared to the baseline condition in the young adults free from sleep complaints and this lasted,

albeit less strongly, during the lights-off period. In the elderly free from sleep complaints, T_{re} was significantly lower during and after the warm SOCKPRE manipulation. In addition, $T_{re\text{-}bed}$ was lower after the warm FBPRE manipulation. The elderly with sleep complaints showed a higher $T_{re\text{-}pre}$ during the warm SOCKPRE condition, which did not last until the lights-off period. Inspection of the figures suggested that the observed differences in T_{re} were already present at the start of the treatments - except for the decreases in T_{re} both prior to and during the lights-off in elderly free from sleep complaints, where a change from the start of block is seen. Both $T_{re\text{-}pre}$ and $T_{re\text{-}bed}$ were modulated by time of day.

In summary: The effects of the warm manipulation were reflected in the foot temperatures during manipulation and were maintained during the subsequent lights-off period. The neutral footbath treatment in the elderly free from sleep complaints actually lowered foot temperature during the lights-off period, probably through evaporative heat loss. Only pre-sleep foot warming, by means of heated bed socks in the elderly free from sleep complaints, appeared to affect rectal temperature.

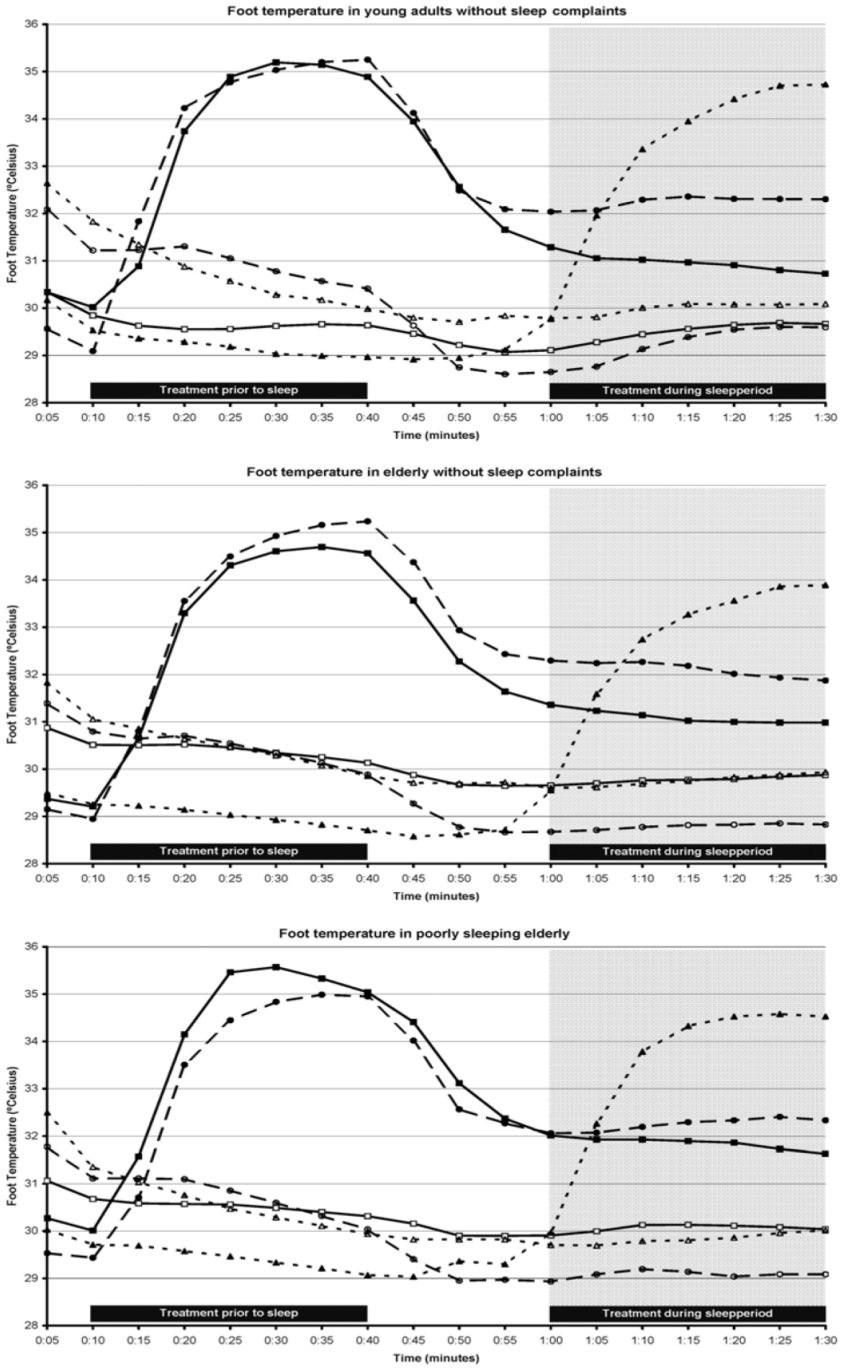

Fig.2. The average foot temperatures (T_{foot}) and core body (next page,$T_{re,}$) for the six treatments throughout every single experimental block per group. Lights-off period is in gray.

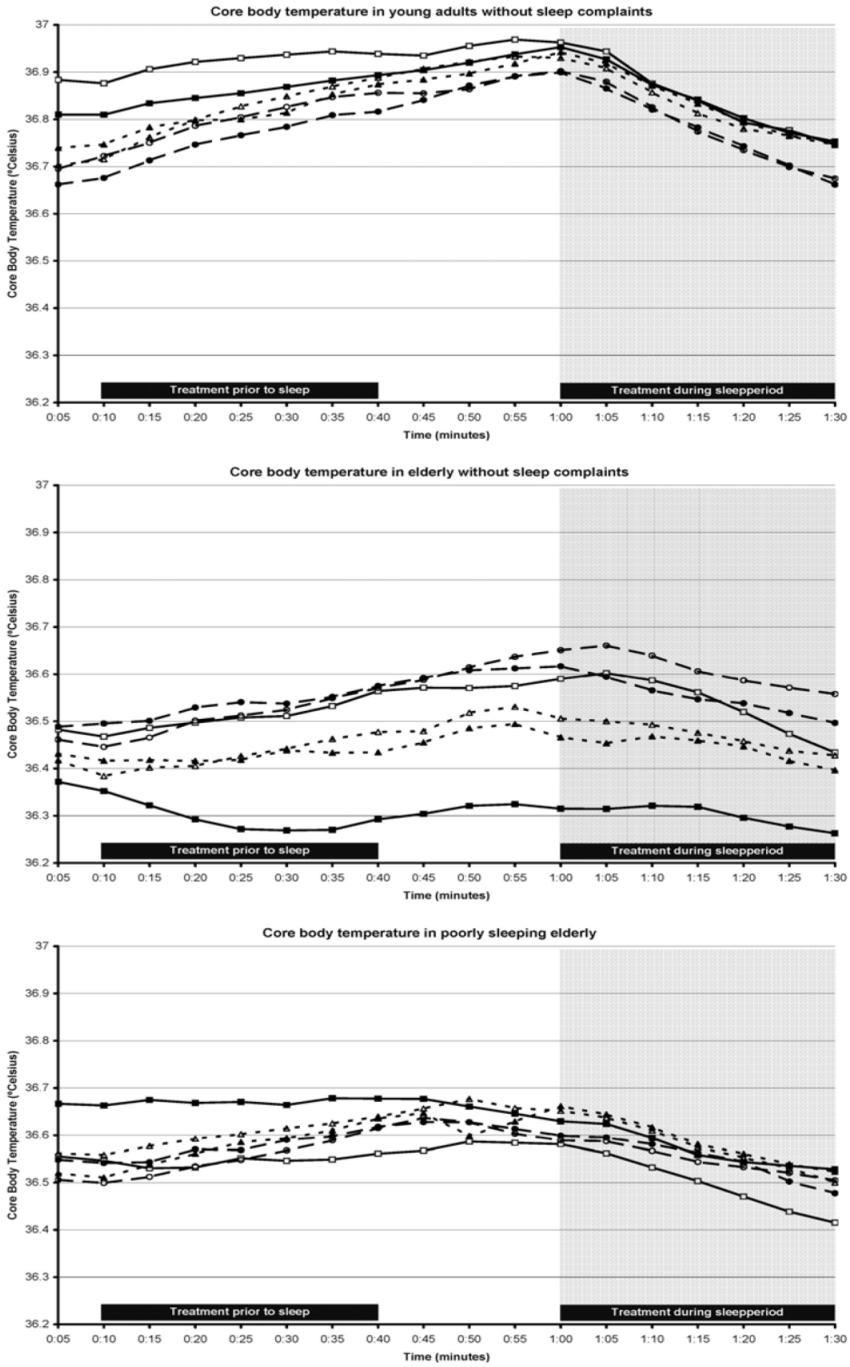

Fig.2[cont]**.** The average foot temperatures (previous page, T_{foot}) and core body ($T_{re,}$) for the six treatments throughout every single experimental block per group. Lights-off period is in gray.

Table 1
The average core body (T_{re}) and foot temperatures (T_{foot}) per treatment condition per group

	Foot temperature (°C)		Core body temperature (°C)	
	$T_{foot\text{-}pre}$	$T_{foot\text{-}bed}$	$T_{re\text{-}pre}$	$T_{re\text{-}bed}$
Young adults free from sleep complaints				
Neutral SOCKPRE (baseline)	**29.62 ± 0.91**	**29.40 ± 0.94**	**37.00 ± 0.15**	**36.90 ± 0.08**
Warm SOCKPRE	35.00±0.85*	31.17±0.67*	36.87±0.07	36.89±0.05
Neutral FBPRE	30.70±0.44	29.04±0.35	36.89±0.07	36.83±0.08
Warm FBPRE	35.06±0.32*	32.28±0.41*	36.83±0.12*	36.82±0.07*
Neutral SOCKBED	30.25±0.42	29.87±0.48	36.91±0.07	36.87±0.10
Warm SOCKBED	29.04±0.64	32.38±0.36*	36.91±0.09	36.90±0.08
Elderly free from sleep complaints				
Neutral SOCKPRE (baseline)	**26.79 ± 3.85**	**29.76 ± 0.59**	**36.63 ± 0.13**	**36.59 ± 0.13**
Warm SOCKPRE	34.55±0.63*	31.22±0.59*	36.35±0.17*	36.31±0.17*
Neutral FBPRE	30.23±0.39	28.78±0.56*	36.54±0.09	36.64±0.08
Warm FBPRE	34.96±0.42*	32.26±0.41*	36.55±0.08	36.58±0.10*
Neutral SOCKBED	30.18±0.81	29.65±0.73	36.45±0.14	36.49±0.14
Warm SOCKBED	28.87±0.80	31.94±0.78*	36.43±0.16	36.44±0.19
Poorly sleeping elderly				
Neutral SOCKBED (baseline)	**30.44 ± 0.48**	**30.04 ± 0.58**	**36.55 ± 0.09**	**36.59 ± 0.10**
Warm SOCKBED	35.35±0.62*	31.90±0.67*	36.67±0.10*	36.62±0.08
Neutral FBPRE	30.44±0.39	29.14±0.36	36.58±0.10	36.57±0.07
Warm FBPRE	34.78±0.56*	32.16±0.44*	36.59±0.09	36.59±0.08
Neutral SOCKBED	30.20±0.70	29.70±0.65	36.62±0.08	36.62±0.09
Warm SOCKBED	29.27±0.73	32.94±1.01*	36.61±0.10	36.61±0.10

Values are means±SE. SOCKPRE=bed sock pre, FBPRE=footbath pre, SOCKBED=bed sock in bed.
Due to missing data, directly comparing averages over time (pre and bed) and over treatment might be cumbersome.
* Significantly different from baseline condition.

Table 2
Estimates of the effects of treatment and time of day on foot (T_{foot}) and core body (T_{re}) temperature per group

	Young adults free from sleep complaints	Elderly free from sleep complaints	Poorly sleeping elderly
Body temperatures prior to sleep (T_{-pre})			
Foot temperature (T_{foot})			
Intercept	29.57±0.60‡	26.79±1.57‡	30.44±0.55‡
Warm SOCKPRE	5.44±0.67‡	7.76±1.99‡	4.91±0.61‡
Warm SOCKBED	−0.58±0.70	2.09±1.99	−1.17±0.61
Neutral SOCKBED	0.63±0.70	3.39±1.99	−0.24±0.61
Warm FBPRE	5.45±0.70‡	8.17±1.99‡	4.34±0.61‡
Neutral FBPRE	1.08±0.70	3.44±1.99	0.00±0.61
no modulation by time			
Core body temperature (T_{re})			
Intercept	37.10±0.09‡	36.55±0.15‡	36.75±0.09‡
Warm SOCKPRE	−0.11±0.06	−0.17±0.07*	0.12±0.06*
Warm SOCKBED	−0.09±0.07	−0.01±0.07	0.08±0.06
Neutral SOCKBED	−0.09±0.07	0.01±0.07	0.10±0.06
Warm FBPRE	−0.17±0.07†	−0.07±0.70	0.08±0.06
Neutral FBPRE	−0.11±0.07	−0.05±0.07	0.07±0.06
Hour	0.10±0.03‡	0.11±0.03‡	0.08±0.02‡
√Hour	−0.29±0.07‡	−0.32±0.07‡	−0.30±0.06‡
Body temperatures after lights-off (T_{-bed})			
Foot temperature (T_{foot})			
Intercept	28.97±0.54‡	29.49±0.57‡	29.79±0.60‡
Warm SOCKPRE	1.73±0.48‡	1.48±0.46‡	1.91±0.59**
Warm SOCKBED	2.47±0.52‡	1.86±0.47‡	2.54±0.61‡
Neutral SOCKBED	0.26±0.48	−0.42±0.47	−0.71±0.61
Warm FBPRE	2.64±0.48‡	2.26±0.46‡	2.00±0.59‡
Neutral FBPRE	−0.56±0.48	−1.20±0.46†	−1.06±0.59
Hour	0.16±0.06†		
Hour^2		0.02±0.01†	0.02±0.01*
Core body temperature (T_{re})			
Intercept	36.86±0.07‡	36.42±0.16‡	36.61±0.08‡
Warm SOCKPRE	−0.03±0.05	−0.18±0.07†	0.00±0.05
Warm SOCKBED	−0.06±0.05	−0.10±0.07	−0.01±0.05
Neutral SOCKBED	−0.08±0.05	−0.04±0.07	0.01±0.05
Warm FBPRE	−0.11±0.05*	−0.15±0.07*	−0.05±0.05
Neutral FBPRE	−0.09±0.05	−0.10±0.07	−0.06±0.05
Hour		0.03±0.01†	
Hour^2	0.003±0.001‡		
Hour^3			0.0002±0.0001*

Values are means±SE. Regression model was as follows: $T_{ij}=\beta_{0ij}+\beta_1$ * warm bed sock $pre_{ij}+\beta_2$ * warm bed sock $bed_{ij}+\beta_3$ * neutral bed sock $bed_{ij}+\beta_4$ * warm footbad $pre_{ij}+\beta_5$ * neutral footbad $pre_{ij}+\beta_6$ * $hour_{ij}+\beta_7$ * $hour2_{ij}+\beta_8$ * $\sqrt{hour_{ij}}+\beta_9$ * $hour^3{}_{ij}$ (see text; subscripts indicate *i*th observation for subject *j*). The treatments were included in the model as dummy coded predictors. Hour (time), defined as the number of hours since the start of the first included sleep latency test, starting with 0 for the first block. Time variables that were not significant in all 3 groups are not displayed. SOCKPRE=bed sock pre, FBPRE=footbath pre, SOCKBED=bed sock in bed. *P 0.05; †P 0.01; ‡P 0.001.

3.2. Sleep onset latency

Table 3 shows the average sleep-onset latencies associated with the different treatments. Table 4 shows the regression model effect sizes of treatment and time on sleep onset latency.

Table 3
Sleep-onset latency by treatment condition per group

	Sleep-onset latency (min.)		
	Young adults free from sleep complaints	Elderly free from sleep complaints	Poorly sleeping elderly
Neutral SOCKPRE (baseline)	15.69±3.47	11.19±3.32	10.50±2.87
Warm SOCKPRE	12.94±3.21	9.81±2.71	9.38±3.41
Neutral FBPRE	15.13±3.29	9.50±2.26	11.81±3.02
Warm FBPRE	15.56±3.45	8.13±1.45*	8.06±1.69
Neutral SOCKBED	11.38±3.21*	8.00±1.83*	7.63±1.57
Warm SOCKBED	11.25±3.77*	10.56±2.33	8.31±1.25

Values are means±SE.
*Significantly different from baseline.

In young adults, the baseline sleep-onset latency averaged 15.69±3.47 minutes. LOG(SOL) was 0.22±0.08 shorter in the warm SOCKBED condition and 0.20±0.08 in the neutral SOCKBED condition as compared to the baseline condition, but unaffected by FBPRE or SOCKPRE manipulations. In the elderly free from sleep complaints, the baseline sleep-onset latency averaged 11.19±3.32 minutes. LOG(SOL) was 0.16±0.06 shorter in the neutral SOCKBED condition and 0.12±0.06 shorter in the warm FBPRE condition, but unaffected by the other manipulations. In the elderly with sleep complaints, the baseline average sleep-onset latency averaged 10.50±2.87 minutes. Sleep-onset latency was not affected by any treatment. In the elderly without sleep complaints, LOG(SOL) was also modulated by $Hour^2$.

We next addressed the question whether SOL could be predicted by the manipulation-induced changes in rectal and foot temperature, either before or after lights-off. Within the young adult group it turned out that the rate of change (ROC) of the $T_{foot\text{-}bed}$ was significantly associated with SOL. The steeper the increase in foot temperature, the faster the sleep onset is. For every 1˚C/min faster increase in $T_{foot\text{-}bed}$, LOG(SOL) decreased by 0.34±0.15. In elderly subjects, both with and without sleep complaints, none of the possible predictors for SOL reached significance.

Subsequently, we found that, in general, the rate of change of foot temperature was significantly less for elderly compared to young adults. In the treatments without warming during the lights-off

period, the rate of change in foot temperature after lights-off was 59% less in the elderly (0.04°C/min) compared to the young adults 0.10°C/min) (p=0.02).

Table 4
Estimates of the effects of manipulations as dummy coded predictor variables and time of day on log transformed sleep-onset latency per group

	Sleep-onset latency LOG(SOL)		
	Young adults free from sleep complaints	Elderly free from sleep complaints	Poorly sleeping elderly
Intercept	1.13±0.11‡	0.90±0.09‡	0.92±0.10‡
Warm SOCKPRE	−0.13±0.08	−0.04±0.06	−0.13±0.09
Warm SOCKBED	−0.22±0.08†	−0.04±0.06	−0.04±0.09
Neutral SOCKBED	−0.20±0.08*	−0.16±0.06†	−0.10±0.09
Warm FBPRE	−0.02±0.08	−0.12±0.06*	−0.07±0.09
Neutral FBPRE	−0.03±0.08	−0.06±0.06	0.07±0.09
$Hour^2$		0.003±0.001†	

Values are means±SE. Regression model was as follows: $LOG(SOL)_{ij}=\beta 0_{ij}+\beta_1 * \text{warm bed sock pre}_{ij}+\beta_2 * \text{warm bed sock bed}_{ij}+\beta_3 * \text{neutral bed sock bed}_{ij}+\beta_4 * \text{warm footbad pre}_{ij}+\beta_5 * \text{neutral footbad pre}_{ij}+\beta_6 * \text{hour}_{ij}+\beta_7 * \text{hour2}_{ij}+\beta_8 * \sqrt{\text{hour}}_{ij}+\beta_9 * \text{hour}^3{}_{ij}$ (see text; subscripts indicate ith observation for subject j). The treatments were included in the model as dummy coded predictors. Hour (time), defined as the number of hours since the start of the first included sleep latency test, starting with 0 for the first block. Time variables that were not significant in all 3 groups are not displayed. SOCKPRE=bed sock pre, FBPRE=footbath pre, SOCKBED=bed sock in bed. *P 0.05; †P 0.01; ‡P 0.001.

In summary: In young adults, sleep onset was accelerated by wearing either warm or neutral bed socks after lights-off, and the rate of change of the foot temperature after lights-off was related to this faster sleep onset. In elderly subjects free from sleep complaints, sleep onset was accelerated by a warm footbath prior to sleep or wearing neutral bed socks during lights-off. In elderly subjects with sleep complaints, none of the foot-warming strategies used was effective in changing SOL. Unlike young subjects, elderly subjects did not show an association between sleep onset latency and the rate of change in foot temperature, or any other temperature variable, and showed an attenuated increase in foot temperature after lights-off compared to the young subjects.

4. Discussion

The aim of the present study was to investigate whether sleep-onset latency could be modulated by home-applicable foot-temperature manipulations, which result in changes in foot temperature of approximately 6°C. Moreover, we addressed the question whether sleep-onset latency is indeed related to the distal skin temperature *prior to* sleep onset, shown to be correlated with

sleep-onset latency[27,28], or rather to the distal skin temperature *during* the period from lights-off to sleep onset. Furthermore, it was investigated whether the effects of distal skin manipulations on sleep onset would be equally effective in elderly, who in general show attenuated thermoreception[53] compared to younger subjects. Results showed that wearing bed socks from the time of lights-off decreased sleep-onset latency, at least in young adults. Whereas we did not find changes in sleep-onset latency during very subtle distal warming[41], the more robust warming with heated bed socks and also the more subtle change in foot temperature due to wearing non-heated bed socks, did affect sleep-onset latency in the present protocol.

Faster increases of foot temperature after lights-off seemed to be involved in this more rapidly sleep onset, suggesting a role for the rate of change rather than the level of distal temperature. The results from the elderly subjects without sleep problems were less clear. Both neutral bed socks during lights-off and a warm footbath prior to sleep decreased SOL, but SOL could not be related to any specific induced temperature change. It might be that, in the elderly, skin temperature is not as effective a sleep-inducing signal as in the young. In fact aging affects thermoreception and peripheral blood flow negatively[53], which in turn reduce the ability to warm the peripheral skin. A post-hoc analysis revealed that the most effective treatment before sleep in elderly subjects without sleep problems was rated as being most comfortable in both these and young subjects. Increased comfort might be a more relevant factor than temperature input in the elderly subjects. The treatments used were not successful in accelerating sleep onset in elderly people with sleep complaints. It might be possible that the manipulation of skin temperature in the feet would be more effective in improving nocturnal sleep at habitual bedtimes.

In young adults, the rate of change of the foot temperature after lights-off appeared crucially involved in sleep-onset latency whereas, in elderly subjects, both the rate of change of foot temperature and the effects of the treatments were significantly less. It is conceivable that the reduced ability to show a fast increase in distal temperature plays a key role in the complaints of difficulties with sleep initiation frequently noted in the elderly. Regular exercise provides a way to improve the vasodilatory response[43], which may be involved in the finding that regular exercise is associated with a reduction in the prevalence of disturbed sleep in a large population of healthy middle-aged to elderly subjects[44].

The average SOL was shorter in the older groups, particularly the poor sleepers. In this particular daytime protocol, they might benefit from their increased daytime sleepiness and their familiarity with daytime napping.

In summary, home-applicable methods for warming the feet may be effective in accelerating sleep onset in young subjects, but the effect is less pronounced in elderly subjects. A steep increase in foot temperature is associated with a rapid onset of sleep. The reduced ability of elderly subjects to show such a steep increase in foot temperature may be involved in the attenuated

efficacy in them of foot warming to promote sleep onset. It is conceivable that sleep-promoting manipulation of temperature may become more effective in elderly subjects if they are supplemented by interventions (such as regular exercise) that improve the vasodilatory response.

Taken together, direct or indirect warming of the skin may accelerate sleep onset. This is in line with the previously proposed neurobiological mechanism that changes in skin temperature modulate brain areas involved in sleep regulation (5). Skin warming may thus be applied to accelerate sleep onset. However, it is not yet known at what location on the body skin warming is most effective. Most correlational studies stress the importance of distal skin temperature, but the only study that applied both proximal and distal skin temperature manipulation simultaneously, showed that proximal skin warming was most effective[41].

Another point of debate is which property of the temperature signal is crucial. Whereas the results of the present study and others show that the level of proximal or distal skin temperature is essential[18,45,41], other suggest the importance of the distal to proximal skin temperature difference, i.e. the *gradient* in skin temperature[27,28,33,20].

Both timing and temperature of the skin warming play a key role. A too warm skin during or just prior to sleep initiation might induce arousal and elevation of core body temperature. Skin warming methods that also induce an increase of core body temperature should therefore be applied at approximately 1.5-2 hours before bedtime, whereas moderate skin warming methods that manipulate the skin temperature close to the ceiling of its normal diurnal pattern *without* affecting core temperature can be applied just prior or during sleep initiation.

In elderly subjects, enhancement of skin vasodilation and its concomittant increase in skin temperature may be crucial to promote sleep onset. Such enhanced skin vasodilation can for example occur after passive body heating, which indeed promoted sleep in elderly subjects[25,12,11,13].

In summary, skin warming is effective in accelerating sleep onset. In young adults the application of a mild thermal skin manipulation is effective, whereas in elderly the induction of a vasodilatory response seems to be crucial for accelerating sleep onset.

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Chapter 4

Cutaneous warming promotes sleep onset

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Summary

Sleep occurs in close relation to changes in body temperature. Both the monophasic sleep period in humans and the polyphasic sleep periods in rodents tend to be initiated when core body temperature is declining. This decline is mainly due to an increase in skin blood flow, and consequently skin warming and heat loss. We have proposed that these intrinsically occurring changes in core and skin temperature could modulate neuronal activity in sleep regulating brain areas[48]. We here provide results compatible with this hypothesis. We obtained 144 sleep onset latencies (SOL) while directly manipulating core and skin temperatures within the comfortable range in 8 healthy subjects under controlled conditions. The induction of a proximal skin temperature difference of only 0.78±0.03°C (mean±SE) around a mean of 35.13±0.11°C changed SOL by 26% (3.09 (95% confidence interval (CI), 1.91 to 4.28) minutes around a mean of 11.85 minutes (CI, 9.74 to 14.41)), with faster sleep onsets when the proximal skin was warmed. The reduction in SOL occurred in spite of a small but significant decrease in subjective comfort during proximal skin warming. The induction of changes in core temperature (∂=0.20±0.02°C) and distal skin temperature (∂=0.74±0.05°C) were ineffective. Previous studies have demonstrated correlations between skin temperature and SOL. Also, sleep disruption by ambient temperatures that activate thermoregulatory defence mechanisms have been shown. The present study is the first to experimentally demonstrate a causal contribution to sleep-onset latency of skin temperature manipulations within the range of its normal nocturnal fluctuations. Circadian and sleep-appetitive behavior induced variations in skin temperature might act as an input signal to sleep-regulating systems.

1. Introduction

Human sleep and body temperature both show a day-night rhythm that appears to be strongly coupled. Habitual sleep onset tends to closely follow the timing of the maximal rate of decline in core body temperature[26,38]. In experimental protocols that disentangle the rhythms by imposing ultra-short[28,30,32,43] or very long[15] sleep-wake cycles while core body temperature maintains its circadian rhythm, the ability to initiate and maintain sleep is maximal during the phase of lowered core body temperature. If sleep is prohibited, as during the so called constant routine protocols, a circadian rhythm in body temperature is still present[30]. These findings demonstrate that the daily decline in core body temperature is not merely the result of sleep. Moreover, they allow for the possibility that the neuronal mechanisms underlying the circadian modulation of sleep propensity and those underlying the circadian modulation of core body temperature share a common component. It may even be proposed that the thermoregulatory state of the body could affect sleep-regulating systems.

Animal experiments indeed have shown that sleep onset and a decline in core body temperature can be induced by a single common stimulus, i.e. local warming of the preoptic anterior hypothalamus (POAH)[35,36]. This structure is considered the thermo-integrative centre of the mammalian brain and plays a key role in the arousal state regulation and is thus involved in the induction of both heat loss and sleep. It has moreover been demonstrated that about two-third of the POAH neurons that spontaneously change their firing rate during sleep show a similar change in firing rate in response to experimental local warming[1]. A similar thermosensitivity in relation to sleep has been demonstrated in the diagonal band[2]. It might thus be argued that sleep would be facilitated when brain temperature exceeds a threshold level[35].

Despite of the robustness of the experimental induction of sleep by local POAH warming, it is highly unlikely that the elevation in brain temperature occurring daily under control of the circadian timing system is causally involved in the circadian modulation of sleep propensity. On the contrary, sleep onset tends to occur on the declining part of the core body temperature rhythm, and the major nocturnal sleep period ends on its rising part. Thus, a circadian modulated input to sleep-related POAH neurons other than local temperature should be postulated if we presume their involvement in the coupling between sleep and temperature rhythms. In fact, this input signal should direct POAH neurons towards their sleep-type firing patterns in spite of local temperature favoring wake-type firing patterns. Putative signals include adenosine and prostaglandin D2, which were found to excite sleep-active neurons[36,45]. We have in addition suggested skin temperature as a candidate to provide such signal to sleep-related neurons[48], because the majority of neurons sensitive to local brain temperature also receive input originating from the skin thermoreceptors[6]. It may thus well be that skin temperature modulates thermo-sensitive neurons in the

POAH and other brain structures involved in arousal-state regulation. It is important to note that this hypothesis goes further than stating that vasodilatation and sleep onset merely coincide because increased activity of a subset of POAH warm-sensitive neurons has the dual effect of promoting sleep and inducing vasodilatation. The hypothesis explicitly states that skin warming, resulting from this vasodilatation or otherwise induced, will cause enhanced activity of sleep-inducing warm-sensitive neurons.

The potential role of skin temperature in sleep, already recognized by Magnussen in 1939, was almost totally neglected[33]. Only at the end of the last century studies on the relation between skin temperature and sleep re-emerged. Kräuchi and colleagues showed that the degree heat loss at the skin of the hands and feet was the best physiological predictor for a fast sleep onset and that during the phase of lowered core body temperature, heat loss is elevated[23,24]. In studies on the close relation between sleep regulation and body temperature, the circadian rhythm in skin temperature has received much less attention than the circadian rhythm in core body temperature. Under constant conditions, keeping subjects supine in a thermoneutral environment without food or drinks, the mean skin temperature is elevated during the night and low throughout the day, thus showing a rhythm inverse to that of the core[34]. In everyday life this day-night difference is even amplified by the nocturnal increase in skin temperature associated with the postural change from upright or sitting to a supine position[25,46], the use of bedding to create a microclimate of 34 to 36°C[19,39,51], and the relaxation associated with the preparedness to sleep signaled by lights off[27]. Since skin warming due to these changes occurs already before sleep onset, it might affect the process of falling asleep. Afferents conveying information about skin temperature have in animal studies been shown to modulate the firing rate thermosensitive neurons in the POAH at least as strong as local brain temperature does, and in case of simultaneous and differential local brain and skin temperature manipulations the response of POAH neurons is dominated by skin temperature[7].

Indirect support for our hypothesis, that sleep onset might be modulated by small changes in skin temperature, was given by Kräuchi and colleagues[23,24] who reported a strong negative correlation between the increase in especially distal skin temperature prior to lights out and sleep onset latency. This finding could however as well be interpreted as indicative of a common mechanism promoting both an increase in skin temperature and sleep onset. We here report the first experimental support for the hypothesis that sleep-onset latency might be modulated by small changes in skin temperature in man. Whereas sleep was found to be disrupted in previous reports where skin temperature was manipulated towards uncomfortable high or low levels, we applied only minute changes in skin temperature within the range covered by the nocturnal skin temperature under thermoneutral conditions.

2. Materials & Methods

2.1. Participants

Eight healthy volunteers (21-39 years old; mean±SE: 27.00±2.41 years, 4 males) participated with informed consent. All participants were free of medication known to affect sleep or the circadian system, cardiovascular medication or psychotropic medication, except for one female that used oral contraceptives. None of the subjects reported sleep complaints and their subjective sleep quality was rated as being good. The scores on the insomnia scale of the 75-item Dutch Sleep Disorders Questionnaire (SDQ)[44] were significantly below the cut-off score of 3 (SDQ-Insomnia; 1.76±0.10; *P*<0.001) and the scores on the Pittsburgh Sleep Quality Index (PSQI)[8] were significantly below the cut-off score of 6 (Global-PSQI; 4.00±0.46; P <0.005). The women participated between *day 4* and *day 12* of the menstrual cycle (mid-follicular phase). The protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam.

2.2. Design and Procedure

Participants were instructed to keep a regular sleep-wake pattern by minimizing variability in bedtime and wake-up time in the two weeks prior to the experiment, which was screened with a sleep diary[31] and with actigraphy (Actiwatch, Cambridge NeuroTechnology Ltd., Cambridge, UK). One week before the experiment subjects visited the sleep laboratory for an introductory session and got habituated to the procedures. Participants were instructed to refrain from caffeine, alcohol and tobacco for 8 hours before arriving at the sleep laboratory. In brief, the experiment consisted of determining 18 sleep onset latencies for each subject over two experimental days, while manipulating core temperature with food and drinks and skin temperature with a thermo-suit. The night before each experimental day, the subjects reported to the sleep laboratory at 22:00 hr where they were prepared for polysomnography, were fitted with a comfortable stretch knit fabric thermo-suit for skin temperature manipulation and where compliance to the instructions was verified by questioning. From midnight until 6:00 hr, lights were turned off and subjects were allowed to sleep. At 6:00 hr they were awakened. The experiment started at 6:30 hr and consisted of a modified constant-routine protocol[14,37] under dim light (<10 Lux) conditions and a fixed body position schedule. Both experimental days consisted of 9 consecutive blocks with a duration of 1.5 hours each. Each block consisted of the following procedures: It started by requiring the subjects to leave the bed and walk 5 meters to use the bathroom if needed. After 10 minutes they returned to bed, were put in semi-supine position and were served a snack and a drink to consume in approximately 10 minutes. Subsequently a self-paced computerized neuropsychological task battery was given, taking around 35 minutes to complete. This battery included assessment of thermal comfort and temperature sensation using 100 mm visual analogue scales (VAS) ranging

from uncomfortable to comfortable and from cool to warm respectively. At 60 minutes, the bed was set in supine position, the lights switched off and the participants were asked to try to sleep. Sleep onset was determined online (Multiple Sleep Latency Test (MSLT))[11,12] and subjects were awakened directly after sleep onset determination (see below). When wakened up, subjects stayed in bed in supine position, with the light turned on (<10 Lux) and they had to stay awake. The maximum time allowed to fall asleep was 30 minutes, finishing up the 1.5 hour of a block. Skin and core temperature were manipulated differently in every block. During the first block skin temperatures were kept at an intermediate temperature. This block served as an adaptation period for participants to wake up and to get used to the protocol. In the remaining 8 blocks core body temperature, proximal skin temperature and distal skin temperature were independently manipulated in either a slightly warmer or cooler direction, but within the comfortable and thermo-neutral range. This 2x2x2 experimental design (core body temperature warm or cool (CBT+ or CBT-), proximal skin temperature warm or cool (PST+ or PST-), distal skin temperature warm or cool (DST+ or DST-)) brings up 8 possible manipulation combinations, that were all tested within a day in every subject (see figure 1). The sequence of the manipulation combinations was different for each subject such that, over all subjects, every manipulation combination was given once in each of the 8 blocks, and every transition from one to any other combination occurred only once.

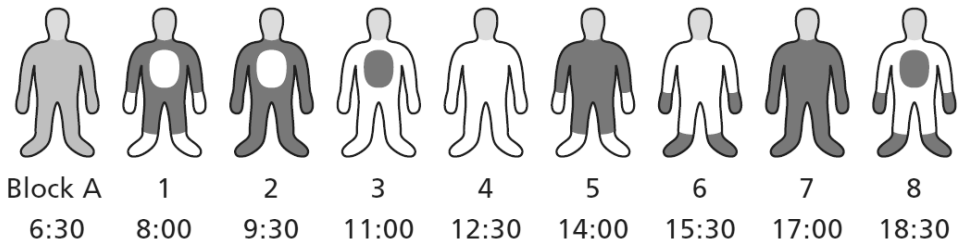

Fig. 1. Schematic view of temperature manipulations within a day within one subject. On the second day temperature manipulation combinations were the opposite of those of the first day to provide a protocol balanced for circadian effects.
Block A = habituation block. White= Cool, Dark grey = Warm.

At the end of the first day subjects went home and returned to the laboratory the next evening for a repeated assessment according to the same procedure, with as only difference that the temperature manipulation combinations were the opposite of those of the first day to provide a protocol balanced for circadian effects. For example if the second block of a specific subject on *day 1* consisted of core warming, proximal skin cooling and distal skin warming, that participant was subjected to core cooling, proximal warming and distal skin cooling during the second block on *day 2*.

2.3. Temperature Manipulations and Measurement.

Core body temperature was manipulated by means of 200 ml hot (heated to 80°C, served 2 minutes later) or cold (0°C, crushed ice) diet (4.25 Kcal), decaffeinated tea (Iced Tea Mix (Diet Decaffeinated Lemon), Lipton, Englewood Cliffs, USA) together with an isocaloric hot or cold snacks at subjects' choice (200 Kcal). Ingestion of food and drinks to manipulate core body temperature manipulation was started 50 minutes before lights off, since it has been shown, at least for core body cooling, that the core body temperature after intake of crushed ice is maximally decreased a time lag of circa 50 minutes, whereas the distal vasoconstriction induced by the intake of crushed ice has to a large extent – though not fully – subsided by that time[27]. Skin temperature (T_{sk}) was manipulated using a thermo-suit (Coretech Cool tube suit, Med-Eng Systems Inc., Ottawa, Canada). The suit provided a full torso, arms, hands and lower body coverage, with a snug fit design for maximum contact for optimal temperature manipulation and optimal comfort and range of motion. It was connected to two computer-controlled bath/circulation thermostats (K6KP, Lauda, Lauda-Königshofen, Germany), one for distal skin temperature manipulation and one for proximal. The thermo-suit trousers and long sleeve shirt induced the proximal skin temperature manipulation, whereas the distal skin temperature manipulation was provided by the socks and the hand gloves of the thermo-suit. The sequence of the temperature manipulations was programmed using Wintherm software (Wintherm, Lauda, Lauda-Königshofen, Germany). During the first 20 minutes of each block the water in the thermostat baths changed to the desired temperature with a programmed ramp of ± 0.2°C /min. For the remaining 70 minutes of the block the bath temperature was kept constant. The water in the bath was 33°C in the cool condition and at 37°C in the warm condition, resulting in temperatures of approximately 31°C and 34°C measured at the tubes just before entering the thermo-suit. Water circulated from and to the thermostat baths via isolated connecting-tubes through the network of micro-tubes inside the thermo-suit. The range of skin temperature manipulations was chosen such as not to differentially trigger major thermoregulatory responses. Subjects were habituated to the diurnal skin manipulation by application of similar nocturnal thermo-suit manipulations (alternating periods of 15 or 30 minutes of 33°C and 37°C water bath temperature, with ramps in between lasting 15 minutes). Manipulation temperature was recorded in the bath with a built-in PT100 element, on the connection-tube just before entering the thermo-suit and on the connection-tube just after departing the thermo-suit (both with a PT100 element (RTD-3-3105, Omega, Stamford, USA) and were recorded and stored on PC once a minute using the Wintherm software. The recordings of the manipulation temperature data were visually checked for possible artefacts. Occasional erroneous recordings characterized by abrupt steep changes (>0.3°C/min) in connection-tube temperature within the time window of interest were removed and linearly interpolated when feasible. Body temperature was obtained using 8 thermistors (P-8432, ICBT, Tokyo, Japan). Core body tempera-

ture (T_{re}) was measured using a rectal thermistor that was self-inserted 13 cm into the rectum. Proximal skin temperature was measured at three places: right mid-thigh on the musculus rectus femoris, abdomen (1 cm above the navel) and the right infraclavicular area. Distal skin temperature was measured at four points: thenar area at the palmar sites of the left and right hand and medial metatarsal area at the plantar sites of the left and right foot. The skin thermistors were attached to the skin with thermal probe covers (ref 090-2764, ConMed Corporation, Utica, USA) that reflect ambient heat and insure a more accurate recording. Temperature was digitally recorded at 1 Hz (Embla A10 and Somnologica software, Flaga hf, Reykjavik, Iceland). Body temperature data were down sampled to 0.1 Hz. Based on visual inspection of the data, an automated procedure was applied to remove occasional artefacts, defined for core body temperature as outside the 35.5˚C-38˚C range and for skin temperature as outside the 32˚C-37˚C range. In addition visually obvious artefacts (abrupt steep changes in skin temperature (>0.3˚C/min) or in core body temperature (>0.1˚C/min)) were removed and linearly interpolated when feasible. Average distal skin temperature (T_{dist}) was calculated as the average of the average of the temperature of both feet and the average temperature of both hands. A weighted average was calculated for proximal skin temperature (T_{prox} = 0.383 * mid-thigh + 0.293 * infraclavicular + 0.324 * abdomen) according to a modification of the method used by Kräuchi et al.[22], who in contrast to our protocol also included forehead temperature. Temperature data averaged over the 5 minutes before lights off were used for further analyses. As a final check, when such a single averaged data point differed more than +/- 2 standard deviations from the other 5-min averages during that day, the non-averaged data were once more checked for artefacts and corrected or removed when needed.

2.4. Sleep

Polysomnographic sleep recordings consisted of electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG). EEG was derived from two bipolar leads FpzCz and PzOz[50] with the E-net and Hydrodot system (Physiometrix Inc., Billerica USA). Submental EMG and horizontal EOG from the outer canthi were recorded using disposable Ag/AgCl electrodes (type 4203 Meditrace, Graphic Controls Corporation, Buffalo USA). All PSG signals were digitally recorded at 200 Hz using the Embla A10 recorder and Somnologica software (both Flaga hf, Reykjavik, Iceland).

Sleep onset was determined online during the experiment according to standard criteria[41], with sleep onset defined as three consecutive 30 sec epochs of Stage 1 sleep or one 30 sec epoch of stage 2 (or deeper) sleep[12]. Online sleep stage determination was aided by the use of spectral views of the EEG signal, facilitating the observation of disappearance of the alpha (8-12 Hz) peak, dominance of the proportion of theta (4-8 Hz) over the proportion of alpha activity, or the clear appearance of spindle (12-15 Hz) peaks. MSLT sleep recordings were once more visually scored

offline by two independent scorers blind to the manipulations, and in case of differences consensus was reached. Sleep-onset latency (SOL) was defined as the time between lights off and the sleep onset. If the subject did not sleep during the 30 minutes, sleep-onset latency was scored as 30 minutes.

2.5. Statistical Analyses

To determine the effects of skin and core temperature manipulation on core body, proximal skin, and distal skin temperatures and on subjective comfort, hierarchical linear modeling (i.e. random coefficient analysis) was applied using the MLwiN software (Centre for Multilevel Modelling, Institute of Education, London, UK). Since the frequency distribution of SOLs may be slightly skewed, longitudinal Poisson regression analysis, also referred to as longitudinal log-linear regression analyses, was used to determine the effects of skin and core temperature manipulations and induced temperatures on sleep onset latency. Both analyses takes into account the interdependency of the data points inherent to the hierarchical structure of the design, in our case the sequential sleep onset observations *i* that were nested within days *j*, once more nested within subjects *k*[47]. The first block of both days (the habituation block) was omitted from analyses. Analyses were run with induced body temperatures (T_{re}, T_{prox} and T_{dist}), subjective comfort and sleep-onset latency as dependent variables and the body temperature manipulations (CBT, PST and DST) as dichotomous predictor variables, with 0 reflecting the cool manipulation and 1 reflecting the warm manipulation. The effects on SOL were additionally (post-hoc) analyzed with the actual induced T_{re}, T_{prox} and T_{dist} as predictor variables. Additional models were run to test for carry-over effects of the temperature manipulations, by adding temperature manipulations of the preceding block (pCBT, pPST and pDST) to the regression models.

A number of variables that might account for variance in the dependent variables were also allowed in the model. More specifically, time of day (Hour) was allowed in the models for induced temperatures to account for possible diurnal variation in core and skin temperature[26]. Both time of day and the number of repeats trying to fall asleep (Repeats) were entered in the models for SOL to account for possible diurnal variation in SOL, and for a possible decrease of SOL with practice[13,29]. 'Repeats' was defined as the number of times allowed to fall asleep since day one. 'Hour' was defined as the number of hours since the start of the first MSLT within each day. Since these effects are likely to be nonlinear, their square root and squared values were allowed in the model in addition to their possible linear contribution. For the longitudinal Poisson regression analysis, all independent variables were centred at the within day level, except for 'Repeats', which was centred at the within subject level over the two days. For all regression analyses we report both

the full model, with all temperature manipulation variables and covariates in the model as well as the optimal model, containing only the significant contributions.

Maximum likelihood was used to estimate the regression coefficients, which were tested for significance with the Wald test[52]. In case of the optimal linear models, additional terms were allowed in the model only if their coefficients were significant and if the model improved according the likelihood ratio test of the models. For the longitudinal Poisson regression analysis, additional terms were allowed in the model only if their coefficients were significant and if the residual error of the model was reduced. Two-tailed significance levels were set at 0.05.

3. Results

3.1. Induced body temperatures

The observed mean sleep-onset latencies and temperatures per temperative condition are shown in Table 1. The observed mean temperatures and SEs per day and time of day are displayed in Table 2. Table 3 shows the effects of temperature manipulations on core and skin temperatures, as derived from the regression analyses. Figure 2, middle, provides an example of measured temperatures in a representative subject throughout the 2 experimental days.

Table 1. *Sleep-onset latency and temperature by temperature condition*

Manipulation	Sleep Onset Latency, min	Core Body Temperature, °C	Proximal Skin Temperature, °C	Distal Skin Temperature, °C
CBT−	12.16±0.88	36.78±0.03	35.15±0.07	34.92±0.09
CBT+	11.52±0.97	36.97±0.03	35.11±0.06	35.36±0.09
PST−	13.44±1.05	36.88±0.03	34.74±0.05	34.95±0.10
PST+	10.25±0.73	36.87±0.03	35.52±0.05	35.33±0.08
DST−	11.96±0.93	36.88±0.03	35.08±0.07	34.77±0.09
DST+	11.73±0.92	36.88±0.03	35.17±0.07	35.51±0.07

Values are means ± SE. CBT, core body temperature; PST, proximal skin temperature; DST, distal skin temperature. + and −, Warm and cool, respectively.

Table 2. *Sleep-onset latency and temperature by day and time of day*

Time	Sleep Onset Latency, min	Core Body Temperature, °C	Proximal Skin Temperature, °C	Distal Skin Temperature, °C
Day 1	13.20±1.04	36.85±0.04	35.15±0.07	35.17±0.09
09:00	13.44±3.04	36.69±0.08	35.19±0.21	35.21±0.20
10:30	12.94±2.55	36.83±0.08	35.16±0.19	35.07±0.29
12:00	11.00±2.91	36.90±0.11	35.21±0.25	35.46±0.18
13:30	12.56±2.02	36.88±0.12	35.12±0.22	35.24±0.16
15:00	12.81±3.70	36.91±0.10	35.12±0.19	35.29±0.19
16:30	11.81±2.95	36.83±0.10	35.03±0.22	34.99±0.22
18:00	12.56±3.12	36.85±0.16	35.17±0.16	35.01±0.38
19:30	18.44±3.50	36.95±0.13	35.17±0.14	35.12±0.31
Day 2	10.49±0.75	36.89±0.03	35.11±0.07	35.11±0.09
09:00	7.81±1.16	36.66±0.08	34.97±0.19	35.26±0.20
10:30	8.94±1.60	36.79±0.08	35.05±0.24	35.29±0.24
12:00	8.25±1.61	36.86±0.05	35.13±0.13	35.21±0.27
13:30	9.00±1.72	36.97±0.05	35.08±0.16	35.15±0.32
15:00	8.56±2.01	36.96±0.05	35.12±0.20	35.18±0.26
16:30	11.13±1.75	36.99±0.08	35.14±0.15	34.97±0.42
18:00	11.13±2.26	36.94±0.07	35.18±0.24	35.01±0.18
19:30	19.13±2.35	37.00±0.06	35.20±0.25	34.78±0.18

Values are means ± SE.

The overall average core body temperature during the 5 minutes prior to lights off was 36.88 ± 0.06˚C (mean±SE). Core body temperature was modulated by time of day (Hour, √Hour) and affected significantly by the core temperature manipulation, with a 0.20 ± 0.02˚C higher core body temperature in the CBT+ condition as compared to the CBT- condition. Entering time of day (Hour, √Hour) into the model accounted for 21% of the variance whereas the addition of the core body temperature manipulation accounted for another 44% of the residual variance in core body temperature. The addition of preceding temperature manipulations, to test for carry-over effects, revealed a positive contribution of pPST (0.11 ± 0.02˚C) that accounted an additional 16% of the variance.

The overall average proximal skin temperature during the 5 minutes prior to lights off was 35.13 ± 0.11˚C. Proximal skin temperature was not only affected by the proximal skin temperature manipulation, but also, albeit very modestly, by distal skin temperature manipulation. Proximal skin temperature was 0.78 ± 0.03˚C higher in the PST+ condition as compared to the PST- condition and 0.09 ± 0.03˚C higher in the DST+ condition as compared to the DST- condition. The manipulations accounted for 82% of the variance in proximal skin temperature.

Table 3. *Estimates of the effects of temperature manipulation and time of sleep initiation on core and skin temperatures*

	Core Body Temperature		Proximal Skin Temperature		Distal Skin Temperature	
	Full model	Optimal model	Full model	Optimal model	Full model	Optimal model
Intercept	36.57±0.07‡	36.57±0.07‡	34.66±0.12‡	34.69±0.11‡	34.44±0.17‡	34.48±0.16‡
Hour	−0.02±0.04	−0.03±0.01†	−0.07±0.07		−0.01±0.10	
Hour^2	0.00±0.00		0.00±0.00		0.00±0.01	−0.003±0.001†
$\sqrt{}$Hour	0.16±0.07*	0.18±0.04‡	0.12±0.12		0.04±0.19	
CBT	0.20±0.02†	0.20±0.02‡	−0.04±0.03		0.44±0.05‡	0.44±0.05‡
PST	0.00±0.02		0.78±0.03‡	0.78±0.03‡	0.38±0.05‡	0.38±0.05‡
DST	0.02±0.02		0.09±0.03†	0.09±0.03†	0.74±0.05‡	0.74±0.05‡

Values are means ± SE. Regression model was as follows: $T_{ijk} = \beta_{0ijk} + \beta_1 \times \text{hour}_{ijk} + \beta_2 \times \text{hour}^2_{ijk} + \beta_3 \times \sqrt{\text{hour}_{ijk}} + \beta_4 \times \text{CBT}_{ijk} + \beta_5 \times \text{PST}_{ijk} + \beta_6 \times \text{DST}_{ijk}$ (see text; subscripts indicate *i*th observation on day *j* for subject *k*). Core body and proximal skin and distal skin temperature manipulations were included in the model as dichotomous variables, with cool and warm coded as 0 and 1. Hour (time), defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900. Full model data show all predictors, whereas optimal model data show only significantly contributing predictors. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

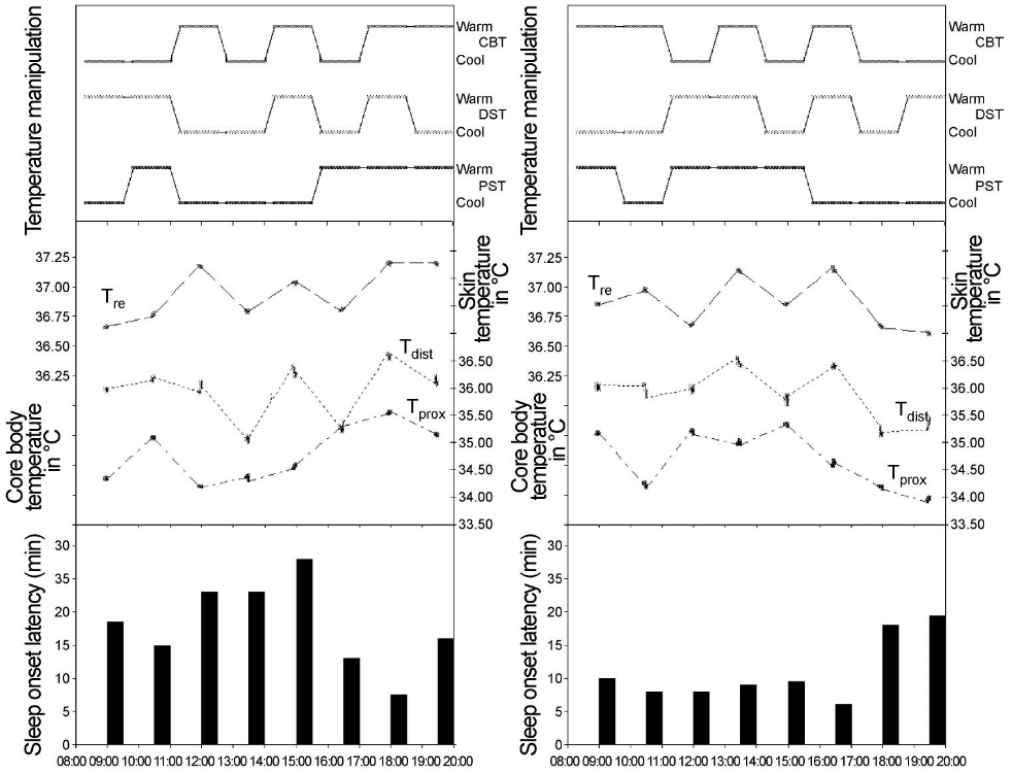

Fig. 2. Example of manipulations and measurements in a representative subject throughout the 2 experimental days. Upper panel: Temperature manipulation combinations. Middle panel: measured body temperatures over 5 minutes prior to lights off, connected by lines for clarity, left axis Tre, right axis Tprox and Tdist. Lower panel: measured SOLs.. For this specific subject, if dichotomized, only two out of sixteen observations (day two, at 10:30 and 16:30 hr) fail to match the general consistent pattern of shorter latencies being restricted to occur during the warm proximal condition.

The overall average distal skin temperature during the 5 minutes prior to lights off was 35.14±0.15˚C. Distal skin temperature was modulated by time of day (Hour^2) and significantly affected by all temperature manipulations. Distal skin temperature was 0.74 ± 0.05˚C higher in the DST+ condition as compared to the DST- condition, 0.38 ± 0.05˚C higher in a PST+ as compared to the PST- condition, and 0.44 ± 0.05˚C higher in a CBT+ as compared to the CBT- condition. Entering time of day into the model accounted for 4% of the variance and adding the manipulations accounted for another 73% of the residual variance in distal skin temperature. The addition of preceding temperature manipulations, to test for carry-over effects, revealed a positive contribution of pPST (0.17 ± 0.06˚C) that accounted an additional 2% of the variance.

Summarizing, the manipulations accounted for a high proportion of the variance in skin and core temperature, but were not fully successful in independently controlling the core body, distal and

proximal skin temperatures. Moreover, a carry-over effect was present in that the previous proximal manipulations slightly affected distal and core temperature.

3.2. Temperature perception

The effect of the temperature manipulations on temperature sensation and thermal comfort is shown in table 4.

Table 4. *Estimates of the effects of temperature manipulation, on temperature sensation and thermal comfort*

	Temperature Sensation	Thermal Comfort
Intercept	47.66±2.27‡	81.49±3.29‡
CBT	12.03±1.62‡	−20.21±2.77‡
PST	13.19±1.62‡	−18.60±2.77‡
DST	4.19±1.62†	−5.91±2.77*

Values are means ± SE. Regression model was as follows: $Y_{ijk} = \beta_{0ijk} + \beta_1 \times \mathrm{CBT}_{ijk} + \beta_2 \times \mathrm{PST}_{ijk} + \beta_3 \times \mathrm{DST}_{ijk}$. Temperature sensation was measured on a visual analog scale ranging from 0 (cool) to 100 (warm), with 50 reflecting thermoneutral. Thermal comfort was measured on a visual analog scale ranging from 0 (uncomfortable) to 100 (comfortable). *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

The overall average rating of thermal comfort prior to lights off was 59.1 ± 2.3. When all conditions were cool (CBT-, PST- and DST-), thermal comfort was rated close to maximal (81.5 ± 3.3 on the 100 mm scale ranging from 0 = uncomfortable to 100 = comfortable). Thermal comfort was slightly but significantly lower in the CBT+, PST+ and DST+ conditions (-20.2 ± 2.8 for CBT+, -18.6 ± 2.8 for PST+, -5.9 ± 2.8 for DST+). The overall average rating of temperature sensation prior to lights off was 62.4± 1.8. When all conditions were cool (CBT-, PST- and DST-), the temperature sensation was neutral (47.66 ± 2.27 on the 100 mm scale ranging from 0 = cool to 100 = warm) Temperature was perceived as significantly higher in the CBT+, PST+ and DST+ conditions (12.03 ± 1.62 for CBT+, 13.19 ± 1.62 for PST+, 4.19 ± 1.62 for DST+).

In summary, the warm conditions were experienced as less comfortable and warmer than the cool conditions.

3.3. Sleep-onset latency

The effects of the temperature manipulations on sleep-onset latency are shown in table 1 and table 5, with the temperature manipulations as dichotomous predictor variables. The observed mean SOLs and standard errors per day and time of day are displayed at table 2.

Table 5. *Estimates of the effects of temperature manipulation, time, and number of repeats on sleep-onset latency*

	Full Model	Optimal Model
Intercept	2.44±0.09‡	2.44±0.09‡
$Hour^2$	0.008±0.001‡	0.007±0.001‡
Repeats	−0.05±0.02*	−0.05±0.02†
CBT	−0.09±0.05	
PST	−0.27±0.05‡	−0.27±0.05‡
DST	−0.02±0.02	

Values are means ± SE. Regression model was as follows: $\ln(SOL_{ijk}) = \beta_{0ijk} + \beta_1 \times hour^2_{ijk} + \beta_2 \times repeats_{ijk} + \beta_3 \times CBT_{ijk} + \beta_4 \times PST_{ijk} + \beta_5 \times DST_{ijk}$ (see text; subscripts indicate the *i*th observation on *day j* for subject *k*). Core body temperature and proximal skin and distal skin temperature manipulations were included in the model as dichotomous variables, with cool and warm coded as −0.5 and +0.5. SOL, sleep-onset latency. Hour (time), defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900. Repeats, defined as the number of times allowed to fall asleep since *day one*, starting with 1. All independent variables were centered at the within-day level, except for 'Repeats', which was centered at the within-subject level over the two days. Covariates without significant contributions in the model are not shown. Full model data show all predictors, whereas optimal model data show only significantly contributing predictors. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

Figure 2, *bottom* provides an example of measured SOLs in a representative subject throughout the 2 experimental days. The overall average sleep-onset latency was 11.85 minutes (95% confidence interval [CI] 9.73 to 14.41). Sleep-onset latency was significantly modulated by time of day (Hour2) and affected by the number of sleep onset repeats (√Repeats) and the proximal skin temperature manipulation. Sleep-onset latency was 3.09 (CI 1.91 to 4.28) minutes shorter in the PST+ as compared to the PST- condition. Sleep-onset latency was not altered by core or distal skin temperature manipulations. The addition of preceding temperature manipulations did not decrease the residual error of the regression model, indicating a lack of significant carry-over effects. Figure 3 gives a graphical representation of the model best fitting the data of all subjects.

Table 6. *Estimates of the effects of actual core and skin temperatures, time, and repeats on sleep-onset latency*

	Full Model	Optimal Model
Intercept	2.44 ± 0.09‡	2.45 ± 0.09‡
Hour^2	0.007 ± 0.001‡	0.008 ± 0.001
Repeats	−0.05 ± 0.02*	−0.05 ± 0.02‡
Core body temperature	0.000 ± 0.000	
Proximal temperature	−0.19 ± 0.07†	−0.23 ± 0.06‡
Distal temperature	−0.07 ± 0.05	

Values are means ± SE. Regression model was as follows: $\ln(SOL_{ijk}) = \beta 0_{ijk} + \beta_1 \times hour^2_{ijk} + \beta_2 \times repeats_{ijk} + \beta_3 \times$ core $temperature_{ijk} + \beta_4 \times$ proximal $temperature_{ijk} + \beta_5 \times$ distal $temperature_{ijk}$. Sleep onset latency was regressed on actual core and skin temperatures (see text; subscripts indicate the *i*th observation on day *j* for subject *k*). SOL, sleep-onset latency. Hour (time), defined as the number of hours since the start of the first included sleep latency test within each day, starting with 0 at 0900. Repeats, defined as the number of times allowed to fall asleep since day one, starting with 1. All independent variables were centered at the within day level, except for 'Repeats', which was centered at the within-subject level over the two days. Covariates without significant contributions in the model are not shown. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

Because the temperature manipulations did not completely independently control core, proximal skin and distal skin temperatures, but did account for most of the variance in these temperatures, we did a post-hoc analysis entering the actually induced temperatures into the model rather than the dichotomous manipulation levels (see table 6). The model best fitting the data turned out to contain the same variables as the aforementioned model with dichotomous manipulation levels. A 1˚C increase in proximal skin temperature shortens sleep-onset latency by 2.68 (CI 1.34 to 4.03) minutes. The effects on sleep-onset latency of time of day and the number of times allowed to fall asleep are highly comparable to the effects in the dichotomous model. Sleep-onset latency was not significantly related the induced changes in core or distal skin temperature.

In summary, sleep onset latencies increase with time over the day, but decrease by 'practice' and proximal skin warming.

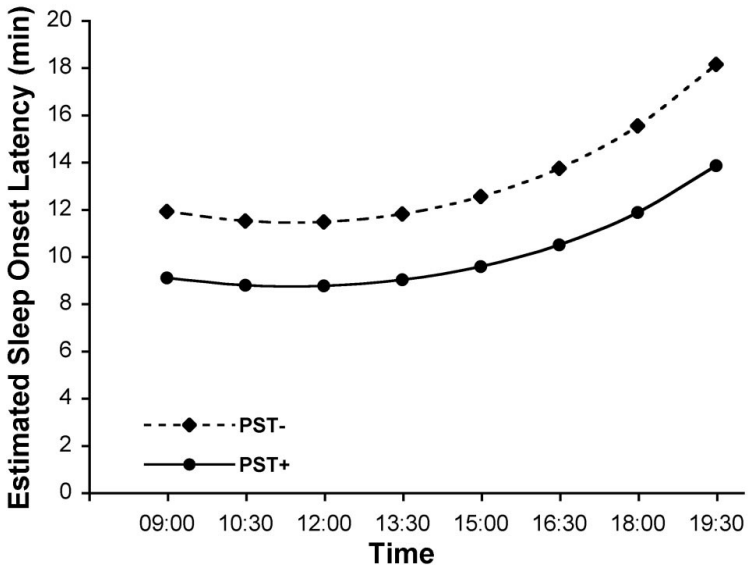

Fig. 3. Graphical representation the effect of PST manipulation in the model best fitting the data of all subjects: $\ln(SOL_{ijk}) = 2.44 + 0.007*Hour^2 - 0.05*Repeats - 0.27*PST$ (where SOL is sleep-onset latency) (see Table 5, right columns and text).

Estimated sleep-onset latency is thus given by: $e^{2.44+0.007*Hour^2-0.05*Repeats-0.27*PST}$
Sleep-onset latency data are given in minutes and PST is coded -0.5 for the cool proximal skin manipulation and +0.5 for the warm proximal skin manipulation (centred dummy coding). 'Repeats' was defined as the number of times allowed to fall asleep since day one, starting with 1 and centred within subject. 'Hour' was defined as the number of hours since the start of the first MSLT within each day, starting with zero at 9:00 hr and was centred within subject within day. For this figure, giving an impression of SOLs obtained on the two experimental days, the average over two days of the centred values of Repeats were used in the model.

4. Discussion

The present study investigated whether sleep-onset latency is affected by manipulating core body and skin temperatures within the range of their normal circadian fluctuations under strictly controlled conditions. It is the first of its kind to experimentally manipulate core and skin temperatures independently with the aim of modifying sleep onset latency. We show that the process of falling asleep is accelerated by warming of the proximal skin within the temperature range normally covered during everyday life under comfortable conditions. This effect occurred in spite of the fact that this warming was perceived as slightly less comfortable.

Before discussing the possible interpretations and implications of our findings, the restrictions of the present study deserve attention. First, we have not been able to fulfill our aim to independently manipulate core body and distal and proximal skin temperatures. Although these areas were primarily and most strongly affected by their respective manipulations, thermoregulatory

responses affecting other areas or carry-over effects from preceding proximal skin temperature manipulations seem to have been elicited. Core temperature manipulations induced not only changes in core body temperature, but also affected distal skin temperature. Proximal skin temperature manipulations affected primarily proximal skin temperature but also distal skin temperature and affected to a lesser extent in core body temperature and distal skin temperature in the next block. Distal skin temperature manipulations affected primarily distal but also proximal skin temperature. We optimized the design to prevent systematic errors due to circadian variation, not only by applying both cool and warm conditions to the same subject at the same time of day, but also by stratified randomization in order to have different sequences for all subjects. Thus, there was also no fixed sequence allowing possible carryover effects to introduce a systematic error. Despite these limitations, the momentary manipulations did account for most of the variability in core and skin temperatures, and a post-hoc analysis regressing sleep-onset latencies on the induced temperatures rather than on the manipulation levels provided essentially the same results, i.e. a reduction of sleep-onset latency associated with a warmer proximal skin.

A second restraint is that one should be cautious with extrapolation of the findings to temperature ranges and times of the day that were not covered in the present experiment. Both animal and human studies have demonstrated disturbed sleep with thermal manipulations that activate heat or cold stress mechanisms[20,40]. Thus, beyond the physiological range we applied, a further increase in skin temperature is likely to disturb sleep onset mechanisms rather than facilitate it at some point. On the other hand, the normal diurnal time course of distal skin temperature reaches values much lower than we have applied. During everyday life, diurnal distal skin temperature easily reaches temperatures of several degrees below the diurnal values measured at the proximal skin[53]. Also under strictly controlled laboratory conditions, the distal 24-hour minimum and maximum and the 24-hour mean skin temperatures were lower than their proximal equivalents[26]. The averaged induced proximal and distal skin temperatures in our study were however comparable to each other (see table 2). Thus we may have manipulated distal skin temperature too close to the ceiling of its normal diurnal pattern, not leaving the range optimal for sleep onset. Whereas the small proximal skin temperature manipulations we applied were sufficient to affect sleep-onset latency, we cannot exclude that applying distal skin temperature manipulations in a slightly lower range would be at least as adequate in affecting sleep-onset latency. In fact, increases in distal skin temperature relative to the proximal skin temperature (the distal-to-proximal gradient, DPG) have previously been shown to be correlated to sleep onset latency[23]. With respect to the gradient findings, it should be noted that all manipulation blocks where distal and proximal temperatures were both warm or both cool resemble the gradient condition found to be correlated to sleep-onset latency by Kräuchi and colleagues[23].

Third, the dichotomous nature of our manipulation is such that the terms 'warm' and 'cool' can be interpreted only as relative to each other. Theoretically, sleep-onset latency might either be increased in the cool condition or decreased in the warm condition. Several arguments favor the interpretation in terms of the warm condition promoting sleep onset rather than the cool condition delaying sleep onset. First, the cool rather than the warm condition was subjectively experienced as most comfortable, with the highest score on the visual analogue scale on comfort. The cool condition was also subjectively experienced as most thermoneutral, with values nearest to 50 on the visual analogue scale ranging from cool (0) to warm (100). Yet, sleep-onset latency was shorter in the warm (subjectively less thermoneutral and slightly less comfortable) condition. Second, although sleep-onset latencies differ strongly from laboratory to laboratory and from clinic to clinic, the average sleep-onset latency we obtained in the warm proximal skin temperature condition (10.25 ±0.73 mean ± SE minutes) tends to be lower than what has been reported in the majority of studies[10,13,17,54,55] in healthy adults. Third, even in the cool condition, the induced average proximal skin temperature (34.7˚C) was slightly higher than the average minimum proximal skin temperature (33.8˚C) reported in the primary controlled study on circadian modulation of skin temperature under laboratory conditions[26].

A related issue is that it is presently not known to which extent the induced skin temperatures of around 35.1˚C are representative of the temperatures that occur in everyday life when preparing for sleep. In an experimental setting, somewhat lower average proximal and distal skin temperatures (34.5˚C) were reported to occur when preparing for sleep after lights off[27]. On the other hand, earlier studies under more natural sleeping conditions, measured skin temperatures of 35 to 36˚C during sleep and bed temperature microclimates of 34 to 36˚C[19,39,51]. Although none of the previously performed studies is of a sample size large enough to provide normative data on the range of skin temperatures under habitual waking and sleeping conditions, these examples at least suggest that the proximal skin temperature was manipulated within or close to the subject's habitual nocturnal range. In fact, it is likely that the temperature we applied closer resembles the natural environmental temperature during sleep than the microclimate temperature in, for example, the studies of Kräuchi et al.[24,26], who provided subjects only with a light bed cover in an ambient temperature of 22˚C. Their experimental setup may well have reflected the habitual daytime environmental temperature, but not have allowed the subjects to attain in the natural nocturnal microclimate temperature of 34-36˚C. In both rodents and humans, the self-selected ambient temperature is higher during the lower part of the core body temperature cycle[49].

As to core body temperatures, we are confident that the range in core body temperatures covered throughout our manipulations should be sufficient to alter sleep-onset latencies if they were indeed dependent on core body temperature as has been proposed previously[5,9,38]. The difference of 0.20˚C in core body temperature we established between the warm and the cool condition is

about half of the reported circadian amplitude in core body temperature (0.44˚C) under controlled conditions[26]. In humans, the onset to the major sleep period tends to closely follow the timing of the maximal rate of decline in core body temperature, halfway its peak and trough[26,38]. In rats, which show a polyphasic sleep pattern and more ultradian fluctuations in core temperature, sleep onset similarly tends to occur near the maximal rate of decline of these fluctuations[16]. It consequently has been proposed that a declining core temperature might be involved in promoting sleep onset[9,38].

Whereas our data do not support the idea that core temperature itself is involved in promoting sleep onset, they do support the notion that the heat loss mechanisms underlying this drop in core temperature are involved. The circadian rhythm in core body temperature is to a large extent due to variations in heat loss[26]: a circadian-regulated nocturnal increase in skin blood flow, resulting in increased skin temperature, promotes heat transfer from the body to the environment. Although our observations have been limited to the human sleep EEG, they are compatible with the idea that, rather than changes in core temperature, the associated warming of the skin could provide a signal to sleep-regulating areas in the brain. This contention is supported by early work of Boulant and Bignall[7], who demonstrated that the activity of the thermosensitive neurons in the POAH is modulated predominantly by skin temperature if local brain temperature and skin temperature is manipulated simultaneously and differentially. Skin warming has moreover been shown to promote sleep-type firing patterns in other brain areas involved in the regulation or expression of sleep[48]. In humans, an increase in (distal) skin blood flow and consequently skin temperature starts around 20:00 h and induces a maximum plateau of skin temperature between 23:00 and 7:00 h[3,4,26,34]. We have previously suggested that, in response to this change in skin temperature, a subpopulation of sleep-related warm-sensitive neurons (WSNs) increase firing rate, thus promoting sleep. This idea can at present only receive indirect support in humans, since the presently available neuro-imaging tools do not yet provide the possibility for ultra-high resolution imaging of changes induced by slowly changing thermal stimuli.

Our findings may at first sight be difficult to reconcile with the inverse circadian rhythms of sleep propensity and proximal temperature under constant routine conditions. If anything, the evening decline in proximal skin temperature that has been shown to occur under constant routine conditions would be predicted, according to our findings, to inhibit the onset of sleep. However, this inhibition would take only as long as the subject has not appropriately prepared for safe sleep by taking a supine position in a relatively warm microclimate due to bedding, and relaxing to allow sleep to occur. Only if these conditions have been met, proximal skin temperature strongly increases after lights off, at least if subjects know that they are allowed to fall asleep. Proximal skin temperature then stays higher than pre-sleep levels throughout most of the night, in contrast its further decline if sleep is not allowed[27]. If safe sleeping conditions have not yet been established,

the low proximal temperature might be of functional importance to support wakefulness when the time awake is usually long and sleep pressure is high. When safe sleeping conditions have been established, its fast increase may promote sleep onset. This tentative idea should be verified by investigating whether sleep-onset latency is related to the steepness of the increase in proximal skin temperature that occurs between lights off and sleep onset. Some caution in interpreting the inverse relation of the circadian rhythms in sleep propensity and proximal temperature is furthermore warranted, given the fact that this relation has been established under constant routing conditions in a 'daytime' environmental temperature[26]. As we noted above, the preferred nocturnal temperature may differ from what has been applied in constant routine studies. The diurnal rhythm in proximal skin temperature under natural living conditions has to our knowledge not been studied in detail, and may differ from the unmasked rhythm obtained in a constant routine protocol.

We have previously suggested that the proposed signaling of skin temperature to sleep-related brain areas may have a functional role: a warm skin is most likely to occur if the sleep-appetitive behaviors of lying down and covering up are fulfilled, and it is thus safe for the organism to fall asleep[48]. A question of considerable interest is whether skin temperature is also involved in the maintenance and depth of sleep.

Our findings may have implications for sleep-onset latency in everyday life. Warming the proximal skin resulted in a 26% decrease in sleep-onset latency, which approximates the order of magnitude that can be obtained with hypnotic compounds. In healthy subjects, daytime administration of melatonin, Temazepam and Zopiclone induced reductions of at most 3 to 7 minutes[18,21,42]. Hence warming of the skin either by promoting peripheral heat loss or by subtle and feedback-controlled warming of the skin within the thermoneutral range might provide a means to improve sleep onset in people who have trouble falling asleep in the beginning of the night, or after nocturnal or after nocturnal or early morning awakening. Such non-pharmacological treatment is likely to lack the adverse effects that characterize chronic use of hypnotics. Although we are not aware of comprehensive studies on the effect on sleep onset of the many pharmaceuticals that induce vasodilatation, some studies at least suggest that vasodilatation is correlated with the ease of sleep onset. For example, the rate of heat-loss induced by melatonin and Temazepam is correlated with their effect on sleep-onset latency[18,24].

In conclusion, our results add to the significance of previous studies demonstrating a correlation between skin temperature changes and sleep-onset latency by demonstrating for the first time that an experimentally induced subtle increase in skin temperature may in fact cause a decrease in sleep-onset latency. The findings are compatible with the model we have previously put forward[48], stating that the diurnal modulation of skin temperature is possibly not only an output

signal of the circadian timing system but may as well act as an input signal to sleep-regulating brain areas.

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Chapter 5

Diminished capability to recognize the optimal temperature for sleep initiation may contribute to poor sleep in elderly people

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Summary

Study Objectives. Sleep propensity and skin temperature are functionally related. In young adults, changes of skin temperature within the comfortable thermoneutral zone affect sleep-onset latency and vigilance performance. Aging is associated with both decreased thermosensitivity and poorer sleep. Our goal was to test whether subtle manipulations of core-body and skin temperature affect sleep onset in elderly people without sleep complaints and in elderly insomniacs and whether the subjective perception of these mild body temperature manipulations is preserved with aging and insomnia.

Design: In a 2-day semi constant–routine protocol, 288 sleep-onset latencies were polysomnographically determined while manipulating core-body and skin temperatures differentially in warm and cold directions within a comfortable thermoneutral range.

Setting: Sleep laboratory of the Netherlands Institute for Neuroscience.

Patients or Participants: Eight elderly subjects without sleep complaints (65.8 ± 2.8 years, mean ± SEM) and 8 elderly insomniacs (59.1 ± 1.9 years).

Measurements and Results: Warming the proximal skin by 0.7˚C facilitates sleep onset equally effective in healthy elderly (by 18% i.e., by 1.84 minutes [95% confidence interval {CI}, 0.76-2.92]) and elderly insomniacs (28%, 2.85 minutes [CI: 2.55-3.18]). These effects were comparable to the results in healthy young subjects, in spite of a marked decrease in the subjective perception of temperature changes in elderly subjects, especially in insomniacs.

Conclusion: The findings show that mild changes in skin temperature have an effect on sleep propensity in elderly and indicate that elderly insomniacs may have a diminished capability to recognize that a slight increase in bed temperature facilitates the initiation or re-initiation of sleep.

1. Introduction

Both skin temperature and core body temperature (CBT) show a day-night rhythm that is functionally linked to the sleep-wake cycle. The circadian rhythm in CBT in humans is characterized by a relatively low temperature throughout the nocturnal sleeping period and a relatively high temperature during the day, while being awake. It is well established that CBT and sleep propensity are negatively related[36] and that sleep onset is most likely to occur when CBT decline is at its maximum rate[1,5,42]. The majority of studies on the interaction between thermoregulation and sleep-wake transitions have focused on the relationship between CBT and sleep. Skin temperature also exhibits a circadian rhythm that is reciprocal to the CBT rhythm[21,40,56,59], i.e., low during the habitual wake period. Its potential role in sleep regulation was already recognized by Magnussen in 1939 but since then has been almost totally neglected[39]. Recently, a renewed interest in the relationship between skin temperature and sleep has emerged. Kräuchi and colleagues have shown that the degree of heat loss at the skin of the hands and feet is the best physiologic predictor for a rapid sleep onset[33,34]. Fronczek et al recently demonstrated that, under less-controlled circumstances, the proximal skin temperature (PST) predicts subsequent sleep-onset latency (SOL) even better than distal skin temperature (DST), in both narcoleptic subjects as well as healthy controls[19]. We have previously addressed the underlying mechanisms of the relationship between skin temperature and sleep propensity and have provided a neurobiological model postulating that autonomous thermoregulatory changes in CBT and especially skin temperature could act as an input signal to modulate neuronal activity in sleep-regulating brain areas[57]. For example, the activity of thermosensitive neurons in the preoptic area/anterior hypothalamus, a key area in both sleep regulation and thermoregulation, is indeed modulated more strongly by changes in skin temperature than by changes in CBT[2]. In support of a feedback mechanism of skin temperature to sleep-regulating brain areas, we have shown that manipulation of the skin temperature within the normal thermophysiological range —without activating thermoregulatory responses— modulates sleepiness in healthy young adults (Chapter 4, this thesis)[45] and patients with narcolepsy (Chapter 7, this thesis)[20] and affects sleep depth (Chapter 8, this thesis)[47].

Insomnia is more prevalent in the elderly[17,35]. Poor sleep in elderly subjects is typically undertreated[27] or treated with pharmacologic interventions with adverse consequences for daytime function[58]. Given the graying society, it is highly relevant to investigate alternative strategies for sleep management in elderly[23,51].

The aims of the present study were 2-fold. The first aim was to evaluate whether subtle skin warming in elderly subjects without sleep complaints and in elderly insomniacs promotes sleep onset in a fashion similar to that reported earlier in healthy young adults (see Chapter 4, this thesis)[45]. The second aim was to evaluate whether the previously reported age-related decrease in

awareness of changes in temperature during the daytime is also present in a sleeping environment and equally so in good sleepers and insomniacs. Preservation of these subjective and objective responses is not trivial because thermosensitivity during wakefulness decreases with age (see Chapter 2, this thesis)[61].

2. Materials & Methods

2.1. Participants

Sixteen elderly subjects were recruited through newspaper and both magazines and Internet sites aiming at an elderly audience. Participants were 8 healthy elderly subjects without sleep complaints (mean ± SEM: 65.8 ± 2.8 years, 4 men) and 8 elderly subjects diagnosed with primary insomnia (59.1 ± 1.9 years, 4 men) according to the qualitative criteria of the *International Classification of Sleep Disorders*[25] and the *Research Diagnostic Criteria for Primary Insomnia*[15], as well as according to proposed quantitative criteria by Lichstein et al[37]. The groups did not differ regarding their mean age (t test, P = 0.38).

Although the study was performed prior to the recently published Recommendations for a Standard Research Assessment of Insomnia[3], it complied with the majority of the recommendations. Diagnosis was performed by accredited sleep specialists and included interviews, sleep diaries, and 2 questionnaires: a Dutch adaptation[53] of the 75-item Sleep Disorders Questionnaire (SDQ)[14] and the Pittsburgh Sleep Quality Index (PSQI)[4]. All elderly subjects suffering from primary insomnia had a PSQI score greater than 5 (10.9 ± 1.1) and an SDQ-Insomnia score greater than 2.5 (3.3. ± 0.1). All elderly subjects without sleep complaints scored within the normal range of these scales: 3.6 ± 0.4 for the PSQI and 2.0 ± 0.1 for the SDQ-Insomnia subscale. The diagnosis of insomnia was supported by sleep diaries kept over a period of 2 weeks just prior to the experiment. Sleep diary data are given in Table 1. The 2 groups differed significantly on subjective sleep efficiency, SOL, and the duration of wake after sleep onset.

None of the subjects scored higher than the cutoff score of 3 on the SDQ subscales Narcolepsy, Apnea, Restless legs, and Psychiatry. Polysomnographic confirmation of disturbed sleep in the absence of apnea and periodic leg movements was demonstrated during the study. A history or present symptoms of medical or psychiatric disorders were furthermore excluded by interview and evaluating the Symptom Check List (SCL-90). All subjects were in good health, and none used hypnotic, psychotropic, or cardiovascular medication. All women were postmenopausal. The data from 8 young and healthy adults (mean ± SEM: 27.0 ± 2.4 years, 4 men) used from a previous study[45] for the comparison all scored within the normal range of these scales: 4.0 ± 0.5 for the PSQI and 1.8 ± 0.1 for the SDQ-Insomnia subscale, respectively. All subjects participated with in-

formed consent. The Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam approved the protocol.

Table 1—Sleep Characteristics from Sleep Diaries of Elderly Subjects Covering 2 Weeks Prior to the Experiment

Sleep Characteristic	Elderly	
	Without sleep complaints	With insomnia
SOL, min	11.23 ± 2.11	46.25 ± 13.50[a]
TIB, min	475.88 ± 16.58	512.70 ± 20.06
TST, min	434.78 ± 18.55	365.72 ± 32.47[b]
WASO, min	7.99 ± 2.15	50.96 ± 9.04[c]
Sleep efficiency, %	91.4 ± 1.1	71.5 ± 5.5[c]

Subjective sleep characteristics, presented as mean ± SEM, for elderly subjects without sleep complaints and elderly subjects with insomnia. P values are determined using independent sample t-tests. SOL refers to sleep-onset latency; TIB, time in bed; TST, total sleep time; WASO, wake time after sleep onset. [a]$P < 0.05$; [b]$P < 0.10$; [c]$P < 0.01$

2.2. Design and Procedure

A previously described design was used that consisted of a modified constant-routine protocol[10,41] over 2 experimental days in which sleepiness was measured using the (Multiple Sleep Latency Test [MSLT])[7,6]. The procedures have been described in detail before (see Chapter 4, this thesis)[45] and are given here in a comprehensive way.

Participants refrained from caffeine, alcohol, and tobacco for 8 hours before arriving at the sleep laboratory at 22:00, where they were prepared for polysomnography and were fitted with a thermosuit (Coretech Cool tubesuit, Med-Eng Systems Inc., Ottawa, Canada) for skin-temperature manipulation. From midnight until 06:00, lights were turned off, and participants were allowed to sleep. The experiment started at 06:30 and consisted of a modified constant-routine protocol under dim-light (<10 lux) conditions and a fixed body-position schedule. Over 2 experimental days, 18 SOLs for each subject were determined while CBT was manipulated with food and drinks and skin temperature was manipulated with a thermosuit.

Both experimental days consisted of 9 consecutive blocks with a duration of 1.5 hours each (see Figure 1). Within the first 60 minutes of each block, CBT and skin-temperature manipulations were applied, and a computerized neuropsychological task battery had to be completed. This battery included assessment of vigilance, thermal comfort, and temperature sensation using 100-mm visual-analog scales. At 60 minutes, the lights were switched off, and the participants were asked to try to sleep. Sleep onset was determined online (MSLT)[7,6], and participants were awakened directly after sleep-onset determination (see below) and stayed awake in bed with the dim

light turned on. The maximum time allowed to fall asleep was 30 minutes. The results of the effects of temperature manipulation on vigilance-task performance have been reported elsewhere (see Chapter 6, this thesis)[44].

CBT, PST, and DST were simultaneously and independently manipulated in either a slightly warmer (+) or cooler (-) direction, within the comfortable and thermoneutral range. This brings up a 2 x 2 x 2 experimental design (CBT warm or cool [CBT+ or CBT-], PST warm or cool [PST+ or PST-], or DST or cool [DST+ or DST-]) with 8 possible manipulation combinations, which were all tested in the 8 blocks within a single day in every participant (see Figure 1 for an example of 1 subject). We have previously demonstrated that the "cool" condition can be regarded as an adequate approximation of the skin temperature during normal sleep in elderly subjects[47]. The sequence of the manipulation combinations was different for each participant such that, over all participants, every manipulation combination was given once in each of the 8 blocks, and every transition from one to any other combination occurred only once. At the end of the first day, subjects went home for a normal night of sleep and returned to the laboratory the next evening for a repeated assessment according to the same procedure. However, on the second day, the temperature manipulation combinations were the opposite of those of the first day to provide a protocol balanced for circadian effects (for example: Day 1, block n: CBT+, PST-, DST+; Day 2, block n: CBT-, PST+, DST-).

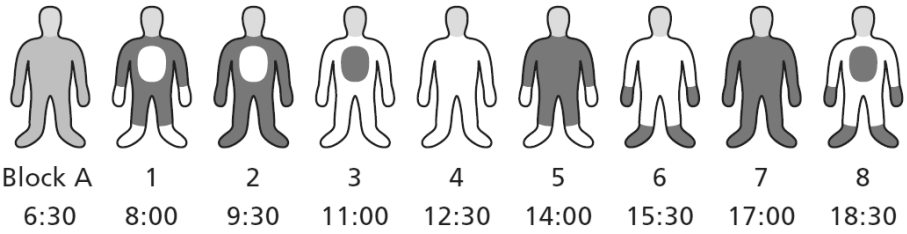

Fig. 1. Schematic view of the temperature manipulations within one day within one subject. Core body, proximal and distal skin manipulation occurs simultaneously during every block. Within the last 30 minutes of each block the MSLT was performed. On the 2nd day, temperature manipulation combinations were the opposite of those of the 1st day to provide a protocol balanced for circadian effects. Block A: Habituation block. White represents cool; dark gray represents warm.

2.3. Temperature Manipulations and Measurement.

Temperature manipulations and measurements have been described in detail previously[45]. In brief, CBT was manipulated by means of 200 mL hot (heated to 80°C, served 2 min later) or cold (0°C, crushed ice) diet (4.25 kcal), decaffeinated tea (iced tea mix [*diet decaffeinated lemon*], Lipton, Englewood Cliffs, NJ) together with an isocaloric hot or cold snack of the subjects' choice (200 kcal). Skin temperatures were manipulated with the use of a water-perfused thermosuit (Core-

tech Cool tube suit, Med-Eng Systems Inc.), connected to 2 computer-controlled bath-circulation thermostats (K6KP, Lauda, Lauda-Königshofen, Germany). The temperatures measured at the tubes just before entering the thermosuit were approximately 31°C and 34°C, a comfortable range of skin temperature manipulations that does not trigger major thermo-regulatory responses. Ingestion of food and drinks to manipulate CBT and skin temperature was started about 50 minutes before lights off.

Body temperature was obtained using 8 thermistors (P-8432, ICBT, Tokyo, Japan). CBT was measured using a rectal thermistor. PST was measured at 3 places: right midthigh, abdomen, and the right infraclavicular area. DST was measured at 4 points: thenar eminence of the left and right hand and medial plantar aspect of the left and right foot. Temperature was digitally recorded at 1 Hz (Embla A10 and Somnologica software, Flaga hf, Reykjavik, Iceland). An automated procedure was applied to remove occasional artifacts and to calculate average DST (T_{dist}) and PST (T_{prox}) using a weighting method, as has been described previously[45]. Temperature data averaged over the 5 minutes before lights off were used for further analyses.

2.4. Sleep

Polysomnographic sleep recordings consisted of electroencephalography from 2 bipolar derivations (FpzCz and PzOz)[63], submental electromyography, and electrooculography. The signals were digitally recorded at 200 Hz using the Embla A10 recorder and Somnologica software (Flaga hf).

Sleep onset was determined online during the experiment according to standard criteria[48], with sleep onset defined as 3 consecutive 30-second epochs of Stage 1 sleep or one 30-second epoch of Stage 2 (or deeper) sleep[7]. Real-time sleep-stage determination was aided by the use of spectral views of the EEG signal. MSLT recordings were once more visually scored offline by 2 independent scorers blind to the temperature manipulations. SOL was defined as the time between lights off and sleep onset. If the participant did not sleep during the 30 minutes, SOL was scored as 30 minutes. This occurred in 8% of the SOL determinations.

2.5. Statistical Analysis

To determine the effects of skin and core-temperature manipulation on body temperatures and subjective comfort, mixed-effect regression analysis (also known as hierarchic or multilevel analysis) was applied using the MLwiN software (Centre for Multilevel Modelling, Institute of Education, London, UK). These analyses were necessary in order to take into account the interdependence of the data points inherent to the hierarchic structure of the design, in our case the sequential sleep onset observations *i* that were nested within days *j*, once more nested within participants *k*[55]. They were necessary as well to independently estimate the effects of the simulta-

neously and differentially manipulated CBT, DST, and PST, a major aim of the present study. Because the frequency distribution of SOLs is skewed, a Poisson distribution rather than normal distribution was assumed in the mixed-effect analyses on the effects of the manipulations on SOL.

We evaluated how CBT (T_{re}) and skin temperatures (T_{prox} and T_{dist}), subjective comfort, and SOL were affected by the manipulations. To do so, the CBT, PST, and DST manipulation levels were dummy coded as dichotomous predictor variables, using -0.5 for the cool and +0.5 for the warm manipulation. A 3-level regression model was fitted (each block (*i*), nested within days (*j*), nested within subjects (*k*)). To account for possible diurnal variation in core body and skin temperature[32] and a possible decrease of SOL with practice[23,8], both time of day (Hour) and the number of repeats trying to fall asleep (Repeats) were entered in the models as covariates. Since these effects are likely to be nonlinear, their square-root and squared values were allowed in the model in addition to their possible linear contribution. Additional models were run to test for confounding effects of the prior temperature manipulations, by adding temperature manipulations of the preceding block (pCBT, pPST, and pDST) to the regression models.

Maximum likelihood was used to estimate the regression coefficients (effect sizes), which were tested for significance with the Wald test[64]. Additional terms were allowed in the model only if their coefficients were significant and the residual error of the model was reduced. Two-tailed significance levels were set at 0.05.

3. Results

3.1. Effects of Temperature Manipulations on CBT and Skin Temperatures

The effects of the temperature manipulations on CBT and skin temperatures for both groups are shown in Table 2. The overall average T_{re} during the 5 minutes prior to lights off was 36.86˚C ± 0.09˚C for elderly subjects without sleep complaints and 36.80˚C ± 0.07˚C for elderly insomniacs. T_{re} was significantly affected by the CBT manipulation, with 0.20˚C and 0.16˚C higher T_{re} in the CBT+ condition, compared with the CBT- condition for elderly subjects and elderly insomniacs, respectively. T_{re} also showed modulation over the time of day, accounting for 47% and 36%, respectively, of the variance. The CBT manipulation accounted for another 33% and 32% of the residual variance in T_{re}. The addition of preceding temperature manipulations to test for confounding effects of the previous manipulations accounted for an additional 27% (by all previous manipulations) and 20% (by previous PST manipulation) of the variance, respectively.

Table 2—Effects of Manipulations on Measured Temperatures of 8 Elderly Subjects Without Sleep Complaints and 8 Elderly Subjects With Insomnia

	T_{re}	T_{prox}	T_{dist}
Elderly without sleep complaints			
Overall mean	36.86 ± 0.09	35.03 ± 0.01	35.00 ± 0.15
CBT	0.20 ± 0.03[a]		0.41 ± 0.06[a]
PST		0.71 ± 0.04 [a]	0.29 ± 0.06[a]
DST			0.82 ± 0.06[a]
Elderly Insomniacs			
Overall mean	36.80 ± 0.07	35.00 ± 0.09	35.18 ± 0.11
CBT	0.16 ± 0.02[a]		0.42 ± 0.05[a]
PST		0.73 ± 0.04[a]	0.27 ± 0.05[a]
DST		0.09 ± 0.04[b]	0.72 ± 0.05

Estimates of the effects, i.e. mean ± SEM difference of temperature (˚C) in the warm relative to cool manipulation conditions, for core body temperature (T_{re}), proximal skin temperature (T_{prox}), and distal skin temperature (T_{dist}) before lights off. CBT, PST, DST manipulation were included in the model as dichotomous variables, with cool and warm coded as 0 and 1. The full regression model was as follows: $T_{ijk} = ß_{0ijk} + ß_1*Hour_{ijk} + ß_2*Hour^2_{ijk} + ß_3*\sqrt{Hour}_{ijk} + ß_4*CBT_{ijk} + ß_5*PST_{ijk} + ß_6*DST_{ijk.}$ Subscripts indicate the i^{th} observation on day j for subject k. Hour = Time of day, not shown.
[a]$P < 0.001$; [b]$P < 0.05$

The overall average T_{prox} during the 5 minutes prior to lights off was 35.03˚C ± 0.01˚C for elderly without sleep complaints and 35.00˚C ± 0.09˚C for elderly insomniacs. T_{prox} was significantly affected by the PST manipulation, with 0.71˚C and 0.73˚C higher T_{prox} in the PST+ condition compared with the PST- condition for elderly subjects and elderly insomniacs, respectively. Moreover, in elderly insomniacs, T_{prox} was significantly affected by the DST manipulation, with 0.09˚C higher T_{prox} in the DST+ condition compared with the DST- condition. T_{prox} showed modulation over the time of day, accounting for 5% and 8% of the variance for elderly subjects and elderly insomniacs, respectively. The PST manipulations accounted for another 76% and 71% of the residual variance in T_{prox}. The addition of preceding temperature manipulations to test for the effects of the previous manipulations accounted for an additional 3% (by previous PST manipulation) of the variance, but only in the elderly without sleep complaints.

The overall average T_{dist} during the 5 minutes prior to lights off was 35.00˚C ± 0.15˚C for elderly without sleep complaints and 35.18˚C ± 0.11˚C for elderly insomniacs. T_{dist} was significantly affected by the DST manipulation, with 0.82˚C and 0.72˚C higher T_{dist} in the DST+ condition compared with the DST- condition for elderly subjects and elderly insomniacs, respectively. T_{dist} was also modulated by proximal skin manipulations (0.29˚C, and 0.27˚C higher T_{dist} in the PST+ condition) and CBT manipulation (0.41˚C, and 0.42˚C higher T_{dist} in the CBT+ condition). In the elderly insomniacs, T_{dist} also showed modulation over the time of day, accounting for 3% of the variance. The DST manipulations accounted for another 70% and 72% of the residual variance in T_{dist}. The

addition of preceding temperature manipulations accounted for an additional 36% (by previous skin temperature manipulations) and 21% (by previous PST manipulation) of the variance, respectively.

In summary, the manipulations accounted for a high proportion of the variance in body temperatures, and their effects were highly comparable between both groups. Only very limited carryover effects of manipulations in the previous block were present. Likewise, crosstalk was limited such that the largest changes of temperature were consistently in the body parts being manipulated.

3.2. Effects of Temperature Manipulations on Temperature Perception

The effects of the temperature manipulations on thermal comfort and temperature sensation for both groups are shown in Table 3. The overall average rating of thermal comfort prior to lights off was 55.6 ± 4 for elderly without sleep complaints and 49.9 ± 7.9 for elderly insomniacs. Only in the elderly without sleep problems was thermal comfort significantly affected by all of the temperature manipulations. In these subjects, comfort was maximal (71.0 ± 4.6 on the 100-mm scale ranging from 0 = uncomfortable to 100 = comfortable) when all conditions were cool (CBT-, PST-, and DST-). Thermal comfort was significantly lower in the warm conditions (-12.6 ± 2.6 for CBT+, -12.6 ± 2.6 for PST+, -5.4 ± 2.6 for DST+). In contrast, none of the temperature manipulations affected thermal comfort in elderly insomniacs.

The overall average rating of temperature sensation prior to lights off was 59.7 ± 2.8 for elderly subjects and 63.2 ± 4.5 for elderly insomniacs. Temperature sensation was significantly affected by the CBT manipulation. The CBT+ condition was rated 12.84 warmer by elderly subjects and 9.35 warmer by elderly insomniacs, as compared with the CBT- condition. Only in elderly subjects without sleep complaints was temperature sensation also significantly affected by the PST manipulation. The PST+ condition was rated 11.48 warmer than the PST- condition. Of note is that, in elderly subjects, the temperature sensation was neutral (47.5 ± 3.2 on the 100-mm scale ranging from 0 = cool to 100 = warm) when CBT manipulation and proximal skin manipulation conditions were cool (CBT- and PST). In elderly insomniacs the temperature sensation was just above neutral (58.5 ± 4.7) when the CBT manipulation was cool (CBT-).

In summary, temperature sensation was affected by the CBT manipulations in all elderly subjects, whereas the PST manipulations were experienced only as warmer than the cool by elderly without sleep complaints. DST manipulations did not affect temperature sensation in either elderly group. All temperature increases were seen as discomforting by elderly good sleepers, but none were discomforting to elderly insomniacs.

Table 3—Effects of Manipulation on Thermal Comfort and Temperature Sensation of 8 Elderly Subjects Without Sleep Complaints and 8 Elderly Subjects With Insomnia

	Thermal Comfort	Temperature Sensation
Without sleep complaints		
Overall mean	55.6 ± 4.0	59.7 ± 2.8
CBT	-12.5 ± 2.6 [a]	12.8 ± 2.3 [a]
PST	-12.6 ± 2.6 [a]	11.4 ± 2.3 [a]
DST	-5.4 ± 2.6[b]	
With insomnia		
Overall mean	49.9 ± 7.9	63.2 ± 4.5
CBT		9.4 ± 2.1[a]
PST		
DST		
Young subjects*		
Overall mean	59.1 ± 2.3	62.4 ± 1.8
CBT	-20.2 ± 2.8 [a]	12.0 ± 1.6[a]
PST	-18.6 ± 2.8 [a]	13.2 ± 1.6[a]
DST	-5.9 ± 2.8[b]	4.2 ± 1.6[c]

Estimates of the effects, i.e. mean ± SEM difference of the visual-analog scale scores (mm) on subjective temperature sensation and thermal comfort in the warm relative to cool manipulation conditions. Core body, proximal skin, and distal skin temperature manipulation (CBT, PST, DST) were included in the model as dichotomous variables, with cool and warm coded as 0 and 1. Thermal Comfort was measured on a visual-analog scale ranging from 0 (uncomfortable) to 100 (comfortable). Temperature sensation was measured on a visual-analog scale ranging from 0 (cool) to 100 (warm), with 50 reflecting most thermoneutral. Only the optimal models are shown, with only the significantly contributing predictors shown. The full regression model was as follows: $Y_{ijk} = ß_{0ijk} + ß_1*CBT_{ijk} + ß_2*PST_{ijk} + ß_3*DST_{ijk.}$ Subscripts indicate the i^{th} observation on day j for subject k.
*Data of young subjects taken from Raymann et al.[15]
[a]$P < 0.001$; [b]$P < 0.05$; [c]$P < 0.01$

3.3. Effects of Temperature Manipulations on SOL

Table 4 shows the effects of the temperature manipulations on SOL. The overall average SOL was 10.43 minutes (95% confidence interval [CI]: 7.13 - 15.26) for elderly subjects and 10.10 minutes (CI: 6.96-14.65) for elderly insomniacs. In elderly good sleepers, SOL was significantly modulated by time (hour2) and affected by the number of sleep-onset repeats (Repeats and √Repeats) and by the proximal skin warming. Sleep onset was 1.84 minutes (CI: 0.76-2.92) shorter in the PST+ condition, compared with the PST- condition. Sleep latency was not significantly affected by core and distal manipulations. As compared to the cool condition, warming of the proximal skin thus resulted in an 18% decrease in the time to fall asleep (see Figure 2). In elderly insomniacs, SOL was significantly modulated by time (Hour) and affected by the number of sleep-onset repeats

(Repeats and Repeats^2) and by both proximal skin warming and core body cooling. Sleep onset was 1.68 minutes (CI: 0.60-2.76) shorter in the CBT- condition, compared with the CBT+ condition, and 1.16 minutes (CI: 0.08-2.24) shorter in the PST+ condition, compared with the PST- condition. Sleep latency was not significantly affected by distal manipulations. Warming of the proximal skin together with cooling of the core thus resulted in a 28% decrease in the time to fall asleep, as compared with the opposite manipulation (see Figure 2).

Table 4—Effects of Manipulation on Sleep Latency in 8 Elderly Subjects Without Sleep Complaints and 8 Elderly Subjects With Insomnia

	Subjects	
	Without sleep complaints	**With insomnia**
Overall mean	10.43 (7.13-15.26)	10.10 (6.96-14.65)
CBT		1.68 (0.60-2.76)[a]
PST	-1.84 (0.76-2.92)[b]	-1.16 (0.08-2.24)[c]
DST		

Estimates of the effects, i.e. mean and confidence intervals difference of sleep onset latency (min) in the warm relative to cool manipulation conditions. This table shows sleep-onset latency in minutes, calculated by taking e to the power of the coefficients, as estimated from the Poisson regression. Temperature manipulations were included in the model as dichotomous variables, with cool and warm coded as -0.5 and +0.5.
The full Poisson regression model was as follows: $Ln(SOL_{ijk}) = ß_{0ijk} + ß_1*Hour_{ijk} + ß_2*Hour^2_{ijk} + ß_3*Repeats_{ijk} + ß_4*Repeat^2s_{ijk} + ß_5*\sqrt{Repeats}_{ijk} + ß_6*CBT_{ijk} + ß_7*PST_{ijk} + ß_8*DST_{ijk}$ (Subscripts indicate *i*th observation on day *j* for subject *k*). Hour (time), defined as the number of hours since the start of the first included sleep-latency test within each day, starting with 0 at 0900. Repeats, defined as the number of times allowed to fall asleep since day 1, starting with 1. Effects of Hour and Repeats are not shown. CBT refers to core body temperature manipulation; PST, proximal skin temperature manipulation; DST, distal skin temperature manipulation; SOL, sleep-onset latency.
[a]$P < 0.01$; [b]$P < 0.001$; [c]$P < 0.05$

In summary, SOLs increase with time over the day but decrease by “practice” and proximal skin warming. In insomniacs, core-body cooling also accelerates sleep onset.

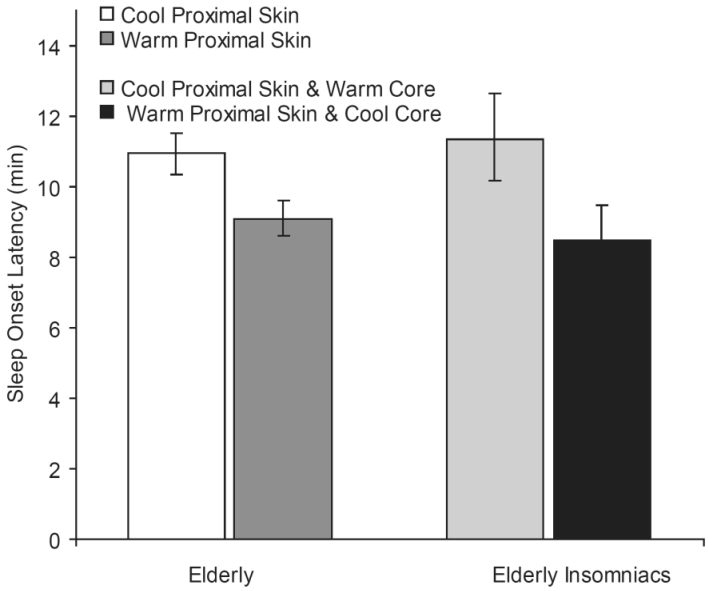

Fig. 2. Sleep onset latencies (± 95% confidence intervals) in elderly and elderly insomniacs. Effect sizes follow from the regression analysis results presented in table 4.

3.4. Effects of Age and Insomnia on Induced Temperature Changes and Subjective Thermosensitivity

To investigate changes in subjective thermosensitivity related to insomnia, we compared the regression model of both groups. To investigate changes in subjective thermosensitivity related to aging, we compared the regression model of both groups with the models of a group of young subjects who underwent the same protocol[45]. Such comparisons were possible because temperature manipulations induced changes in CBT and skin temperatures of similar magnitude in all 3 groups (all Z-tests: $P > 0.10$).

Between-groups comparison of the effects of the temperature manipulations on thermal comfort and temperature sensation indicated only a minor loss in temperature perception with aging, per se, and a major loss in elderly insomniacs. When comparing thermal comfort in the young and the elderly without sleep complaints, it was found that thermal comfort was affected highly similarly by PST and DST manipulations (both Z-tests: $P > 0.10$) and significantly less by CBT manipulations in the elderly (Z-tests: $P < 0.05$). However, in the elderly insomniacs, none of the temperature manipulations affected thermal comfort. When comparing temperature sensation in the young and the elderly without sleep complaints, it was found that temperature sensation was affected similarly by CBT and PST manipulations (both Z-tests $P > 0.50$) but not by DST, which affected temperature sensation only in young subjects. In the elderly insomniacs, only CBT manipulation

affected temperature sensation, and this effect was comparable to the effect seen in the young and the elderly (both Z-tests $P > 0.25$).

In summary, the applied ranges of temperature manipulations affected the skin temperatures and CBT in a highly similar fashion in all 3 groups, and all manipulations affected the thermal comfort and sensation, but only in the young group. However, with age, the effect of the applied CBT range on thermal comfort attenuates, and the effect of the applied DST range on temperature sensation disappears. In elderly insomniacs, only the effect of the applied CBT range on temperature sensation holds on. It indicates that the subjective effects of thermal manipulation are slightly weakened with aging and more strongly so in elderly insomniacs.

3.5 Effects of Age and Insomnia on the Effects of Temperature Manipulations on SOL

Between-groups comparison indicated no differences on the effects of PST manipulations on SOL (all Z-Tests $P > 0.05$). Increases of PST resulted in decreases of SOL in all groups. Only in the elderly insomniacs did decreases of CBT result in decreases of SOL.

4. Discussion

The aims of the present study were (1) to evaluate whether subtle manipulation of CBT and skin temperature within the range that is naturally occurring during the circadian cycle in elderly without sleep complaints and elderly insomniacs affects SOL in a similar fashion as reported earlier in healthy young adults[45] and (2) to evaluate whether the previously reported age-related decrease in awareness of changes in temperature at daytime is also present in a sleeping environment. Whereas it has been shown that elderly in general show attenuated thermosensitivity[29,60,61] compared with younger subjects when awake, no prior studies have addressed such possible attenuation during attempts to fall asleep and/or maintain sleep within the microclimate of the bed. Of note, our experimental approach of manipulating CBT and skin temperatures and quantifying their effect on thermal appreciation and sleep onset allowed for a cause-and-effect interpretation, in contrast with correlation studies.

With regard to the effect of skin temperature on sleep initiation, our study showed that proximal skin warming, in particular, facilitated sleep onset in elderly with and without sleep complaints. The effect was comparable in both groups of elderly and also did not differ significantly from the effect found in young adults, reported in our earlier study[15]. In elderly insomniacs, core body cooling also accelerated sleep onset, an effect that was not present in either younger or older participants without sleep complaints.

The failure of distal warming to affect sleep latency is in line with the results of our previous study on foot warming and sleep onset that reported an attenuated sensitivity of sleep propensity to foot warming in elderly[46]. Moreover, the normal diurnal time course of DST reaches values much lower than we have applied, and, hence, both our cool and warm DST manipulation might be interpreted as being warm. Whereas the subtle PST manipulations we applied were sufficient to affect SOL, we cannot exclude that applying DST manipulations in a slightly lower and wider range would be at least as adequate in affecting SOL.

Although the present study demonstrates a proof of principle, it remains to be addressed in a larger sample whether CBT and skin-temperature manipulations will be of clinical relevance in real-life situations. A reduction of 2.8 minutes (28%) in the SOL of elderly insomniacs, induced by the optimal combination of a warmer proximal skin in the absence of a warmer core, may not seem clinically relevant at first sight. However, it approximates the order of magnitude that can be obtained with hypnotic compounds. In adult and elderly insomniacs, comparable improvements have been reported with the administration of melatonin (eg, 17%)[38] or benzodiazepines (4.2 minutes on average in a meta-analysis)[24]. Moreover, control of skin temperature not only affects SOL, but also sleep depth[47]. Further work is necessary to evaluate the clinical efficacy of the manipulations in insomniacs with an objectively verifiable very long SOL. In the present sample of insomniacs, the daytime SOLs under strictly controlled laboratory conditions did not differ from those of elderly without sleep complaints, even though the insomniacs reported much increased sleep latencies in the diaries on their sleep at home. Such discrepancy has been reported previously for laboratory-based studies of nocturnal sleep[49] and for laboratory-based studies on SOL under constant-routine conditions comparable with our present study[22].

With respect to our investigation of an age-related decrease in awareness of changes in temperature in a sleeping environment, the results show that elderly insomniacs have a notable deficit in the detection of subtle changes in skin temperature —even though the temperature manipulations affected their skin temperatures and CBTs, as they did in younger and older subjects without sleep complaints. This attenuation of subjective thermosensitivity was much less in elderly without sleep complaints who, as compared with young subjects, only failed to detect the distal warming condition as being warmer than the distal cooling condition. Elderly insomniacs did not discriminate temperature changes associated with either PST or DST manipulations nor did they rate any of the manipulations of core and skin temperature as affecting subjective comfort. The only sensitivity that the elderly insomniacs preserved similar to young and elderly without sleep complaints was that they rated the core warming condition as warmer than the core cooling condition.

These findings are in agreement with those of previous studies reporting a decrease in the sensitivity of subjective thermal perception with age, especially for warm stimuli and particularly in the

distal parts[30,31]. Our results also show a reduced contribution of the CBT to the subjective experience of thermal comfort at advanced age. In elderly insomniacs, none of the applied temperature manipulations affected thermal comfort. This finding is in agreement with studies showing that elderly tolerate larger deviations in temperature before discomfort is noticed, at least when awake[9,18,26,54]

To our knowledge, this is the first experimental finding of a pronounced attenuation of subjective thermosensitivity in elderly insomniacs within the small range of normal bed temperatures. It should be noted that our results cannot be extrapolated to a wide range of temperatures, including those outside of the thermoneutral range; it cannot be concluded that insomniacs have a generalized failure to recognize temperature changes over a range of several degrees. Since subjective thermosensitivity is better preserved in elderly without sleep complaints, we consider the possibility that an attenuated thermosensitivity could contribute to suboptimal sleep in elderly subjects. A suboptimal temperature of the bed may go unnoticed even though it could adversely affect the capability to initiate or reinitiate sleep and adequate countermeasures may not be taken.

A limitation of the study is that the manipulation of CBT, DST, and PST was not completely independent. However, the combined manipulations still did account for most of the variability observed throughout the day in CBT and skin temperatures.

A surprising finding was that the average SOL of the elderly insomniacs did not differ from that of the elderly without sleep complaints, although the groups differed in reported SOL in the 2 weeks prior to the experiment, as shown in Table 1. It may be that, in our particular protocol, the elderly insomniacs benefited from increased daytime sleepiness due to the restricted sleep allowed during both nights preceding the experimental days. Moreover, the elderly insomniacs frequently reported that the environment of the sleep laboratory, with no sound, very low light levels, and a comfortable temperature, was rather ideal to them. Also, sleep onset occurred increasingly faster throughout the 2 experimental days, supporting the previous notion of Harris et al[23] that sleep onset can improve with frequently repeated training. Finally, the application of relatively high distal temperatures in both cool and warm condition might have optimized sleep-onset conditions and, thus, contributed to the elimination of possible differences in SOL between elderly groups.

Our findings may have implications for SOL in elderly and elderly insomniacs in everyday life. In both elderly and elderly insomniacs, warming the proximal skin resulted in a decrease in SOL. Hence, warming of the skin either by promoting peripheral heat loss or by subtle and feedback-controlled warming of the skin within the thermoneutral range provides a means to improve sleep onset in elderly who have trouble falling asleep in the beginning of the night or after nocturnal or early morning awakening. Since our results indicate that the sleep onset in elderly insomniacs is accelerated by CBT cooling, it is of importance that the applied skin-warming strategy

is not resulting in an influx of heat to the core of the body. Application of, for instance, an electric blanket throughout the night (ie, continuous heating) results in an increase in the CBT and disturbs nocturnal sleep[16,43.] Feedback control of the heating is clearly necessary to keep the microclimate in bed at such a level that the skin is warmed slightly only when skin-temperature measurement indicates that it falls below a critical value. Such procedure should be optimized to prevent an increase in CBT.

In conclusion, our results confirm that even mild changes in skin temperature, likely to occur in normal sleeping circumstances, can have an effect on sleep propensity in elderly subjects, just as we previously demonstrated in young adults[45]. The sensitivity of the sleep-regulating systems in the brain to small variations in skin temperature is thus preserved at advanced age. In contrast, the subjective appreciation of subtle induced changes in skin temperature is decreased in elderly subjects, especially so in insomniac elderly. As a consequence, elderly insomniacs may lie awake awaiting sleep onset without noticing that the bed microclimate might not be supportive for falling asleep and, consequently, without taking the appropriate behavioral action, e.g., a change of bedding or clothing, to optimize the bed microclimate. Especially elderly insomniacs may benefit from interventions that increase skin temperature, e.g., by passive body heating before sleep (resulting in an increased drop in CBT and an elevated skin temperature)[11,12,13,28] or by controlled warming of the beds microclimate. It is essential that this warming should not be timed too close to bedtime because elevated body temperature does not favor sleep[50] and, only after about 2 hours after body warming, the CBT becomes lower than without warming while skin temperature is still elevated[52].

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DAYTIME VIGILANCE

Chapter 6

Time-on-task impairment of psychomotor vigilance is affected by mild skin warming and changes with aging and insomnia

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Summary

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

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

Setting: Sleep laboratory of the Netherlands Institute for Neuroscience.

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

Measurements and Results: During the 7-minute PVTs, response speed typically declined with increasing time-on-task. Proximal skin warming by only ±0.6˚C accelerated this decline by 67% ($P = 0.05$) in young adults and by 50% ($P<0.05$) in elderly subjects. In elderly insomniacs, proximal warming slowed down the mean response speed already from the onset of the task (3%, $P<0.001$). Response speed tended to decrease with age ($P<0.10$), reaching significance only in elderly insomniacs ($P<0.05$). Speed decrements occurred mostly towards the end of the time-on-task in young adults; earlier and more gradually in elderly without sleep complaints; and very early and in a pronounced fashion in insomniacs. Interestingly, the worsening by warming followed the time pattern already present within each group.

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

1. Introduction

There is a close relationship between the circadian rhythm of core body temperature (CBT) and the daily variation in vigilance, as shown by Kleitman[16]. Vigilance is optimal during the circadian phase of increased CBT[6,15,22,39,40]. Under controlled conditions, the rhythm in CBT results to a large extent from the rhythm in skin blood flow, which determines skin temperature, and the resulting heat transfer gradient from the body to the environment. Skin temperature thus shows a circadian rhythm that is reciprocal to the CBT rhythm, i.e., low during the habitual wake period[20,32,35], although a reversal of the proximal skin temperature has been found under specific conditions[17]. We have proposed that these intrinsic changes in both CBT and skin temperature could modulate neuronal activity in vigilance regulating brain areas[33]. A likely brain structure linking vigilance with core body and skin temperature is the preoptic area/anterior hypothalamus (POAH), the major thermo-regulatory center of the mammalian brain as well as a key structure in vigilance state control. Both local brain temperature and skin temperature modulate the firing rate of thermo-sensitive neurons in the POAH and other brain areas involved in vigilance regulation[4,33].

Support for a causal contribution of skin, but not core, temperature to vigilance regulation has been provided by a strictly controlled laboratory study, demonstrating accelerated sleep onset with very subtle warming of the skin in a comfortable and thermoneutral range (Chapter 4, this thesis)[28]. The simultaneous and independent induction of changes in core body temperature did not affect sleep propensity. These findings suggest that the previously reported positive phase relation of the circadian rhythm in core body temperature and the circadian rhythm in vigilance[6,15,22,39,40] might also be an indirect reflection of a reciprocal phase relation of the circadian rhythm in skin temperature and the circadian rhythm in vigilance.

A limited number of experimental studies have investigated the effect of skin tmperature manipulation on vigilance. These studies manipulated ambient temperature to induce skin temperatures beyond the range of the normal diurnal fluctuations in skin and core body temperature. A recent meta-analysis on the effects of temperature manipulation on task performance indicates an inverted U-shape, not surprisingly demonstrating that both high and low temperatures that activate thermoregulatory responses adversely affect performance[26.] Thus, both heat and cold stress negatively affected sustained vigilance[14,23]. This makes sense from the point of view that the brain needs to readdress its resources from optimal task performance towards thermal stress defense. These findings cannot be generalized to the normal diurnal range of in skin temperature. Consequently, no conclusion can be drawn regarding a causal contribution of the circadian rhythm in skin temperature to the circadian rhythm in vigilance.

The aim of the present study was to investigate whether the induction of changes in skin and core body temperature within the comfortable range of normal diurnal rhythm could causally affect

vigilance. Our recently developed experimental set-up[28] allowed us to induce subtle changes in core body temperature (+ and - 0.1˚C) and proximal and distal skin temperature (+ and - 0.3˚C) in a balanced protocol. As the dependent variable, we obtained sustained response speed as measured with the psychomotor vigilance task (PVT)[10]. We investigated the effect of core body and skin temperature manipulations on psychomotor vigilance not only in healthy young adults, but also in elderly without sleep problems and elderly who complained of poor sleep. Elderly subjects are of particular interest because (1) thermosensitivity decreases with aging[36]; (2) aging slows the response speed during a psychomotor vigilance task[1,2,24,25]; (3) elderly are at a higher risk of chronic poor sleep[34], and acute sleep restriction affects vigilance—although less so in well sleeping elderly subjects than in young adults[1,2,24,25].

2. Materials & Methods

2.1. Subjects

Eight healthy young adults free from sleep complaints (21-39 years old; mean±s.e.m.: 27.0±2.4 years; 4 males), 8 healthy elderly free from sleep complaints (56-80 years old; 65.8 ± 2.8 years; 4 males), and 8 poorly sleeping healthy elderly (51-66 years old; 59.1 ± 1.9 years; 4 males) participated with informed consent. The protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam. All participants were free of medication known to affect thermoregulation, sleep or the circadian system, cardiovascular medication, and psychotropic medication. One female used oral contraceptives. Subjective sleep quality and complaints were measured using a Dutch adaptation[29] of the 75-item Sleep Disorders Questionnaire (SDQ)[11] and the Pittsburgh Sleep Quality Index (PSQI)[5]. Poor sleepers were defined by a PSQI score > 5 and an SDQ-Insomnia score >2.5. None of the subjects scored higher than the cutoff score of 3 on the SDQ subscales Narcolepsy, Apnea, Restless legs, and Psychiatry. In the young adult group, females participated between day 4 and day 12 of the menstrual cycle (midfollicular phase or pseudofollicular phase). All elderly females were postmenopausal.

2.2. Design and Experimental Procedures

One week before the experiment, subjects visited the laboratory for an introductory session and habituation to the procedures. The vigilance task was trained for 3 times to minimize possible subsequent learning effects[9]. Participants were instructed to refrain from caffeine, alcohol, and tobacco for 8 hours before arriving at the sleep laboratory. Subjects were interviewed to verify compliance with the instructions. The night before each of the 2 experimental days, the subjects reported to the sleep laboratory at 22:00, when they were prepared for polysomnography and

fitted with a comfortable stretch knit fabric thermosuit for skin temperature manipulation. From midnight until 06:00, lights were turned off and subjects were allowed to sleep. They were awakened at 06:00, so sleep duration was restricted to a maximum of 6 hours.

The experiment consisted of measuring psychomotor vigilance 18 times for each subject over 2 experimental days, while manipulating CBT with food and drinks and skin temperature with a thermosuit. An experimental day started at 06:30 and consisted of a modified constant-routine protocol[21,7] under dim light (<10 Lux) conditions and a fixed body position schedule. Both experimental days consisted of 9 consecutive blocks of 1.5 hours each.

Each block was conducted as follows: The subjects were required to leave the bed and walk 5 meters to use the bathroom if needed. At minute 10 of each block, skin temperature manipulation was started and subjects were seated in a bed in semi-supine position, and were served a snack and a drink to consume in approximately 10 minutes. Subsequently a self-paced computerized neuropsychological task battery was completed. This task battery included assessment of psychomotor vigilance, as described below in detail. At 60 minutes, the bed was set in supine position, the lights switched off, and the participants were asked to try to sleep. Maximum lights-off time was 30 minutes, completing the 90 minutes of each block. Results of the effects of temperature manipulation on sleep latency in healthy young adults have been reported elsewhere (Chapter 4, this thesis)[28] and the results in the elderly are in preparation.

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

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

was subjected to core cooling, proximal warming, and distal skin cooling during the second block on day 2.

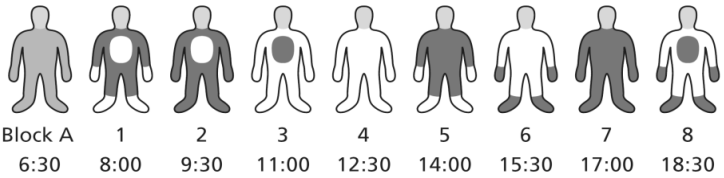

Fig. 1. Schematic view of temperature manipulations within a day within one subject. On the second day, temperature manipulation combinations were the opposite of those of the first day. Block A = habituation block. White= Cool, Dark grey = Warm.

2.3. Temperature Manipulations and Measurement

Temperature manipulations and measurements have been described in detail previously (see Chapter 4, this thesis)[28]. In brief, core body temperature was manipulated by means of 200 ml hot (heated to 80°C, served 2 minutes later) or cold (0°C, crushed ice) tea (4.25 Kcal), (Iced Tea Mix [*Diet Decaffeinated Lemon*], Lipton, Englewood Cliffs, NJ, USA) together with an isocaloric hot or cold snack of the subject's choice (200 Kcal). Skin temperatures (T_{sk}) were manipulated using a thermosuit (Coretech Cool Tube Suit, Med-Eng Systems Inc., Ottawa, Canada). It was connected to two computer-controlled bath-circulation thermostats (K6KP, Lauda, Lauda-Köningshofen, Germany), one for distal and one for proximal skin temperature manipulation. The water in the bath was 33°C in the cool condition and 37°C in the warm condition, resulting in temperatures of approximately 31°C and 34°C measured at the tubes just before entering the thermosuit.

This range of skin temperature manipulations was chosen to be comfortable and not trigger major thermoregulatory responses. Ingestion of food and drinks to manipulate core body temperature manipulation and skin temperature manipulations were started about 25 minutes before the start of the PVT. Subjects were well habituated to the thermosuits and skin temperature manipulation; during the prior night they had slept in the suits, while being subjected to slow temperature variations within the same range (reported elsewhere, see chapter 8, this thesis).

Body temperature was obtained using 8 thermistors (P-8432, ICBT, Tokyo, Japan). Core body temperature (T_{re}) was measured using a rectal thermistor. Proximal skin temperature was measured at 3 places: right mid-thigh on the musculus rectus femoris, abdomen (1 cm above the navel), and the right infraclavicular area. Distal skin temperature was measured at 4 points: thenar area at the palmar sites of the left and right hand and medial metatarsal area at the plantar sites of the left and right foot. Average distal skin temperature (T_{dist}) and a weighted average for proximal skin temperature (T_{prox}) were calculated as described previously[28]. Temperature data were averaged over 20-minute intervals surrounding the PVT assessments and used for further analyses. As a

final check, when a single averaged data point differed more than 2 standard deviations from the other 20-minute averages during that day, the non-averaged data were once more checked for artifacts and corrected or removed when needed.

2.4. Vigilance Measurement

Vigilance was assessed using a 7-minute version of the Psychomotor Vigilance Task (PVT)[10] that can be regarded as a viable alternative to the standard 10-minute PVT test[19]. During the task, subjects focused on a blank box in the middle of a computer screen. At random intervals, a millisecond counter started to scroll, and subjects had to press a key to stop the counter as quickly as possible. After pressing the key, the counter displayed the achieved reaction time (RT, in milliseconds) for 1 second, providing the subject with feedback on performance. Interstimulus intervals ranged randomly from 2 to 10 seconds, and the task lasted 7 minutes. Response speed, calculated as reciprocal RT (RRT = 1000/RT) was averaged per minute. The vigilance measure of interest was the characteristic decline of response speed with increasing time-on-task. This decline was modelled using up to second order regression fits over the subsequent one-minute means, starting at the second minute. The first minute of data was excluded from analyses because many subjects showed unrepresentative long reaction times at the start of the PVT (see also Figure 2).

2.5. Statistical Analysis

To determine the effects of skin and core body temperature manipulation on body temperatures and on vigilance, hierarchical regression analysis was applied (also known as multilevel or random coefficient analysis) using the MLwiN software package (Centre for Multilevel Modelling, Institute of Education, London, UK). The regression takes into account the multileveled interdependency of the data points inherent to the hierarchical structure of the design[30].

It was first evaluated how core body and skin temperatures (T_{re}, Tprox, and Tdist) were affected by the manipulations. To do so, CBT, PST, and DST were dummy coded as dichotomous predictor variables, with 0 reflecting the cool manipulation and 1 reflecting the warm manipulation. A 3-level regression model was fitted (the sequential 20-minute average temperatures in each block (*i*), nested within days (*j*), nested within subjects (*k*). Additional models were run to test for carryover effects of the temperature manipulations, by adding temperature manipulations of the preceding block (pCBT, pPST, and pDST) to the regression models.

Subsequently, 4-level regression models were applied to PVT response speed: the sequential one-minute averaged response speeds (*i*), nested within measurements (blocks, (*j*)), nested within each day (*k*), nested within subjects (*l*). The final regression model included the best of linear and nonlinear approximations for the rate of decline in response speed (linear, second order, and

square root, i.e., Minutes, Minutes^2, and √Minutes). Two series of regression analyses were run. The first series evaluated the effect of the dummy coded (factorial) temperature manipulations on response speed and its rate of decline with increasing time-on-task. The second series evaluated the relation of the actual momentary body temperatures to response speed.

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

3. Results

3.1. Induced temperatures

The effects of the temperature manipulations on core body and skin temperatures for all groups are shown in Table 1 and Table 2. Note that the values reflect the temperatures during task performance and therefore differ slightly from the previously reported temperatures after completion of the task, just prior to sleep onset latency determination[17].

T_{re} was significantly affected by the core body temperature manipulation, with 0.25˚C, 0.20˚C, and 0.18˚C higher T_{re} in the CBT+ condition, compared with the CBT- condition for young adults, elderly subjects, and elderly insomniacs, respectively. T_{re} also showed modulation over the time of day, accounting for respectively 20%, 47%, and 37% of the variance. The core body temperature manipulation accounted for another 51%, 32%, and 35% of the residual variance in Tre. The addition of preceding temperature manipulations to test for carryover effects accounted for an additional 14%, 24%, and 20% of the variance, respectively.

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

residual variance in $T_{prox.}$ The addition of preceding temperature manipulations to test for carryover effects accounted for an additional 1%, 7%, and 1% of the variance, respectively.

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

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

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

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

Table 2—Multilevel estimates of effects (± s.e.m.) of manipulations and time on body temperatures. Regression model: $T_{ijk} = ß_{0ijk} + ß_1*Hour_{ijk} + ß_2*Hour2_{ijk} + ß_3*\sqrt{Hour}_{ijk} + ß_4*CBT_{ijk} + ß_5*PST_{ijk} + ß_6*DST_{ijk}$

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

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

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

3.2. Effect of Temperature Manipulation on Vigilance

The first minute of the PVT performance was characterized by long reaction times in both groups of elderly, suggesting some difficulty initiating the right mind-set for the task (see Figure 2). Analyses were therefore limited to the minutes 2 to 7. There was a typical worsening, i.e., a decline in response speed (RRT), with increasing time-on-task (see Table 3 and Figure 2). Proximal warming accelerated this decline by 67% in young adults (PST x $Minute^2$, P = 0.05) and by 50% in the elderly

subjects (PST x Minute, P<0.05). In the elderly insomniacs, proximal warming lowered the overall response speed by 3%, independent of time-on-task (PST, P<0.001). There was no significant difference in response speed between the cool and warm core body and distal skin temperature manipulations in any group.

Since the effects of the temperature manipulations were not always restricted to the body sites aimed for, and some carryover effects of previous temperature manipulations occurred, we also analyzed the relation of the actually measured temperatures T_{re}, T_{prox}, and T_{dist} (regressor variables) to response speed. In young adults, a higher T_{prox} was marginally associated with a faster decline in response speed with increasing time-on-task (T_{prox} x Minute2, P = 0.05). In the elderly insomniacs a higher T_{prox} also tended to be associated with a lower response speed, but now independent of time-on-task (T_{prox}, P<0.10). For these both groups, the model best fitting the data was comparable to the aforementioned models with dichotomous manipulation levels. In the elderly subjects, lower T_{re} was associated with lower response speed independent of time-on-task (T_{re}, P<0.05).

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

3.3. Effect of Age and Insomnia on Vigilance

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

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

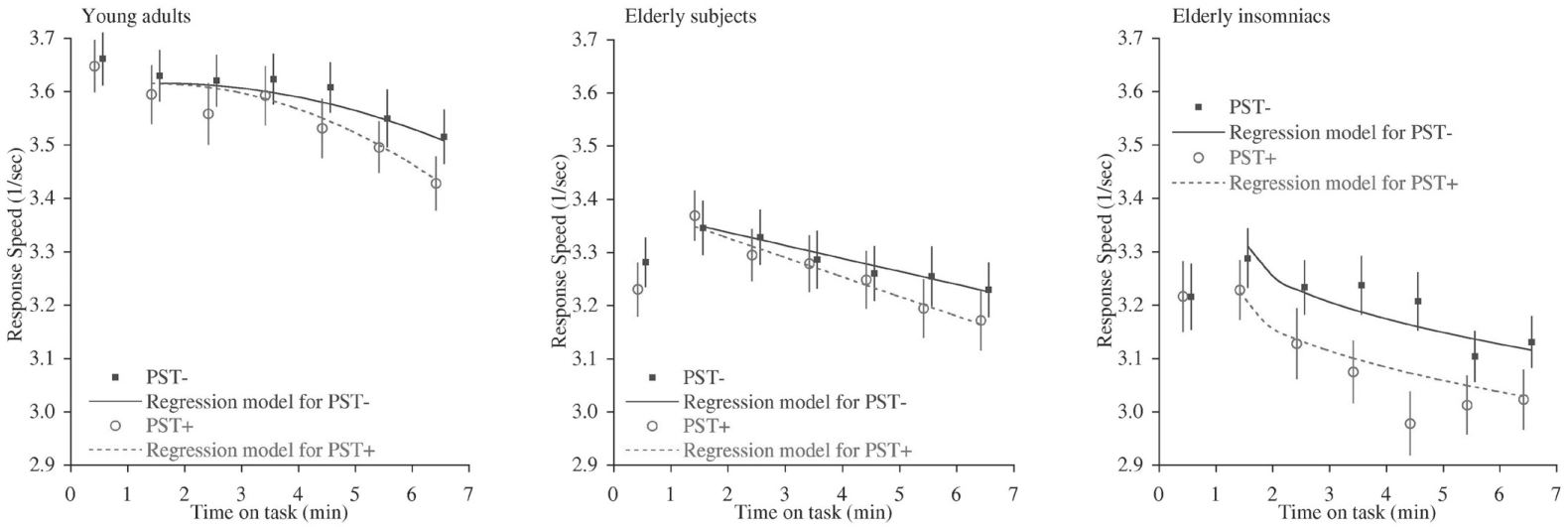

Figure 2—Means (± standard error) and regression models of response speed over the 7 subsequent minutes of PVT performance during proximal cooling (closed squares, solid line) and warming (open circles, dashed line) for young adults (left panel), elderly without sleeping problems (middle panel), and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

Table 3—Multilevel estimates of effects (± s.e.m.) of manipulations, time and repeats on responce speed of the PVT

	Young adults without sleep complaints	Elderly without sleep complaints	Elderly Insomniacs
Intercept	3.61±0.10[c]	3.35±0.12[c]	3.31±0.13[c]
√Repeats(c)	0.05±0.02[a]		
Minute		-0.025±0.005[c]	
Minute^2	-0.004±0.001[c]		
√Minute			-0.087±0.010[c]
PST			-0.087±0.026[c]
PST x Minute		-0.012±0.006[a]	
PST x Minute^2	-0.003±0.002[a]		

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

4. Discussion

Psychomotor vigilance is partly determined by the endogenous circadian clock[6,15,22,39,40], but the mechanisms involved in this circadian modulation are not known. We investigated whether subtle changes in core body and skin temperatures, mimicking those that are naturally occurring during the circadian cycle, could contribute to changes in psychomotor vigilance. In order to prevent cause-and-effect interpretation difficulties inherent to correlations, we chose to experimentally manipulate core body and skin temperatures and observe the effects on PVT performance. Our study is the first of its kind to study relative changes in vigilance under conditions of simultaneously and differentially controlled core body and skin temperatures. In young and elderly subjects without sleep complaints, the decline in response speed with increasing time-on-task became stronger with slight warming of the proximal skin area. In elderly insomniacs, the overall response speed decreased with such subtle proximal skin warming. Since all manipulations induced changes in the temperature range normally seen in everyday life, the circadian modulation of these temperatures could indeed contribute to the circadian modulation in vigilance. During the circadian phase of habitual nocturnal sleep there is a parallel increase in vigilance impairment[31] and average or proximal skin temperature[32,20], although the proximal skin temperature profile may reverse under colder laboratory conditions[17], as discussed recently[35].

A mechanism that may be involved is that skin warming has been shown to increase neuronal activity in the preoptic and anterior hypothalamic area in rodents[4] and humans[13], comprising areas critically involved in both sleep and arousal regulation. Such a mechanism is also supported by our recent finding that subtle skin warming accelerates sleep onset in young healthy adults, despite being experienced as less comfortable[28]. Our studies provide indirect support for a modulatory role of skin temperature on brain areas involved in the regulation of sleep propensity and vigilance[33]. Drummond and colleagues[12] reported that slower reaction times in the PVT task were associated with greater activity in a "default mode network"[27] that consists of frontal and posterior midline regions. Our findings suggest that the activity in this network is sensitive to skin temperature, possibly indirectly through a signaling pathway from the preoptic and anterior hypothalamic area to this network.

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

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

In the elderly good sleepers, a significant association emerged between vigilance performance and rectal temperature. This is compatible with previous reports on a worsening of vigilance during the circadian phase of lowered CBT[6,15,22,39,40].

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

The range in *core* temperatures covered throughout our manipulations should have been sufficient to alter vigilance, if vigilance was indeed causally affected by the normal circadian variation in core body temperature. The difference of about 0.2˚C on average in T_{re} we established between the warm and the cool conditions is about half of the reported circadian amplitude in core body temperature (0.44˚C) under controlled conditions[17]. The normal diurnal time course of distal skin temperature reaches values much lower than we have applied. During everyday life, distal skin temperature reaches temperatures of several degrees below the values measured at the proximal

skin[38]. Also under strictly controlled laboratory conditions, the distal 24-hour minimum, maximum, and 24-hour mean skin temperatures were lower than their proximal equivalents[17]. The averaged induced T_{prox} and T_{dist} in our study were however comparable to each other (see Table 1). We may thus have been manipulating distal skin temperature too close to the ceiling of its normal diurnal pattern, hence we cannot exclude that applying distal skin temperature manipulations in a slightly lower range could be at least as effective in modulating vigilance.

In order to investigate whether the changes in subjective thermal comfort and thermal sensation might have contributed to the findings, we post hoc added both variables that were included in the neuropsychological test battery[17] to the optimal models. Neither subjective thermal sensation nor thermal comfort was associated with response speed in any of the groups (thermal sensation: $P = 0.69$, $P = 0.26$, and $P = 0.67$ and thermal comfort: $P = 0.78$, $P = 0.90$, and $P = 0.51$ for young adults, elderly without sleeping problems, and elderly insomniacs, respectively). Hence the performance impairment is a direct effect of the change in temperature rather than an effect of the concurrent change in subjective thermal comfort or thermal sensation. We also performed a post hoc analysis to test whether the polysomnographically assessed sleep duration or efficiency during the previous night might have been involved in the group differences in response speed. No significant contribution to response speed could be demonstrated (sleep duration: $P = 0.41$, sleep efficiency: $P = 0.36$), indicating that the group differences cannot be attributed to the sleep pattern of the nights directly preceding the vigilance assessment days.

Our data also revealed a number of age-related and insomnia-related changes in performance on the PVT under strictly controlled and balanced conditions. Of note, elderly subjects who were good sleepers responded only marginally less fast than young adults ($P<0.10$). Only if elderly were poor sleepers, their response speed became significantly worse than that of young adults ($P<0.05$). Whereas previous studies have also reported PVT response speed slowing with aging[1,3], our data suggest that a part of the "age-related cognitive slowing" may in fact be due to sleep changes inherent to aging. The fact that only elderly insomniacs showed a robust worsening of PVT response speed supports the possible involvement of what one could call "poor sleep-related cognitive slowing" in "age-related cognitive slowing." On the other hand, it may be that elderly good sleepers are not representative for the cognitive alterations present in the aged population. Whereas some previous studies on the effects of aging on vigilance may have been biased by selecting well-sleeping elderly only, we purposely included separate groups of well-sleeping and poorly-sleeping elderly, thus allowing us to separate sleep-related changes from changes associated with aging.

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

First, whereas young adults show a slowing of speed only starting halfway the 7 minutes time-on-task, the slowing was linear in elderly subjects and occurred at the beginning of the task in elderly insomniacs. Thus, aging results in an earlier onset and more gradual decline in response speed with increasing time-on-task. Insomnia, on the other hand, results in a near maximal drop in response speed by the third minute, indicating that insomnia specifically affects the cognitive resource "reserve" that is required to maintain a highly vigilant state for a prolonged period of time. This specific defect associated with insomnia was mirrored also in the effects of proximal warming on the response speed. Whereas the effect of proximal warming developed slowly with increasing time-on-task in young and elderly subjects without sleep complaints, the effect was present at the onset of the task in the elderly insomniacs. It is remarkable that the group differences in the profile of speed decline with increasing time-on-task-related were mirrored in the worsening with mild warming: only late in young adults, gradual in elderly subjects and at onset in elderly insomniacs. The fact that the group differences in the profile of temperature effect were exactly similar to the overall time-on-task effects within the groups provides strong support for the robustness of the group differences in time-on-task effects. Interestingly, the gradual change from (1) a performance decline starting only halfway the task (young adults), to (2) a linear performance decline starting soon after onset of the task (elderly without sleep complaints), to (3) a performance decline that is very pronounced already soon after onset of the task – closely resembles previously reported effects of increasing sleep propensity on time-on-task profiles[8].

Second, we observed marked group differences in the mean response time within the first minute of the PVT. Whereas the young adults showed the fastest responses during the first minute, the elderly subjects reached their fastest response speed only by the second minute. The data of Kribbs and Dinges[18] also clearly show a delay of the fastest response in adults with obstructive sleep apnea. The initial poor performance indicates that elderly experience some difficulty initiating the right mind-set for the task. The finding is compatible with the fact that aging affects executive functioning in general, and task switching in particular[37]. Our novel finding that this age effect is also present in repeated PVT assessments has consequences for the use and interpretation of its most commonly calculated outcome measures (median RT, mean of the fastest 10% RT, mean of the slowest 10% reciprocal RTs, SD of the RT, and number of lapses [RT > 500 ms]) when comparing different age groups. None of these measures adequately describe the typical decline in response speed with increasing time-on-task, in which we found the most interesting age- and insomnia- related changes. We favor the opinion of Kribbs and Dinges[18] that "analysis of the overall mean response often does not truly reflect the entire impairment process and, in fact, may sometimes obscure actual performance impairment." We suggest others include an examination of time-on-task effects before aggregating data. In age-related studies on such time-on-task effects, the first minute of PVT response data may be excluded.

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

In conclusion, our results add to the significance of previous correlational studies[39] on the relation between body temperature and vigilance by now demonstrating for the first time that an experimentally induced subtle increase in skin temperature may in fact *cause* a decrease in vigilance performance. The findings are compatible with the model we have previously put forward, stating that the diurnal modulation of skin temperature should be regarded not only as an output signal of the circadian timing system but also as an input signal modulating vigilance regulating brain areas[33]. We also demonstrated that a minute-by-minute analysis of the PVT helps to reveal and disentangle age- and insomnia- related changes in vigilance regulation.

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

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Chapter 7

Manipulation of core body and skin temperature improves vigilance and maintenance of wakefulness in narcolepsy

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Summary

Context: Impaired vigilance and sleepiness are two major daily complaints of patients with narcolepsy. We previously showed their sleepiness to be correlated to an abnormally regulated skin temperature, i.e., increased distal skin temperature compared with proximal skin temperature.

Objective: Our goal was to investigate a possible causal contribution of skin temperature disturbances to impairments in the ability to maintain vigilance and wakefulness in narcolepsy.

Design: In a modified constant routine protocol, the Psychomotor Vigilance Task (PVT) and the Maintenance of Wakefulness Test (MWT) were repeatedly assessed. Meanwhile, skin and core body temperatures were mildly manipulated within the thermoneutral range of the normal diurnal rhythm using a thermosuit and hot or cold food and drinks.

Setting: Tertiary narcolepsy referral center in a university hospital.

Patients or Other participants: Eight patients (5 males) diagnosed with narcolepsy with cataplexy according to the ICSD-2 criteria (mean age ± SD: 28.6 ± 6.4, range 18-35 years).

Intervention(s): None

Main Outcome Measure(s): MWT sleep latency and PVT response speed.

Results: Compared to core cooling, core warming attenuated the typical decline in PVT response speed with increasing time-on-task by 25% ($P = 0.02$). Compared to distal skin warming, distal skin cooling increased the time that the patients were able to maintain wakefulness by 24% (distal warming: 1.88 min. vs. distal cooling: 2.34 min.; $P < 0.01$).

Conclusions: Core body and skin temperatures causally affect vigilance and sleepiness in narcolepsy. This could lead to future practical applications.

1. Introduction

Narcolepsy is a syndrome characterized by excessive daytime sleepiness (EDS) and cataplexy[17]. Although sleepiness in narcolepsy is generally described as inadvertently falling asleep, a perhaps equally important aspect is impaired performance in the waking state due to disturbed vigilance[6,23].

In healthy controls, both sleepiness and vigilance show a relationship with core body temperature and skin temperature. When core body temperature is high during daytime, skin temperature is relatively low, a combination that is correlated to optimal vigilance[3,8,9,16,27,28]. In contrast, core body temperature is low at night time, when skin temperature is relatively high, and this combination is correlated to optimal sleep[3,8,9,16,27,28]. Skin temperature thus shows a circadian rhythm that is the inverse to the core body temperature rhythm[13]. Furthermore, a relatively high temperature of the distal skin (hands and feet) compared to the temperature of the proximal skin has been shown to be related to the process of falling asleep: a higher distal-to-proximal gradient (DPG) promotes sleep onset[10]. A causal contribution of core body temperature and skin temperature to vigilance and sleepiness has been shown to exist in healthy subjects, in whom mild warming of the proximal skin leads to an accelerated decline in vigilance and to an earlier onset on sleep (Chapter 4 and Chapter 6, this thesis)[20,21]. It has been proposed that changes in both core body temperature and skin temperature modulate neuronal activity of thermosensitive neurons in brain areas that regulate vigilance and sleepiness[13,24].

In a previous study, we reported an altered pattern of skin temperature regulation in narcolepsy[7]. Narcoleptic subjects showed a combination of higher distal skin temperatures and lower proximal skin temperatures, which in healthy subjects is associated with the process of falling asleep[10]. We suggested that this pattern may even contribute to sleepiness[7].

In this paper, we investigate whether direct manipulations of core body and skin temperature induce corresponding changes in the degree of sleepiness and vigilance in narcolepsy. We measured vigilance and the ability to maintain wakefulness in narcoleptic subjects while subtly manipulating skin and core body temperature within the thermoneutral range of their normal diurnal rhythm in a modified constant routine protocol.

2. Materials & Methods

2.1. Subjects

Eight narcoleptic subjects (5 males, 18-35 years of age; mean ± SD: 28.6 ± 6.4 years) participated with informed consent. All suffered from excessive daytime sleepiness (EDS) and typical cataplexy according to the ICSD-2 criteria for narcolepsy with cataplexy[1]. The protocol was approved by the local Medical Ethics Committee. All subjects were free of medication, except for one female sub-

ject using oral contraceptives. Females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase). Subjects were excluded when they suffered from conditions that could influence their peripheral vascular bed, such as the metabolic syndrome, diabetes mellitus, thyroid function disorder, and cardiovascular pathological conditions.

2.2. Design

A previously described design was used (see Chapter 4, this thesis)[21], that consisted of a modified constant routine protocol[4,14] over 2 experimental days during which vigilance was measured using the Psychomotor Vigilance Task (PVT) and sleepiness was measured using the Maintenance of Wakefulness Test (MWT). Meanwhile, proximal and distal skin temperature were subtly manipulated using a thermosuit, while core body temperature was manipulated using hot or cold food and drinks (see Figure 1).

2.2.1. Constant Routine protocol

Subjects first visited the sleep laboratory to get familiar with the test environment and to practise the PVT. One week later, the actual experiment was performed. Subjects refrained from caffeine, alcohol, and tobacco for 8 hours before reporting at the sleep laboratory at 22:00, where they were prepared for polysomnography and fitted with the thermosuit. At midnight, lights were turned off and subjects were allowed to sleep until 06:00. The experiment started at 06:30 under dim-light conditions (10 lux) with a fixed body position (semi-supine) and consisted of 9 consecutive blocks with durations of 1.5 hours each (described below). At the end of the first day subjects went home and returned to the laboratory the next evening for a repeated assessment according to the same procedure, but with a different temperature manipulation scheme (see Figure 1).

2.2.2. Block Design

Each block was similar: It started by having the subjects get out of bed and walk 5 meters, using the bathroom if needed. Ten minutes after the start of each block, skin temperature manipulation was started and subjects were served a snack and a drink to consume in approximately 10 min. Subsequently a self-paced computerized neuropsychological task battery was completed, including the PVT (see below) and assessment of thermal comfort and temperature sensation, with the use of 100-mm visual analogue scales ranging from uncomfortable to comfortable and from cool to warm. During these tests a researcher was present to keep subjects awake if necessary. After 60 min, the researcher left the room and subjects were asked to remain awake while lying quietly[15]. If sleep was attained (see the sleep scoring subsection)[22] subjects were awakened and kept awake for the remaining part of the MWT time of 30 min.

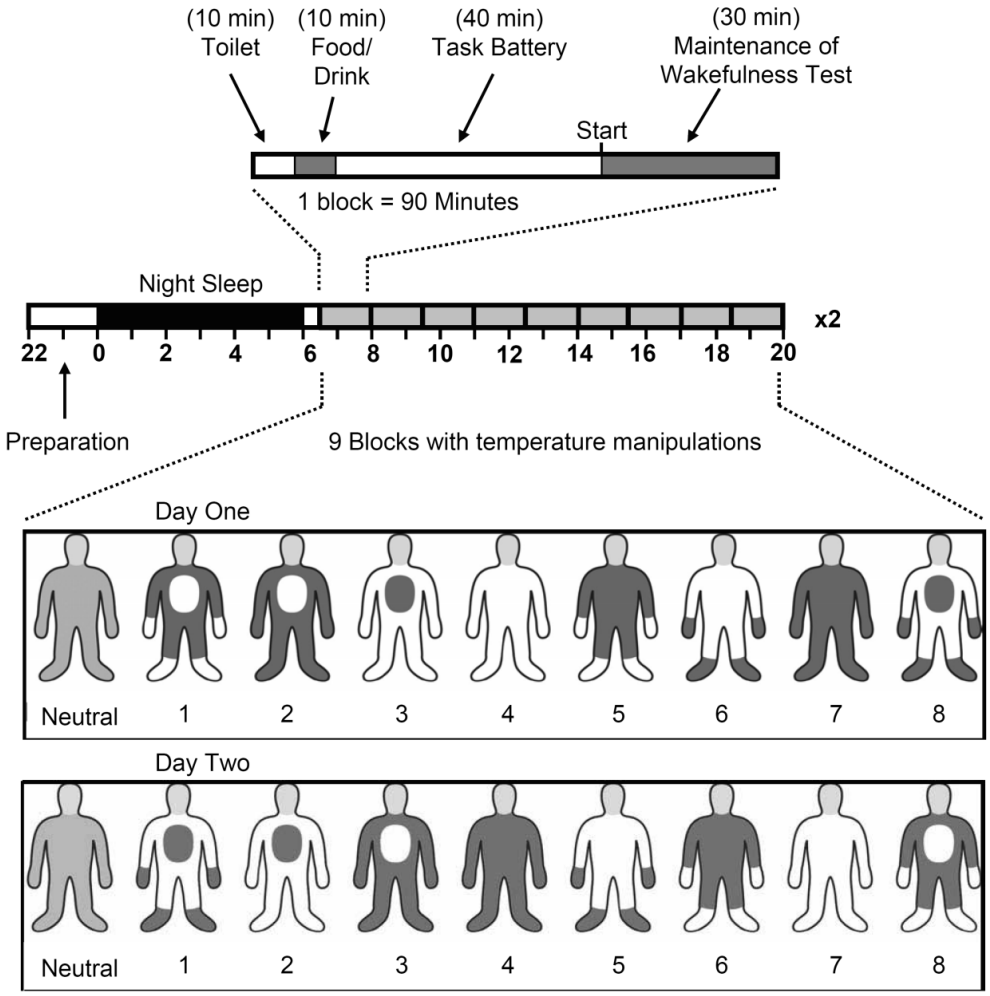

Fig. 1. Study Design. This figure shows a schematic overview of the two experimental days. Each day, subjects entered the lab at 22:00 and were prepared for temperature manipulation and sleep registration. After 6 hours of night sleep, a modified constant routine protocol was started with 9 identical 90 minute blocks. During each block, subjects walked to the toilet (10 min), consumed hot or cold food and drinks (10 min), performed tests on a computerized task battery (including PVT, 40 min), and underwent a MWT (30 min). Core body and proximal and distal skin manipulation occurred during every block. Manipulation patterns are shown in the human outlines with white representing cooling and dark grey representing warming. On the second day, the protocol was identical, but temperature manipulations were exactly the opposite of day one.

2.3. Temperature Manipulations

2.3.1. Manipulation Sequence

Skin and core body temperature were manipulated differentially in every block according to a method described before (see Chapter 4, this thesis)[21]. In short, the 2x2x2 design consisted of 3 body sites of manipulation: core body (CB), proximal skin (PS), and distal skin (DS). At each, temperature could be increased or decreased (T+ and T-), resulting in 8 combinations (CBT+, CBT-, PST+, PST-, DST+, DST-). All 8 were tested in one day (Figure 1). The sequence differed between subjects in order to balance the protocol, such that over all subjects, every manipulation combination was given once in each of the 8 blocks, and every transition from one to any other combination occurred no more than once for each time of day. To balance for circadian effects, the second experimental day temperature manipulation combinations were the inverse of those of the first day (for example: day 1, block 1, CBT+, PST-, DST-; day 2, block 1, CBT-, PST+,DST+, figure 1).

2.3.2. Manipulation Method

Core body temperature was manipulated by means of 200 mL hot (heated to 80°C, served 2 min later) or cold (0°C, crushed ice) diet decaffeinated tea (4.25 Kcal, Diet Decaffeinated Iced Tea Mix, Lipton, Englewood Cliffs, USA) together with a hot or cold snack of subjects' choice (200 Kcal). Skin temperature was manipulated using a full-body thermosuit (Coretech Cool tube suit, Med-Eng Systems Inc., Ottawa, Canada) connected to two computer-controlled circulation thermostat baths (K6KP, Lauda, Lauda-Königshofen, Germany). During the first 20 min of each block, the water in the thermostat baths changed to the desired temperature, while the bath temperature was kept constant for the remaining 70 min of the block. The water in the tubes was ~31°C and ~34°C just before entering the thermosuit. This range of skin temperature was chosen to avoid major thermoregulatory responses.

2.4. Body Temperature Recordings

Core body temperature was measured using a rectal thermistor. *Proximal skin temperature* was measured at 3 places: right on the middle of the frontal aspect of the thigh, abdomen (1 cm above the navel), and the right infraclavicular area. *Distal skin temperature* was measured at four points: thenar eminence of the left and right hand and medial plantar aspect of the left and right foot. Temperature was measured using thermistors (P-8432, ICBT, Tokyo, Japan) and digitally recorded at 1 Hz (Embla A10 and Somnologica software, Flaga, Reykjavik, Iceland). An automated procedure was applied to remove occasional artifacts and to calculate average distal and proximal skin temperature by a weighted average as described before (see Chapter 4, this thesis)[21]. Tempera-

ture data were averaged over 20-min intervals surrounding the PVT assessments and over the 5 min before the start of the sleep latency test (Figure 1).

2.5. Sleep Scoring

Polysomnographic sleep recordings were performed according to standard procedures[22]. Sleep onset was determined online during the experiment according to standard criteria, defined as 3 consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep[15]. Sleep-onset latency was defined as the time between the start of the MWT and sleep onset. If the subject did not sleep during the 30 min, sleep-onset latency was scored as 30 min. One data point could not be included in the analysis due to loss of EEG data.

2.6. Vigilance

Vigilance was assessed using a 7-min version of the psychomotor vigilance test (PVT)[5,12]. Subjects focused on a blank rectangle in the middle of a computer screen. At random intervals (2-10 sec), a reaction time counter started, shown as the number of milliseconds since start, in the rectangle. Subjects had to press a key to stop it as quickly as possible. The obtained reaction time (RT) count was shown for 1 second, providing performance feedback. Because the distribution of reaction times deviates from normal, PVT results are as a standard reported as response speed, i.e., reciprocal RT (RRT=1000/RT). In order to quantify the typical performance decline with increasing time-on-task response speed, averages were calculated per minute. The vigilance measure of interest was the decline of response speed with increasing time-on-task.

2.7. Statistical Analysis

To determine the effects of skin and core temperature manipulations on actual measured temperatures (core body, proximal skin, and distal skin) and on PVT performance and subjective comfort, hierarchical regression analysis was applied using MLwiN software (Centre for Multilevel Modelling, Institute of Education, London, UK). Because the frequency distribution of sleep-onset latencies was skewed, longitudinal Poisson regression analysis was used to determine the effects of skin and core temperature manipulations and induced temperatures on MWT sleep onset latency. The hierarchical regression analyses take into account the interdependency of the data points inherent to the hierarchical structure of the design, in our case the sequential sleep-onset observations, *i*, that were nested within days, *j*, once more nested within subjects, *k* [26]. The first block of both days (the habituation block) was omitted from analyses. Analyses were run with induced body temperatures (core body, proximal skin, and distal skin), subjective comfort, ther-

mal comfort, time-on-task decline of PVT response speed, and sleep-onset latency as dependent variables and body temperature manipulations as centred dichotomous predictor variables (with -0.5 reflecting the cool manipulation level and 0.5 reflecting the warm manipulation level, for ease of interpretation of the intercept, now showing the overall average). For the longitudinal Poisson regression analysis, all independent variables were centred at the within-subject single-day level.

A second series of analyses was performed, now not evaluating the manipulation conditions but rather how the actually measured core body, proximal and distal skin temperatures, and the distal-to-proximal gradient (DPG) predicted the time-on-task decline of PVT response speed and MWT sleep-onset latency.

Time (hour, $hour^2$ and √hour; defined as the number of hours since the start of the first included PVT or MWT within each day, starting with 0 at 09:00) was allowed in the models for induced temperatures to account for possible diurnal variations in core and skin temperature[11]. For all regression analyses, we calculated the full model, with all temperature manipulation variables and covariates in the model and subsequently stepwise removed non-significant terms to obtain optimal models, containing only the significant contributions. Maximum likelihood was used to estimate the regression coefficients, which were tested for significance with the Wald test[26]. In order to obtain the optimal linear models, additional terms were allowed in the regression equation only if their coefficients were significant and only if their inclusion improved the regression model according to the likelihood ratio test. In order to obtain the optimal Poisson regression models, additional terms were allowed in the regression equation only if their coefficients were significant and if the residual error of the model was reduced. The following regression models were used:

[1] effects of manipulation on measured temperature:

$$T_{ijk} = \beta_{0ijk} + \beta_1 \times Hour_{ijk} + \beta_2 \times Hour^2_{ijk} + \beta_3 \times \sqrt{Hour_{ijk}} + \beta_4 \times CBT_{ijk} + \beta_5 \times PST_{ijk} + \beta_6 DST_{ijk}$$

[2] effects of manipulation on PVT response speed:

$$PVT_{ijkl} = \beta_{0ijkl} + \beta_1 \times CBT_{ijkl} + \beta_2 \times PST_{ijkl} + \beta_3 \times DST_{ijkl} + \beta_4 \times \sqrt{Minute_{ijkl}}$$

[3] relation of measured temperatures on PVT response speed:

$$PVT_{ijk} = \beta_{0ijkl} + \beta_1 \times Tre_{ijkl} + \beta_2 \times Tprox_{ijkl} + \beta_3 \times Tdist_{ijkl} + \beta_4 \times \sqrt{Minute_{ijkl}}$$

[4] effects of manipulation on sleep latency:

$$ln(latency) = \beta_{0ijk} + \beta_1 \times CBT_{ijk} + \beta_2 \times PST_{ijk} + \beta_3 \times DST_{ijk} + \beta_4 \times Hour^2_{ijk}$$

[5] effects of measured temperatures on sleep latency:

$$\ln(\text{latency})_{ijk} = \beta_{0ijk} + \beta_1 \times Tre_{ijk} + \beta_2 \times Tprox_{ijk} + \beta_3 \times Tdist_{ijk} + \beta_4 \times Hour^2_{ijk} (+ \beta_5 \times DPG_{ijk})$$

[6] effects of manipulation on temperature sensation and comfort: $Outcome\text{-}variable_{ijk} = \beta_{0ijk} + \beta_1 \times CBT_{ijk} + \beta_2 \times PST_{ijk} + \beta_3 \times DST_{ijk} + \beta_4 \times Hour^2_{ijk}$.

(Subscripts indicate *i*th observation on day *j* for subject k in equations 1,4,5 & 6 and *i*th minute during the *j*th PVT on day *k* for subject *l* in equations 2 & 3)

In the tables the optimal models are shown, with only the significant contributing factors. Note that the values in the tables represent the effect coefficients as estimated from the Poisson regression analysis: in order to transform these coefficients to the number of 30-sec epochs, one should calculate *e* to the power of the regression equation. Transformation to minutes subsequently takes a division by two. In the results section, sleep latencies have thus been transformed and are reported in minutes. Two- tailed significance levels were set at 0.05.

3. Results

3.1. Effects of Manipulations on Temperature and Comfort

The effects of the manipulations on core body and skin temperatures during the PVT and before the start of the MWT are shown in Table 1. Core body and distal skin temperature were significantly modified by time of day ($P < 0.001$), accounting for 10% to 25% of variance during the PVT and the MWT.

The core body temperature manipulation was the sole factor influencing core body temperature during the PVT and the MWT (effect size: 0.10–0.12°C, $P < 0.001$) and accounted for 29% of the variance during the PVT and 17% of the variance during the MWT.

Proximal and distal skin temperatures during the PVT and the MWT were mainly affected by their respective skin temperature manipulation (effect size: 0.45–0.62°C, $P < 0.001$), but also to a lesser extent by core body temperature and by the other skin temperature manipulation (effect size: 0.14–0.56°C, $P < 0.001$). The temperature manipulations accounted for 60% of the variance during the PVT and the MWT.

The effects of the manipulations on thermal comfort and temperature sensation, measured before the MWT are shown in Table 2. In summary, the warm conditions were experienced as less comfortable and warmer than the cool conditions. Comfort was significantly lower when the core body and proximal skin were warmed ($P < 0.001$), with a trend for warming of the distal skin ($P = 0.06$). The highest comfort was achieved when cooling was induced at all 3 sites. Temperature was perceived as higher in the core body and proximal skin warming condition ($P < 0.001$). Subjects did not perceive the distal skin warming condition as a significantly warmer condition than the distal skin cooling condition ($P = 0.26$).

Table 1—Estimates of the Effects of Temperature Manipulation and Time of Day on Core and Skin Temperatures During the PVT and 5 Minutes Before Start of Sleep Latency Test

	Core Body Temperature (T_{re})	Proximal Skin Temperature (T_{prox})	Distal Skin Temperature (T_{dist})
PVT - Temperature during test			
Intercept	36.47 ± 0.14	34.74 ± 0.15	35.11 ± 0.11
$Hour^2$	n.s.	n.s.	-0.004 ± 0.001***
√Hour	0.08 ± 0.01***	n.s.	n.s.
CBT:+/-	0.14 ± 0.02***	0.21 ± 0.05***	0.56 ± 0.06***
PST:+/-	n.s.	0.50 ± 0.05***	0.22 ± 0.06***
DST:+/-	n.s.	0.14 ± 0.05**	0.45 ± 0.06***
MWT - Temperature 5 minutes before start of sleep latency test			
Intercept	36.46 ± 0.14	34.78 ± 0.15	35.12 ± 0.10
Hour	0.05 ± 0.01***	n.s.	n.s.
$Hour^2$	-0.003 ± 0.001***	n.s.	-0.005 ± 0.001***
CBT:+/-	0.10 ± 0.02***	0.15 ± 0.04***	0.36 ± 0.06***
PST:+/-	n.s.	0.62 ± 0.04***	0.32 ± 0.06***
DST:+/-	n.s.	0.15 ± 0.04***	0.57 ± 0.06***

Intercepts represent means. Values are ± standard error. Significance levels are indicated as *P < 0.05, **P < 0.01, ***P < 0.001.

Table 2—Estimates of the effects of temperature manipulation on temperature sensation and thermal comfort.

	Subjective Measures	
	Temperature Sensation	**Thermal Comfort**
Intercept	64.27 ± 4.34	47.24 ± 2.62
CBT:+/-	11.31 ± 2.81***	-15.00 ± 3.62***
PST:+/-	14.95 ± 2.80***	-13.50 ± 3.62***
DST:+/-	n.s.	n.s.

Values are means ± standard error. Temperature sensation was measured on a visual analog scale ranging from 0 (cool) to 100 (warm), with 50 reflecting thermoneutral. Thermal comfort was measured on a visual analog scale ranging from 0 (uncomfortable) to 100 (comfortable). Significance levels are indicated as *P < 0.05, **P < 0.01, ***P < 0.001.

3.2. Effects of Temperature Manipulation on Psychomotor Vigilance

The overall average RRT of narcoleptic subjects was 2.46 ± 0.20 sec^{-1}. There was a typical worsening, i.e., a decline in response speed, with increasing time-on-task (see Figure 2). This decline was best approximated by a square root function of time-on-task (√Minutes, P < 0.001). As evident from figure 2, these profiles indicate that vigilance declined quickly after starting the task. As compared to core body cooling, core body warming attenuated this decline by 25% (CBT x Minute, P = 0.02), while effects induced by proximal or distal skin temperature manipulations were not significant (P > 0.20).

Regressing PVT on the actually induced temperatures showed essentially the same effects: a higher core body temperature was associated with an attenuated decline in response speed over the time-on-task (T_{re} x Minute, P = 0.004). Moreover, a higher DPG was associated with an accelerated decline in response speed (DPG x Minute, P = 0.04).

3.3. Effects of Temperature Manipulation on Maintenance of Wakefulness

Figure 3 shows the effects of the temperature manipulations on maintenance of wakefulness as derived from the regression analysis. Overall average sleep latency was 2.10 min (95% CI: 1.52–2.90). Sleep onset latency was significantly modulated by time ($hour^2$) and the distal skin manipulation, with an estimated shorter latency (1.88 min; CI: 1.60–2.21) in the DST+ condition compared to a longer latency (2.34 min; CI: 1.99–2.75) in the DST− condition (P < 0.01, figure 3). Cooling the distal skin thus meant that subject remained awake for 24% longer as when the distal skin was warmed. Sleep latency was not significantly affected by core and proximal manipulations (all P > 0.20).

a. Effects of manipulation (see c.)

	Response Speed (1/RT)	
Intercept	2.46 ± 0.20	
√Minute	-0.28 ± 0.02	***
CBT:+/- * √Minute	0.07 ± 0.03	***
PST:+/- * √Minute	n.s.	
DST:+/- * √Minute	n.s.	

b. Effects of measured temperatures

	Response Speed (1/RT)	
Intercept	2.47 ± 0.20	
√Minute	-0.25 ± 0.02	***
T_{re}/°C * √Minute	0.30 ± 0.10	**
T_{prox}/°C * √Minute	n.s.	
T_{dist}/°C * √Minute	n.s.	
DPG/°C * √Minute	-0.031 ± 0.015	*

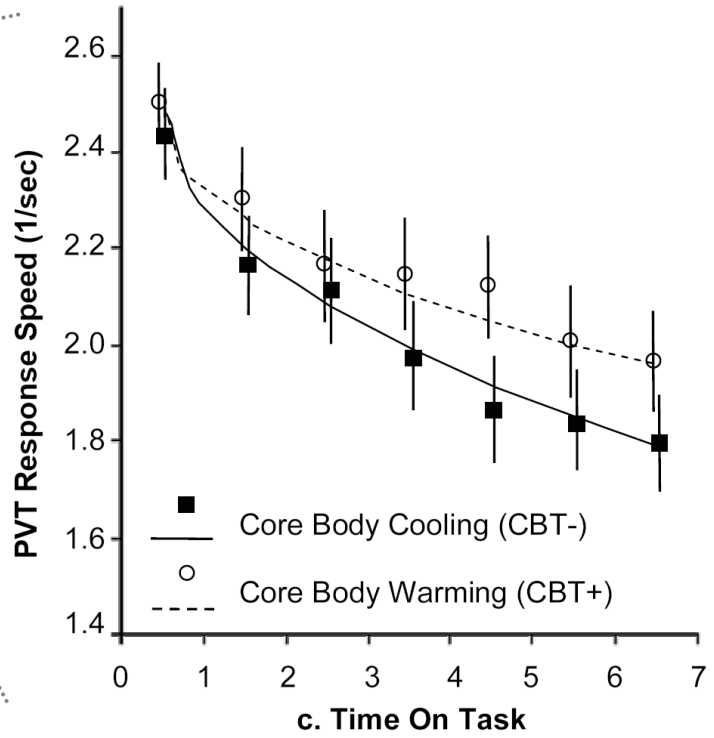

Figure 2—Psychomotor Vigilance Task. Estimates of the effects of temperature manipulation and time on task on PVT response speed (a), estimates of the effects of actual measured temperatures and time on task on PVT response speed (b) and regression model of response speed over the 7 subsequent min of PVT performance in the core warming (CBT+, open circles) and core cooling (CBT-, solid squares) conditions (c). Intercepts represent overall means. Values are means ± standard error. Significance levels are indicated as *P < 0.05, **P < 0.01, ***P < 0.001. Narcoleptic subjects show a low response speed and a time on task effect with a fast decline already during the first minutes. The response speed improves during the core body warming condition.

a. Effects of manipulation (see c.)

	Sleep Latency (min)		
	mean	confidence interval	
Intercept	2.10	1.52 – 2.90	
$Hour^2$	0.50	0.50 – 0.50	***
CBT:+/-	n.s.		
PST:+/-	n.s.		
DST:+/-	-0.40	0.34 – 0.47	**

b. Effects of measured temperatures

	Sleep Latency (min) (factorial model)			Sleep Latency (min) (DPG model)		
	mean	confidence interval		mean	confidence interval	
Intercept	2.10	1.52 – 2-91		2.10	1.52 – 2-91	
Hour^2	0.50	0.50 – 0.50	***	0.50	0.50 – 0.50	***
T_{re}/°C	n.s.					
T_{prox}/°C	n.s.					
T_{dist}/°C	-0.40	0.34 – 0.48	**			
DPG/°C				-0.40	0.33 – 0.49	*

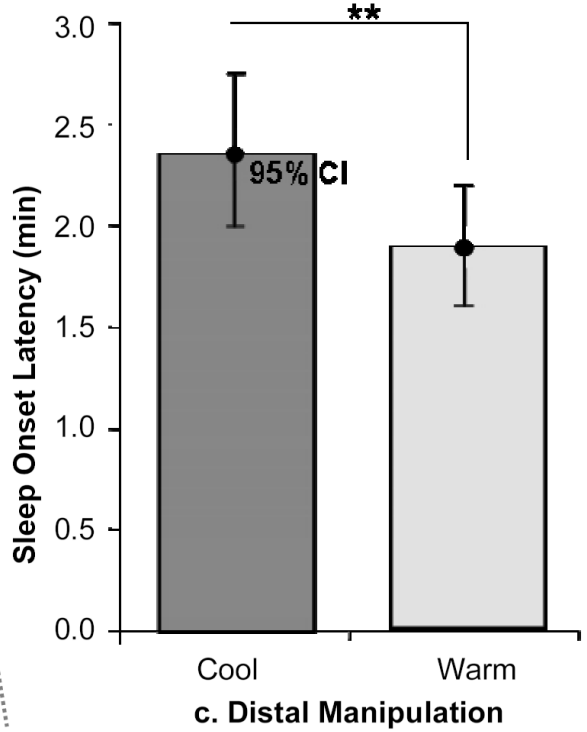

Figure 3—Maintenance of Wakefulness. Estimates of the effects of temperature manipulation and time of day on sleep latency (a), estimates of the effects of measured temperatures and time of day on sleep latency (b) and the means (± 95% CI) of sleep latency in the distal cooling (left bar) and distal warming (right bar) conditions (c). Intercepts represent overall means. Significance levels are indicated as *P < 0.05, **P < 0.01, ***P < 0.001. Narcoleptic subjects were characterized by very short sleep latencies. Sleep latency was longer in the distal skin cooling condition as compared to the distal skin warming condition (**P < 0.02).

Regressing MWT on the actually measured temperatures resulted in significance for the same variables: sleep onset latency was significantly modulated by time (hour^2) and by distal skin temperature. The regression coefficients, transformed to minutes (Figure 3a & 3b), can be interpreted as follows: patients could stay awake for 1.89 (CI: 1.60–2.24) min when distal skin temperature was 0.5°C higher than the average distal skin temperature, compared with 2.34 (CI: 1.97–2.77) min when distal skin temperature was 0.5°C lower than the average distal skin temperature ($P < 0.01$, Figure 3c). One degree of decrease in distal skin temperature thus increased the time patients succeeded to maintain wakefulness by 24%. Sleep latency was not significantly related to core and proximal temperatures (all $P > 0.31$).

4. Discussion

We investigated whether subtle manipulations of core body and skin temperatures within the natural range of the diurnal cycle, affected vigilance and sleepiness in narcolepsy.

First, patients were better able to maintain vigilance when core body temperature was increased than when it was lowered. In short, vigilance in narcolepsy can be altered simply by altering the temperature of food and drinks. Second, the ability to maintain wakefulness was better when distal skin temperature was lowered than when it was increased. We were thus able to influence the process of falling asleep in narcoleptic subjects by gently cooling or warming their hands and feet. The acceleration of sleep onset by distal skin warming occurred in spite of the fact that warming was perceived as slightly less comfortable.

Our data furthermore showed a number of narcolepsy-related aspects on PVT performance and maintenance of wakefulness under strictly controlled and balanced conditions. In agreement with previous investigations[6], narcoleptic subjects showed a very poor average PVT response speed, not only compared with matched controls, but also compared with elderly good sleepers and elderly insomniacs previously submitted to the same protocol (see Chapter 6, this thesis)[20]. Although untreated narcolepsy is already characterized by a very short MWT sleep latency (around 6 min)[15], in our constant routine protocol all patients had great difficulties remaining awake for longer than 3 min. These shorter MWT values relative to previous reports may be due to the restricted time allowed for sleep during the night prior to the investigation (6 h) and continuous low-light, stimulus-free, semi-supine circumstances, known to promote falling asleep[2]. The more remarkable it is that even under these high sleep pressure inducing conditions, distal skin cooling significantly increased sleep latency by 24%.

Note that in this study, sleep-onset was defined as 3 consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2 (or deeper) sleep. This differs from the definition of one 30-s epoch of stage 1 (or deeper) sleep that is commonly used in the clinical setting. In our study design, sleep scoring was performed online and subjects had to be woken up immediately after the onset of

sleep. For this purpose, we had to be absolutely sure of sleep onset, and therefore used the three 30-s epoch criterion. To compare results with other studies, the exact definition of sleep onset needs to be taken into account. However, using the clinical definition of sleep onset would not have changed the outcome of this study, since there was no occasion when a subject showed an epoch of wake after the occurrence of stage 1 sleep.

It is known that the clinical efficacy of commonly used stimulants, such as modafinil, is not adequately revealed by its small effects on sleep latency as measured in the MWT[19]. Although the definition of sleep onset may have differed between studies, the changes in sleep latency in our study are comparable to those seen with modafinil. Temperature manipulations may thus have a more significant clinical effect.

We initiated this study based upon our previous findings that narcoleptic subjects have an increased distal relative to proximal skin temperature (distal-to-proximal gradient, DPG) that was related to an increased sleepiness[7]. In that previous study, we did not measure core body temperature. Other studies have reported conflicting results regarding core body temperature. Therefore, we compared the T_{core} measured in this study in narcoleptic subjects, with the earlier published T_{core} measured in healthy controls that underwent the same protocol and matched on age and gender[21]. Core body temperature was lower in narcolepsy than in controls (T_{re}: narcolepsy 36.47 ± 0.14°C; controls, 36.88 ± 0.06°C; P = 0.01 [Z-test]). A partial normalization of the low core body temperature in the core warming condition may have been involved in its positive effects on PVT performance. This interpretation is supported by the positive relation between core body temperature and vigilance we previously found in elderly subjects in an identical protocol (see Chapter 6, this thesis)[20] and by previous work showing a correlation between the circadian modulation of vigilance and of core body temperature[8,27,3,16,28]. The effects of distal skin warming and cooling on maintenance of wakefulness in narcoleptic subjects are in line with our earlier findings of an abnormally increased distal skin temperature that correlated with the ease of falling asleep in narcolepsy[7]. In previous studies of our group, both young and elderly subjects without sleep problems and insomniac elderly showed worsening of PVT performance and shorter sleep latencies with proximal skin warming (Chapter 4 and Chapter 6, this thesis)[20,21]. Given the repeatability of the proximal warming results over the 3 groups in those previous studies, the more remarkable it is that narcoleptic subjects do not show sensitivity of vigilance performance and sleepiness to proximal warming. It is not unlikely that this difference with healthy controls—and with elderly subjects reported previously—is related to the markedly lower core and proximal temperature of narcoleptic subjects in combination with a higher distal skin temperature, even under the strictly controlled conditions of the present experiment and found previously under less controlled circumstances[7].

Of note, the present study differs from previous work[11,18,25] in that mild manipulations within the thermoneutral zone were applied. Since such manipulations induced only changes within the temperature range normally covered during everyday life, the circadian modulation of these temperatures could contribute to the circadian modulation in vigilance and sleepiness.

In conclusion, our results demonstrate a modulatory role for body temperature in the regulation of vigilance and maintenance of wakefulness in narcolepsy. Experimentally induced subtle changes in core body and skin temperature caused changes in vigilance and ability to maintain wakefulness. A practical implication of our findings is that temperature manipulations may be of value in the management of vigilance and sleepiness problems in narcolepsy. An ultimate practical application could for example be clothing with integrated measurement and regulation of skin temperature. For the time being, the advice may be to utilise a warm drink or meal in combination with cooling of the extremities to aid their fight against vigilance impairment and daytime sleepiness.

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SLEEP DEPTH &
SLEEP MAINTENANCE

Chapter 8

Skin deep: cutaneous temperature determines sleep depth

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Summary

With aging, an increasingly disturbed sleep is reported as a significant complaint affecting the health and well-being of many people. The available treatments for sleep disturbance have their limitations, so we have adopted a different approach to the improvement of sleep. Since, in animal and human studies skin warming has been found to increase neuronal activity in brain areas that are critically involved in sleep regulation, we investigated whether subtle skin temperature manipulations could improve human sleep. By employing a thermosuit to control skin temperature during nocturnal sleep, we demonstrate that induction of a mere 0.4˚C increase in skin temperature, whilst not altering core temperature, suppresses nocturnal wakefulness ($P<0.001$) and shifts sleep to deeper stages ($P<0.001$) in young and, especially, in elderly healthy and insomniac participants. Elderly subjects showed such a pronounced sensitivity, that the induced 0.4˚C increase in skin temperature was sufficient to almost double the proportion of nocturnal slow wave sleep and to decrease the probability of early morning awakening from 0.58 to 0.04. Therefore, skin warming strongly improved the two most typical age-related sleep problems; a decreased slow wave sleep and an increased risk of early morning awakening. EEG frequency spectra showed enhancement of low frequency cortical oscillations. The results indicate that subtle feedback control of in-bed temperature through very mild manipulations could have strong clinical relevance in the management of disturbed sleep especially in the elderly, who have an attenuated behavioural response to suboptimal environmental temperature, which may hamper them from taking appropriate action to optimize their bed temperature.

1. Introduction

With advancing age, an increasing number of people complain about their sleep quality[18,28]. Nocturnal awakenings occur more frequently, especially in the morning, and the time spent in slow wave sleep decreases. Non-pharmacological interventions are of value in the management of age-related sleep complaints, since they may be at least as effective as hypnotics and lack the adverse effects that occur with chronic use[44]. In this report, we investigate a novel non-pharmacological approach to improve sleep by maintaining skin temperature within a narrow comfortable range.

The major sleep period occurs during the trough of the circadian rhythm of core body temperature (CBT). Habitual sleep onset closely follows the maximal rate of decline in CBT during the evening[36] and the probability of waking up increases during the early morning rise of CBT. Experimental protocols have been designed to desynchronize the sleep and temperature rhythms. Results confirm that the ability to initiate and maintain sleep is maximal during the phase of lower CBT[11,29,30,43]. These findings suggest that sleep-regulating systems are regulated in parallel with the circadian variation in body temperature, or may even be affected directly by it.

The site at which sleep regulation is likely to be linked with body temperature is the preoptic area/anterior hypothalamus (POAH), which is the major thermoregulatory centre of the mammalian brain and a key structure in arousal state control. One source of input affecting activity of the POAH is its local brain temperature, which modulates the firing rate of thermosensitive neurons. A subpopulation of warm-sensitive POAH neurons (WSNs) spontaneously increases its firing rate at sleep onset. Experimental warming of the POAH induces a similar increase in this firing rate, and ultimately facilitates sleep[1,34,35]. It has, therefore, been proposed that sleep would be facilitated when brain temperature exceeds a threshold level[34]. However, the finding that experimental POAH warming promotes sleep renders it unlikely that the diurnal rhythm in *brain* temperature is causally involved in the circadian modulation of sleep propensity, because sleep propensity is low rather than high during the circadian phase of increased brain temperature[11,29,30,43]. Thus, a circadian modulated source of input to sleep-related POAH neurons *other* than local brain temperature should be present if their involvement in the coupling between sleep and temperature rhythms is presumed. Such a putative input signal should show a diurnal modulation that is inverse to the CBT rhythm, i.e. direct POAH neurons towards their sleep-type firing patterns in spite of the low local brain temperature, presumed to disfacilitate sleep-type firing patterns[51].

We have proposed that skin temperature is a candidate for such an input signal[52]. Skin temperature shows a diurnal rhythm that is inversely related to the CBT rhythm, i.e. skin temperature peaks during the habitual sleep period[33]. Under normal conditions the nocturnal increase of skin temperature is further amplified by postural change[26,47], a warm microclimate resulting from insulating bedding[20,37,38] and pre-sleep relaxation signalled by lights off[27]. A functional link between

skin temperature and sleep has been suggested before[25], but hard evidence concerning the directionality of the relationship was lacking. Nevertheless, in a recent report, we showed that mild direct skin warming within the thermoneutral range reduced sleep onset latency by 27%, in spite of this warming being perceived as slightly less comfortable[40]. Skin warming moreover accelerated the decline in vigilance associated with the prolonged performance of a monotonous task[39].

A recent study involving human neuro-imaging demonstrated that hypothalamic activation occurs with skin warming[16]. Data from animal studies show that afferents conveying information about skin temperature modulate the firing rate of thermosensitive neurons in the POAH at least as strong as local brain temperature does, and even dominate the POAH response in case of simultaneous differential manipulations of brain and skin temperature[3,4]. We proposed that the modulation in neuronal firing rate and sleep propensity that can be experimentally induced by local brain warming, might similarly be induced by the warming of the skin that occurs under natural sleeping conditions.

2. Materials & Methods

Using a water-perfused thermosuit, we manipulated proximal and distal skin temperature ($T_{skin\text{-}prox}$; $T_{skin\text{-}dist}$) directly and differentially, while monitoring sleep depth polysomnographically in eight young adult and eight elderly participants without sleep complaints and in eight elderly insomniacs. Unlike in previous studies the manipulations we made were so subtle that they affected only skin temperature, and only within a very narrow range (0.4˚C) of the thermoneutral and comfortable zone.

2.1. Subjects

Twenty-four healthy volunteers participated with informed consent. They included eight young adults (mean ± s.e.m.: 27.0±2.4 years, 4 males), eight elderly subjects without sleep complaints (65.8 ± 2.8 years, 4 males) and eight elderly subjects diagnosed with primary insomnia (59.1 ± 1.9 years, 4 males) according to the qualitative criteria of the International classification of sleep disorders (ICSD[10]) and the Research Diagnostic Criteria for Primary Insomnia[15], as well as according to the quantitative criteria proposed by Lichstein et al.[31], i.e. sleep onset latency or wake time after sleep onset of more than 30 minutes, occurring at least three times a week for at least half a year. Although the study was performed prior to the recently published 'Recommendations for a Standard Research Assessment of Insomnia[7], it still complied with the majority of these recommendations. Diagnosis was performed by accredited sleep specialists. Author EVS is a clinical sleep-wake expert accredited by the Netherlands Society for Sleep-Wake Research and Health Care Psychologist registered by the Netherlands Central Information Centre for Professional Practitioners in

Health Care; Author RR is a sleep expert accredited by the Holland Sleep Research School, Westeinde Hospital, The Hague. Diagnostic tools included interviews, questionnaires and sleep diaries. Polysomnographic confirmation of disturbed sleep in absence of apnoea and periodic leg movements was demonstrated during the study as described below. Subjective sleep quality and complaints were measured using interview, sleep diaries, a Dutch adaptation[46] of the75-item Sleep Disorders Questionnaire[14] and the Pittsburgh Sleep Quality Index[8]. All elderly subjects suffering from primary insomnia had a PSQI score > 5 (10.9 ± 1.1) and an SDQ-Insomnia score >2.5 (3.3.± 0.1). Young adult and elderly subjects without sleep complaints all scored within the normal range of these scales, respectively 4.0 ± 0.5 and 3.6 ± 0.4 for the PSQI, and 1.8 ± 0.1 and 2.0 ± 0.1 for the SDQ-Insomnia subscale. None of the subjects scored higher than the cut-off score of 3 on the SDQ subscales Narcolepsy, Apnoea, Restless legs and Psychiatry. A history of, or present symptoms of medical or psychiatric disorders were furthermore excluded by interview and evaluating the Symptom Check List (SCL-90[9]). All subjects were in good health and none used hypnotic, psychotropic or cardiovascular medication. One of the young adult females used oral contraceptives. The younger females participated during the mid-follicular phase (or pseudo-follicular phase) of the menstrual cycle. Elderly females were post-menopausal. The Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam approved the protocol.

2.2. Procedure

Subjects refrained from caffeine, alcohol and tobacco for 8 hours before reporting to the sleep laboratory at 22:00 hr. They were then prepared for polysomnography and fitted with a thermosuit for skin temperature manipulation. At midnight, lights were turned off and subjects were allowed to sleep until 06:00 hr. The nocturnal sleep period was limited to six hours because the subjects were subjected to a semi-constant routine procedure starting at 6:00 hr, as reported previously (see chapters 4,5 & 6, this thesis)[39,40]. Starting at 0:30 hr., $T_{skin\text{-}prox}$ and $T_{skin\text{-}dist}$ were differentially manipulated by thermosuit water perfusion of slowly cycling temperatures (figure 1). After sleeping for one night at home subjects returned for a second night, with the temperature manipulation sequences inversed compared to that of the first night.

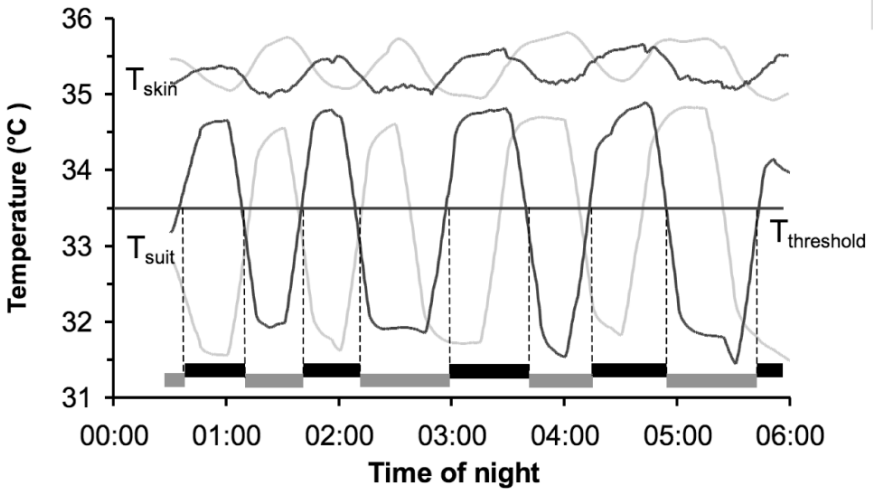


Fig. 1. Single-case, one-night example of the temperature profiles induced in the proximal (grey) and distal (black) parts of the thermosuit (lower traces),$T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$. The upper traces show the induced slowly cycling proximal (grey) and distal (black) average skin temperature, $T_{skin\text{-}prox}$ & $T_{skin\text{-}dist.}$ During the second experimental night (not shown) the thermosuit temperature profiles were inversed to provide a balanced protocol. The horizontal line illustrates the proximal thermosuit threshold - 35.5˚C for this example - that was determined such that the proportion of wakefulness during the time spent above this temperature (black rectangles) differed maximally from the proportion of wakefulness during the time spent below this temperature (grey rectangles).

2.3. Temperature Manipulations and Measurement

Skin temperature was manipulated from 00:30 hr. until 6:00 hr. using a thermosuit (Coretech Cool tube suit, Med-Eng Systems Inc., Ottawa, Canada) connected to two computer-controlled bath/circulation thermostats (K6KP, Lauda, Lauda-Königshofen, Germany) that controlled the temperature of the water flowing through the tubes of the thermosuit. As shown in figure 1, the temperature levels were changed slowly throughout the night. The sequence of these temperature level changes was programmed on two control computers (Wintherm Software, Lauda, Lauda-Königshofen, Germany), one for distal (hands and feet) and one for proximal (trunk and limbs) skin temperature manipulation. During each of the two nights, the T_{suit} temperature cycled between alternating constant plateaus of high and low temperature levels that lasted either 15 or 30 minutes. Transitions between the plateaus were accomplished with slow temperature changes, taking 15 minutes for each transition. The order of the sequences of skin temperature manipulations was different for each subject within its group and chosen in such a way that it resulted in an optimal uniform distribution of combinations of high and low $T_{suit\text{-}prox}$ & $T_{suit\text{-}dist}$ levels throughout the night over all subjects in one group, i.e. at any time of night there was an equal proportion of warm and cool periods. The actual manipulation temperature T_{suit} was measured once per minute on the tubes that supplied the temperature controlled water to thermosuit, us-

ing PT100 thermistors (RTD-3-3105, Omega, Stamford, USA). T_{suit} cycled between 31.7 ± 0.1°C in the 'cool' and 34.6± 0.1°C in the 'warm' condition. This range was specifically chosen specifically to match the previously reported range of temperatures normally present in the bed microclimate[20,27,37,38]. Importantly, we have also demonstrated previously that these temperatures are both close to maximal comfort, with the warm condition being experienced as slightly less comfortable and thermoneutral[40].

Body temperature was sampled at 1 Hz from 8 thermistors (P-8432, ICBT, Tokyo, Japan; Embla A10 recorder and Somnologica software, Flaga hf, Reykjavik, Iceland). Core body temperature (T_{re}) was obtained using a thermistor that was self-inserted 13 cm into the rectum. $T_{skin\text{-}prox}$ was measured at three places: right mid-thigh on the musculus rectus femoris, abdomen and the right infraclavicular area, and a weighted average was calculated[40]. $T_{skin\text{-}dist}$ was calculated as the average of four points: the thenar area at the palmar sites of both hands and medial metatarsal area at the plantar sites of both feet. Temperature data were averaged over 30 second intervals synchronized to the sleep stage epochs.

2.4. Sleep recordings and analysis

Polysomnographic sleep recordings consisted of electroencephalography (EEG) from two bipolar derivations (FpzCz and PzOz)[55] obtained with the E-net system (MVAP, Newbury Park, CA), submental electromyography (EMG) and electrooculography from the outer canthi (EOG), both recorded using disposable Ag/AgCl electrodes (type 4203 Meditrace, Graphic Controls Corporation, Buffalo USA). The signals were recorded digitally with a sampling frequency of 200 Hz using the Embla A10 recorder and Somnologica software (Flaga hf, Reykjavik, Iceland). An assessor who was blind to the temperature conditions scored sleep in 30 sec epochs according to standard criteria[42]. Epoch classification stages 3 and 4 were merged into the single class slow wave sleep (SWS). For each artifact-free 30 second epoch scored as non-REM-sleep, the average power spectra were calculated over 50% overlapping periods of 512 samples with a Hamming window, using the Somnologica software (Flaga hf, Reykjavic, Iceland). Power was averaged in 1 Hz bins in the frequency range from 0.4 to 25 Hz, the first bin ranging from 0.4 to 1.0 Hz.

2.5. Statistical Analysis

2.5.1. Descriptive analysis: determination of the thermosuit temperature threshold for sleep enhancement.

For an ultimate practical applicability, e.g. in a system to control the bed microclimate temperature, a first requirement is to have an indication of the lower limit of the temperature that should be maintained in order to promote sleep. A first descriptive analysis therefore aimed to deter-

mine an average thermosuit temperature above which wakefulness would be maximally suppressed and sleep maximally promoted as well as to determine its variability both within and between groups. It can be assumed a priori that some individual variability will exist in the temperature that should be reached before favourable effects on sleep surfaces. Therefore, for each individual night, we systematically varied the whole range of possible thresholds between the 31.7 ± 0.1°C 'cool' and 34.6 ± 0.1°C 'warm' T_{suit} boundaries and selected the temperature that maximized the difference in the proportion of wakefulness during the time spent above this temperature and the proportion of wakefulness during the time spent below this temperature. An example is shown in figure 1.

If for example, for a specific night, wakefulness is present for 20% of the time that the proximal suit temperature is above of 33.5˚C and 30% of the time that the suit temperature is below 33.5˚C, and at no other temperature the difference is larger than this 10%, the threshold is determined to be 33.5˚C for this night. In this way, an optimal threshold temperature can be determined for each night, as well as well as two sets of percentage for each wake and sleep stage. The first set of percentages represents the time spent in each sleep stage and wakefulness relative to the total amount of time spent below the temperature threshold. The second set of percentages represents the time spent in each sleep stage and wakefulness relative to the total amount of time spent above the temperature threshold. The optimal temperature thresholds and corresponding distributions of wake and sleep stages were averaged over nights and subjects and are shown in table 2.

2.5.2. Statistical testing of the effect of thermosuit temperature on sleep

For statistical testing, mixed effect (or multilevel) regression analysis was applied to account for the interdependency of the data points inherent to the hierarchical structure of the dataset, i.e. epochs within nights within subjects (MLwiN software, Centre for Multilevel Modelling, Institute of Education, London, UK). The regression models included parameters to account for nonlinear changes over time that could lead to correlated residual error. The analyses included all epochs during the skin temperature manipulation (i.e. from 00:30 hr. until 6:00 hr.). To determine the effects of skin temperature manipulation on the probability of occurrence of sleep stages, longitudinal multilevel logistic regressions were applied for each sleep stage classification, with the current presence or absence of that stage as dummy coded dichotomous dependent variable and $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ as predictor variables. In addition to main effects, regression equations included terms as needed in order to account for variability due to time (including a linear, second order, and square root term) and its interaction with $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$. Optimal regression models were selected using the likelihood ratio chi-square test[48]. Odds ratios were translated into sleep stage probabilities at every time point during the night for the maximal and minimal ther-

mosuit temperature levels using the transformation $e^x/(1+e^x)$, where x represents the regressor part of the best fitting model. Two separate plots were generated to visualize the regression prediction for the cumulative sleep stage probability during the 34.6˚C upper and 31.7˚C lower T_{suit} levels. The effect of T_{suit} on the EEG spectral power bands was investigated using multilevel linear regression. Two-tailed significance levels were set at 0.05 for all analyses.

3. Results

3.1. Manipulation effects on core and skin temperature

Unlike in previous studies -and due to the fact that the manipulations forced the skin temperature to slowly cycle only within a very subtle range of 0.4˚C (see figure 1)- core body temperature (T_{re}) was left virtually unchanged: skin temperature manipulations accounted for only 1.4 % of the variance of T_{re}. Manipulation of the proximal part of the thermosuit accounted for 49.2 % of the variance in mean $T_{skin\text{-}prox}$, which was on average 35.37 ± 0.07˚C (mean ± s.e.m.) versus 34.98 ± 0.07˚C for the warmest and coolest levels respectively. Likewise, the independently manipulated temperature of the distal part of the thermosuit accounted for 43.0% of the variance in mean $T_{skin\text{-}dist}$, which was 35.38 ± 0.08˚C versus 35.02 ± 0.07˚C for the warmest and coolest levels respectively.

3.2. Manipulation effects on the occurrence of sleep versus wakefulness

In general, subjects showed less wakefulness and more sleep with increasing temperature of the thermosuit, especially in the proximal region. In order to obtain a first model-free description we therefore focused on the proximal thermosuit temperature ($T_{suit\text{-}prox}$) threshold above which sleep was most promoted. Individual $T_{suit\text{-}prox}$ temperature values were determined for each night, such that the proportion of wake during the time spent above that temperature differed maximally from the proportion of wake during the time spent below it. There were no significant differences between the average thresholds of young adults (33.5 ± 0.4˚C), elderly subjects without sleep complaints (33.2 ± 0.4˚C) and elderly people with sleep complaints (33.1 ± 0.4˚C) (Z-tests, all p>0.48). Although there was some variance between subjects and nights, the thresholds *on average* occurred midway between the 'cool' (31.7 ± 0.1ºC) and 'warm' (34.6 ± 0.1 ºC) T_{suit} temperatures. Table 2 shows the thresholds and the percentage of wakefulness relative to the time spent below ('cool') and the time spent above ('warm') the threshold, as well as the distribution of sleep stage percentages corresponding to the optimal bipartition. Because the effects of distal manipulations were less pronounced relative to the effects of proximal manipulation, a determination of thresholds and corresponding wake and sleep stage proportions

Table I Average distal skin, proximal skin and core body temperatures (mean ± SEM) induced during the 'cool' and 'warm' distal and proximal manipulation periods of the night, shown for each group separately

	Distal manipulation		Proximal manipulation	
	Cool	Warm	Cool	Warm
Distal skin temperature				
Young adults	35.10 ± 0.10	35.46 ± 0.09	35.24 ± 0.09	35.33 ± 0.11
Elderly without sleep complaints	34.84 ± 0.13	35.18 ± 0.11	34.94 ± 0.12	35.05 ± 0.13
Elderly insomniacs	35.12 ± 0.12	35.50 ± 0.11	35.25 ± 0.11	35.36 ± 0.13
Proximal skin temperature				
Young adults	35.35 ± 0.13	35.26 ± 0.17	35.12 ± 0.14	35.49 ± 0.14
Elderly without sleep complaints	35.04 ± 0.12	35.01 ± 0.12	34.85 ± 0.11	35.19 ± 0.11
Elderly insomniacs	35.24 ± 0.09	35.16 ± 0.13	34.98 ± 0.09	35.43 ± 0.10
Core body temperature				
Young adults	36.31 ± 0.05	36.30 ± 0.04	36.32 ± 0.04	36.30 ± 0.04
Elderly without sleep complaints	36.26 ± 0.05	36.25 ± 0.05	36.28 ± 0.04	36.23 ± 0.05
Elderly insomniacs	36.42 ± 0.07	36.40 ± 0.07	36.42 ± 0.07	36.39 ± 0.07

for distal temperature was difficult due to strong masking effects of simultaneous proximal temperature changes. The descriptive data in table 2 suggest that not only a reduction in wakefulness occurred but also that a deepening of sleep was induced by the warmer thermosuit temperatures. This was tested using logistic regression analyses as described below.

Table 2 Proximal thermosuit temperature thresholds (mean ± SEM) and sleep stage distribution (percentage mean ± SEM over all nights), during the time spent below ('Cool') and above ('Warm') the individualized $T_{suit\text{-}prox}$ thresholds.

	Cool	Warm
Young adults		
Temperature threshold *(33.5 ± 0.4° C)*		
% Wake	12.2 ± 6.5	1.4 ± 1.2
% S1	3.8 ± 0.8	2.6 ± 0.7
% S2	43.4 ± 4.0	46.2 ± 4.4
% SWS	18.0 ± 3.6	25.9 ± 6.1
% REM	19.8 ± 2.9	22.9 ± 3.4
% MT	2.8 ± 1.8	1.1 ± 0.6
Elderly without sleep complaints		
Temperature threshold *(33.2 ± 0.4° C)*		
% Wake	33.7 ± 9.0	6.9 ± 2.2
% S1	6.5 ± 1.3	4.8 ± 0.9
% S2	31.1 ± 5.7	50.9 ± 4.2
% SWS	8.4 ± 2.2	16.5 ± 3.0
% REM	20.1 ± 6.4	20.5 ± 4.2
% MT	0.2 ± 0.1	0.4 ± 0.2
Elderly insomniacs		
Temperature threshold *(33.1 ± 0.4° C)*		
% Wake	38.7 ± 8.4	12.6 ± 3.9
% S1	7.0 ± 1.2	5.8 ± 1.2
% S2	37.1 ± 6.2	46.3 ± 4.9
% SWS	7.6 ± 2.0	11.8 ± 2.5
% REM	7.5 ± 2.5	21.9 ± 4.3
% MT	2.2 ± 0.8	1.6 ± 0.6

Temperature and% Sleep stages: mean ± SE.
MT=movement time, a polysomnographic classification of an epoch with artifacts that excludes it from sleep staging. The percentage values represent the time spent in wake and sleep stages relative to the time spent below (left column) or above (right column) the proximal thermosuit temperature threshold that was determined for each individual night in each subject, such that the proportion of wake during the time spent above that temperature differed maximally from the proportion of wake during the time spent below it (see example in Fig. 1).

3.3. Manipulation effects on sleep stage probability and distribution

3.3.1. Main effects

In order to evaluate in detail the effect of temperature manipulation on the probability of occurrence of sleep stages, logistic regression was applied. As shown in figure 2 and 3, thermosuit temperature ($T_{suit\text{-}prox}$; $T_{suit\text{-}dist}$) significantly affected the odds ratios for occurrence of wakefulness (Wake) and the sleep stages 1 (S1), 2 (S2), slow wave sleep (SWS) and rapid eye movement sleep (REM sleep). Odds ratios were translated into cumulative probability distribution plots for these stages throughout the night to provide a graphical representation of the regression-model-predicted sleep stage distribution during the periods of minimal T_{suit} (31.7˚C, upper panels) and during the periods of maximal T_{suit} (34.6˚C, lower panel).

The data in figure 2 and table 3 show that *distal skin* warming enhanced REM sleep and suppressed S1 in the young adults and the elderly people without sleep complaints. In contrast, it suppressed REM sleep and marginally enhanced S1 in elderly insomniacs. Its effects on the other sleep stages were less uniform over the age groups. Distal skin warming suppressed S2 in young adults, enhanced S2 in elderly people without sleep complaints, and did not affect S2 in elderly insomniacs. In both groups of elderly, but not in young adults, distal skin warming suppressed Wake. Moreover, distal skin warming strongly enhanced SWS in elderly insomniacs, but not in young and elderly participants without sleep complaints. *Proximal skin* warming enhanced the deeper stages SWS and S2 at the cost of S1 and Wake in young adults and even more so in elderly without sleep complaints. In the elderly insomniacs, proximal skin warming promoted SWS and REM sleep at the cost of S1, S2 and Wake.

3.3.2. Modulation of manipulation effects by time of night within groups

Two questions of relevance to the utility of an ultimate home-applicable system for sleep optimization by skin temperature control are whether a certain temperature level is equally effective from the beginning to the end of the night and whether this is of the same magnitude in young subjects, elderly without sleep complaints and elderly insomniacs. Within each group, we evaluated how the time of night modulated sleep stage probabilities and their sensitivity to temperature manipulations. Therefore, we added (nonlinear) time and time by temperature interaction terms to the logistic regression models. The parameter estimates and a more detailed description of their meaning are available in a supplementary file. They are also visualized in figure 3, which shows the predicted development of sleep stage probabilities throughout the night under conditions where distal and proximal skin would both be kept at ‘cool’ (left column) versus ‘warm’ (right column) levels continuously. Some temperature by time of night interaction

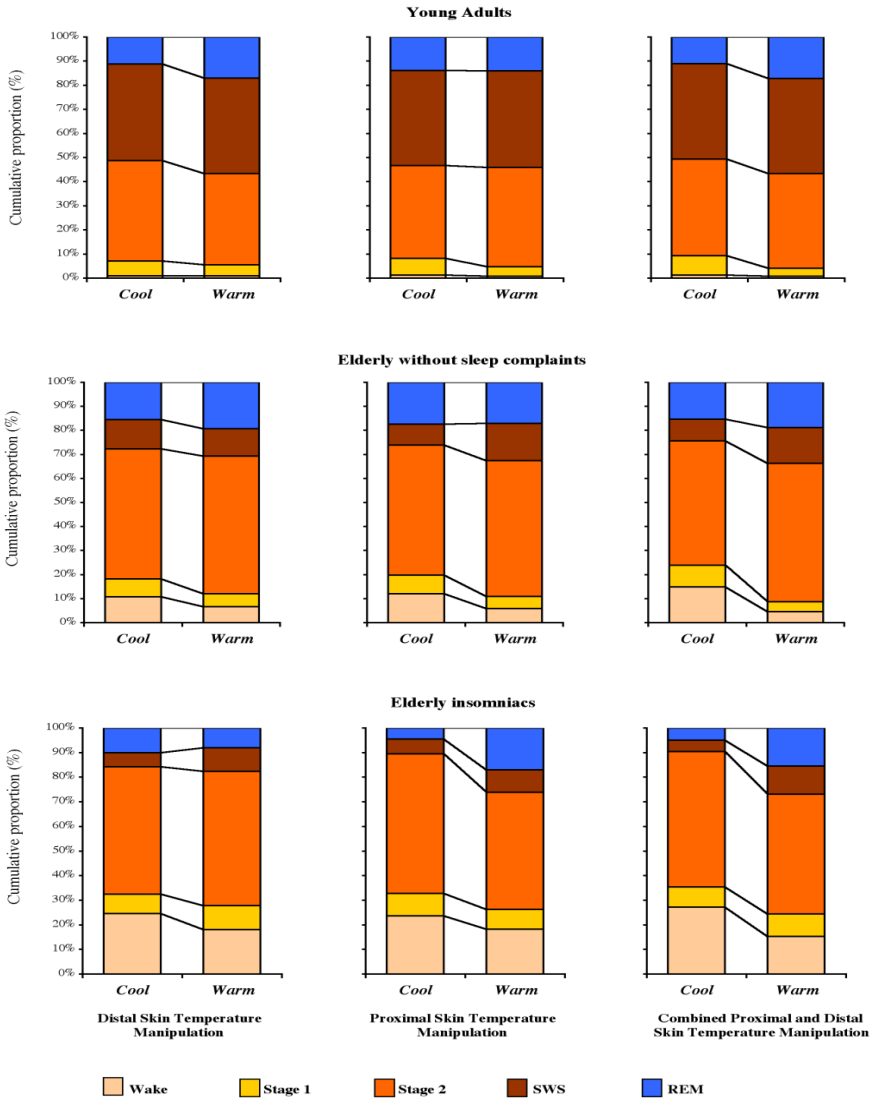


Fig. 2. Graphical representation of the main effects logistic regression results. The stacked areas visualize the cumulative proportion of each sleep stage occurring over the whole night in case of the cool versus warm thermosuit temperatures for young adults (top panels), elderly without sleep complaints (middle panels) and insomniac elderly (bottom panels). Effects of distal warming versus cooling ($T_{suit\text{-}dist}$ at their minimal level of 31.7˚C (stacked bars left) and at their maximal level of 34.6˚C (stacked bars right)) are displayed in the left column, effects of proximal warming versus cooling ($T_{suit\text{-}prox}$ at their minimal level of 31.7˚C (stacked bars left) and at their maximal level of 34.6˚C (stacked bars right)) are displayed in the middle column and effects of total skin warming versus cooling (both $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ at their minimal level of 31.7˚C (stacked bars left) and at their maximal level of 34.6˚C (stacked bars right)) are displayed in the right column. The actual predicted cumulative proportion over all sleep stages may slightly exceed or fall behind 100% since the proportions were derived in separate logistic regressions for each sleep stage. For graphical purposes only, rescaling to 100% has been applied to correct for minor deviations in figure 2 and 3.

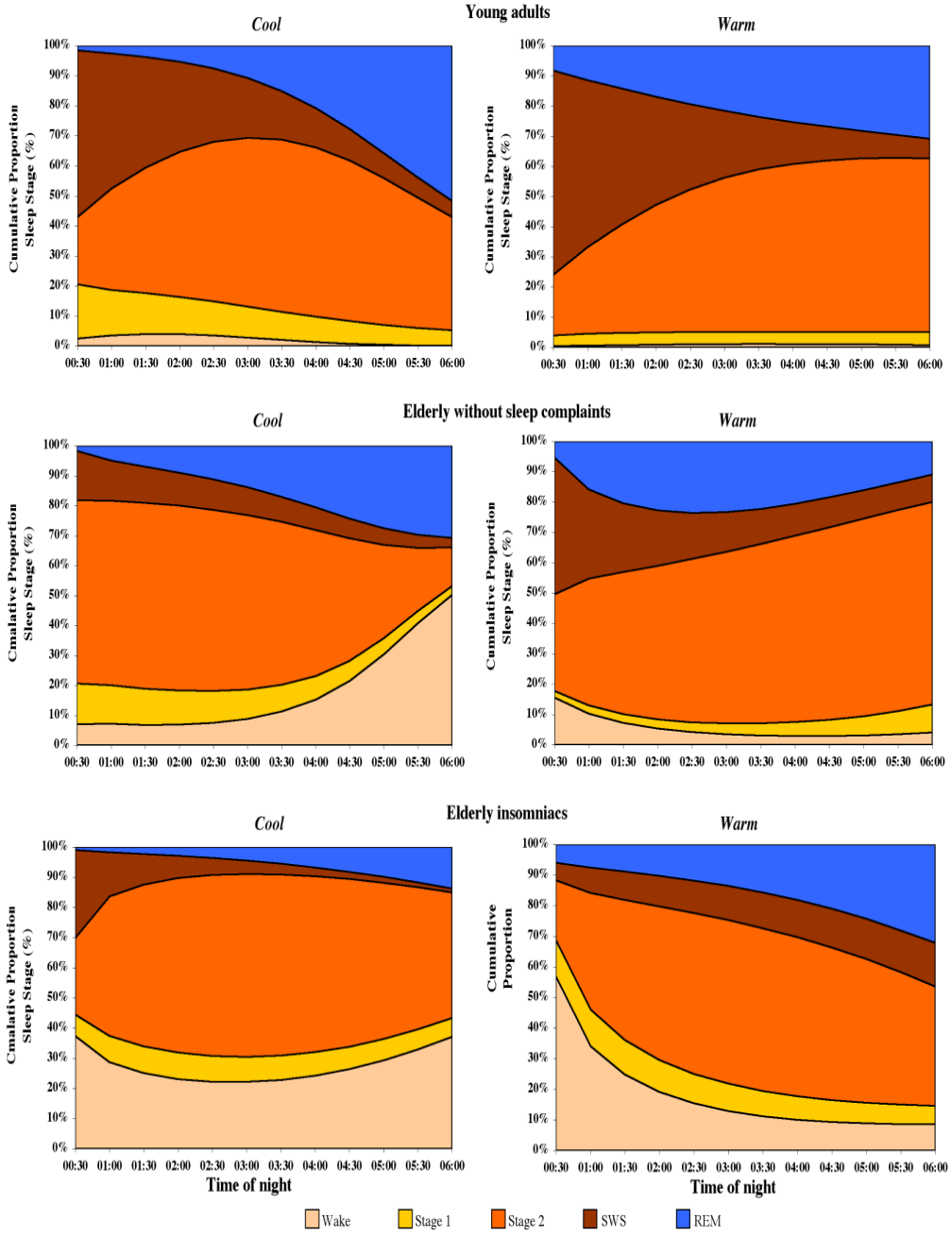


Fig. 3. Graphical representation of the results of the logistic regression analyses that included main effects, time of night modulation and manipulation by time of night interactions. Stacked areas represent the model-predicted cumulative proportion of each sleep stage occurring at each time of the night in case of cool (minimal proximal and distal T_{suit} (both 31.7˚C), left panels) versus warm (maximal proximal and distal T_{suit} (both 34.6˚C), right panels) thermosuit temperatures for young adults (upper panels), elderly without sleep complaints (middle panels) and insomniac elderly (lower panels).

Table 3 Summary of the main effects of temperature manipulations on sleep stages

Stage	Young adults		Elderly without sleep complaints		Elderly insomniacs	
	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*
Wake	0.84 (0.77–0.92)***		0.77 (0.73–0.81)***	0.86 (0.81–0.90)***	0.87 (0.84–0.91)***	0.86 (0.82–0.90)***
S1	0.80 (0.73–0.89)***	0.89 (0.81–0.98)*	0.86 (0.81–0.92)***	0.91 (0.85–0.97)**	0.94 (0.88–0.99)*	1.06 (1.00–1.13)*
S2	1.04 (1.01–1.08)*	0.95 (0.92–0.98)**	1.04 (1.01–1.08)*	1.09 (1.06–1.13)***	0.87 (0.84–0.89)***	
SWS	1.08 (1.03–1.13)**		1.25 (1.19–1.32)***		1.14 (1.08–1.20)***	1.18 (1.12–1.25)***
REM		1.20 (1.15–1.26)***		1.12 (1.07–1.17)***	1.62 (1.53–1.71)***	0.91 (0.86–0.95)***

Odds ratio (OR), confidence interval (CI) and significance (*P*) for the occurrence of each sleep state are given per C modulation of the temperature of the thermosuit ($T_{suit\ prox}$ and $T_{suit\ dist}$) warming the distal and proximal skin areas. Note that whereas the odds ratios are given per 1°C, the thermosuit temperature was actually modulated over a 3°C range, i.e. resulting in stronger actual effects than shown in the table: Fig. 2 shows a representative interpretation of the effect sizes. A supplementary file contains a Table 4 which provides models including changes over time and interactions effects of T_{suit} by time. $^{***}P<0.001$, $^{**}P<0.01$, $^{*}P<0.05$.

effects on sleep stage probabilities can be highlighted as having practical relevance. First, the net effect of distal and proximal temperature by time of night interactions indicates that skin warming enhances SWS most effectively in the beginning of the night in young and elderly subjects without sleep complaints. In contrast, SWS enhancement by skin warming commenced only after about one and a half hour of sleep in elderly insomniacs, and continued throughout the night. Second, in both elderly subject without sleep complaints and elderly insomniacs, the net wake-suppressing effect of skin warming increased towards the end of the night, when its sleep-preserving effect was very marked and consequently prevented early morning awakening.

3.4. Manipulation effects on sleep-EEG spectral power

In addition to the qualitative assessment of sleep stages, the effects of skin temperature manipulations on the quantitative NREM sleep (NREM sleep = non REM sleep, i.e. S1, S2 and SWS) EEG spectral power were examined using multilevel linear regressions for each 1 Hz bin. Figure 4 presents the average spectra for the fronto-central and parieto-occipital EEG leads, as well as the percentage of change in spectral power per ˚C change in T_{suit} for those frequency bins that were significantly ($p<0.05$) affected.

In *young adults*, *proximal* skin warming enhanced EEG power in the sleep-propensity-related frequency range at both the fronto-central (FpzCz) (all $p<0.0001$ for the 0.4-12 Hz range) and parieto-occipital (PzOz) (all $p<0.04$ for the 0.4-12 Hz range) derivations. Proximal warming also enhanced the sigma frequency range where sleep spindles occur, both at FpzCz ($p<0.01$ for the 13-14 Hz bin) and at PzOz ($p<0.002$ for the 13-15 Hz range). Proximal skin warming moreover attenuated EEG power in the 16-30 Hz frequency range typical of alert wakefulness (for FpzCz, all $p<0.0002$ for the 16-30 Hz range; for PzOz, all $p<0.003$ for the 19-24 Hz range). *Distal* skin warming increased the sleep-related 1-3 Hz range power at FpzCz (all $p<0.03$), and 5-7 Hz range power at PzOz (all $p<0.002$). It also enhanced the 14-15 Hz sleep spindle range power at both FpzCz ($p<0.006$) and PzOz ($p<0.002$). Nevertheless, at PzOz, distal warming also enhanced the wake-related lower beta frequencies (15-21 Hz, $p<0.03$). Finally, distal skin warming attenuated EEG-power in the alpha frequency range at both FpzCz (all $p<0.0001$ for the 7-12 Hz range) and PzOz (all $p<0.001$ for the 9-12 Hz range).

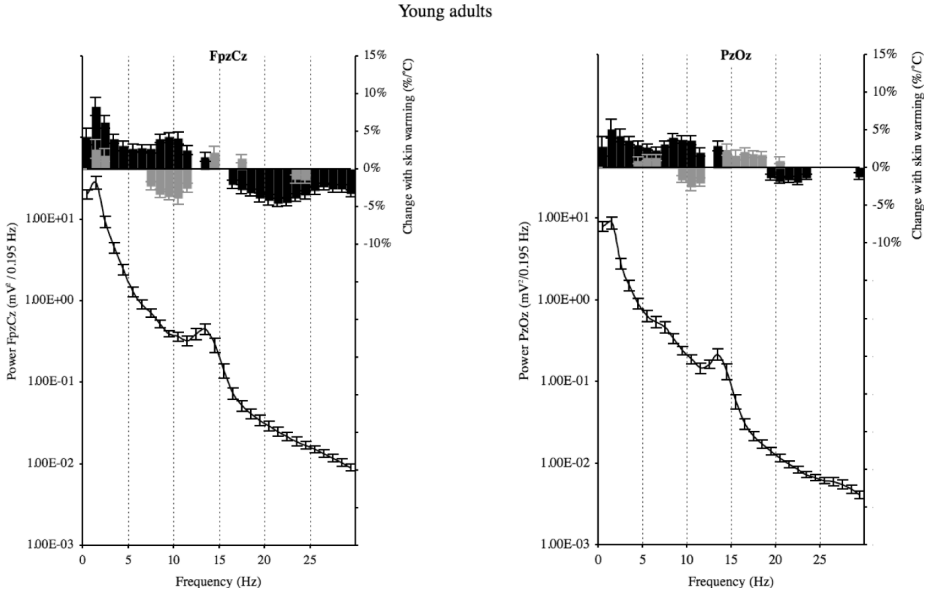
In *elderly without sleep complaints*, *proximal* skin warming enhanced the fronto-central expression of the sleep-related 1-9 Hz range ($p<0.03$) and the higher sleep spindle frequency bin (14-15 Hz, $p<0.0004$), and suppressed a lower sleep spindle frequency bin (12-13 Hz, $p<0.002$) and the wake-related beta range (16-25 Hz, $p<0.03$). Proximal warming also enhanced the parieto-occipital expression of the sleep related 0.4-9 Hz range ($p<0.05$) and suppressed the 10-29 Hz range ($p<0.02$). *Distal* skin warming suppressed the fronto-central expression of the alpha range (7-12 Hz, $p<0.005$) and enhanced the 14-23 Hz range ($p<0.05$). Parieto-occipital, distal warming

suppressed the sleep related 0.4-6 Hz range ($p<0.03$) and enhanced a few frequency bins between 10 and 23 Hz ($p<0.04$).

As compared to the elderly people without sleep complaints, the overall EEG power spectra of *elderly insomniacs* (see figure 4) were characterized by a notable fronto-central reduction in the lower frequency range (0.4-5 Hz, all $p<0.02$, z-test) and sleep spindle peak frequency (13-14 Hz, $p=0.03$). The effects of temperature manipulation on the power spectra of the insomniac elderly were more restricted. Other than some minor spectral changes, only the enhancement of the sleep-related parieto-occipital slow wave sleep related 0.4-2 Hz range by proximal warming stood out ($p<0.001$).

To summarize the strongest effects of *proximal* warming: it especially enhanced the slow oscillation (0.4-1 Hz) frequency range at PzOz in all groups and at FpzCz in young subjects only; and enhanced the slow wave (delta, 1-4 Hz) frequency range at PzOz in all groups and at FpzCz in young and elderly well sleeping subjects only. Moreover, it enhanced the higher sleep spindle frequency bin (14-15 Hz) in young adults and elderly without sleep complaints, but rather suppressed it in elderly insomniacs. Proximal warming also suppressed the wake-related higher frequencies in young adults and elderly without sleep complaints, but somewhat enhanced it (fronto-central only) in elderly insomniacs.

To summarize the strongest effects of *distal* warming: its effects were more equivocal, and mainly present in young adults and elderly without sleep complaints. It suppressed the alpha range (8-12 Hz) and induced some increase in the beta range (15-23 Hz). Only in elderly without sleep complaints and only on PzOz, it suppressed the slow oscillation, delta, and lower theta ranges (0.4-6 Hz) – which is compatible with the shift towards S2 and REM sleep indicated by the logistic regression analyses.



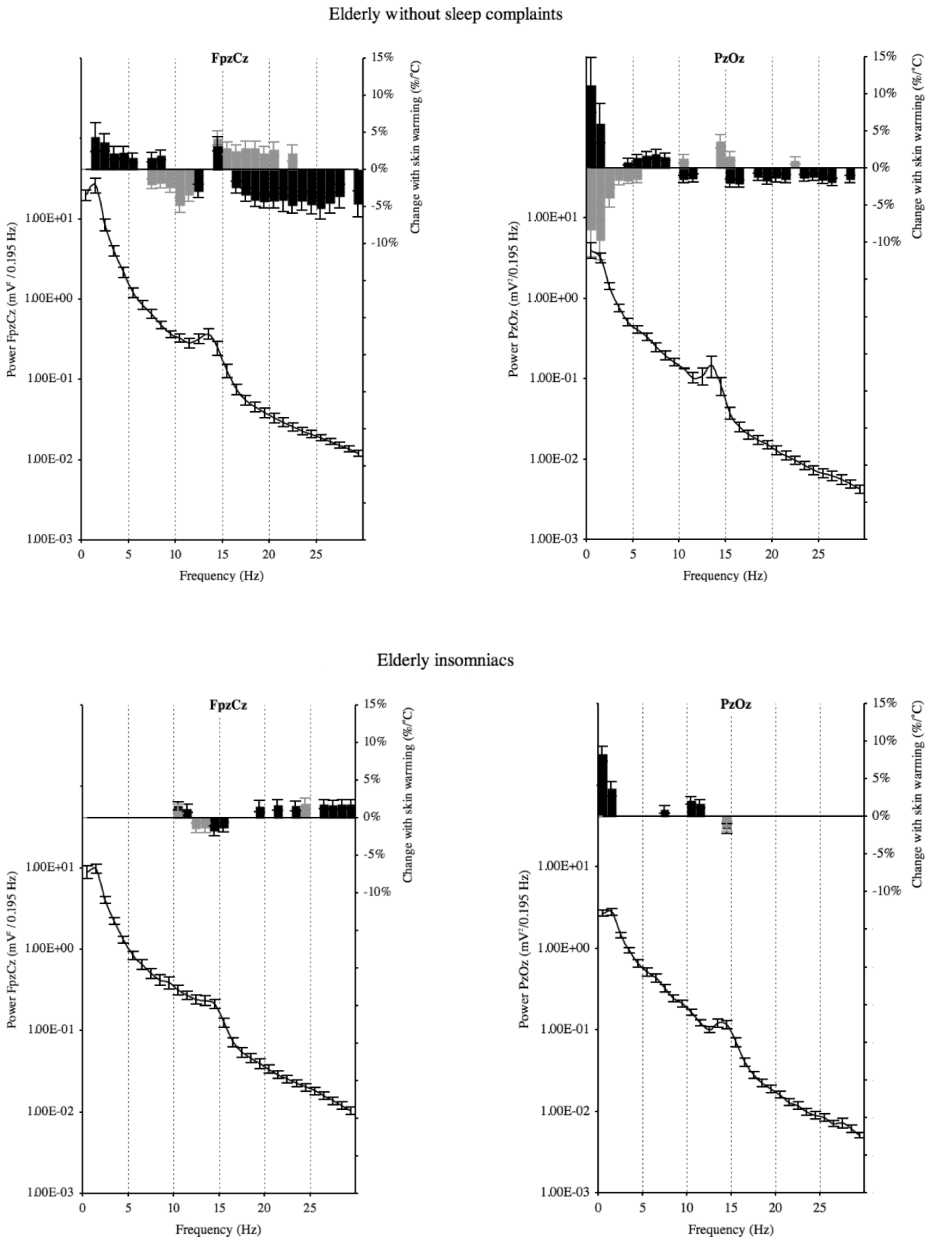


Fig. 4. EEG power spectra averaged over all artifact-free 30 second epochs scored as NREM sleep throughout the night from FpzCz (left panels) and PzOz (right panels) for young adults (upper panels), elderly without sleep complaints (middle panels) and insomniac elderly (lower panels). The traces give the mean±SEM spectra for each group, given in milli-volt^2/0.2 Hz bin. The bars indicate, for each 1 Hz bin, the percent change (±SEM in power per °C change in Tsuit, if significant ($p<0.05$). Note that the actually induced changes may be three times as much, given the range of thermosuit manipulation (3˚C). Black bars represent power changes induced by manipulation of the proximal part of the thermosuit. Gray bars represent power changes induced by manipulation of the distal part of the thermosuit. (lower panels).

4. Discussion

The results of the present study have demonstrated for the first time that sleep depth is strongly affected by direct mild manipulation of skin temperature within the thermoneutral zone that normally occurs during everyday life under comfortable sleeping conditions. Of note, core body temperature remained unchanged and could thus not have mediated any of the effects. After demonstrating the effect of skin temperature manipulations in young adults, the robustness of the effects was verified in elderly with, and without, sleep complaints, in whom both thermosensitive and thermoregulatory capacities are changed (Chapter 2, this thesis)[54]. In young and older subjects without sleep complaints, proximal warming resulted in deeper sleep and suppressed wakefulness, whereas distal skin warming enhanced REM sleep and suppressed light sleep (see figure 2 and table 3). Elderly insomniacs responded somewhat differently, in that proximal warming enhanced slow wave sleep and REM sleep, whereas distal warming enhanced slow wave sleep and suppressed REM sleep (see figure 2 and table 3). The fraction of SWS (see table 2) reported here may seem high for elderly and insomniacs and could result from the fact that we limited the allowed sleep time to 6 hrs (5.5 hrs analysed) in the present protocol. The even higher fraction of SWS in the skin warming condition suggests that this procedure can raise the amount SWS to a level not habitually seen in elderly people. Most importantly, the results show that mild skin temperature manipulations can be chosen such as to significantly reduce early morning awakening and enhance deeper sleep stages (see figure 3). Early morning awakening and a lack of deep sleep are typical findings even in elderly people who do not have sleep complaints. Elderly participants showed such a pronounced sensitivity to skin temperature manipulations, that the induction of a relatively small (0.4˚C) increase in skin temperature lowers the probability of being awake at 6:00 in the morning (P(W|6:00)) by a factor 14 (from 0.58 to 0.04) for elderly without sleep complaints, and by a factor 5 (from 0.36 to 0.07) in elderly insomniacs (see figure 3). In addition, subtle skin warming significantly restored the age-related decrease in SWS - often considered the most physiologically restorative stage of sleep. The induction of a 0.4˚C increase in skin temperature doubled the overnight occurrence of slow wave sleep from 8% to 14% in elderly without sleep complaints and from 4% to 9% in elderly insomniacs (see figure 3). Frequency spectra of the NREM sleep EEG (see figure 4) confirmed that skin warming enhanced low frequency cortical oscillations, in agreement with the previously reported slowing of EEG with skin warming in a primate study[2].

An important question to be evaluated in further studies is whether the mild skin warming procedure would be equally effective if it was applied continuously during the whole night instead of intermittently as in the present study. It might be argued that our finding of increased sleep depth with mild warming could be due to a 'rebound' of deeper sleep stages during the warming periods if their normal development would have been suppressed during the 'cool' periods. In brief, be-

cause our hypothesis was that mild skin warming would enhance sleep, we made sure that our baseline ('cool') would be optimally comfortable, such that it would not suppress sleep. During pilot studies, we determined the baseline ('cool') level so that is was perceived as optimally comfortable and thermoneutral. This was verified in one published study (Chapter 4, this thesis)[40], in which we demonstrated that the 'cool' condition was in fact perceived as even slightly more comfortable than the warm condition. We also ensured that the skin temperatures induced in our present protocol did not drop below normal proximal and distal skin temperatures measured using ambulatory equipment[49] under habitual sleeping conditions at home. In 15 well-sleeping elderly (7 m, 8 f, age 62 ± 2 years mean ± s.e.m.) and 20 insomniac elderly (8 m, 12 f, age 59 ± 1 years) the mean distal skin temperature measured at home in the 00:30-6:00 hr period was 34.4 ± 0.2˚C and 34.8 ± 0.1˚C, respectively (unpublished data). Our present manipulations never induced the mean distal skin temperature to drop below 34.84˚C, even in the 'cool' conditions (see table 1). Similarly, the mean proximal skin temperature measured in bed at home was 34.6 ± 0.2˚C for well-sleeping elderly and 34.8 ± 0.1˚C for elderly insomniacs, while our present manipulations never induced the mean distal skin temperature to drop below 34.85˚C, even in the 'cool' conditions. In conclusion, because the baseline ('cool') condition was already somewhat warmer than the habitual sleep microclimate at home, it is unlikely that it suppressed the normal development of sleep. Warming studies over the whole nocturnal period are warranted to verify that the sleep-enhancing effect and sleep-depth-enhancing effect of mild skin warming can indeed be sustained. Future research should also be designed in a way that is more suitable to evaluate temperature effects on REM sleep; mainly for reasons of logistics our protocol finished at 6:00 hr in the morning and may thus have compromised the typical enhanced expression of REM sleep at the end of the night.

Previous studies reported skin and bed temperature microclimates of 34 to 36˚C during sleep[20,37,38]. In the present study, skin temperature was manipulated within a narrow 0.4˚C range around a mean of 35.1˚C, i.e. well within the normal comfortable skin temperature range during sleep. Of note, the sleep-enhancing effects of slight warming cannot simply be attributed to changes in comfort, since we previously demonstrated that the upper limit of the manipulated range is in fact perceived as slightly less comfortable[40]. Of further importance for perceived comfort is the fact that our study is unique in the sense that skin temperature manipulations were applied while keeping the temperature of the environmental air – which was breathed and to which the face was exposed – at 21˚C. We do not expect that elevating ambient temperature instead of directly manipulating the proximal and distal skin, would lead to any comparable sleep improvements, because elevated air temperatures may be experienced as uncomfortable. Worse sleep has indeed been reported with an air temperature of 30˚C, as compared to 18˚C and 23˚C[19].

It thus appears of utmost importance to limit the manipulations to the proximal and distal skin area, i.e. the area normally covered by bedding.

The finding that skin temperature modulates sleep depth may provide a possible explanation for the sleep improvement that previous researchers found to occur following passive body heating[6,12,13,21,22,23,24,45]. The increase in core body temperature induced by passive body heating activates heat loss mechanisms including increased skin blood flow, resulting in increased skin temperature. This increase in skin temperature may have been involved in the reported acceleration of sleep onset and increase in slow wave sleep. Such an explanation is supported by the results of the only passive body heating study that included both polysomnography and skin temperature measurements[45]: in this study, the sleep-promoting effects subsided as soon as the hot bath induced increase in skin temperature had normalized after two hours of sleep. In keeping with data from previous studies in which an association between sleep propensity and distal skin temperature was reported[5,25,26,32] our present and recently reported studies[39,40] support the view that there is not only a correlation, but actually a causal effect of skin temperature on sleep.

The magnitude, body location and timing of the skin temperature manipulation are of crucial importance for its application to improve sleep. Our results indicate that a clinically-useful thermal sleep treatment should aim at individualized and time-of-night dependent control of proximal skin temperature within the small range of reported skin and bed temperature microclimates during sleep[20,37,38]. Our results moreover suggest that bed microclimate temperature should ideally be kept, on average, above 33.5˚C, 33.2˚C and 33.1˚C for young adults, elderly subjects without sleep complaints and elderly people with sleep complaints respectively. It is not sufficient to merely apply heating blankets, which warm up the skin and core body without knowledge about the actual body temperatures, which may become too high and adversely affect sleep[17] – most likely by activating heat stress responses. Whereas our thermosuit cannot be regarded as optimally suited for application at home, it is conceivable to develop a system integrated in the bedding that both measures skin temperature and controls the bed microclimate within a feedback control loop.

In the absence of such a system and its validation, how can a clinician at present utilize the advancing insight on the importance of skin temperature for sleep with yet available methods? For a patient reporting with sleep complaints, a first valuable step would be to measure his or her skin temperature during habitual sleep at home. Low-cost small and unobtrusive temperature sensors have recently been validated for such purpose[49]. Since we recently found a marked decrease in the subjective perception of optimal sleeping temperatures in old age, especially in insomniacs[41], it may well be that that people sleep under thermal conditions that do not favour sleep, without realising this fact. If skin temperature measurements suggest this to be the case, what temperature manipulation methods are available? In the case of low skin temperature measurements, a first approach would be to optimize the sleeping microclimate by heat insulation (additional

clothes or bedding) or by pre-warming of the bed with an electric heating blanket. As mentioned above, it is important to switch off the heating blanket during actual sleep. A second approach is to increase the heat load of the body prior to bedtime. This can be accomplished using passive body heating (e.g. bathing, sauna) or active body heating (exercise); both will help to maintain skin temperature elevated during subsequent sleep[52,53]. For complaints of early morning awakening, one may try an electrical heating blanket set at its lowest capacity and connected to an AC power timer to accomplish a delayed start.

In conclusion, the present results show a strong modulating effect of skin temperature on sleep depth, which is compatible with the hypothesis that skin temperature affects sleep-regulating areas in the brain[51] The finding may be involved in the suboptimal sleep that many elderly complain of, because their previously reported attenuated behavioural response to off-neutral environmental temperature[50] may keep them from taking the behavioural actions necessary to optimize the thermal microclimate of the bed. The effects of even very minimal temperature manipulations within the thermoneutral comfortable range are so pronounced that they warrant further research into practical thermal manipulation applications to improve sleep.

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Chapter 9

Manipulation of skin temperature improves nocturnal sleep in narcolepsy

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Summary

Objective: Besides excessive daytime sleepiness, disturbed nocturnal sleep is a major complaint of patients with narcolepsy. Previously, alterations in skin temperature regulation in narcoleptic patients have been shown to be related to increased sleepiness. This study tests the hypothesis that direct control of nocturnal skin temperature might be applied to improve the disturbed sleep of narcoleptic patients.

Methods: Participants were eight patients (five males) diagnosed as having narcolepsy with cataplexy according to the ICSD-2 criteria, mean (SD) age 28.6 (6.4) years, range 18–35 years. During two nights, sleep was recorded polysomnographically while proximal and distal skin temperature were manipulated using a comfortable thermosuit that induced skin temperature to cycle slowly with an amplitude of only 0.4°C within the comfortable range normally observed during sleep. Logistic regression was used to evaluate the effect of skin temperature manipulation on the probability of occurrence of different sleep stages and nocturnal wakefulness.

Results: Proximal skin warming significantly suppressed wakefulness and enhanced slow wave sleep (SWS). In contrast, distal skin warming enhanced wakefulness and stage 1 sleep at the cost of SWS and REM sleep. The optimal combination of proximal skin warming and distal skin cooling led to a 160% increase in SWS, a 50% increase in REM sleep and a 68% decrease in wakefulness, compared with the least beneficial combination of proximal skin cooling and distal skin warming.

Interpretation: Subtle skin temperature manipulations under controlled conditions significantly improved the typical nocturnal sleep problems in narcolepsy.

1. Introduction

The four classical symptoms of narcolepsy are excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis[11]. In recent years, disturbed nocturnal sleep has gained increasing attention as a fifth core symptom that severely affects quality of life[11]. Nocturnal polysomnography in patients with narcolepsy shows a fragmentation of the normal sleep pattern with frequent arousals and a decrease in slow wave sleep[6,8,10]. Several hypnotics, including sodium oxybate (gammahydroxy-butyrate), are currently used to improve nocturnal sleep in narcolepsy[2]. Narcolepsy is caused by a loss of the neuropeptide hypocretin (orexin), a neurotransmitter that is produced by neurons in the lateral hypothalamus[12,17].

There is a relation between sleep and both core body and skin temperature[20,21] In everyday life and under laboratory conditions with a comfortable to warm environmental temperature, core body temperature is lower and the average skin temperature is higher during the night than during the day[9,21]. Sleep-onset latency is negatively correlated to the temperature of distal skin areas (hands and feet)[7]. There seems to be a causal relation, since mild warming of the skin compromises sustained vigilance (see Chapter 4, this thesis)[13] and facilitates sleep initiation (see Chapter 6, this thesis)[14]. Moreover, mild active manipulation of the skin temperature within the comfortable and circadian range affects night-time sleep in healthy controls (see Chapter 8, this thesis)[15].

In a previous study, we reported disturbances in skin-temperature regulation in narcolepsy[3]. Narcoleptic subjects showed a combination of a higher distal skin temperature and a lower proximal skin temperature, which in healthy subjects is associated with the process of falling asleep[7]. In a follow-up study, we were able to improve both daytime vigilance and maintenance of wakefulness by mild manipulation of skin temperature and core body temperature (see Chapter 7, this thesis)[4]. To test the hypothesis that manipulation of skin temperature might be applied to ameliorate the disturbed nocturnal sleep in narcolepsy as well, we performed subtle manipulations of proximal and distal skin temperature during two nocturnal sleep episodes in eight narcoleptic patients.

2. Materials & Methods

2.1. Subjects

Eight narcoleptic patients (five males, 18–35 years of age; mean (SD): 28.6 (6.4) years) participated with informed consent. All suffered from excessive daytime sleepiness and typical cataplexy according to the ICSD-2 criteria for narcolepsy with cataplexy[1.] All subjects were free of medication, except for one female subject using oral contraceptives. All females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase or pseudo-follicular phase). All sub-

jects participated in the summer season (July/August). The protocol was approved by the Medical Ethics Committees of the Academic Medical Center in Amsterdam and the Leiden University Medical Center. The same eight subjects were used in the aforementioned study, where both skin temperature and core body temperature were manipulated during daytime (see Chapter 7, this thesis)[4].

2.2. Design

A previously described design was used to differentially manipulate proximal and distal skin temperature, and to determine the effects of these manipulations on sleep depth (see Chapter 8, this thesis)[15]. Subjects refrained from caffeine, alcohol and tobacco for 8 h before reporting at the sleep laboratory at 22:00. There they were prepared for polysomnography and fitted with a thermosuit. At midnight, lights were turned off, and subjects were allowed to sleep until 06:00. From 00:30 until 06:00, their proximal and distal skin temperatures were manipulated. After this, subjects slept one night at home, after which they returned for a second night in the sleep laboratory, during which the temperature manipulation sequence (see below) was inverted to that of the first night.

2.3. Temperature Manipulations and Measurement.

Starting at 0:30, the temperature of the proximal skin ($T_{skin\text{-}prox}$) and the temperature of the distal skin ($T_{skin\text{-}dist}$) were differentially manipulated by slowly altering the temperature of the water that perfused the thermosuit (fig 1). The suit temperature (T_{suit}) stayed at constant plateaus of either 15 or 30 min with slow (15 min) transitions in between. The order of the sequences of skin temperature manipulations was different for each subject within its group and chosen in such a way that it resulted in an optimal uniform distribution of combinations of high and low $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ levels throughout the night over all subjects, that is at any time of night there was an equal proportion of ''warm'' and ''cool'' periods. T_{suit} cycled between 31.9 (0.1)°C (mean (SE)) in the ''cool'' and 34.8 (0.1)°C in the ''warm'' condition, as measured once per minute on the isolated inflow tubes at their connections with the thermosuit using PT100 thermistors (RTD-3-3105, Omega, Stanford). This range was specifically chosen to match the previously reported range of temperatures normally present in the bed microclimate[5]. The environmental temperature was kept at 21°C. Skin and core body temperature was recorded as described previously (see Chapter 6, this thesis)[14].

2.4. Sleep Recordings

Polysomnographic sleep recordings were performed according to standard procedures[22]. An experienced sleep technician blind to the temperature conditions scored sleep stages in 30-second epochs according to the Rechtschaffen and Kales criteria using Somnologica software[16].

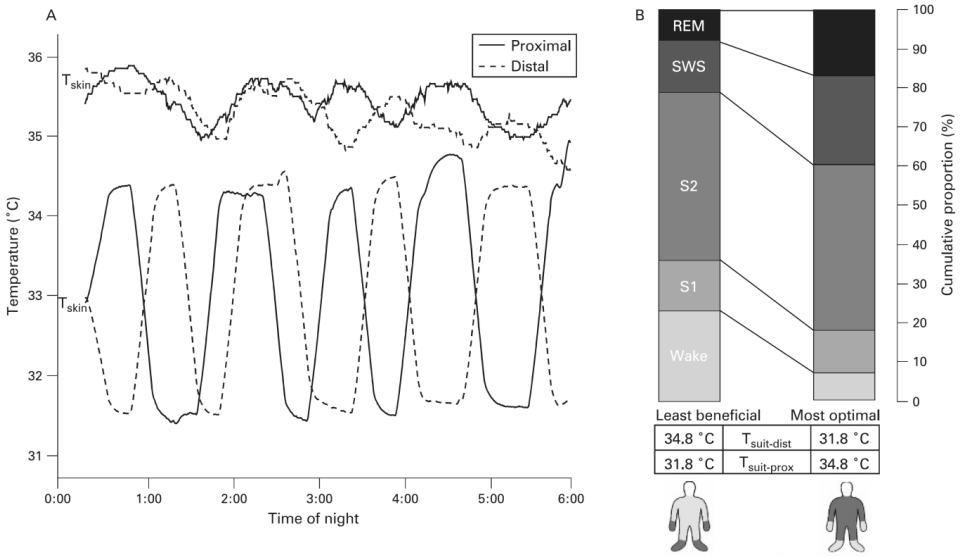

Fig. 1. (A) Example of a temperature profile induced in one patient during a single night. The lower traces show the temperature of the proximal (solid line) and distal (dotted line) parts of the thermosuit. The upper traces show the actually induced proximal and distal skin temperatures. (B) Graphical representation of the proportion of the sleep stages during the optimal (distal cooling and proximal warming) and least beneficial (distal warming and proximal cooling) manipulation scheme. The proportions were derived in separate logistic regressions for each sleep stage. For graphical purposes only, the figure was rescaled to 100%. S1: stage 1 sleep, S2: stage 2 sleep, SWS: slow-wave sleep, REM: rapid-eye-movement sleep.

2.5. Statistical Analysis

The main outcome measures of this study were the effects of proximal and distal skin warming or cooling on the odds ratios for the occurrence of each sleep stage (stage 1, stage 2, slow-wave sleep, REM sleep and wakefulness). Mixed effect (or multilevel) regression modelling was applied to account for the interdependency of the data points inherent to the hierarchical structure of the dataset: sleep epochs within nights within subjects (MLwiN software, Centre for Multilevel Modelling, Institute of Education, London)[19]. The analyses included all epochs during the skin temperature cycles (from 00:30 until 6:00). To determine the effects of skin temperature manipulation on the probability of occurrence of each sleep stage or wakefulness, longitudinal multilevel logistic

regressions were applied for each sleep stage classification, with the current presence or absence of that stage as dummy coded dichotomous dependent variable and $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ as predictor variables. Two-tailed significance levels were set at 0.05. For a graphical representation, odds ratios (OR) were translated into whole-night sleep stage probabilities for two conditions, reflecting the most and least profitable combination of upper (34.8 (0.1)°C) and lower (31.9 (0.1)°C) T_{suit} levels (see results). These probabilities can easily be calculated using the transformation $e^x/(1+e^x)$, where x represents the regressor part of the best-fitting regression model.

3. Results

3.1. Induced Temperatures

With the thermosuit approach, we were able to differentially manipulate proximal and distal skin temperature (see example of one night in one patient in fig 1). The temperature manipulations of the proximal part of the thermosuit accounted for 53.8% of the variance in mean $T_{skin\text{-}prox}$. $T_{skin\text{-}prox}$ averaged 35.1 (0.1)°C (mean (SEM)) at the warmest level versus 34.7 (0.1)°C at the coolest level. Likewise, the independently manipulated temperature of the distal part of the thermosuit accounted for 44.0% of the variance in mean $T_{skin\text{-}dist}$. $T_{skin\text{-}dist}$ averaged 35.5 (0.05)°C at the warmest level versus 35.1 (0.05)°C at the coolest level. Thus, the manipulations forced the skin temperature to cycle slowly within a very subtle 0.4°C range (see temperature graph in fig 1). The manipulations left core body temperature virtually unchanged (skin temperature manipulations accounted for only 2.5% of the variance in core body temperature).

3.2. Effects of Temperature Manipulations on Sleep Stage Distribution

Thermosuit manipulation of the temperature of the proximal and distal skin significantly affected sleep depth and the occurrence of wakefulness. Table 1 shows that proximal warming suppressed wakefulness (OR 0.81, CI (0.77 to 0.84), $p<0.001$) and enhanced slow-wave sleep (OR 1.23 (1.17 to 1.29), $p<0.001$; all OR expressed per 1°C increase in T_{suit}). In contrast, distal warming enhanced wakefulness (OR 1.11 (1.06 to 1.16), $p<0.001$) and stage 1 sleep (OR 1.22 (1.16 to 1.28), $p<0.001$) sleep at the cost of slow-wave sleep (OR 0.85 (0.81 to 0.89), $p<0.001$) and REM sleep (OR 0.87 (0.83 to 0.92), $p<0.001$). There were no significant effects on the occurrence of stage 2 sleep. A graphical representation of the sleep-stage distribution is given in fig 2. As compared with the least favourable skin temperature combination, the optimal combination led to a 160% increase in slow-wave sleep, a 50% increase in REM sleep and a 68% decrease in wakefulness.

Table 1 Odds ratio (OR), CI and p value for the occurrence of each sleep state as modulated by the temperature of the thermosuit warming the distal ($T_{suit-dist}$) and proximal ($T_{suit-prox}$) skin (per 1°C)

	$T_{suit-prox}$		$T_{suit-dist}$	
	OR (95% CI)	**p Value**	**OR (95% CI)**	**p Value**
Wake	0.81 (0.77 to 0.84)	<0.001	1.11 (1.06 to 1.16)	<0.001
S1	0.98 (0.93 to 1.03)	NS	1.22 (1.16 to 1.28)	<0.001
S2	1.02 (0.99 to 1.05)	NS	1.01 (0.98 to 1.04)	NS
SWS	1.23 (1.17 to 1.29)	<0.001	0.85 (0.81 to 0.89)	<0.001
REM	0.98 (0.93 to 1.03)	NS	0.87 (0.83 to 0.92)	<0.001

REM, rapid-eye-movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow-wave sleep.

4. Discussion

This study shows that subtle manipulation of proximal and distal skin temperatures has beneficial effects on nocturnal sleep in narcolepsy. When the proximal skin was warmed, slow-wave sleep increased, and wakefulness was suppressed. In contrast, warming of the distal skin suppressed slow-wave and REM sleep, while enhancing wakefulness and stage 1 sleep.

Fragmented nocturnal sleep is a major and difficult to treat problem for many patients with narcolepsy. Currently, treatment of this invalidating symptom is based on hypnotics, most notably sodium oxybate[2], which increases slow-wave and REM sleep, while suppressing wakefulness[8,18].

The present study was designed in such a way that different manipulation schemes were equally and randomly distributed over the test subjects in a balanced way. As such, the effects cannot have been caused by time of night or circadian effects, but can be solely attributed to the manipulation of skin temperature. The fact that subtle changes in skin temperature affect sleep in both narcoleptic patients and healthy controls (see Chapter 8, this thesis)[15] shows that the basic hypothalamic circuitry involved in temperature and sleep regulation is still responsive to manipulation in narcolepsy despite the hypocretin deficiency. In this study, no subject experienced the optimal or least beneficial combination of proximal and distal manipulations continuously during a full night. Furthermore, sleep time was restricted from midnight to 06:00. It would now be of interest to confirm the positive effects found in this study using a controlled trial in which the optimal or least beneficial temperature conditions are applied continuously throughout a full night.

In conclusion, despite the hypocretin deficiency, the basic hypothalamic circuitry involved in temperature and sleep regulation is still responsive to manipulations in narcolepsy. These results raise the intriguing possibility that selective manipulation of skin temperature within the comfortable range might in theory be applied to ameliorate one of the core symptoms of narcolepsy; disturbed nocturnal sleep.

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CONCLUSION

Chapter 10

Summary, general discussion and future perspectives

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General Discussion

At this very moment, let us recall the situations described in the first chapter of this thesis. The first situation was 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 was: *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?* Both questions were addressed to explain *sleep-permissive* and *wake-promoting* effects. Body temperature can act as both *sleep-permissive* and *wake-promoting* factors. As mentioned before a relatively cool core body temperature and a relative warm, but not to warm, skin temperature act as a sleep-permissive signal, whereas a relatively warm core body temperature and a relatively cool skin temperature acts as a wake-promoting factor.

On *anecdotal* level we mentioned the sleep permissive effect of the warmth of the sun, when lying on the beach, the red earlobes of young children getting tired, the use of the fan and air conditioner in the car to stay alert when driving during a hot summer day, the warm rosy feeling after being deprived from sleep, or the difficulties facing when attempting to fall asleep with cold feet. On *scientific* level studies provided 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[49]. A number of studies that investigated spontaneous or indirectly experimentally induced fluctuations in skin temperature however, strongly support an association with vigilance and sleep. Healthy people fall asleep more easily if their skin temperature or bed temperature is higher[24,25,48]. 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[28]; and for narcoleptic patients, where skin temperature is correlated to their daytime sleep propensity[15]. With respect to the ability to maintain alert wakefulness, healthy people perform better during the troughs of their normal daytime skin temperature fluctuations[35]. These aforementioned correlational studies can be interpreted as merely indicating that skin temperature reflects an underlying process of vigilance regulation. But what is the actual *experimental* support for a causal contribution of skin temperature to vigilance regulation in humans? That was the scope of the current thesis.

The present thesis addressed *sleep-permissive* and *wake-promoting* effects of small changes in skin temperature as occur naturally within the thermoneutral zone. Under well-controlled conditions we evaluated the effect of skin temperature manipulations on the onset and maintenance of

sleep, and alertness. A number of controlled experiments were specifically designed to evaluate the following hypotheses.

Hypotheses

1. Within the thermoneutral range, mild skin warming promotes sleep onset (1a) and sleep depth (1b) and impedes vigilance (1c).
2. Skin temperature manipulations yield stronger effects than core body temperature manipulations.
3. Distal skin temperature manipulations yield stronger effects than proximal skin temperature manipulations.
4. Skin temperature manipulations yield stronger effects the more sleep is compromised, i.e. small effects in young people without sleep complaints, medium effects in elderly people without sleep complaints and strong effects in elderly people suffering from chronic insomnia and patients diagnosed with narcolepsy.

In order to evaluate these hypotheses, we first address the use of home applicable foot temperature interventions and studied its effects on sleep onset (Chapter 3). Next, an innovative, well-controlled experimental set-up was build, using a water-perfused thermosuit – during wakefulness in combination with hot and cold food and drinks – to study the effects of mild manipulations of skin temperature and core body temperature on sleep onset (Chapters 4 and 5), on daytime vigilance (Chapters 6 and 7) and on sleep depth and maintenance (Chapter 8 and 9). Below, the specific aims and major findings of the studies reported in Chapter 3 to 9 will be summarized, after which the hypotheses will be revisited.

Summary

The effects of skin warming and core body cooling on sleep onset were addressed in Chapter 3 to Chapter 5. In ***Chapter 3*** we aimed at improving sleep onset using home-applicable distal warming techniques. To do so, we manipulated foot temperature using a footbath before lights off, heatable bed socks before lights-off and heatable bed socks after lights-off in adults without subjective sleep complaints, elderly without subjective sleep complaints and elderly with subjective sleep complaints. Multiple Sleep Latency Test (MSLT) protocol guidelines were followed to quantify sleep onset latency (SOL) polysomnographically. In adults, sleep onset latency was accelerated by warm and neutral bed socks after lights-off and it correlated to the increase in foot temperature. This increase was attenuated in elderly subjects. In elderly subjects without sleep difficulties, sleep onset could be accelerated with neutral bed socks after lights-off and a warm footbath prior

to lights-off. In elderly insomniacs, none of the treatments accelerated sleep onset. We concluded that elderly subjects show an attenuated increase in foot temperature after lights-off and lose the relationship between pre-sleep heat loss activation and sleep latency. The sensitivity of sleep propensity to foot warming changes with age and is attenuated in age-related insomnia.

In ***Chapter 4*** we also intended to accelerate sleep onset, but now using mild skin warming and core body cooling, using a water-perfused thermosuit, in adults without subjective sleep complaints. A 2 day semi constant-routine protocol was followed and each day consisted of a 2x2x2 experimental design to apply different warming and cooling combinations. MSLT protocol guidelines were followed to quantify sleep onset latency polysomnographically. Hence we obtained 144 sleep onset latencies while directly manipulating core and skin temperatures within the comfortable range in 8 healthy subjects under controlled conditions. The induction of a proximal skin temperature difference of only 0.78°C changed SOL by 26% (3.09 minutes), with faster sleep onsets when the proximal skin was warmed. The reduction in SOL occurred in spite of a small but significant decrease in subjective comfort during proximal skin warming. The induction of changes in core temperature of 0.20°C and distal skin temperature of 0.68°C were ineffective. We demonstrated a causal contribution to sleep-onset latency of skin temperature manipulations within the range of its normal nocturnal fluctuations and concluded that circadian and sleep-appetitive behavior induced variations in skin temperature might act as an input signal to sleep-regulating systems.

In ***Chapter 5*** it was studied if the results found in the study described in Chapter 4 could be replicated within a group of elderly adults with and without subjective sleep complaints. The experimental design and innovative setup was identical to the one described in Chapter 4. 288 sleep onset latencies were determined, while directly manipulating core and skin temperatures within the comfortable range in 8 elderly without subjective sleep complaints and 8 elderly with subjective sleep complaints under controlled conditions. Warming the proximal skin by on average 0.72˚C facilitated sleep onset equally effective in healthy elderly by 18% (1.84 minutes) and elderly insomniacs 28% (2.85 minutes). These effects were comparable to the results in healthy young subjects as reported in chapter 4, in spite of a marked decrease in the subjective perception of temperature changes in elderly subjects, especially in insomniacs. We concluded that mild changes in skin temperature have an effect on sleep propensity in elderly and indicate that elderly insomniacs may have a diminished capability to recognize that a slight increase in bed temperature facilitates the initiation or re-initiation of sleep.

The effects of skin warming and core body cooling on daytime vigilance were addressed in Chapter 6 and Chapter 7. In ***Chapter 6*** we tried to impede daytime vigilance using mild skin warming and core body cooling. This study was conducted in the same 3 groups (adults without subjective sleep complaints and elderly both with and without subjective sleep complaints), using the same

experimental design and the same setup as described in Chapter 4 and Chapter 5. Vigilance was assessed using a 7 minute version of the Psychomotor Vigilance Task (PVT) and 432 PVTs were completed, while core and skin temperatures were manipulated within the comfortable range. During the PVTs, response speed typically declined with increasing time-on-task. Proximal skin warming by only 0.68˚C and 0.56˚C respectively accelerated this decline by 67% in young adults and by 50% in elderly subjects. In elderly insomniacs, proximal warming slowed down the mean response speed already from the onset of the task, independent of time-on-task, with 3%. Response speed tended to decrease with age, however reaching significance only in elderly insomniacs. Speed decrements occurred mostly towards the end of the time-on-task in young adults; earlier and more gradually in elderly without sleep complaints; and very early and in a pronounced fashion in insomniacs. Interestingly, the worsening by warming followed the time pattern already present within each group. We concluded that the endogenous circadian variation of skin temperature could modulate vigilance regulating brain areas and thus contribute to the circadian rhythm in vigilance. Minute-by-minute PVT analyses revealed effects of age and insomnia not previously disclosed in studies applying time-point aggregation. Our data indicated that "age-related cognitive slowing" may result, in part, from age-related sleep problems.

In ***Chapter 7*** we addressed the effects of changes in skin and core temperature on daytime vigilance in narcoleptic patients, in order to reveal a possible causal contribution of skin temperature disturbances to impairments in the ability to maintain vigilance and wakefulness in narcolepsy. For optimal comparability, the experimental design and setup was identical to the ones used in the studies described in Chapter 4 to Chapter 6, however, the MSLT procedure was replaced by a Maintenance of Wakefulness Test (MWT) procedure. 144 MWT sleep latencies and PVTs acquired during manipulation of core body and skin temperature within the comfortable range in 8 patients diagnosed with narcolepsy with cataplexy were analyzed. Compared to core cooling, core warming attenuated the typical decline in PVT response speed with increasing time-on-task by 25%. Compared to distal skin warming, distal skin cooling increased the time that the patients were able to maintain wakefulness by 24% (distal warming: 1.88 minutes versus distal cooling: 2.34 minutes). It was concluded that core body and skin temperatures causally affect vigilance and sleepiness in narcolepsy and that this could lead to future practical applications.

The effects of skin warming (but not core body cooling) on sleep macro- and sleep micro- structure were addressed in Chapter 8 and Chapter 9. In ***Chapter 8*** we tested if nocturnal sleep could be improved using mild skin warming in adults without subjective sleep complaints, elderly without subjective sleep complaints and elderly with subjective sleep complaints. Sleep was recorded polysomnographically during two nights while proximal and distal skin temperature were manipulated using a comfortable thermosuit (the same intervention method as used in the sleep onset and the daytime vigilance studies) that induced skin temperature to cycle slowly within the com-

fortable range normally observed during sleep. It was shown that an induction of a mere 0.4˚C increase in skin temperature, whilst not altering core temperature, suppressed nocturnal wakefulness and shifted sleep to deeper stages in young adults and, especially, in elderly healthy and insomniac participants. Young adults showed a decrease in the relative proportion S1 and S2, and an increase of REM, as result of the distal skin warming. Proximal warming resulted in a decrease of Wake and S1, and an increase in S2 and SWS. Elderly healthy participant showed a decrease in the relative proportion Wake and S1, and an increase of S2 and REM, as result of the distal skin warming. Proximal warming resulted in a decrease of Wake, and S1 and an increase in S2 and SWS. Elderly insomniacs showed a decrease in the relative proportion S1 and REM, and an increase of S1 and SWS, as result of the distal skin warming. Proximal warming resulted in a decrease of Wake, S1 and S2, and an increase in SWS and REM. Elderly subjects showed such a pronounced sensitivity, despite the diminished capability to perceive temperature changes, that the induced 0.4˚C increase in skin temperature was sufficient to almost double the proportion of nocturnal slow wave sleep and to decrease the probability of early morning awakening from 0.58 to 0.04. EEG frequency spectra showed enhancement of low frequency cortical oscillations. Skin warming strongly improved the two most typical age-related sleep problems; a decreased amount of slow wave sleep and an increased possibility of early morning awakening. As such, subtle feedback control of in-bed temperature through very mild manipulations could have strong clinical relevance in the management of disturbed sleep especially in the elderly, who have an attenuated behavioural response to suboptimal environmental temperature, which may hamper them from taking appropriate action to optimize their bed temperature.

In ***Chapter 9*** an experimental protocol identical to the one described in Chapter 8 was used in a population of narcoleptic patients, in order to improve the disturbed nocturnal sleep habitually seen in these patients using mild skin warming. As a result of our temperature manipulations, proximal and distal skin temperature cycled slowly with an amplitude of only 0.4°C within the comfortable range normally observed during sleep. Proximal skin warming significantly suppressed wakefulness and enhanced slow wave sleep. In contrast, distal skin *cooling* enhanced SWS and REM sleep at the cost of wakefulness and stage 1 sleep. The cooling of the distal skin most likely brings the habitually nocturnal increased distal skin temperature in narcoleptic patients within the range that is less disturbing for sleep. The optimal combination of proximal skin warming and distal skin cooling led to a 160% increase in SWS, a 50% increase in REM sleep and a 68% decrease in wakefulness, compared with the least beneficial combination of proximal skin cooling and distal skin warming. It was that subtle skin temperature manipulations under controlled conditions significantly improved the typical nocturnal sleep problems in narcolepsy.

Evaluation of hypotheses

Hypothesis 2, 3 and 4 need to be revised as a result of these studies. Firstly, we tested the effect of core body temperature manipulation only during daytime. With the setup that was used we could not apply core body manipulations whilst the participant was asleep. Consequently we can only confirm that skin temperature manipulations yield stronger effects than core body temperature manipulations in changing sleep onset and vigilance at daytime.

We cannot confirm that distal skin temperature manipulations yielded stronger effects than proximal skin temperature manipulations; we mainly could observe the opposite pattern. As mentioned in several of the chapters, we manipulated the proximal skin temperature within or close to the subject's habitual nocturnal range, whereas we might have manipulated distal skin temperature slightly below the subject's habitual nocturnal range. The sleep-permissive effects of distal skin warming might be revealed in a protocol that induces skin temperatures in 2 different ranges for distal skin and proximal skin temperature. However, at the start of the series of studies and also up to now, no normative data on the range of skin temperatures under habitual sleeping conditions are available.

We also cannot confirm that skin temperature manipulations yielded stronger effects the more sleep is compromised, i.e. small effects in young people without sleep complaints, medium effects in elderly people without sleep complaints and strong effects in elderly people suffering from chronic insomnia and patients diagnosed with narcolepsy. For sleep onset we reported the strongest effects in the healthy young adults. With regard to nocturnal sleep, the strongest effects could be observed in the elderly without sleep complaint. Hence the severity of the sleep complaint is not playing a key role in determining if the temperature intervention might be effective. It should also not left unnoted that our data showed relatively more pronounced effects of distal temperature in the 2 groups were sleep was comprised as compared to the two groups without subjective sleep complaints.

One might argue that the efficacy of the temperature treatment might also be affected by the current thermoregulatory state of the body during sleep onset and nocturnal sleep. Only if mild skin warming is facilitating the body to achieve a thermal balance, without the need to activate thermoregulation, the sleep permissive state will be achieved. It is known that both insomniacs and narcoleptics are prone to compromised thermoregulation. As a consequence, a possible intervention can be optimized by using the current thermoregulatory state of the body as an input to fine-tune the skin temperature manipulation.

Based on the current result we conclude:

1. Within the thermoneutral range, mild skin warming promotes sleep onset (1a) and sleep depth (1b) and impedes vigilance (1c).
2. Skin temperature manipulations yield stronger effects than core body temperature manipulations in changing sleep onset and vigilance at daytime.
3. *Proximal* skin temperature manipulations yield stronger effects than *distal* skin temperature manipulations.
4. The effects of skin temperature manipulations on sleep and vigilance is not related to the severity of the disturbed sleep, but might be related to the degree of warming as compared to the actual thermoregulatory state of the body.

General conclusion and perspectives

The findings provide support for the notion that skin temperature modulates vigilance regulation, and more than core temperature does. It has been demonstrated in younger and older healthy adults, as well as in patients suffering from either insomnia or narcolepsy, that very mild skin cooling enhances vigilance and the ability to maintain wakefulness (Chapter 6 and 7, this thesis)[17,32], while mild skin warming facilitates sleep onset (Chapter 4 and 5, this thesis)[29,33] and promotes slow wave sleep and sleep maintenance (Chapter 8 and 9, this thesis)[16,31]. Skin temperature manipulations may thus even complement available research tools to experimentally affect slow cortical oscillations during sleep[27,37]. Concertedly, these findings now provide strong support for a causal contribution of skin temperature to vigilance regulation, as was suggested from animal studies[39].

The studies therefore allowed for the conclusion that, within the comfortable thermoneutral range that does not directly trigger thermoregulatory responses, the effect of a proximal skin temperature manipulation is stronger than the effect of manipulating either core temperature or distal skin temperature. Predominance of skin 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[6] 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.

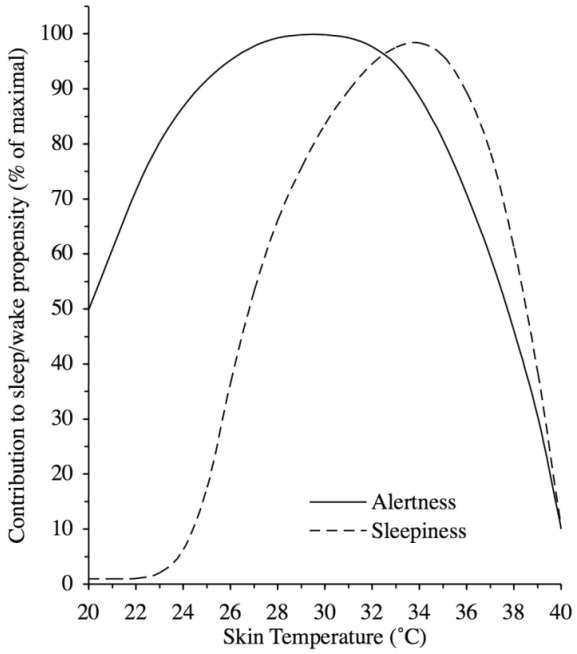

Fig. 1. Schematic representation of how we envision skin temperature may affect sleep and wake propensity regulation. Both the capacity to initiate or maintain sleep or to perform /performance on a sustained attention tasks are compromised at low and high temperatures, because the brain will prioritize 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.

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

As extensively reviewed before[39,40,41,42] and briefly touched upon in the introductory Chapter 1, most of the neuroanatomical and neurophysiological support for thermosensitivity of vigilance-regulating networks in the brain stems from animal studies that were moreover not specifically and primarily designed to address this specific association. An important recommendation to follow-up on the present apparently quite robust findings, is to apply functional Magnetic Resonance Imaging (fMRI) in humans with protocols specifically designed to address the association. Technological developments have recently made it feasible to obtain resting state electroencephalography (EEG) during fMRI protocols, and to subsequently separate physiological signals from the abundant artifacts that are introduced by switching of magnetic fields and by motion (e.g. scanner vibration and ballistocardiac) of the head inside the high magnetic field[1,21,26,47]. The following type of protocol can therefore now be proposed to identify and further study which vigilance-regulating networks in the human brain show changes in activity in association with observed behavioral and physiological changes in vigilance level as induced by mild manipulations of skin temperature. First, in a simultaneous EEG-fMRI recording of subjects throughout wake and sleep, one may use the EEG to either determine fluctuations in sleep depth or repeatedly determine transitions between wake and sleep. These fluctuations can then be convolved with a haemodynamic response function and blood oxygenation level dependent (BOLD) changes in MRI signal, in order to determine the areas that (de)activate in association with changes in vigilance, just as has e.g. been done for fluctuations in alpha oscillations in the resting state EEG[18]. Second, one may use the thermosuit within the MRI environment[11] and observe the pattern of BOLD changes in response to enforced mild increases and decreases in skin temperature. The third step is then to overlay the statistical parameter maps of significant (de)activations obtained in the two protocols, i.e. do a conjuction analysis to determine the overlapping areas. This approach will be of use to determine where in the brain incoming signals, induced by thermal changes, affect vigilance regulation. A similar approach can be followed to do conjunction analyses of temperature-induced changes and changes associated with lapses or slow reaction times in sustained attention tasks.

Perspectives: towards practical applications of sleep enhancement

An important question that ensues from our controlled *direct skin temperature manipulation* studies using a dedicated water-perfused thermosuit set-up in the laboratory, is to what extent they can be applied in daily life. It turns out that a translation towards a practical application is not trivial. Field studies trying to improve sleep with a heating blanket actually show that it disrupts

sleep[14]. The most likely reason for this failure is that a heating blanket continues to add heat to the body, thus increasing core body temperature. The situation of an elevated skin temperature while core temperature does not decrease should alarm the thermoregulatory systems of the organism to note that a thermally undesirable and possibly dangerous situation is present, and disrupt sleep in favor of autonomic or behavioral thermoregulatory defense mechanisms. If our rationale is correct, one may argue that only more subtle approaches of direct skin temperature are likely to produce the desired sleep-promoting effect. Surprisingly, within a very small temperature range it appears theoretically possible to impose a slightly warmer skin temperature, yet promoting rather than inhibiting heat loss and thus lowering skin temperature. In humans, the environmental temperature that the skin is exposed to strongly determines the volume of blood flowing through the skin vasculature, and thus the efficiency of exchanging heat from the body to the environment. The skin is a relatively good insulator, keeping the heat within the body up to an environmental temperature of about 33˚C. However, it dramatically loses its heat insulating properties and allows for a much more effective heat transfer to the environment once it is exposed to, and takes on, an environmental temperature of ~35˚C (see Fig. 2.) [3,12,13]. Thus, while the temperature gradient between the core and the environment *decreases* if the environment is warmed, the possibility to lose heat does not necessarily decrease and may even *increase*. The large increase in skin blood flow with this small increase in skin temperature effectively reduces the heat insulation properties the skin normally provides, and facilitates heat flow from the core to the environment. Thus, while the gradient between a core body temperature of 37˚C and an environment of ~35˚C is less than a gradient of 37˚C versus 33˚C, it may still be easier to reach lower core body temperatures because the insulating property of the skin is much reduced. Efforts to improve sleep by external heating should obtain feedback from the skin to create a closed loop manipulation, ensuring that it keeps the skin temperature within a range that still allows for the core body temperature to drop – settings which may even differ between individuals. Ultimately, this closed loop manipulation may lead to home-applicable versions of the methodology that showed efficacy in laboratory studies on young and elderly people, without sleep complaints or suffering from insomnia or narcolepsy (Chapter 4, 5, 8, 9 this thesis)[16,29,31,33].

Another, *indirect possibility to increase skin temperature* during the sleep period without impeding the nocturnal drop in core body temperature is to make use of normal thermoregulatory mechanisms. This alternative to direct warming of the skin during the desired sleep period is to heat the body prior to sleep, for example by exercising or taking a hot bath or sauna. Body heating activates heat dissipation for a duration that outlasts the heat stress, and consequently may keep skin blood flow higher for a few hours. Indeed this indirect endogenous skin warming procedure has shown to improve subsequent sleep in several studies (reviewed in Chapter 3, this thesis)[30]. It is important to note that this sleep enhancement seems to occur mostly when the heat stress is

annihilated, i.e. core temperature is no longer elevated, while skin temperature is still somewhat increased due to the overshoot in heat dissipation[4,5,7,8,9,10,19,20,22,23,36]. Thus, because of the restricted interval of increased sleep propensity, this procedure may be applied to enhance sleep onset and improve sleep in the first hours of the night. But it is unlikely to show an effect on complaints of early morning awakening, which may only be alleviated using direct skin temperature manipulation, as demonstrated in our laboratory studies (Chapter 8, this thesis)[31].

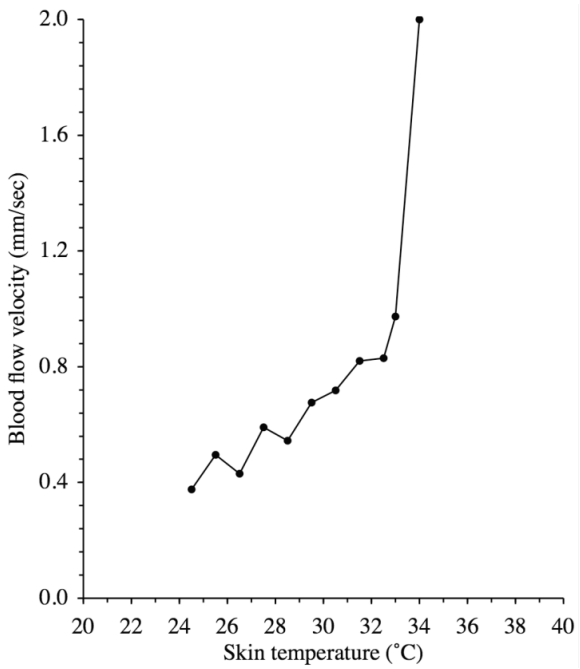

Fig. 2. Relationship between skin temperature and resting blood flow velocity (CBV) in one nailfold capillary of a healthy 37-year-old man. Notice the marked increase in CBV occurring at 34˚C. Figure and legend text above are after Fagrell and Intaglietta[13], who investigated the effect of skin warming 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.

An important question is whether skin temperature control to promote sleep would be necessary at all? If one examines time lapse videos of sleeping humans it seems evident that people, during brief arousals from sleep, apply behavioral thermoregulation by kicking away the blankets or duvet to expose limbs to the cooler environment alternating with covering oneself to create a warm microclimate. But what if this behavior is somehow compromised? Or what if there is a deficit in the conscious or unconscious evaluation of the most appropriate temperature. It has never been evaluated systematically whether nocturnal thermoregulatory behavior differs between insom-

niacs and people without sleep complaints. We have an indication however, that at least some phenotypes of insomnia may not recognize the most comfortable thermal microclimate that is conductive to sleep[33]. Interestingly, these observations were recently supported by our finding[2] that the severity of their sleep complaints correlated with structural abnormalities in the part of the orbitofrontal cortex that is essential for the evaluation of comfort[11,34].

Skin warming may thus be helpful for some insomnia phenotypes. However, we have unpublished data suggesting that in some insomniacs, metabolic heat production and heat dissipating mechanisms are both elevated. In this case, further enhancement of heat dissipation may not be possible or useful. Any endeavor to evaluate the application of skin temperature control to promote sleep in insomniacs may thus profit from rigorous phenotype profiling and selection. Since the reliable long-term assessment of skin temperature in field studies has recently become as feasible as actigraphic assessments of sleep-wake rhythms has been for many years[38,43,45,46], it would be of value to assess skin temperature profiles in large cohorts of people with and without sleep complaints. In addition, web-based surveys [like www.sleepregistry.org[see 44]] for multivariate assessment of insomnia phenotypes could include extensive questioning on subjective thermosensitivity and behavioral thermoregulation. Concertedly, we estimate that it will be feasible within years to support the sleep of at least a subgroup of insomniacs using mild skin temperature manipulations.

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Nederlandse Samenvatting

Lichte opwarming van de huid, een methode om slaap en waakzaamheid te veranderen zonder medicijnen.

Ondanks medicatie, gedragstherapie en tal van huis-, tuin- en keukenmiddeltjes blijft het tobben voor wie kampt met slaapproblemen. Om goed in slaap te komen en in slaap te blijven, moeten zowel het lichaam en de geest tot rust kunnen komen. Een lichaamsproces dat parallel loopt aan de overgang tussen slaap en waken is de variatie in kerntemperatuur (de temperatuur in het lichaam). Gedurende de nacht is de kerntemperatuur lager dan overdag. De temperatuur van de huid laat het tegengestelde patroon zien: warmer gedurende de nacht, en kouder overdag. Uit literatuur was al bekend dat slaap gekoppeld is aan het verloop van de kerntemperatuur, maar het was Van Someren die in 2000 stelde dat vooral de *huid*temperatuur van invloed is op de neuronale activiteit van slaapregulerende hersengebieden. De bevindingen in dit proefschrift laten zien dat een minimale wijziging van de huidtemperatuur inderdaad een groot positief effect op slaap kan hebben.

In **hoofdstuk 1** wordt de huidopwarmingshypothese en de relatie tussen met slaap, waakzaamheid en thermoregulatie nader uitgelegd. Het blijkt dat informatie over temperatuur en aansturing van slaap en waakzaamheid in hetzelfde gebied van de hersenen (pre-optisch gebied van de anterieure hypothalamus) verwerkt worden. Een koude huid lijkt slaap tegen te gaan en waakzaamheid (vigilantie) te bevorderen, terwijl een warme huid slaap lijkt te bevorderen en de vigilantie te doen afnemen.

In **hoofdstuk 2** wordt een overzicht gegeven van de fysiologische principes van temperatuurwaarneming en temperatuurregulatie en de verandering hierin binnen de dag (24 uur) en over de duur van het leven. Op oudere leeftijd zijn de temperatuurwaarneming, de warmteproductie, de centrale temperatuur regulatie, en de capaciteit om warmte te behouden en af te geven niet meer optimaal. Dit resulteert uiteindelijk in een afgevlakt 24-uurs temperatuurritme in ouderen. Dit kan, gezien de relatie tussen slaap en kerntemperatuur weer een gevolg hebben voor de slaap van ouderen.

De huidopwarmingshypothese werd in dit proefschrift getoetst in diverse populaties. Gezonde jongeren werden onderzocht om meer inzicht te krijgen in de fysiologische en psychologische effecten van temperatuurmanipulatie op slaap en vigilantie. Ouderen werden onderzocht om inzicht te krijgen in de effecten van temperatuurmanipulatie op slaap in een populatie waar de

thermoregulatie niet optimaal is. Ouderen met slaapproblemen en de narcolepsiepatiënten tenslotte, werden onderzocht om inzicht te krijgen in de effecten van temperatuurmanipulatie op slaap in populaties waar zowel de thermoregulatie als de slaap niet optimaal is. Alle vier groepen doorliepen hetzelfde onderzoeksprotocol.
Om subtiele temperatuurveranderingen op de huid te bewerkstelligen werd een pyjama met ingeweven flexibele buisjes aangesloten op een systeem dat water van een gecontroleerde temperatuur door de buisjes pompt (hoofdstukken 4-9). De veranderingen in huidtemperatuur waren zo gering (tussen de 0.4°C en 0.7°C) dat er geen thermoregulatoire reactie van het lichaam optrad (d.w.z. het lichaam ondernam geen poging zelf weer de temperatuur te veranderen). Tijdens deze verandering van huidtemperatuur werd zowel de micro- en macro-structuur van de slaap gemeten in de nacht. Daarnaast werd overdag op verschillende tijdstippen de inslaapneiging en de waakzaamheid/vigilantie gemeten.

In een toegepaste studie, beschreven in **hoofdstuk 3,** werden eenvoudige manieren om de huidtemperatuur van de voeten te veranderen, zoals warme bedsokken en een warm voetenbad voor het slapen, gebruikt. Gemeten werd of verwarming van de voeten alleen inslaapneiging kon verbeteren. Bij gezonde jongeren bleek het dragen van al dan niet verwarmde bedsokken tijdens het inslapen het meest effectief. Bij de gezonde ouderen daarentegen was het dragen van de niet verwarmde bedsokken tijdens het inslapen en het warme voetenbad voorafgaand aan de slaappoging het meest effectief. Bij de ouderen met slaapklachten verkortte geen de interventies de inslaaptijd. Inslaaptijd bleek daarnaast korter wanneer de opwarmsnelheid van de voet groter was, zij het alleen bij de jongeren. In beide groepen ouderen werd deze relatie niet gevonden en het bleek dat bij ouderen de voeten tijdens de poging om in slaap te vallen minder snel opwarmen dan de voeten van de jongeren.

In de **hoofdstukken 4, 6 & 8** worden de effecten van temperatuurmanipulaties bij **jongeren** beschreven. Alle temperatuurmanipulaties hadden een effect op de beleving van de temperatuur. Alle warme condities werden als minder comfortabel en warmer beoordeeld. De milde verwarming van de huid van de romp, armen en benen zorgde, zoals verwacht, voor een afname van de inslaaptijd (met 26%) tijdens de inslaapmomenten overdag (hoofdstuk 4) en een 67% snellere afname van de waakzaamheid gedurende een 7 minuten durende vigilantietaak (hoofdstuk 6). Veranderingen van de temperatuur van de handen en voeten en van de kerntemperatuur hadden geen effect op inslapen of vigilantie.
De verwarming van de handen en voeten van jongeren tijdens hun nachtelijke slaap zorgde voor een afname in de relatieve proportie lichte slaap (slaapstadia S1 en S2) en een toename van de REM-slaap. Gelijktijdig zorgde een verwarming van de romp, armen en benen tijdens de nachtelij-

ke slaap voor een afname in de relatieve proportie wakker en S1, en toename van de lichte (S2) en de diepe slaap (hoofdstuk 8). Concluderend: lichte huidverwarming versnelt het inslaapproces, verdiept de slaap en vermindert de vigilantie van jongeren.

In de **hoofdstukken 5, 6 & 8** worden de effecten van temperatuurmanipulaties bij **gezonde ouderen** beschreven. Bijna alle temperatuurmanipulaties hadden een effect op de beleving van de temperatuur. Alle warme condities werden als warmer en minder comfortabel beoordeeld, alleen het verwarmen van de handen en de voeten werd niet als warmer beoordeeld. Ook in deze groep zorgde een verwarming van de romp, armen en benen zorgde voor een verkorting van de inslaaptijd (van 18%) overdag (hoofdstuk 5) en een 50% snellere afname van de waakzaamheid gedurende de vigilantietaak (hoofdstuk 6). Veranderingen van de temperatuur van de handen en voeten en van de kerntemperatuur hadden ook in deze populatie geen effect.
De verwarming van de handen en voeten tijdens de nachtelijke slaap zorgde voor een afname in de relatieve proportie wakker en S1, en toename van de lichte slaap (S2) en de REM-slaap. Gelijktijdig zorgde een verwarming van de romp, armen en benen tijdens de nachtelijke slaap ook voor een afname in de relatieve proportie wakker en S1, en toename van de lichte (S2) en de diepe slaap (hoofdstuk 8).
Concluderend: evenals bij jongeren versnelt een lichte huidopwarming het inslaapproces, verdiept het de slaap en vermindert het de vigilantie van ouderen.
Hiermee laat deze studie zien dat een milde verwarming van de huid een oplossing kan bieden voor de twee meest gerapporteerde slaapproblemen van ouderen, namelijk het minder diep slapen en vroeger ontwaken. De verwarming van de huid leidde in deze studie tot verdubbeling van de hoeveelheid diepe slaap over de hele nacht en een vermindering van de kans op vroeg ontwaken van 58% tot 4%. Vergeleken met de andere groepen was het effect van de nachtelijke huidverwarming zelfs het sterkst in deze groep van ouderen zonder slaapproblemen.

In de **hoofdstukken 5, 6 & 8** worden de effecten van subtiele temperatuurmanipulaties bij **ouderen met slaapklachten** onderzocht. Op één na had geen enkele van de temperatuurmanipulaties een effect op de beleving van de temperatuur. Alleen de kerntemperatuurverwarming werd door deze oudere insomniepatiënten beoordeeld als warmer. Dit verminderd vermogen om de temperatuurverandering waar te nemen, is een opmerkelijk verschil met de andere onderzochte populaties. Bij insomniepatiënten kan het niet adequaat kunnen beoordelen van hun thermische staat wellicht een rol spelen in het ontstaan en het in stand houden van hun slaapprobleem. Ondanks de verminderde temperatuurperceptie is de huidverwarming wel effectief: lichte verwarming van de huid van de romp, armen en benen gecombineerd met een kleine verlaging van de kerntemperatuur zorgde voor een verkorting van de inslaaptijd van 28% overdag (hoofdstuk 5). Verwarming

van de huid van de huid van de romp, armen en benen zorgde voor 3% tragere reactietijden gedurende de vigilantietaak (hoofdstuk 6). Veranderingen van de temperatuur van de handen en voeten had geen effect.
De verwarming van de handen en voeten van de ouderen met slaapproblemen tijdens de nachtelijke slaap zorgde voor een afname in de relatieve proportie S1 en REM slaap, en toename van de lichte slaap (S1) en de diepe slaap. Gelijktijdig zorgde een verwarming van de romp, armen en benen tijdens de nachtelijke slaap ook voor een afname in de relatieve proportie wakker en lichte slaap (S1 & S2), en toename van de diepe slaap en REM slaap (hoofdstuk 8). Concluderend: Lichte huidverwarming versnelt het inslaapproces, verdiept de slaap en vermindert de vigilantie bij ouderen met slaapklachten, ondanks de sterk verminderde temperatuurperceptie.

In de **hoofdstukken 7 & 9** worden de effecten van subtiele temperatuurmanipulaties bij **narcolepsiepatiënten** beschreven. Voor narcolepsiepatiënten, die vaak verminderde waakzaamheid en verhoogde slaperigheid overdag rapporteren, is het bevorderen van de waakzaamheid en het tegengaan van de slaperigheid overdag van groot belang. In deze groep zou het koelen van de huid en het verhogen van de kerntemperatuur voor deze verbetering moeten zorgen.
De kerntemperatuurmanipulaties en de temperatuurmanipulaties van de huid van de romp, armen en benen hadden een effect op de beleving van de temperatuur, de temperatuurmanipulaties van de huid van de handen en voeten hadden dat niet. De verwarming van de kerntemperatuur en de proximale huidtemperatuur werden als minder comfortabel en warmer beoordeeld. Het koelen van de handen en voeten zorgde voor het verlengen van de waaktijd met 24% tijdens de waaktesten overdag (hoofdstuk 7). Een lichte verwarming van de kerntemperatuur zorgde voor een 25% langzamere afname van de waakzaamheid gedurende de vigilantietaak (hoofdstuk 7). De veranderingen van de temperatuur van de romp, armen en benen had geen effect.
Narcoleptiepatiënten rapporteren een verstoring van de nachtelijke slaap. Tijdens hun slaap is de huidtemperatuur van hun handen en voeten relatief hoog. Door de manipulaties is getracht de temperatuur van de handen en voeten te normaliseren tot een huidtemperatuur niveau zoals deze bij gezonde mensen gebruikelijk is. Daarnaast werd ook de temperatuur van de romp, armen en benen licht verhoogd om de slaap te verbeteren, net zoals beschreven bij de hierboven genoemde groepen.
Het koelen van de handen en voeten tijdens de nachtelijke slaap zorgde voor een afname in de relatieve proportie wakker en lichte slaap (S1), en toename van de diepe slaap en de REM slaap. Gelijktijdig zorgde een verwarming van de romp, armen en benen tijdens de nachtelijke slaap voor een afname in de relatieve proportie wakker, en toename van de diepe slaap (hoofdstuk 9). Concluderend: het koelen van de huid van de handen en voeten verlengt de waaktijd, het verhogen van de kerntemperatuur verbetert de vigilantie en de combinatie van handen en voeten koe-

len met het verwarmen van de huid van de armen, benen en romp herstelt de nachtelijke slaap in narcolepsie patiënten.

In **hoofdstuk 10** worden de onderzoeksresultaten samengevat. Op basis van het onderzoek kunnen we het volgende concluderen

1. Lichte opwarming van de huid, binnen de thermoneutrale zone, versnelt het inslaap- proces, verdiept de slaap en vermindert de vigilantie.
2. Het effect van huidtemperatuurmanipulatie op inslaapneiging en vigilantie tijdens de dag is sterker dan het effect van kerntemperatuurmanipulatie.
3. Het effect van het veranderen van de huidtemperatuur van de romp, benen en armen op slaap en vigilantie is sterker dan het effect van manipulatie van de distale huid.
4. De sterkte van effect van huidtemperatuurmanipulaties op slaap en vigilantie is niet gerelateerd aan de ernst van het slaapprobleem, het zou eerder gerelateerd kunnen zijn aan de sterkte van verwarming in relatie tot de thermoregulatoire staat van het lichaam.

De resultaten uit dit proefschrift zijn verwerkt in een model voor huidtemperatuur en slaap en vigilantieregulering. Er is zowel voor slaap als voor vigilantie een optimale range van huidtemperaturen. Huidtemperaturen buiten deze range hebben een sterk negatief effect op slaap en vigilantie. Gezien de resultaten is een toepassing van lichte manipulatie van huidtemperatuur als middel om slaap of vigilantie te beïnvloeden goed denkbaar. De haalbaarheid zal afhangen of men in staat is een systeem te maken dat op subtiele wijze temperatuurveranderingen kan induceren, rekening houdend met de momentane huidtemperatuur.

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Curriculum Vitae

Roy Raymann was born February 20, 1971 in Venlo. In 1989 he graduated from high school (Gymnasium β) achieved at the st. Thomascollege in Venlo. In 1992 he started his study Biological Psychology at Utrecht University. He graduated in 1996, after conducting EEG and MEG experiments on visual attention at Utrecht University and TU-Twente and emotional startle response studies at the Centre for the Study of Emotion and Attention (CSEA) at the University of Florida. After graduation he studied biological determinants of occupational fatigue at Utrecht University and in the end of 1999 he started his work in the field of sleep research, conducting studies on sleep and thermoregulation at the Netherlands Institute for Neurosciences (an institute of the Royal Netherlands Academic of Arts and Sciences).

He continued his professional career at TNO (Dutch organization for applied scientific research) in Soesterberg (2006-2008) and TU-Delft (2007-2008), before he joined Philips Research in 2008. Within Philips Research he is mainly working on non-pharmacological solutions to address sleep complaints (including thermoregulation), alternative ways to quantify sleep, subtyping of insomnia, sleep in newborns and the effects of light on sleep and cognition.

He is accredited by the Holland Sleep Research School, Westeinde Hospital, The Hague as sleep expert. He is appointed as an associate editor for the Open Sleep Journal and editor of the Dutch Sleep Annuals and is taking part in the scientific committee of the Dutch Sleep-Wake Society and the European Insomnia Network. He is member of the Sleep Research Society, the European Sleep Research Society, the Dutch Sleep-Wake Society and the Society for Ambulatory Assessment.

In 2005 the manuscript on sleep onset and temperature (chapter 4 this thesis) was selected as Highlight from the Literature by the journal Physiology. In 2006, the European Sleep Research Society (ESRS) awarded the work on sleep and temperature in narcoleptic patients with the Helgi Kristbjarnarson Award for innovative research. In 2011 the work on LED coloured ambient lighting, well-being and cardiac reactivity received the Best Paper Award in the "Ergonomics and Health Aspects of Work with Computers" Thematic Area of the HCI (Human-Computer Interaction) International conference.

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