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# Skin deep: enhanced sleep depth by cutaneous temperature manipulation

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**With ageing, 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.**

**Keywords:** insomnia; sleep; ageing; temperature manipulation; thermoregulation; electroencephalography

**Abbreviations:** CBT = core body temperature; POAH = preoptic area/anterior hypothalamus; REM = rapid eye movement; SWS = slow wave sleep

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## Introduction

With advancing age, an increasing number of people complain about their sleep quality (Foley *et al.*, 1995; Kryger *et al.*, 2004). 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 (Sivertsen *et al.*, 2006). 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 (Murphy and Campbell, 1997) and the probability of waking increases during the early morning rise in temperature. 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 (Dijk and Czeisler, 1995; Lack and Lushington, 1996; Shochat *et al.*, 1997; Kubota *et al.*, 2002). 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 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 (McGinty and Szymusiak, 1990; Alam *et al.*, 1995; McGinty and Szymusiak, 2001). It has, therefore, been proposed that sleep would be facilitated when brain temperature exceeds a threshold level (McGinty and Szymusiak, 1990). 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 (Dijk and Czeisler, 1995; Lack and Lushington, 1996; Shochat *et al.*, 1997; Kubota *et al.*, 2002). 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 (Van Someren, 2000).

We have proposed that skin temperature is a candidate for such an input signal (Van Someren, 2004). Skin temperature shows a diurnal rhythm that is inversely related to the CBT rhythm, i.e. skin temperature peaks during the habitual sleep period (Marotte and Timbal, 1982; Van Someren, 2006). Under normal conditions the nocturnal increase of skin temperature is further amplified by postural change (Tikuisis and Ducharme, 1996; Kräuchi *et al.*, 1997), a warm microclimate resulting from insulating bedding (Goldsmith and Hampton, 1968; Muzet *et al.*, 1984; Okamoto *et al.*, 1997) and pre-sleep relaxation signalled by lights off (Kräuchi and Wirz-Justice, 2001). A functional link between skin temperature and sleep has been suggested before (Kräuchi *et al.*, 1999), 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 (Raymann *et al.*, 2005). Skin warming moreover accelerated the decline in vigilance associated with the prolonged performance of a monotonous task (Raymann and Van Someren, 2007).

A recent study involving human neuroimaging demonstrated that hypothalamic activation occurs with skin warming (Egan *et al.*, 2005). 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 (Boulant and Bignall, 1973; Boulant, 1981). 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.

## Materials and 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.

### Subjects

Twenty-four healthy volunteers participated with informed consent. They included eight young adults (mean ± SEM: 27.0 ± 2.4 years, four males), eight elderly subjects without sleep complaints (65.8 ± 2.8 years, four males) and eight elderly subjects diagnosed with primary insomnia (59.1 ± 1.9 years, four males) according to the qualitative criteria of the International classification of sleep disorders (ICSD) (Diagnostic Classification Steering Committee, 1990) and the Research Diagnostic Criteria for Primary Insomnia (Edinger *et al.*, 2004), as well as according to the quantitative criteria proposed by Lichstein *et al.* (2003), i.e. sleep onset latency or wake time after sleep onset of more than 30 min, 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' (Buysse *et al.*, 2006), 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 later. Subjective sleep quality and complaints were measured using interview, sleep diaries, a Dutch adaptation (Sweere *et al.*, 1998) of the 75-item Sleep Disorders Questionnaire (SDQ, Douglass *et al.*, 1994) and the Pittsburgh Sleep Quality Index (PSQI, Buysse *et al.*, 1989). All elderly subjects suffering from primary insomnia had a PSQI score >5 (10.9 ± 1.1) and an

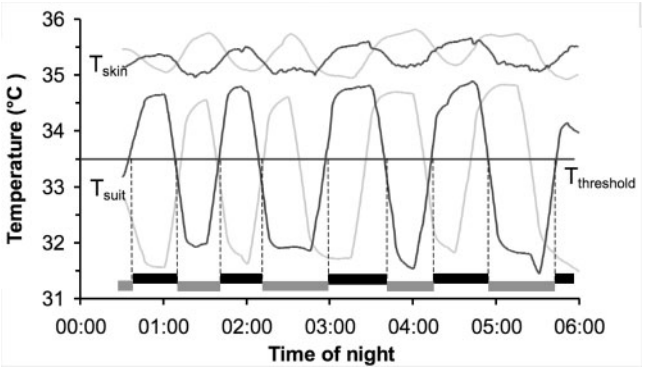


**Fig. 1** Single-case, one-night example of the temperature profiles induced in the proximal and (grey) distal (black) parts of the thermosuit (lower traces), $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$. The upper traces show the induced slowly cycling proximal (grey) and distal (black) average skin temperature, $T_{skin\text{-}prox}$ and $T_{skin\text{-}dist}$. 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).

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, Derogatis *et al.*, 1973). 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.

## Procedure

Subjects refrained from caffeine, alcohol and tobacco for 8 h before reporting to the sleep laboratory at 22:00 h. 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 h. The nocturnal sleep period was limited to 6 h because the subjects were subjected to a semi-constant routine procedure starting at 6:00 h, as reported previously (Raymann *et al.*, 2005; Raymann and Van Someren, 2007). Starting at 0:30 h., $T_{skin\text{-}prox}$ and $T_{skin\text{-}dist}$ were differentially manipulated by thermosuit water perfusion of slowly cycling temperatures (Fig. 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.

## Temperature manipulations and measurement

Skin temperature was manipulated from 00:30 h until 6:00 h. 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 Fig. 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 min. Transitions between the plateaus were accomplished with slow temperature changes, taking 15 min 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 $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ 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, using 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 (Goldsmith and Hampton, 1968; Muzet *et al.*, 1984; Okamoto *et al.*, 1997; Kräuchi and Wirz-Justice, 2001). 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 (Raymann *et al.*, 2005).

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 (cf. Raymann *et al.*, 2005). $T_{skin\text{-}dist}$ 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 s intervals synchronized to the sleep stage epochs.

## Sleep recordings and analysis

Polysomnographic sleep recordings consisted of electroencephalography (EEG) from two bipolar derivations (FpzCz and PzOz, see van Sweden *et al.*, 1990) 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 s epochs according to standard criteria

(Rechtschaffen and Kales, 1968). Epoch classification stages 3 and 4 were merged into the single class slow wave sleep (SWS). For each artifact-free 30 s epoch scored as non-rapid eye movement (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.

## Statistical analysis

### *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 determine 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 $31.7 \pm 0.1$°C 'cool' and $34.6 \pm 0.1$°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 Fig. 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.

### *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 non-linear 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 h until 6:00 h). 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 (Twisk, 2003). Odds ratios were translated into sleep-stage probabilities at every time point during the night for the maximal and minimal thermosuit 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.

# Results

## 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 (Fig. 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 $35.37 \pm 0.07$°C (mean ± SEM) versus $34.98 \pm 0.07$°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 $35.38 \pm 0.08$°C versus $35.02 \pm 0.07$°C for the warmest and coolest levels, respectively. Table 1 shows the average temperatures during the warmest and coolest levels of the manipulations separately for each of the three groups.

## 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 ($33.5 \pm 0.4$°C), elderly subjects without sleep complaints ($33.2 \pm 0.4$°C) and elderly people with sleep complaints

**Table 1** 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 |

(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 ± 0.1°C) and 'warm' (34.6 ± 0.1°C) $T_{suit}$ 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 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 later.

## Manipulation effects on sleep-stage probability and distribution

### *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 Figs 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), SWS and 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 Fig. 2 and Table 3 show that *proximal skin warming* enhanced the deeper stages SWS and S2 at the cost

**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).

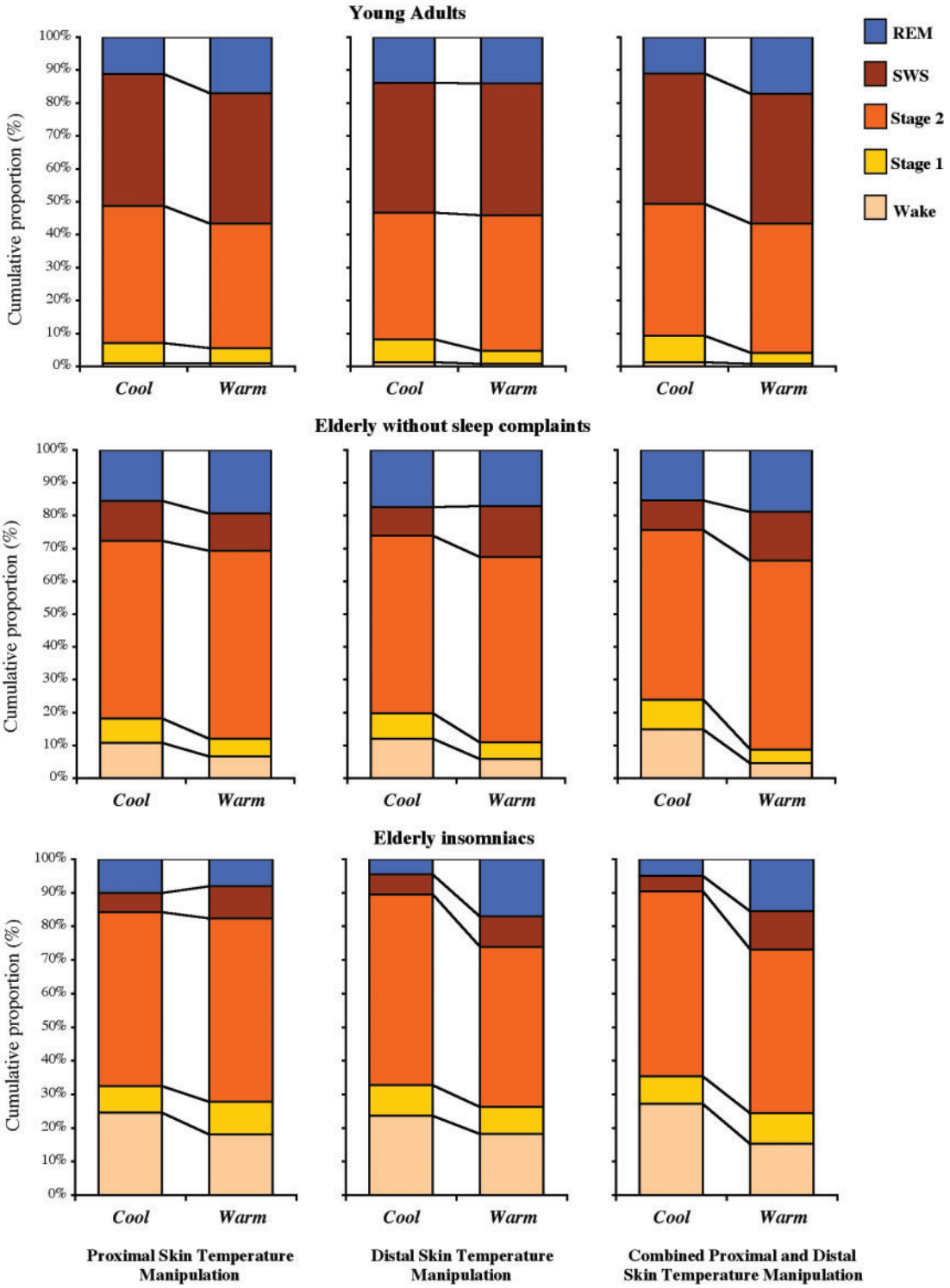


**Fig. 2** Graphical representation of the main effects logistic regression results. The stacked areas visualize the cumulative proportion of each sleep stage occurring over the whole night in case of the cool versus warm thermosuit temperatures for young adults (top panels), elderly without sleep complaints (middle panels) and insomniac elderly (bottom panels). Effects of proximal warming versus cooling [$T_{suit\ prox}$ 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 left column, effects of distal warming versus cooling [$T_{suit\ dist}$ 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 middle column and effects of total skin warming versus cooling [both $T_{suit\ prox}$ and $T_{suit\ dist}$ 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 Figs 2 and 3.

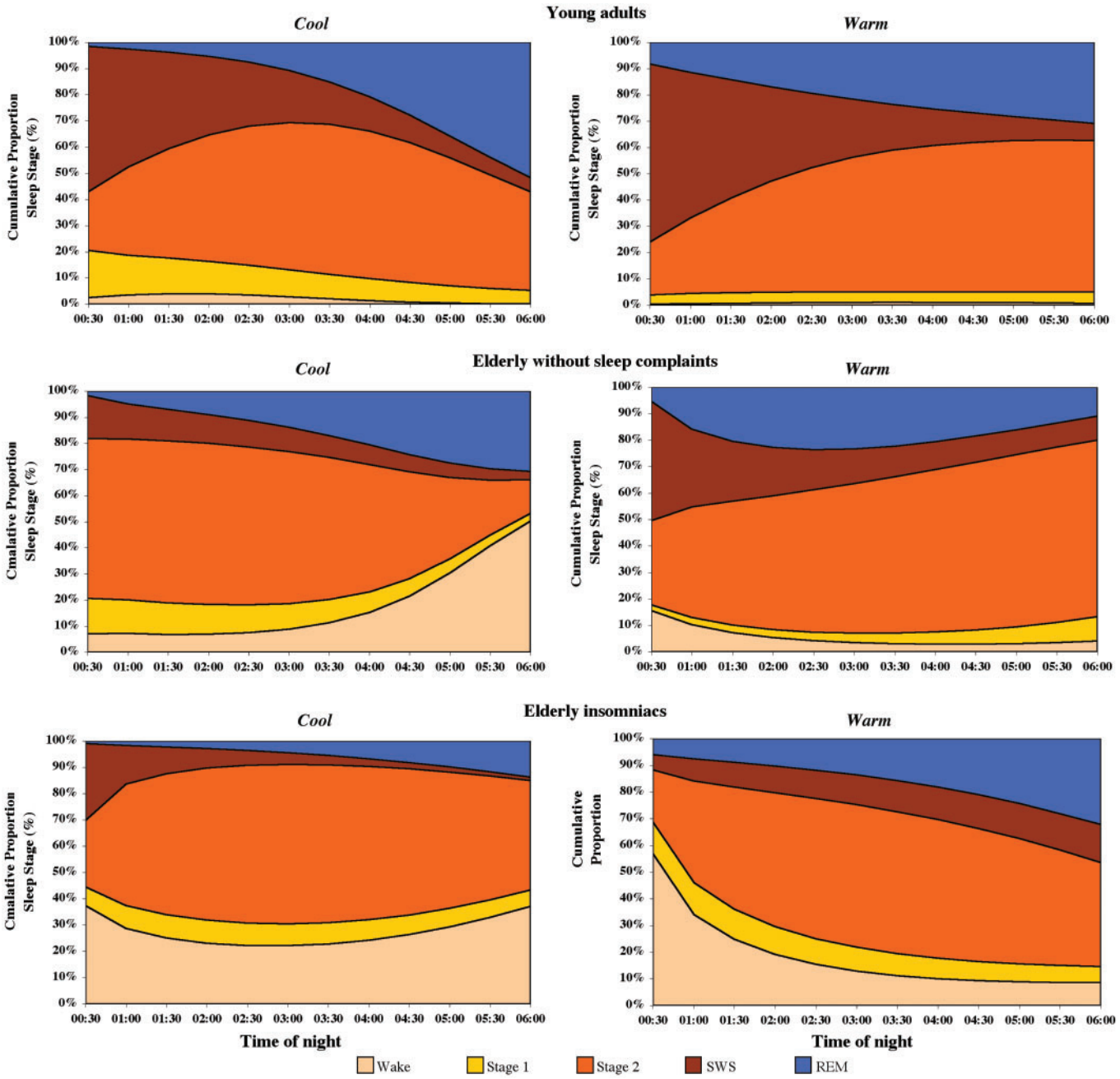


**Fig. 3** Graphical representation of the results of the logistic regression analyses that included main effects, time of night modulation and manipulation by time of night interactions. Stacked areas represent the model-predicted cumulative proportion of each sleep stage occurring at each time of the 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).

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. *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.

**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. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

### *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 (non-linear) 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 Fig. 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 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.

## 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

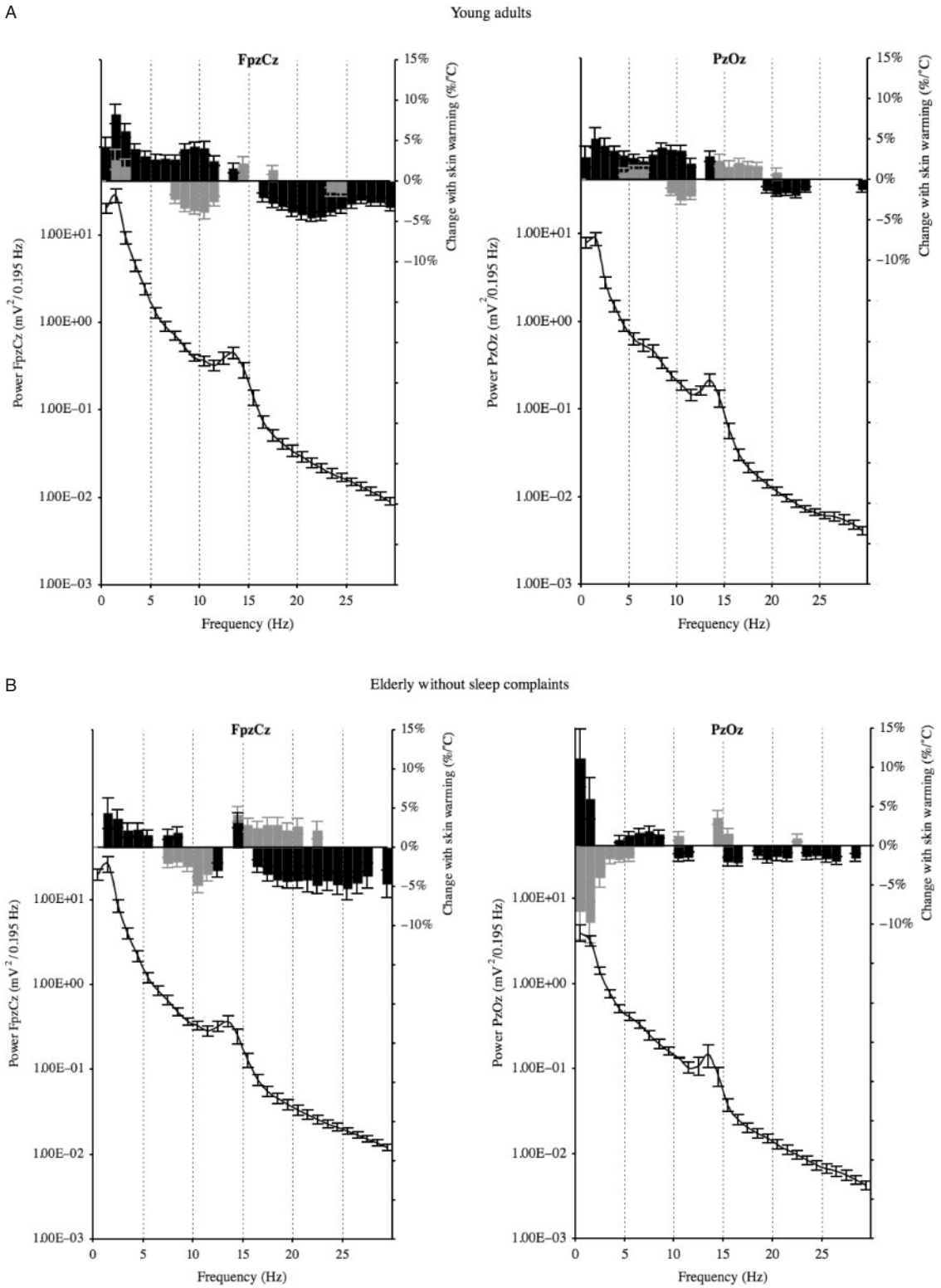


**Fig. 4** EEG power spectra averaged over all artifact-free 30 s epochs scored as NREM sleep throughout the night from FpzCz (left panels) and PzOz (right panels) for young adults (upper panels), elderly without sleep complaints (middle panels) and insomniac elderly (lower panels). The traces give the mean ± SEM spectra for each group, given in millivolt$^2$/0.2 Hz bin. The bars indicate, for each 1 Hz bin, the percent change (±SEM) in power per °C change in $T_{suit}$, 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.

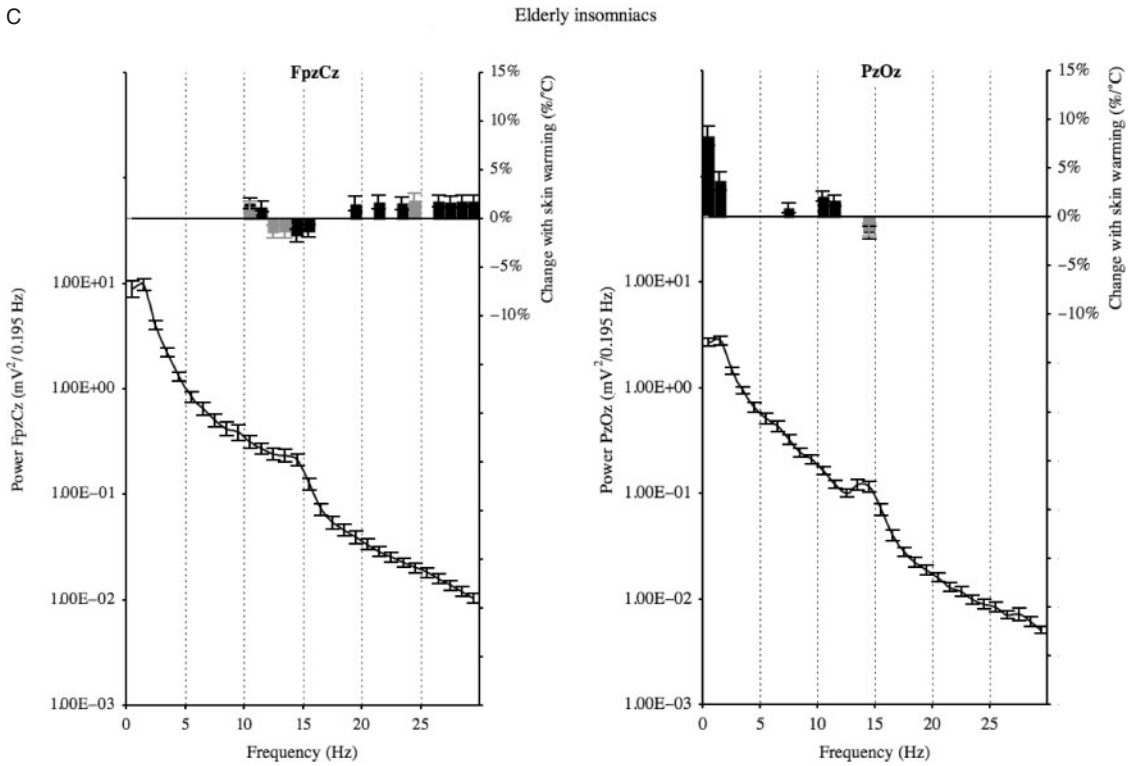


**Fig. 4** Continued.

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* (Fig. 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.

## 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 (Van Someren *et al.*, 2002). 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 Fig. 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 (Fig. 2 and Table 3). The fraction of SWS (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 h (5.5 h 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 (Fig. 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 (Fig. 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 (Fig. 3). Frequency spectra of the NREM sleep EEG (Fig. 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 (Baker *et al.*, 1976).

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, because 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 (Raymann *et al.*, 2005), 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 (van Marken Lichtenbelt *et al.*, 2006) under habitual sleeping conditions at home. In 15 well-sleeping elderly (7 males, 8 females, age 62 ± 2 years mean ± SEM) and 20 insomniac elderly (8 males, 12 females, age 59 ± 1 years) the mean distal skin temperature measured at home in the 00:30–6:00 h 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 (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 proximal 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 h 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 (Goldsmith and Hampton, 1968; Muzet *et al.*, 1984; Okamoto *et al.*, 1997). 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 (Raymann *et al.*, 2005). 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 and 23°C (Freedman and Roehrs, 2006). 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 (Horne and Reid, 1985; Horne and Shackell, 1987; Bunnell *et al.*, 1988; Jordan *et al.*, 1990; Dorsey *et al.*, 1996, 1999; Kanda *et al.*, 1999; Sung and

Tochihara, 2000). 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 (Sung and Tochihara, 2000): in this study, the sleep-promoting effects subsided as soon as the hot bath induced increase in skin temperature had normalized after 2 h of sleep. In keeping with data from previous studies in which an association between sleep propensity and distal skin temperature was reported (Magnussen, 1939; Brown, 1979; Kräuchi *et al.*, 1997, 1999) our present and recently reported studies (Raymann *et al.*, 2005; Raymann and Van Someren, 2007) 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 (Goldsmith and Hampton, 1968; Muzet *et al.*, 1984; Okamoto *et al.*, 1997). Our results moreover suggest that bed microclimate temperature should ideally be kept, on average, above 33.5, 33.2 and 33.1 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 high and adversely affect sleep (Fletcher *et al.*, 1999)—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 (van Marken Lichtenbelt *et al.*, 2006). Since we recently found a marked decrease in the subjective perception of optimal sleeping temperatures in old age, especially in insomniacs (Raymann and Van Someren, under revision), it may well be that people sleep under thermal conditions that do not favour sleep, without realizing 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 earlier, 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 (Van Someren, 2004, 2006). 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 (Van Someren, 2000). 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 (Van Someren, 2007) 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.

## Supplementary Material

Supplementary Material is available at *Brain* online.

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