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

Raymann, R.J.E.M.

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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 comfortable 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.