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1 **TITLE**

2 Assessment of time window for sleep onset on the basis of continuous wrist temperature
3 measurement

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21

22 ABSTRACT

23 The interactions of the principal circadian clock with the homeostatic sleep process create the
24 time-sensitive window for easy falling asleep in the evening, which is affected by a
25 thermoregulatory process. It has been hypothesized that the changes in skin and core body
26 temperatures before the sleep onset might play a direct role in sleep regulation. To determine
27 this time window, we recorded from 20 healthy participants (11 women and 9 men), aged 26–
28 58 years, one overnight own-home ambulatory polysomnography and measured continuously
29 wrist skin temperature with a wrist-worn accelerometer containing a skin temperature
30 thermometer. Wrist skin temperatures which were read out from the thermometer of the
31 accelerometers were modeled using linear mixed models, and the linear effect of time before
32 the sleep onset on wrist temperature was analyzed using a mixed model with the sex and age
33 as the covariates. We found that wrist skin temperatures increased on average by 0.6° (of
34 Celcius) in 10 minutes prior to the sleep onset and could be tracked robustly along a slope of
35 time ($p=0.004$). Our current findings may be useful in further characterizing the window of
36 time and its boundaries for easy falling asleep.

37 KEYWORDS

38 ambulatory monitoring, peripheral temperature, sleep stage, timing of sleep

39

40 INTRODUCTION

41 To understand sleep and its problems, sleep must be considered as part of the circadian
42 rhythm (Hofstra and de Weerd 2008). The natural timing and structure (quantity and quality)
43 of sleep are determined by both the intrinsic circadian rhythm of the nervous system and the
44 need for sleep during wakefulness. These two interacting processes give rise to the sleep
45 behavior of a person which can be observed, even by the naked eye, or recorded with
46 polysomnography (PSG) for example. The circadian process is the dominant of these two
47 (Kawato et al. 1982) and results from the functions of the cells located in the suprachiasmatic
48 nucleus of the anterior hypothalamus, or the body's central internal clock, the outputs of
49 whose contribute to the generation and maintenance of circadian rhythms. This clock also
50 controls the emergence of a specific sleep stage after sleep onset, i.e., rapid eye movement
51 (REM) sleep, but not that of non-REM (NREM) sleep. Moreover, the interactions of this
52 clock with the homeostatic sleep process create the time-sensitive windows for easy falling
53 asleep as well as refreshed waking-up after the night-time sleep, if the time slept fulfilled the
54 individual sleep need in terms of quantity as well as quality (Wehr et al. 2001). Moreover, it
55 has been hypothesized that the changes in skin and core body temperatures before the sleep
56 onset might play a direct role in sleep regulation (Gilbert et al. 2004). Changes in body
57 temperature, whether measured as core body temperature or peripheral (such as wrist skin)
58 temperature, are highly correlated with the likelihood of falling asleep, but the degree of heat
59 loss from the skin and the subsequent change in peripheral body temperature was a stronger
60 predictor for the sleep onset than the change in core body temperature, irrespective of the
61 circadian phase (Kräuchi et al. 2000).

62 During sleep, the sleep stages alternate in a healthy person according to a particular pattern or
63 formula of the cycle of NREM-to-REM sleep stages (Kleitman and Ramsaroop 1948;
64 Kleitman et al. 1948; Kleitman 1949, 1960). After falling asleep, healthy adults follow in

65 their night-time sleep the same cycling pattern, if not disturbed. During their natural night-
66 time sleep, a person usually sleeps for 4 or 5 sleep cycles, short sleepers for fewer cycles and
67 long sleepers for more cycles, and the average length of the NREM-to-REM sleep stages
68 cycle in an adult is approximately 90 minutes on average, ranging from 80 to 110 minutes
69 (Merica and Gaillard 1986; Le Bon et al. 2002). The opening of the sleep-friendly time
70 window allows a person to have a sufficiently long night-time sleep during which the NREM-
71 to-REM sleep stages cycle according to the formula. Finally, the need for sleep becomes
72 fulfilled and the night-time sleep comes to its end, when another time window for a refreshed
73 wake-up opens.

74 To determine these two time windows, a person's daily rest-activity or sleep-wakefulness
75 rhythm must be measured. It can be reliably determined by measuring body temperature
76 under controlled conditions (Gilbert et al. 2004). The circadian rhythm of body temperature
77 can be measured, for example, from the skin using a measuring device placed over the radial
78 artery (Sarabia et al. 2008; Martinez-Nicolas et al. 2013; Bonmati-Carrion et al. 2014). In
79 such case, the measuring device for use is compact, taped to the skin and worn by the person
80 for several days. The wrist temperature increase onset calculated from these measurements
81 reliably reports the phase of the circadian rhythm of skin temperature and correlates, e.g.,
82 with the phase of the circadian rhythm of melatonin as calculated on the basis of the dim light
83 melatonin onset (Lewy et al. 2007).

84 Circadian rhythm sleep-wake disorders due to disturbances of the body's central internal
85 clock often result in insomnia, tiredness or hyperactivity (Abbott et al. 2015). Of these,
86 insomnia and tiredness are very common symptoms in the general population among adults
87 as well as adolescents (Chattu et al. 2018). Partly because of this, they are also big diagnostic
88 and therapeutic challenges. A key therapeutic goal is to regularize the sleep-wakefulness

89 schedule, which favors the opening of the window of time suitable for falling asleep in the
90 evening hours (van Straten et al. 2018).

91 Delayed sleep (delayed sleep phase syndrome) is the most common one of the circadian
92 rhythm sleep disorders, especially in younger age groups, but it also affects 1.5% to 9% of
93 adults (Nesbitt 2018). Concomitant or comorbid substance abuse disorders, mood disorders
94 or anxiety disorders are common as well (Abbott et al. 2018), thus the circadian rhythm sleep
95 disorders are relevant and important in terms of public health. Finding new ways to determine
96 and regularize the sleep-wakefulness patterns is therefore justified.

97 **Aims**

98 The purpose of this study is to determine, whether the continuous measurement of wrist skin
99 temperature can determine the time window for falling asleep. Earlier, there is a view on that
100 the increase in heat loss prior to sleep increases sleep propensity, thereby facilitating the sleep
101 onset (for review, see Gilbert et al. 2004). To make it clear, we do not claim that the idea of
102 thermoregulatory responses in relation to falling asleep is new, but herein, we wanted to
103 answer the following two research questions. First, is there a characteristic, rapid and
104 relatively large variation in wrist skin temperature in the evening? If it were, it would be due
105 to changes in thermoregulation (such as an increase in wrist skin temperature) which are
106 irrespective of the circadian phase able to trigger directly sleep and wakefulness promoting
107 areas of the brain to initiate sleep, and then the second question would be, whether the
108 moment of falling asleep is trackable and reliably predictable from this characteristic
109 variation?

110 **MATERIALS AND METHODS**

111 **Participants**

112 We recruited 20 participants (11 women and 9 men), aged 26–58 years (mean = 39 years,
113 standard deviation = 11.01 years), through word of mouth. They were interviewed in person
114 and assessed as psychologically healthy. Any potential individuals who had current health
115 problems or were taking medication known to affect thermoregulation or sleep were excluded
116 from participating. For the 24 hours prior to each session the participants abstained from
117 alcohol and caffeine.

118 All participated voluntarily with no monetary compensation. Potential participants were fully
119 informed of the procedure before they agreed to participate: they were given a detailed
120 written procedure description and an overall verbal explanation of the measurements. All
121 participants gave their written consent and were aware that interrupting their participation
122 was possible at any phase of the study. The study was conducted in accordance with the
123 Declaration of Helsinki and its amendments. The detailed research protocol was approved by
124 the Helsinki University Hospital Coordinating Ethics Committee (#HUS/652/2017).

125 **Assessments**

126 All of the participants scheduled an overnight, own-home ambulatory PSG with the research
127 nurse according to their own timetables. In addition to the PSG, the participants also filled in
128 a short background questionnaire, and used wrist-worn accelerometers (for actigraphy) and
129 skin temperature loggers for three days starting from the PSG night. Details regarding these
130 measurements are described in the following paragraphs.

131 *Polysomnography*

132 All recordings were done using SOMNOscreen plus (SOMNOmedics GmbH, Germany). A
133 trained research nurse attached gold cup electrodes at 6 EEG locations (frontal (F)
134 hemispheres: F3, F4; central (C) hemispheres: C3, C4; occipital (O) hemispheres: O1, O2)
135 and two for the mastoids (A1, A2) accordingly. The electro-oculogram (EOG) and the

136 electromyogram (EMG) were measured by using disposable adhesive electrodes (Ambu
137 Neuroline 715, Ambu A/S, Denmark), two locations for EOG and three locations for EMG.
138 In addition, an online reference Cz and a ground electrode in the middle of forehead were
139 used. PSG data were scored manually using the DOMINO program (v2.7; SOMNOmedics
140 GmbH, Germany) in 30-second epochs into Stage 1, Stage 2, SWS and REM sleep according
141 to AASM guidelines.

142 *Actigraphy*

143 GENEActiv Sleep actigraphs (Activinsights Ltd., Kimbolton, UK) are wrist-worn, tri-axial
144 accelerometers which can be initialized to collect raw 12-bit MEMS acceleration data at
145 selected frequencies and contain linear active thermistor sensors which measure temperature
146 with 0.25°C resolution and have the accuracy of $\pm 1.0^\circ\text{C}$ from 0°C to +60°C. They include
147 memory for storing data on the temperature and time recordings, and measure temperature
148 every 30 seconds. Participants were instructed to wear the actigraph device on their non-
149 dominant wrist for three days and nights. They were given a sleep log booklet to fill in
150 alongside the actigraphy measurement period, and were instructed to write down sleep onset
151 and offset times, as well as all times when the device was not worn on the wrist. The devices
152 were set to sample activity at a frequency of 50 Hz, and their data were downloaded onto a
153 computer and aggregated into 30-second epochs.

154 *Temperature logger*

155 ThermoChron iButtons (DS1922L, Maxim Integrated, San Jose, CA, USA) are small, light
156 (about 3 g), round, stainless steel data loggers with thermometers. They contain digital
157 thermistor sensors which measure temperature with 0.0625°C resolution and have the
158 accuracy of $\pm 0.5^\circ\text{C}$ from -10°C to $+65^\circ\text{C}$. They include memory for storing data on the
159 temperature and time recordings, and can be initialized to the desired logging frequency. In

160 the current study, we selected the measurement rate to be one per minute. The research nurse
161 attached the iButton onto the wrist (inner side, approximately upon the radial artery) using a
162 comfortable adhesive medical tape, and instructed the participants to write down all times
163 when the device was removed from the wrist. The data were read with the USB Port Adapter
164 as connected to the PC 1-Wire Connectivity Reader, and extracted with the OneWireViewer
165 software (Maxim Integrated, San Jose, CA, USA).

166 *Background questionnaire*

167 The participants were given a short questionnaire, which included questions regarding their
168 current health (a self-rated Likert-like scale from 1 to 4, where 1=excellent, 2=good,
169 3=moderate, 4=poor), and an open field to describe their current health in more detail if
170 desired. The questionnaire also included three further questions on height, weight, and
171 handedness.

172 **Statistical analysis**

173 Sleep onset can be and has been defined in different ways in the literature. For this reason, in
174 this study, we used the following three definitions for sleep onset. First (Definition 1), sleep
175 onset was met after three consecutive epochs of N1 sleep. Second (Definition 2), sleep onset
176 was met at after the first epoch of N2, N3 or REM sleep. Third (Definition 3), sleep onset
177 was met after the first epoch of N1, N2, N3 or REM sleep. Of these, the Definitions 1 and 2
178 are classic, i.e., gold standards (Rechtschaffen et al. 1968), and the Definition 3 is the updated
179 version of the classical definitions (Iber et al. 2007). This allowed us also to compare and
180 analyze, whether the definition affected the outcome.

181 We derived the wrist temperature read-outs from both devices, and after the initial inspection
182 and preliminary analyses, we decided to use the 1-second epoch data derived from the
183 actigraphy (GENEActiv Sleep actigraphs) for analysis, because the data derived from the

184 temperature loggers (Thermochron iButtons), with the 60-second epochs, were not reactive
185 nor sensitive enough to capture changes in temperature. For the analysis, the 1-second epoch
186 data derived from actigraphy (GENEActiv Sleep actigraphs) were aggregated into 30-second
187 epochs which matched with the epochs of polysomnography.

188 First, the curves of wrist skin temperature were visualized as a function of time, i.e., from 30
189 minutes before the onset of sleep to 5 minutes after the onset of sleep and calculated with
190 linear mixed models using splines of time as the fixed effect, with the knots for 20, 10 and
191 zero minutes before the sleep onset minute by minute, which covered the data well. We used
192 the intercept of individuals as the random effect. Cubic splines with knots is a piece-wise
193 cubic polynomial with continuous derivatives upto order 2 (the 1st and the 2nd derivatives) at
194 each knot. Secondly, we modelled the fixed linear effect of time before the sleep onset on
195 wrist temperature using a mixed model, with the sex and age as the fixed covariates, and
196 including only data for 10 minutes prior to the sleep onset. In this model, we also included the
197 intercept of individuals as the random effect, and we tested whether the slope was different
198 from zero using the Wald type test. For this analysis, the R software (R Core Team 2015) was
199 used and we give the codes computed in the Appendix. The model was used to calculate the
200 adjusted curves we present in the figures.

201 **RESULTS**

202 There were increases in wrist temperature on average were 0.62 (95% confidence interval of
203 0.52-0.72), 0.47 (0.33-0.61) and 0.60 (0.50-0.71) degrees (of Celsius) in 10 minutes as
204 calculated from the slopes minute by minute prior to the sleep onset for definitions 1, 2 and 3,
205 repectively (Figures 1-3).

206 Of the definitions for sleep onset, the Definitions 1 and 3 yielded very similar, almost equal,
207 associations of wrist temperatures with the estimated slope of time prior to the sleep onset
208 (Table 1). The Definition 2 was in contrast to the remaining.

209 **DISCUSSION**

210 Concerning our two research question we proposed a priori for this study, we are able to give
211 the following answers. To the first question, whether there is a rather rapid and relatively
212 large variation in skin temperature in the evening close to falling asleep, the answer was that
213 there was such variation. The skin temperature increased on average by 0.6° (of Celcius) in
214 10 minutes prior to the sleep onset. Later during the night when the individual is asleep there
215 are larger, but however slower, variations in temperature (Sarabia et al. 2008), but as we
216 focused on the sleep onset we did not analyze these fluctuations in the current study.

217 To the second question, whether the moment of falling asleep is reliably predictable from this
218 variation, the answer was that it may be able to be predicted, since we applied the usage of
219 splines of time for our data analysis and of the inter-individual variation we were able
220 identify a significant slope of time prior to the sleep onset. However, we did not conduct a
221 further study to test the predictive values, but such tests remain to be done and the second
222 research question of ours awaits an answer.

223 Our analysis showed that on average the wrist skin temperatures tended to increase before
224 falling asleep, and this finding was robust and independent of the definition for sleep onset. It
225 supports, but does not confirm, the hypothesis that changes in thermoregulation including a
226 co-occurring change in body temperature, a characteristic increase in wrist skin temperature
227 and a characteristic decrease in core body temperature, being irrespective of the circadian
228 phase, triggers directly sleep and wakefulness promoting areas of the brain to initiate sleep.
229 This is recorded and assessed as the sleep onset with polysomnography. However, the

230 criterion chosen for the PSG-defined sleep onset revealed diversity in wrist temperature
231 dynamics at cross-sections, as visualized at 5 minutes before the sleep onset pending on
232 definition. The Definition 2 was in contrast to the remaining, so it appears that if the sleep
233 onset was defined to be met only at after the first epoch of N2 sleep stage, not paying
234 attention to epochs of N1 sleep stage the peripheral skin temperature fluctuated more during
235 the period of time from the first N1 epoch(s) to the first N2 epoch.

236 In addition to the circadian and homeostatic processes which underlie and contribute to the
237 sleep-wakefulness cycle, it is known that sleep propensity is affected by a thermoregulatory
238 process, and thus it is plausible that the changes in skin and core body temperatures before
239 the sleep onset might play a direct role in sleep regulation (Gilbert et al. 2004). Earlier,
240 among men who were aged 19 to 27 years and healthy good sleepers, a significant increase in
241 hand skin temperature contributed to the concomitant decrease in rectal core temperature
242 which occurred at 20 minutes prior to sleep initiation (van den Heuvel et al. 1998). However,
243 while changes in these body temperatures were evident before the sleep onset, the amplitude
244 of pre-sleep effects was less than the evoked effects of sleep on the body temperatures.
245 Mechanistically, it appears that selective vasodilation of distal skin regions and their heat loss
246 facilitates the onset of sleep (Kräuchi et al. 2000).

247 As our study was based on recordings for one night only, however, our study was not free of
248 limitations. On the other hand, we included both women and men in our study sample and
249 provided data on both genders, whereas earlier studies on this subject (van den Heuvel et al.
250 1998; Kräuchi et al. 2000) were on men only. Allowing the subjects to sleep according to
251 their preferred schedule at their homes is an additional strength of the current study.

252 As we see these findings of ours from the current study, they may be useful in further
253 characterizing the window of time and its boundaries for easy falling asleep. Continuous
254 recording of wrist skin temperature before the bedtime may be useful to discover such

255 window of time. This information might thus be used as a source of input for machine
256 learning procedures to identify the opening of window of time favoring sleep onset and to
257 provide feedback to the individual about this. It may be seen as an automated component for
258 a guided self-care intervention as part of the formal cognitive behavioral treatment for
259 insomnia or anyone who is interested in identifying and thereby becoming more aware of an
260 opportune moment for bedtime and starting night sleep.

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263 carrying out the polysomnographic recordings. This study was based on the agreement
264 between the University of Helsinki and Night Train Oy (Oulu, Finland) and supported in part
265 by a grant from the latter party which was not involved in the design, interpretation, or
266 writing of the manuscript.

267 **DISCLOSURE OF INTEREST**

268 Timo Partonen, Liisa Kuula and Anu-Katriina Pesonen declare as co-inventors for a patent
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272

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APPENDIX

We modelled the linear effect of time before the sleep onset on wrist temperature using a mixed model, with the sex and age as the covariates, and including only data less 10 minutes before the sleep onset. For this analysis, the R software (R Core Team 2015) was used and the codes were computed as follows.

(1) $uni.m0 <- lmer(ga.temp \sim I(24 \times 60 \times ga.aika) + (1 | PID), data=apu.data.1.B)$

(2) $uni.m1 <- lmer(ga.temp \sim I(24 \times 60 \times ga.aika) + sex+age+(1 | PID), data=apu.data.1.B)$

(3) $uni.m1.sp <- lmer(ga.temp \sim ga.aika.1 + I(ga.aika.1^2) + I(ga.aika.1^3) + pmax(0,(ga.aika.1-(-20))^3) + pmax(0,(ga.aika.1-(-10))^3) + pmax(0,(ga.aika.1-(0))^3) + (1 | PID), data=tmp.data)$

The first one was without the background variables (sex and age), whereas the second one included the two background variables. Time ($ga.aika$) was transformed into minutes (24×60), and the dependent variable was wrist temperature ($ga.temp$). The individual was used as a random effect in these models [(1 | PID)]. The third model is with the splines of time. The model was used to calculate the adjusted curves which we present in the figures.

TABLES

Table 1. Associations of wrist skin temperatures on average (standard deviation) with the sleep onset. Slopes from mixed effect models with fixed effect linear time (minutes), sex and age, and individual intercept as random effect.

Sleep onset definition ^a	Wrist temperature 5 minutes before the sleep onset, mean (s.d.)	Wrist temperature at the sleep onset, mean (s.d.)	Wrist temperature 5 minutes after the sleep onset, mean (s.d.)	Slope of time before the sleep onset (per 1 minute)	Standard error of the slope	t-value	p-value
#1	32.13 (2.33)	32.47 (2.35)	32.78 (2.28)	0.0622937	0.0007921	78.641	0.0040
#2	32.53 (2.41)	32.37 (2.52)	32.82 (2.20)	0.047087	0.001087	43.303	0.0073
#3	32.15 (2.31)	32.47 (2.35)	32.76 (2.29)	0.0603308	0.0008039	75.049	0.0042

^a Definition 1 = sleep onset was met after three consecutive epochs of N1 sleep; Definition 2 = sleep onset was met at after the first epoch of N2, N3 or REM sleep; Definition 3 = sleep onset was met after the first epoch of N1, N2, N3 or REM sleep.

FIGURE LEGENDS

Figure 1. Wrist skin temperature (in degrees of Celsius) as a function of time, i.e., from 30 minutes before the onset of sleep, as assessed with the Definition 1 and indicated with the vertical dashed line, to 5 minutes after the onset of sleep. The predicted values based on random effects model with splines together with their 95% confidence limits are given. In the background, the read-outs for each individual are presented.

Figure 2. Wrist skin temperature (in degrees of Celsius) as a function of time, i.e., from 30 minutes before the onset of sleep, as assessed with the Definition 2 and indicated with the vertical dashed line, to 5 minutes after the onset of sleep. The predicted values based on random effects model with splines together with their 95% confidence limits are given. In the background, the read-outs for each individual are presented.

Figure 3. Wrist skin temperature (in degrees of Celsius) as a function of time, i.e., from 30 minutes before the onset of sleep, as assessed with the Definition 3 and indicated with the vertical dashed line, to 5 minutes after the onset of sleep. The predicted values based on random effects model with splines together with their 95% confidence limits are given. In the background, the read-outs for each individual are presented.





