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# Circadian skin temperature rhythms, circadian activity rhythms and sleep in individuals with self-reported depressive symptoms

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ABSTRACT

*Background:* Disturbed circadian rhythms have been associated with depression. New body-worn devices allow the objective recording of circadian parameters such as physical activity, skin temperature and sleep. The objective of this study was to investigate whether circadian skin temperature and circadian activity rhythms are altered in depressed individuals.

*Methods:* Data on skin temperature, physical activity and sleep were available for 1610 subjects from a population-based cohort study. In a matching process two groups were formed for analysis: 121 participants with pronounced depression symptoms (CES-D Score > 21) and n = 121 matched non-depressed controls (CES-D Score < 15). Circadian rhythms were investigated by analyzing non-parametric rhythm indicators of 24-h skin temperature and physical activity data. Sleep timing, continuity and quantity were calculated from actigraphy.

*Results:* No differences between the groups were found when all participants were considered. After excluding antidepressant medicated participants, the depression group was found to have a lower skin temperature amplitude t(208) = 2.45, p = .015 and a less stable skin temperature rhythm t(208) = 2.40, p = .017. The amplitude predicted the group status (beta = −5.529, *p* = .016). No effects were found for activity or sleep.

*Conclusion:* The results indicate that skin-temperature rhythms are blunted in unmedicated depressed individuals. This could be a promising non-invasive marker for further analysis.

## 1. Introduction

Sleep disturbances and altered psychomotor activities such as a decrease in motor activity are often reported by patients with depressive disorders. Furthermore, changes in circadian rhythms have been reported in patients with depression (Zaki et al., 2018). During depressive episodes circadian rhythms are often disrupted (Edgar and McClung, 2013). Furthermore, the degree of desynchronization in circadian rhythms correlates with the severity of depressive symptoms (Hasler et al., 2010). Improvement of symptoms is often accompanied by a normalization of the rhythms (Bunney and Bunney, 2012).

The suprachiasmatic nucleus (SCN) of the anterior hypothalamus is the major circadian pacemaker. The SCN regulates rhythmic clock-controlled gene expression which controls many physiological functions, such as the sleep–wake cycle, hormone release or thermoregulation (Takahashi et al., 2008). The intrinsic circadian rhythm is slightly longer than 24 h and it is synchronized to a 24-h rhythm by environmental time cues. Light is the major time cue, which involves retinal ganglion cells that project to the SCN. The involvement of circadian rhythms and external time cues in the pathophysiology of depression has been supported by the effects of bright light therapy in seasonal and non-seasonal depression (Oldham and Ciraulo, 2014).

Actigraphy is a useful assessment tool to quantify sleep and daytime activity. Applied in a time window of at least 24-h, actigraphy can be used to collect data on circadian rhythms non-invasively. In the past, several studies have used actigraphy to obtain data on either activity during night- or daytime, reviewed by Burton et al. (2013). However; only a few recent studies have applied actigraphy over a 24 h period or more, making it possible to investigate circadian activity rhythms in depressed patients: Luik et al. (2015) found in a community sample that depression was positively associated with an intradaily variability index of the 24-h activity time series. Robillard et al. (2015) investigated young people with several emerging mental disorders. One finding was that 24-h activity rhythms were phase delayed in depression compared

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to a control group. Hori et al. (2016) compared actigraphically measured 24-h activity rhythms and sleep between patients suffering from depression and heathy controls. They found lower mean activity levels and lower amplitude of the circadian activity curve in the patient sample.

These studies have used data on activity counts from actigraphy, an indirect measure of activity. The advantage of this technology is its easy and cost-efficient application. One disadvantage however is that actigraphy recordings are influenced by artifacts that may mask the true rhythm since activity is strongly related to external conditions such as work schedules or other obligations. Physiological markers such as core body temperature however, follow a strict circadian rhythm paced by the SCN when measured in lab conditions (Hiddinga, Beersma, & Van Den Hoofdakker, R. H, 1997).

The core body temperature plays a critical role in biological function. A change of 1 °C can modify circadian gene expression (Saini et al., 2012). Core body temperature rises in the early morning and decreases in the late evening. Evidence has shown that core body temperature curves in depressed patients are blunted (Avery et al., 1999; Elsenga et al, 1988) and phase shifted (Hasler et al., 2010). Common methods to measure core body temperature are invasive (inserting rectal or oesophageal measuring tools). Hence, studies on core body temperature in depression are limited, mostly done in labs and with small sample sizes which reduces the ecological validity. One alternative could be to measure skin temperature. Skin temperature is phase-advanced and inversely related to core body temperature (Sarabia et al., 2008). It is suggested that skin temperature drive the core body temperature rhythms due to heat loss through the skin of the extremities (Kräuchi and Wirz-Justice, 1994; Raymann, Roy J E M, Swaab, & Van Someren, Eus J W, 2005; van Sommeren, Eus J. W., 2003). Compared to core body temperature, skin temperature can be measured non-invasively with body-worn devices. However, skin temperature measurements in free-living conditions can be highly masked by activity, changing environmental temperature, eating and much more factors. Nevertheless, being able to study much larger sample sizes could partially mitigate these limitations.

New body-worn devices of the life style industry (e.g. fitness tracker) are already widespread. These devices often have multiple sensors installed, including heat sensors. Analyzing this data for medical purposes has great potential and data on skin temperature may be of particularly interest for detecting circadian changes in depression.

The primary objective of this study was to test whether alterations in 24 h rhythms of skin temperature could be found in individuals with self-reported depressive symptoms using a non-invasive body worn device. In analogy to previous findings of core body temperature the following hypotheses were tested:

A. Skin temperature curves are phase shifted in depressed individuals compared to healthy controls, operationalized by the start time of the highest 5 h of the 24-h skin temperature data
B. Skin temperature rhythms are blunted in depressed individuals compared to healthy controls, operationalized by a lower relative amplitude of the skin temperature curve

Since studies on 24-h activity rhythms in depression are scarce, a secondary aim of this study was to test whether alterations in 24-h activity rhythms measured with actigraphy could be found in individuals with self-reported depressive symptoms.

In addition, we analyzed actigraphic sleep and expected sleep continuity, sleep timing and sleep quantity to be altered in individuals with self-reported depressive symptoms. Sleep alterations were operationalized by the following parameters: sleep efficiency, mid-sleep time and total sleep time.

Moreover, we tested the predictive effects of circadian parameters on the group status (depressed vs. non-depressed).

## 2. Materials and methods

### 2.1. Participants

Data was drawn from the database of the LIFE project (Leipzig Research Center for Civilization Diseases), which aimed to assess the prevalence and incidence of common diseases and subclinical disease phenotypes within a representative German population. In one LIFE sub-project an adult cohort of 10 000 inhabitants of the city of Leipzig in Germany was investigated, for a closer description see (Loeffler et al., 2015). The basic assessment consisted of standardized interviews (e.g. for sociodemographic information and medical history), several physical and medical examinations (e.g. anthropometric measurements), questionnaire (e.g. concerning aspects of mental health and sleep) as well as laboratory tests (e.g. blood sampling). In addition to the basic assessment, a random subgroup of 2995 participants wore an actigraphy device for seven consecutive days to assess sleep-wake behavior and physical activity. All procedures were conducted according to the Declaration of Helsinki and approved by the University of Leipzig Medical Faculty's ethics committee (registration-number: 263-2009-14122009). Subjects gave written informed consent to participate in the examinations.

In a first step, we identified a subsample of LIFE participants that had completed a screening questionnaire for depression severity (CES-D, see below) and had participated in the actigraphy assessment. In a second step, several inclusion and exclusion criteria were applied to the subsample: Subjects had to be between 40 and 79 years of age, free of known neurological disorders (Parkinson disease, multiple sclerosis, epilepsy and stroke) or heart insufficiency. Subjects who took hypnotics and sedatives or who engaged in shiftwork were excluded. Furthermore, the actigraphy recordings needed to include analyzable data for at least six days (at least 4 week days plus 2 weekend days).

This resulted in a subsample of 1610 subjects of which n = 121 participants met the criterion for pronounced depression symptoms (CES-D Score > 21). This sample is hereinafter referred to as the “depressed group”. In a propensity score matching based on sex, age and BMI, n = 121 matched non-depressed controls (CES-D Score < 15) were selected which are hereinafter referred to as the “non-depressed group”.

### 2.2. Objective measures

Objective measures of skin temperature, physical activity and sleep were collected with the SenseWear® Pro 3 actigraph (BodyMedia Inc.; Pittsburgh, Pennsylvania). The device is attached to the upper right arm and records 2-axis acceleration, heat flux, galvanic skin response and skin temperature. Subjects were instructed to wear the device for a total of 7 days and to keep a sleep diary to log sleep and bedtimes. Skin temperature is measured with a thermistor sensor placed on the backside of the SenseWear device. Activity was expressed in metabolic equivalents (METs) per minute. A MET is a measure that expresses the energy cost of physical activity in which 1 MET represents the energy expenditure under rest condition. Several studies have shown that the SenseWear device provides accurate estimates of energy expenditure during rest and daily life activities (Casiraghi et al., 2013; Reece et al., 2015; Scheers et al., 2013; van Hoye, et al, 2014). Furthermore, the SenseWear software classifies each recording minute as either “lying” vs. “non-lying” and “awake” vs. “asleep”. The sleep detection algorithm of the device was validated in several studies (Alsaadi et al., 2014; O'Driscoll et al., 2013; Shin et al., 2015) including the sleep onset and sleep offset time (Sunseri et al., 2009).

Minute by minute data was exported from the SenseWear software output to a Microsoft Excel template with Visual Basic for Applications (VBA) macros, which was used for further analysis. On average 23.03 h of data was available per day. Daily skin temperature and activity data were analyzed using nonparametric indicators that describe the

activity/skin temperature rhythm without making strict assumptions about the shape of the curves (Van Someren et al., 2009). Using the r package nparAct (Blume et al., 2016) the interdaily stability (IS), intradaily variability (IV) and relative amplitude (RA) were computed. In addition, for the activity data, the 5 h with the lowest average activity (L5) and the 10 h with the highest average activity (M10) and their respective start times were calculated. For the skin-temperature data, the 5 h with the highest average temperature (M5) and the 10 h with the lowest average temperature (L10) were computed. IS is an indicator for the stability of the rhythm indicating the extent to which the rhythms of the individual days resemble each other ranging from 0 (Gaussian Noise) to 1 (perfect fit). IV is an indicator for the fragmentation of the rhythms describing the frequency and extent of transitions between rest and activity ranging from ~0 (perfect sine wave) to ~2 for Gaussian noise. RA is the difference between M10 and L5 normalized by their sum. Concerning sleep, the following parameters were calculated based on the classification of the SenseWear Software: Total sleep time (TST), sum of all minutes classified as sleep during a day; Sleep efficiency (SE), ratio of all minutes classified as sleep and all minutes classified as lying down during a day in %; Mid-sleep time (MST), half-time between sleep onset and sleep offset. Sleep onset and sleep offset time were defined as the first and last minute classified as sleep by the sleep algorithm during the night sleep interval based on the bedtime information from the sleep diary (lights off and get up time).

### 2.3. Statistical analysis

Differences in demographic, skin temperature, activity and sleep parameters between the two groups were analyzed using Pearson $\chi 2$ and independent t-tests. A forward stepwise logistic regression analysis was conducted to examine the predictive effects of skin temperature, activity and sleep on the group status (depressive vs. control). Statistical significance was set to $p < 0.05$ (two-tailed). Since most of the indicators were analyzed exploratively, no p value adjustment was made. However, p values relating to the hypotheses, i.e. the phase indicators (M5/10 start-time and L5/10 start-time) and the amplitude indicators (RA, M5/10, and L5/10) are additionally reported after FDR correction for multiple comparisons. Statistical analyses were conducted in SPSS 24.

## 3. Results

Demographic characteristics of the depressed and the non-depressed participants matched with regard to sex, age and BMI are shown in Table 1. No significant differences between matched and unmatched demographic characteristics (age, sex, BMI, Country of birth, education, professional situation or marital status) were found between depressed and non-depressed individuals.

None of the activity or skin temperature rhythm indicators (IS, IV, RA, M5/10, L5/10)) showed a significant difference between the groups. The same applied for the sleep parameters: No significant differences between the groups were found for MST, SE or TST. Since antidepressant medication can have an influence on sleep and other circadian parameters, we repeated the analyses after the exclusion of antidepressant medicated participants (n = 32). After exclusion of medicated participants, there were still no significant differences between the groups concerning sex ($\chi^2(1) = 0.03$, $p = .866$), age ($t(208) = 0.89$, $p = .374$) or BMI ($t(240) = 0.04$, $p = .970$). Unmedicated depressed individuals showed significantly lower relative amplitude compared to the non-depressed control group ($p = .045$, FDR corrected). In addition, interdaily stability was found to be lower in unmedicated depressed individuals ($p = .017$). No significant differences between the groups were found for any activity rhythm indicator or sleep parameter. Results of skin temperature and activity rhythm indicators as well as sleep parameters for unmedicated participants are presented in Table 2. Figs. 1 and 2 are showing 24-h mean activity and skin temperature curves for unmedicated participants.

With regard to the prediction of the group status, a significant effect of the logistic regression model was found for unmedicated participants ($Chi^2(1) = 5.977$, $p = .014$, Nagelkerkes $R^2 = 0.038$). The relative amplitude of the skin temperature was the only predictive coefficient (beta = −5.529, $p = .016$). All other regression coefficients were excluded from the model.

## 4. Discussion

In this study, 121 participants with pronounced depressive symptoms were compared to 121 non-depressed controls matched by age, sex and body-mass index concerning 24-h skin temperature und activity rhythms. Moreover, actigraphic sleep timing, sleep quantity and sleep continuity measures were compared between the two groups.

Contrary to our first hypothesis, no differences were found between the groups regarding a phase shift of the skin temperature rhythms. This is in contrast to previews studies on circadian rhythms in depression that investigated cortisol, melatonin or core body temperature to measure circadian rhythms and that found larger phase angles between dim light melatonin onset and cortisol acrophase (Buckley and Schatzberg, 2010) as well as larger phase angles between the time of the core body temperature minimum and the midsleep time (Hasler et al., 2010).

Contrary to our second hypothesis, there was no difference in the amplitude of the skin temperature curves between the two groups. This is in contrast to previous studies on core body temperature in depressed patients that have revealed changes in amplitude of the temperature rhythms (Avery et al., 1999; Souêtre et al., 1989)). However, when participants taking antidepressant medications were excluded, the relative amplitude of the skin temperature curve was found to be significant lower in the depressed compared to the non-depressed control group. This result supports our second hypothesis and is comparable to the studies of Avery et al. (1999) and Souêtre et al. (1989) that investigated core body temperature rhythms in depression. However, in contrast to previews studies, we measured skin temperature rhythms instead of the core body temperature. Especially with regard to large-scale clinical applications, the measurement of skin temperature has significant advantages, since devices with skin temperature sensors are already inexpensive and widely used. As an example, a long-term monitoring of skin temperature data in patients might be useful as an indicator for the effects of interventions that focus on circadian rhythms such as bright light therapy or interpersonal and social rhythm therapy (IPSRT) (Frank et al., 2000; Oldham and Ciraulo, 2014) as well as other interventions that were found to have an effect on temperature rhythms (Szuba et al., 1997). In addition, data on circadian skin temperature might even be used to derive treatment implications. However, this is beyond the scope of this study and can only be tested in further longitudinal and interventional studies. To our knowledge, only one other study investigated circadian rhythms of skin temperature in depression so far (Ávila Moraes et al., 2013). The authors used a cosine fitting to calculate the amplitude of the skin temperature but found no difference between depressed and healthy female subjects. However, the sample sizes of the investigated groups were quite small, thus it is difficult to judge whether similar effects would have been found by the authors especially if non-parametric statistics instead of a cosine fitting would have been applied to operationalize the skin temperature rhythm.

Beside the amplitude and phase shift of the temperature rhythm we investigated whether other non-parametric rhythm indicators differed between the groups. No differences were found in the total sample (including antidepressant medicated participants) but a significant difference was found regarding the interdaily stability of the skin temperature rhythm after medicated participants were excluded indicating a less stable rhythm in unmedicated depressed individuals. To our knowledge no study exists that has previously investigated the interdaily stability of skin temperature rhythms.

**Table 1**
Demographic information of depressed and non-depressed individuals.

| Demographic information | Depressed (n = 121) | Non-depressed (n = 121) | Group comparison |
|---|---|---|---|
| Age, M (SD) | 56.52 (9.96) | 57.01 (10.50) | $t(240) = 0.37$, $p = .711$ |
| Sex, n (%) | | | $\chi^2(1) = 0.09$, $p = .763$ |
| Female | 28 (23) | 30 (25) | |
| Male | 93 (77) | 91 (75) | |
| BMI, M (SD) | 27.75 (5.15) | 28.30 (5.72) | $t(240) = 0.78$, $p = .439$ |
| Country of birth, n (%) | | | $\chi^2(1) = 0.50$, $p = .479$ |
| Germany | 116 (96) | 117 (97) | |
| Other | 5 (4) | 3 (2) | |
| School graduation, n (%) | | | $\chi^2(4) = 6.39$, $p = .172$ |
| Lower secondary school | 6 (5) | 5 (4) | |
| Secondary school | 70 (58) | 58 (48) | |
| Advanced technical college | 3 (2) | 10 (8) | |
| Higher education | 41 (34) | 47 (39) | |
| Other | 1 (1) | 0 (0) | |
| Professional situation, n (%) | | | $\chi^2(2) = 0.94$, $p = .626$ |
| Full time employed | 48 (40) | 55 (46) | |
| Part time employed | 19 (16) | 17 (14) | |
| unemployed | 54 (45) | 48 (40) | |
| Marital status, n (%) | | | $\chi^2(3) = 0.78$, $p = .854$ |
| Single | 16 (13) | 17 (14) | |
| Married | 68 (56) | 71 (59) | |
| Divorced | 23 (19) | 22 (18) | |
| Widowed | 14 (12) | 10 (8) | |
| Socioeconomic status, n (%) | | | $\chi^2(2) = 3.52$, $p = .172$ |
| Low | 24 (20) | 14 (12) | |
| Medium | 68 (56) | 79 (66) | |
| High | 29 (24) | 27 (23) | |

Note. M = mean, SD = standard deviation.

Our results underline the importance of taking antidepressant medication into account when analyzing circadian skin temperature rhythms since antidepressant drug treatment, including tricyclic medications, can influence the circadian rhythms including the amplitude of the temperature rhythm (Goetze and Tölle, 1987). Taking this into account, our results support the increasing evidence for a strong link between circadian rhythms and depression which have been shown in a variety of studies. In addition to findings on temperature or hormone rhythm disruptions, recent studies focused on rhythmic patterns of gene expression that were found to be disrupted in depressive patients (Li et al., 2013) or on gastrointestinal microorganisms that were found to interact with circadian genes that in turn are associated with depression (Li et al., 2018).

Surprisingly, we did not find any differences in 24-h activity rhythms between depressed and non-depressed individuals. Even after the exclusion of antidepressant medicated participants, no differences in any activity rhythms parameter was found. In addition, no differences in sleep timing, quantity or continuity were found. Regarding the prediction of the group status, a similar pattern was observed: The relative amplitude of the skin-temperature rhythm was the only predictive parameter of the group status in the unmedicated sample (depressive vs. non-depressed). These results might reflect the problem of

**Table 2**
Circadian parameters of skin temperature, METs and sleep in antidepressant free depressed individuals and non-depressed controls.

| Parameter | Depression | Control | Group comparison | Effect |
|---|---|---|---|---|
| | M (SD) | M (SD) | | Cohens d |
| Skin Temperature | | | | |
| RA | 0.15 (0.06) | 0.17 (0.06) | t(208) = 2.45, p = .015 | 0.34 |
| M5 start-time | 23.83 (3.45) | 24.56 (1.94) | t(208) = 1.82, p = .072 | 0.25 |
| M5 | 33.66 (0.72) | 33.78 (0.70) | t(208) = 1.20, p = .233 | 0.17 |
| L10 | 31.45 (0.85) | 31.23 (0.84) | t(208) = 1.90, p = .059 | 0.26 |
| L10 start-time | 8.21 (3.22) | 8.91 (3.01) | t(208) = 1.62, p = .106 | 0.23 |
| IS | 0.42 (0.18) | 0.48 (0.19) | t(208) = 2.40, p = .017 | 0.33 |
| IV | 0.54 (0.18) | 0.53 (0.17) | t(208) = −0.44, p = .661 | −0.06 |
| METs | | | | |
| RA | 0.15 (0.08) | 0.36 (0.07) | t(208) = 0.74, p = .460 | 0.10 |
| L5 start-time | 24.52 (1.22) | 24.49 (1.15) | t(208) = −0.23, p = .820 | −0.03 |
| L5 | 0.83 (0.10) | 0.82 (0.12) | t(208) = −0.33, p = .744 | −0.05 |
| M10 | 1.79 (0.45) | 1.79 (0.37) | t(208) = −0.02, p = .983 | −0.00 |
| M10 start-time | 8.39 (1.59) | 8.59 (1.57) | t(208) = 0.94, p = .349 | 0.13 |
| IS | 0.48 (0.12) | 0.49 (0.12) | t(208) = 0.33, p = .742 | 0.05 |
| IV | 0.85 (0.21) | 0.81 (0.20) | t(208) = −1.18, p = .241 | −0.16 |
| Sleep | | | | |
| TST [h:m] | 6:17 (0.55) | 6.29 (1.00) | t(208) = 1.49, p = .139 | 0.21 |
| SE [%] | 83.60 (7.30) | 83.64 (8.46) | t(208) = 0.04, p = .968 | 0.01 |
| MST [h:m] | 3:11 (0:53) | 3:13 (0:53) | t(208) = −0.21, p = .833 | −0.03 |

Note. M = mean, SD = standard deviation, IS = interdaily stability, IV = intradaily variability, RA = relative amplitude, L5/10 = 5/10 h with the lowest average activity/temperature, M10/5 = 10/5 h with the highest average activity/temperature.

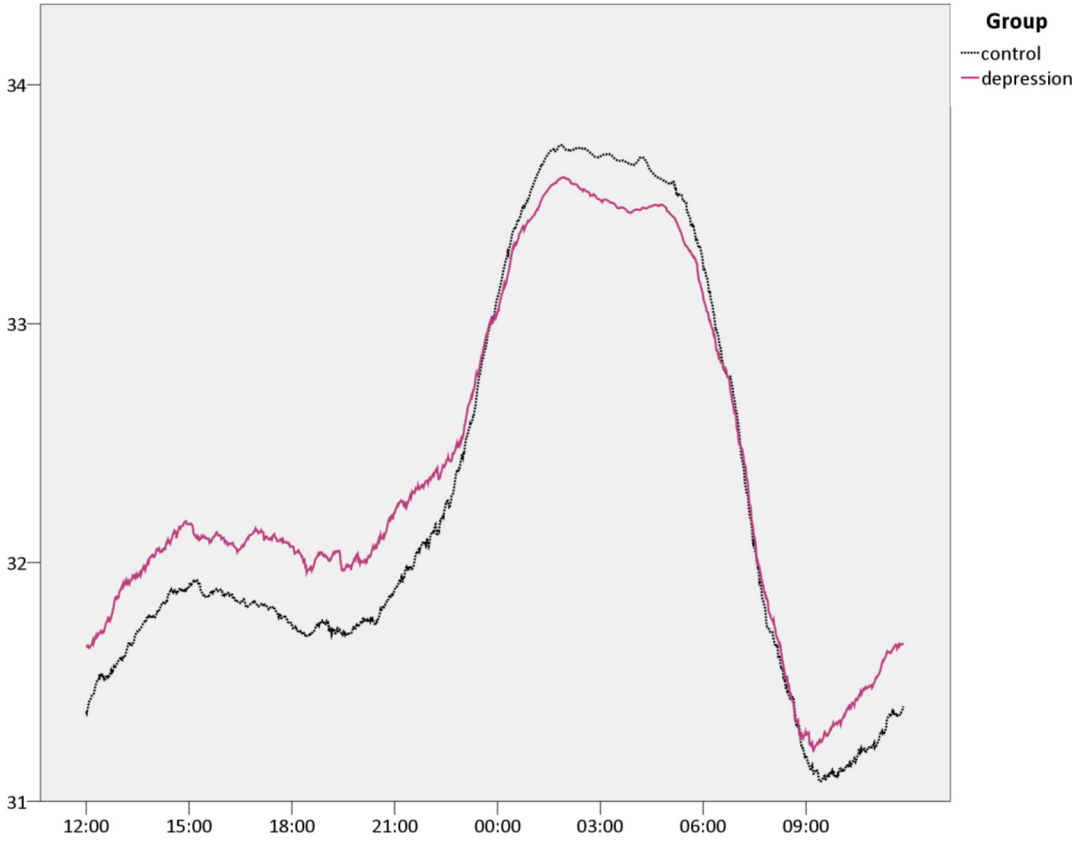


**Fig. 1.** Mean 24-h skin temperature rhythm dived by group.

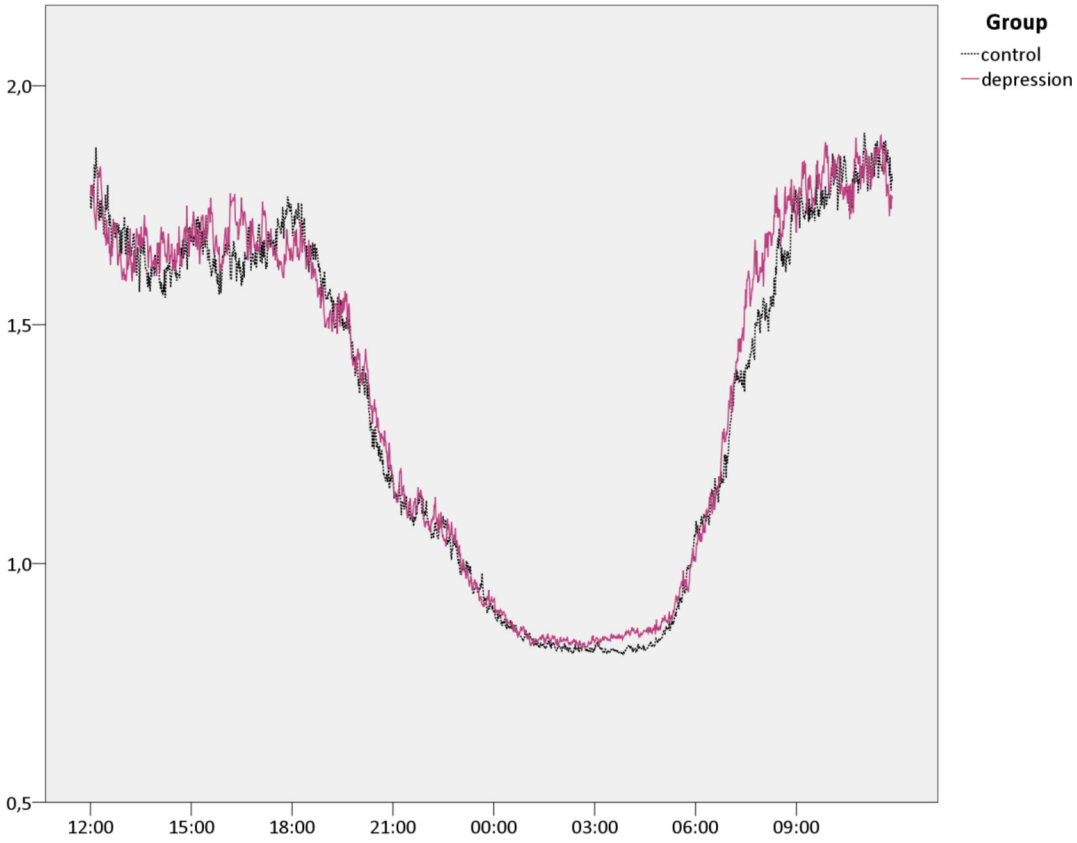


**Fig. 2.** Mean 24-h activity rhythm dived by group.

inter-individual differences that occur especially in more naturalistic studies and lead to heterogeneous groups. Another explanation could be that major changes in skin temperature and physical activity only become visible in a pronounced depressive episode and fade away afterwards. Thus, longitudinal studies should be carried out that can take these inter-individual and temporal factors into account. However, the fact that we did not find any differences between depressed individuals and non-depressed controls concerning actigraphically measured physical activity contradicts reasonable expectations and is in contrast to previous actigraphic findings in depression (Burton et al., 2013). Another explanation for this could be that a large part of previous studies have been conducted in hospital settings where patients are displaced from their normal routines due to clinical time schedules that may mask the activity rhythms and lead to artificial differences between the investigated groups. The absence of any differences in sleep timing, sleep quantity or continuity between the two groups is surprising, since sleep problems are found in most patients with major depression (Baglioni et al., 2016). An explanation for this could be that we did not choose the participants based on a clinical interview that would allow us to include only patients with the clinical diagnosis of depression into the study.

## 5. Limitations

It must be considered that the measured circadian rhythms are likely to be masked by various external factors because we measured skin temperature in free-living conditions allowing activity, changing environmental temperature, eating and other factors to influence the data. Precise circadian temperature rhythms can only be measured in lab conditions using unmasking study protocols. This limits our results in terms of drawing conclusions about circadian rhythms. Furthermore, it should be noted that we did not examine diagnosed depressive patients, but people with self-reported depressive symptoms. Therefore, conclusions about depression disorders should be taken with caution.

## 6. Conclusion

Recently, there have been a number of studies investigating the opportunities associated with the use of mobile devices and connected sensors in depression (Callan et al., 2017). In particular, there was a strong interest in investigating the associations between objective behavioral features collected with wearable devices and depressive symptoms in patients with affective disorders (Dogan et al., 2017). Several promising correlations were found (Rohani et al., 2018). In these studies, however, circadian features such as 24-h skin temperature rhythms have received little attention so far. As the technology improves, long-term monitoring of physiological parameters and their circadian rhythms may become increasingly applicable. Further studies should therefore investigate the benefits of adding these parameters to the relevant studies in depression.

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## Disclosure statement

All authors declare no conflict of interests.

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