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Actimetry-Derived 24 h Rest–Activity Rhythm Indices Applied to Predict MCTQ and PSQI

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Abstract: The aim of this study was to identify wrist actimetry-based indices associated with the sleep–wake rhythm characteristics of healthy individuals. The study involved 79 healthy subjects of both sexes (age range 15–62 years (mean: 21.5 ± 9.6 years, women: 77.8%)). Each participant provided personal data, filled out two questionnaires, the Munich ChronoType Questionnaire (MCTQ) and the Pittsburgh Sleep Quality Index (PSQI), and wore a wrist actimeter for a week. A significant positive association of the chronotype with the mid-phase of the most active 10 h period (M10t: $B = 0.252$, $p = 0.015$), the mid-phase of the least active 5 h period (L5t: $B = 0.338$, $p = 0.005$), and the interdaily stability (IS: $B = -0.021$, $p = 0.017$) was noted, as well as the sleep duration with the M10t ($B = -0.257$, $p = 0.003$), L5t ($B = -0.340$, $p = 0.001$), and IS ($B = 0.042$, $p = 0.003$). There was a significant association of social jetlag ($B = 0.320$, $p = 0.032$) and sleep quality ($B = 0.990$, $p = 0.013$) with motor activity in bed, as well as sleep efficiency with the acrophase ($B = -0.043$, $p = 0.007$). Nonparametric indices of the 24 h rest–activity rhythm are useful tools for assessing the sleep–wake rhythm of healthy individuals.

Keywords: wrist actimetry; the Munich ChronoType Questionnaire; the Pittsburgh Sleep Quality Index; 24 h rest–activity rhythm indices; sleep–wake rhythm characteristics

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Citation: Borisenkov, M.; Tserne, T.; Bakutova, L.; Gubin, D. Actimetry-Derived 24 h Rest–Activity Rhythm Indices Applied to Predict MCTQ and PSQI. *Appl. Sci.* **2022**, *12*, 6888. https://doi.org/10.3390/app12146888

Academic Editor: Jesús García Pallarés

Received: 14 June 2022
Accepted: 5 July 2022
Published: 7 July 2022

1. Introduction

In modern society, the rhythm of activity and rest in humans is largely determined by social rhythms (work/school schedules, etc.). At the same time, the role of the circadian system in the regulation of physiological function and sleep–wake rhythms remains substantial [1]. The discrepancy of mid-sleep phase between work and free days, most common in individuals with the late chronotype [2], leads to a mismatch in the function of the circadian system, defined as 'social jetlag' (SJL) [3]. Numerous studies have shown that SJL is associated with cognitive impairment [4], low academic performance [5], and a predisposition to depression [6], bad habits [3], obesity [7], and type 2 diabetes [8].

A comprehensive review of the circadian misalignment concept, its contribution to chronobiology [9,10], shortcomings [9,11], possible practical applications [12,13], and directions for further development [9] is currently underway. The most reliable and reproducible results have been obtained regarding the association of SJL with cognitive decline in students [4,5]. Researchers have found practical application in changing the working hours of educational institutions in order to increase the efficiency of the educational process: a one-hour delay in the start of classes [12,14,15] and a flexible school start time, taking into account the chronotype of students [13,16].

Currently, the most serious problem for addressing circadian misalignment is the lack of objective data on the causal relationship between SJL and the clinical manifestations of this form of circadian misalignment. To solve this problem, additional research at a qualitatively higher level is required. The need for the further development of this area of chronobiology was assessed by one of the authors of the concept: "*In fact, most studies investigating the associations between SJL and health are cross-sectional. Further longitudinal studies are needed not only to confirm causal associations but also to clarify under how much and for how long one needs to be exposed to SJL for its consequences to show*" [9].

Based on the foregoing, there is a need to search for and put into practice objective indicators that make it possible to quantify the degree of circadian system misalignment. These methods should be fairly simple and inexpensive. It is important that these methods can be used in conditions as close to natural as possible. It is also important that they allow continuous recording of indicators for a significant amount of time to obtain a time series.

Some progress has been made in this direction. A chronotype or phase of entrainment (MSFsc) [2,9] and SJL have been shown to correlate with the dim-light melatonin onset (DLMO) [17–19] and the cortisol awakening response (CAR) [20–22], indicators that have long been widely used to assess the state of the circadian system. However, the use of these indicators is difficult due to the high cost of consumables and the complexity of the analyses. There was also a correlation between SJL and the amplitude of the 24 h rhythm of the wrist temperature [23]. This method satisfies the above requirements as much as possible. One of its disadvantages is the fact that it only indirectly reflects the state of the circadian system; thus, it must be used in combination with other methods, such as wrist actimetry

Currently, wrist actimetry is widely used to assess the state of the circadian system [24–28] and sleep function [28,29]. An important advantage of the method is that it has been used to develop and test a wide range of indicators that have long been actively used in clinical practice [30–32]. Wrist actimetry is used to calculate parametric (Midline Estimating Statistic of Rhythm (MESOR), amplitude (A), and acrophase (φ) [33,34]) and nonparametric (interdaily stability (IS), intradaily variability (IV), the least active 5 h period (L5) that is nocturnal activity, and the most active 10 h period (M10) that is daily activity [30,31,35]) indices. It is of interest to study the relationship of the indicators of the state of the circadian system and sleep function, assessed by the questionnaire survey method, with the objective indicators obtained by the method of wrist actimetry, which will enable future determination of approaches for a reliable assessment of the contribution of the circadian system misalignment to the development of various pathologies.

The aim of this study was to analyze the relationship between the subjective indicators characterizing the state of the circadian system and sleep function on the one hand and the objective indicators characterizing the 24 h rest–activity rhythm on the other hand.

In this article, in accordance to standard procedure [36], we first calculated basic statistics of the studied indicators (mean, standard deviations, and normality of distribution). We converted some values to normalize them, if necessary, and then analyzed the association between subjective and objective indicators in two ways: (1) we carried out an analysis of covariance for a preliminary assessment of the relationship between the studied indicators and (2) the final conclusion about the presence and nature of relationships between the indicators was made on the basis of multiple regression analysis adjusted for concomitant factors (sex, age, and BMI).

2. Materials and Methods

2.1. Subjects and Data Collection

The study was conducted from February 2019 to March 2020 upon 79 voluntary and anonymous participants aged 15 to 62 years (average age: 21.5 ± 9.6 years, women: 77.8%). Persons working on night shifts, as well as those with sleep disorders, were excluded from the study. The self-assessment method was used to identify sleep disorders. The study was carried out in two stages. At the first stage, the study participants completed a battery of tests. In it, we, among other things, asked the following questions: Do they have sleep disorders? Do they take sleeping pills prescribed by a doctor? In the case of a positive answer to these questions, we did not include this participant in the second stage of the study, where we conducted an experiment with actimeters. Each study participant indicated their sex, age, height, and weight and completed the Munich ChronoType Questionnaire (MCTQ) [2] and the Pittsburgh Sleep Quality Index (PSQI) [37].

2.2. Data Treatment

Weight and height were used to calculate body mass index (BMI) as weight in kilograms divided by height in meters squared. Sex- and age-specific BMI percentiles were calculated using BMI growth charts [38]. Four groups of participants were identified according to their BMI values (BMIc): (1) underweight (BMI percentile below 5%), (2) normal weight (BMI percentiles ranging from 5% to 84.9%), (3) overweight (BMI percentile in a range from 85% to 94.9%), and (4) obese (BMI percentile over 95%).

2.3. Instruments

2.3.1. MCTQ

The MCTQ contains questions about the time of falling asleep and waking up, the time required for final falling asleep and waking up on school/work days, the use of an alarm clock, and the length of the school/work week. Based on these data, the following indicators were calculated: chronotype (MSF_{SC}), social jetlag (SJL), average weekly sleep duration (SlD), and sleep efficiency (SlE). The formulas and calculation methods of the characteristics listed above have been described previously [39].

2.3.2. PSQI

To assess the quality of sleep, we used the Russian version of the PSQI [40]. This measure consists of 19 questions related to sleep quality, including sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime sleepiness for a period of one month. Global PSQI scores range from 0 to 21 points; in our sample the scores ranged from 1 to 12, with an overall group mean $\pm$ SD of 5.7 $\pm$ 2.8. In accordance with the recommendation of the test authors [37], a PSQI score $\leq$ 5 was considered to be indicative of a good-quality sleeper and a PSQI score > 5 was considered to be indicative of a poor-quality sleeper.

2.3.3. Wrist Actimetry

Each participant wore an actimeter 'Daqtometer v2.4' (Daqtix, Germany) (Figure 1) on the wrist of the non-dominant hand for 1 week, continuously.

Figure 1. Actimeter 'Daqtometer v2.4' (Daqtix, Germany).

The activity was measured at 1 Hz, and the values were summed once per minute and expressed in arbitrary units (a.u.). Activity was recorded by a dual axis accelerometer that records dynamic (motion) as well as static (gravity, i.e., change in position) acceleration. The following algorithm was used to quantify the activity. In the sampling interval of 1 s, the value for each axis (x_i and y_i) of the sensor was read. The linear difference between two subsequent readings was summarized for the number of sampling intervals (bin = 1 min).

This number was then saved for the specific bin. The value stored for each bin was computed as (1):

$$\text{Saved value for bin} = \sum_{i=1}^{60} (x_i - x_{i-1}) + (y_i - y_{i-1}) \tag{1}$$

The study participants kept a diary in which they indicated the time that they removed the actimeter when engaging in activities involving water, as well as the times that they went to bed in the evening and rose in the morning. Time intervals when measurements of motor activity were not made were removed from the actograms, and the time in bed was also indicated. Figure 2 shows a 7-day actogram for one of the study participants. Using the Chronos-Fit software package (Zuther P. and Lemmer B., Frankfurt, Germany), the parametric indices of the 24 h rest–activity rhythm (MESOR, A, and φ) were calculated. Nonparametric indices (IS, IV, L5, mid-phase of L5 (L5t), M10, and mid-phase of M10 (M10t)) were calculated as described in [30,31,35]. In addition, the average weekly motor activity in bed (AciB) and outside of bed (AcoB) was calculated.

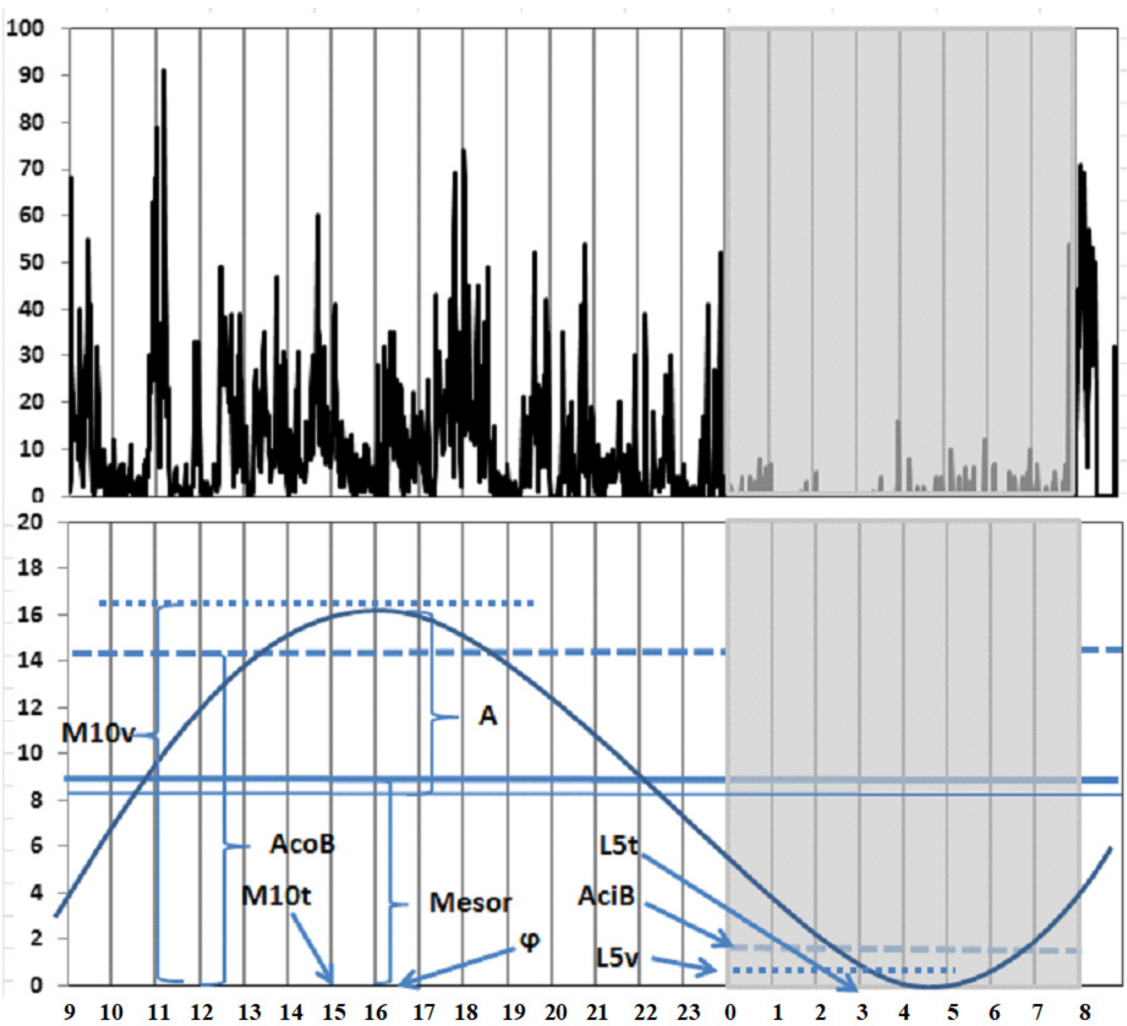

Figure 2. Example of 24 h rest–activity rhythm (**upper panel**) and 24 h rest–activity rhythm characteristics (**lower panel**). The abscissa axis represents the local time in hours, the ordinate axis represents the level of motor activity in arbitrary units, and the measurement step is 1 min. Rectangles highlighted in color: time in bed; MESOR: Medline estimating statistics of rhythm; A: amplitude; φ: acrophase; M10(t): most active 10 h period (mid-phase of M10); L5(t): least active 5 h period (mid-phase of L5); AcoB: motor activity outside of bed; AciB: motor activity in bed at night.

2.4. Statistical Analysis

To analyze the relationship between the sleep–wake rhythm and the 24 h rest–activity rhythm characteristics, the continuous indicators (MSFsc, SlD, SlE) of the sleep–wake rhythm were transformed into categorical values. To calculate the boundaries of the categorical values, tertiles were used as described in [41]:

(1)	(2)	(3)
MSFsc < 03:45	03:45 ≤ MSFsc < 05:02	MSFsc ≥ 05:02
SlD < 6.5 h	6.5 ≤ SlD < 7.5 h	SlD ≥ 7.5 h
SlE < 85 %	85 ≤ SlE < 94 %	SlE ≥ 95 %

Table 1 presents the mean values, standard deviations, and estimates of the normality of the distribution of the samples of the indicators used in the work. The distribution of the samples of two of the indicators (L5 and AciB) differed from normal; therefore, in further analyses, transformed indicators (2 + ln(L5) and 1 + ln(AciB)), which had a normal distribution, were used (Table 1).

Table 1. Descriptive statistics parameters studied.

Parameter	Instrument	Mean	*SD*	*S*	*K*
Age, years	Self-report	21.51	9.64	0.79	0.86
BMI, %	Self-report	47.51	25.33	0.26	−0.63
PSQI, global score	PSQI	5.65	2.82	0.37	−0.83
SlE, %	MCTQ	88.64	5.53	−0.67	−0.12
SlD, min	MCTQ	413	72	−0.94	0.19
SJL, min	MCTQ	114	80	0.71	−0.77
MSFsc, hh:min	MCTQ	04:13	01:22	0.07	−0.10
MESOR, a.u.	Actimetry	10.36	1.97	0.09	−0.27
A, a.u.	Actimetry	7.49	2.07	0.17	−0.47
φ, hh:min	Actimetry	14:52	01:07	0.17	−0.20
M10, a.u.	Actimetry	17.28	3.29	0.21	−0.45
M10t, hh:min	Actimetry	15:16	01:29	0.59	0.69
L5, a.u.	Actimetry	0.60	0.24	2.25	9.95
2 + ln(L5), a.u.	-	1.42	0.36	0.29	0.76
L5t, hh:min	Actimetry	03:14	01:17	−0.10	0.82
IS, a.u.	Actimetry	0.51	0.11	−0.14	−0.76
IV, a.u.	Actimetry	0.92	0.19	0.40	−0.16
AcoB, a.u.	Actimetry	14.84	2.61	−0.09	−0.49
AciB, a.u.	Actimetry	1.65	1.01	1.97	4.47
1 + ln(AciB), a.u.	-	0.36	0.52	0.53	0.02

PSQI: sleep quality; SlD: average weekly sleep duration; MSF_{SC}: chronotype; SJL: social jetlag; SlE: sleep efficiency; MESOR/A/φ: 24 h time series mean/amplitude/acrophase of 24 h rest–activity rhythm; M10(t): most active 10 h period (mid-phase of M10); L5(t): least active 5 h period (mid-phase of L5); IS: interdaily stability; IV: intradaily variability; AcoB/AciB: mean values of motor activity out of bed/in bed; a.u.: arbitrary units; *SD*: standard deviation; *S*: skewness; *K*: kurtosis.

The SPSS version 20 (SPSS, Inc., Chicago, IL, USA) software package was used for the statistical analyses of data. Four series of one-way analyses of covariance (ANCOVAs) were performed as follows: in the first model we used MSFsc categorical as a fixed factor; '24 h rest–activity rhythm characteristics (MESOR, A, φ, IS, IV, 2 + ln(L5), L5t, M10, M10t, AcoB, 1 + ln(AciB))' were specified as dependent variables; and 'sex (1: female, 2: male)', 'age', and 'BMIc (1: underweight, 2: normal weight, 3: overweight, 4: obese)' were included in the model as covariates. In the second model we used SJL categorical (1: SJL ≤ 1 h; 2: 1 < SJL ≤ 2 h; 3: SJL > 2 h) as a fixed factor; '24 h rest–activity rhythm characteristics' were specified as dependent variables; and 'sex', 'age', and 'BMIc' were included in the model as covariates. In the third model we used SlE categorical as a fixed factor; '24 h rest–activity rhythm characteristics' were specified as dependent variables; and 'age', 'sex', and 'BMIc' were included as covariates. In the second model we used 'PSQI categorical (1: PSQI ≤ 5, 2: PSQI > 5)' as fixed factor; '24 h rest–activity rhythm characteristics' were specified as dependent variables; and 'age', 'sex', and 'BMIc' were included as covariates.

A series of multiple regression analyses were performed in which the continuous values 'MSFsc', 'SJL', 'SlD', 'SlE', and 'PSQI global score' were used as dependent variables and 'age', 'sex', 'BMIc', and '24 h rest–activity rhythm characteristics' were included as independent variables. A procedure of stepwise inclusion of predictors in the model was used. Only predictors with significant regression coefficients were included in the final model. The variance inflation factor was used to evaluate multicollinearity in the model, as described in [42]. Predictors were excluded from the model if the variance inflation factor was equal to or greater than five.

3. Results

Mean values of MSF_{SC} in study participants was 04:13 (Table 1). Early chronotype was observed in 39%, intermediate in 35%, and late in 25% of participants (Table 2). The average value of SJL in our study was 1 h and 90 min (Table 1). SJL > 1 h was observed in 75% and SJL > 2 h in 43% of study participants (Table 3). The average sleep duration was 6 h and 53 min (Table 1). The study participants were approximately equally distributed in three groups: less than 6.5 h, from 6.5 to 7.5 h, and more than 7.5 h (Table 4). Low sleep quality (PSQI > 5) was observed in 42% of study participants (Table 5).

Table 2. Association of chronotype with 24 h rest–activity rhythm characteristics.

Parameter	MSFsc < 03:45	03:45 ≤ MSFsc < 05:02	MSFsc ≥ 05:02	F	p	η^2
N	31	28	20			
MESOR, a.u.	10.64 ± 1.74	10.44 ± 2.07	9.81 ± 2.00	0.830	0.440	0.022
A, a.u.	7.93 ± 1.54 ^{C}	7.61 ± 2.46	6.65 ± 1.89 ^{c}	1.758	0.179	0.045
φ, hh:mm	14:34 ± 01:05	14:58 ± 01:05	15:10 ± 01:05	1.571	0.215	0.041
M10, a.u.	17.31 ± 2.87	17.92 ± 3.51	16.45 ± 3.48	0.731	0.485	0.019
M10t, hh:mm	14:37 ± 01:08 ^{b,c}	15:26 ± 01:28 ^{C}	15:55 ± 01:34 ^{B}	**5.435**	**0.006**	**0.128**
& L5, a.u.	0.58 ± 0.30	0.59 ± 0.21	0.63 ± 0.18	0.211	0.810	0.006
L5t, hh:mm	02:41 ± 01:02 ^{b}	03:26 ± 01:03 ^{B}	03:44 ± 01:30 ^{B}	**5.618**	**0.005**	**0.138**
IS, a.u.	0.53 ± 0.10 ^{C}	0.53 ± 0.10 ^{C}	0.46 ± 0.12 ^{c}	**3.520**	**0.035**	**0.091**
IV, a.u.	0.88 ± 0.14	0.93 ± 0.22	0.96 ± 0.20	0.580	0.563	0.015
AcoB, a.u.	15.11 ± 2.28	15.08 ± 2.77	14.14 ± 2.64	0.425	0.656	0.012
& AciB, a.u.	1.59 ± 1.14	1.62 ± 0.82	1.75 ± 1.03	0.055	0.947	0.002

Abbreviations as in Table 1. & Since these indicators differ from the normal distribution, transformed indicators were used in the analyses: 2 + ln(L5) and 1 + ln(AciB), respectively, having a normal distribution. A series of one-way analyses of covariance were performed using 'MSFsc categorical' as a fixed factor, '24 h rest–activity rhythm characteristics (MESOR, A, φ, M10(t), 2 + ln(L5), L5t, IS, IV, AcoB, 1 + ln(AciB))' as dependent variables, and 'age', 'sex', and 'BMI categorical' as covariates; data are presented as mean ± standard error; F: Fisher test; p: significance of F; η^2: effect size; bold values = statistically significant F-tests; differences between values marked with the letters are significant: A > a—$p < 0.001$, B > b—$p < 0.01$, C > c—$p < 0.05$ (post hoc comparisons, Tukey test).

Table 3. Association of social jetlag with 24 h rest–activity rhythm characteristics.

Parameter	SJL < 1 h	1 ≤ SJL < 2 h	SJL ≥ 2 h	F	p	η^2
N	20	25	34			
MESOR, a.u.	10.87 ± 0.40	10.14 ± 0.33	10.20 ± 0.38	1.062	0.351	0.028
A, a.u.	8.22 ± 0.40	7.41 ± 0.29	7.09 ± 0.42	1.313	0.275	0.034
φ, hh:mm	15:15 ± 01:14	14:37 ± 01:13	14:47 ± 01:11	2.580	0.083	0.065
M10, a.u.	18.06 ± 3.26	19.98 ± 2.30	17.05 ± 3.77	1.151	0.322	0.030
M10t, hh:mm	15:34 ± 01:11	14:45 ± 01:22	15:28 ± 01:37	1.410	0.251	0.037
L5, a.u.	0.52 ± 0.15 ^{c}	0.62 ± 0.33	0.63 ± 0.19 ^{C}	1.706	0.189	0.044
L5t, hh:mm	03:14 ± 00:47	03:02 ± 01:29	03:24 ± 01:19	0.202	0.817	0.006
IS, a.u.	0.54 ± 0.10 ^{C}	0.52 ± 0.11	0.48 ± 0.11 ^{c}	2.305	0.107	0.058
IV, a.u.	0.89 ± 0.16	0.88 ± 0.19	0.97 ± 0.21	1.487	0.233	0.038
AcoB, a.u.	15.32 ± 0.52	14.75 ± 0.41	14.61 ± 0.514	0.454	0.637	0.012
AciB, a.u.	1.18 ± 0.13 ^{b,c}	1.71 ± 0.20 ^{C}	1.88 ± 0.19 ^{B}	**5.901**	**0.004**	**0.138**

Abbreviations as in Table 1. For details see footnote to Table 2.

Table 4. Association of sleep duration with 24 h rest–activity rhythm characteristics.

Parameter	SlD < 6.5 h	6.5 ≤ SlD < 7.5 h	SlD ≥ 7.5 h	F	p	η^2
N	25	26	28			
MESOR, a.u.	9.81 ± 2.06 [c]	10.94 ± 1.80 [C]	10.34 ± 1.95	2.284	0.109	0.061
A, a.u.	6.86 ± 1.92 [c]	7.46 ± 2.02	8.04 ± 2.05 [C]	1.895	0.158	0.051
φ, hh:mm	15:11 ± 01:10 [C]	14:58 ± 01:09	14:30 ± 00:53 [c]	2.340	0.104	0.063
M10, a.u.	16.50 ± 3.48	17.58 ± 3.11	17.71 ± 3.09	1.050	0.355	0.029
M10t, hh:mm	15:44 ± 01:17 [C]	15:17 ± 01:37	14:49 ± 01:23 [c]	**3.203**	**0.047**	**0.084**
L5, a.u.	0.56 ± 0.18	0.66 ± 0.32	0.57 ± 0.20	1.582	0.213	0.043
L5t, hh:mm	03:52 ± 01:10 [A]	03:14 ± 01:20	02:42 ± 01:00 [a]	**5.913**	**0.004**	**0.145**
IS, a.u.	0.46 ± 0.09 [a]	0.50 ± 0.11	0.56 ± 0.10 [A]	**5.033**	**0.009**	**0.126**
IV, a.u.	0.97 ± 0.22	0.89 ± 0.17	0.90 ± 0.18	0.589	0.558	0.017
AcoB, a.u.	13.99 ± 2.72	15.09 ± 2.14	15.33 ± 2.66	1.928	0.153	0.051
AciB, a.u.	1.44 ± 0.59	1.67 ± 1.00	1.81 ± 1.25	1.809	0.171	0.049

Abbreviations as in Table 1. For details see footnote to Table 2.

Table 5. Association of sleep quality with 24 h rest–activity rhythm characteristics.

Parameter	PSQI ≤ 5	PSQI > 5	F	p	η^2
N	37	27			
MESOR, a.u.	10.38 ± 0.30	10.00 ± 0.42	0.027	0.869	0.000
A, a.u.	7.82 ± 0.33 [a]	6.78 ± 0.35 [A]	2.333	0.131	0.033
φ, hh:mm	14:48 ± 00:56	15:15 ± 01:18	1.474	0.229	0.021
M10, a.u.	17.87 ± 3.35	16.65 ± 3.24	0.898	0.548	0.043
M10t, hh:mm	15:03 ± 01:14	15:34 ± 01:44	3.794	0.056	0.054
L5, a.u.	0.55 ± 0.17 [c]	0.68 ± 0.30 [C]	0.599	0.822	0.010
L5t, hh:mm	03:11 ± 00:59	03:31 ± 01:32	1889	0.174	0.027
IS, a.u.	0.53 ± 0.11 [B]	0.46 ± 0.09 [b]	1.846	0.066	0.056
IV, a.u.	0.91 ± 0.20	0.93 ± 0.19	0.789	0.650	0.028
AcoB, a.u.	15.15 ± 0.40	14.02 ± 0.51	0.768	0.384	0.011
AciB, a.u.	1.20 ± 0.08 [a]	1.55 ± 0.10 [A]	**12.969**	**0.001**	**0.160**

Abbreviations as in Table 1. For details see footnote to Table 2.

As a result of ANCOVAs (Tables 2–6), a significant positive association of chronotype (MSFsc) with M10t (F = 5.435, p = 0.006) and L5t (F = 5.618, p = 0.005) and negative with IS (F = 3.520, p = 0.035; Table 2) was noted. There was also a significant positive relationship between SJL and AciB (F = 5.901, p = 0.004; Table 3). There was a significant negative association SlD with M10t (F = 3.203, p = 0.047) and L5t (F = 5.913, p = 0.004), as well as a positive relationship with IS (F = 5.033, p = 0.009; Table 4). A significant positive relationship between PSQI and AciB (F = 12.969, p = 0.001; Table 5) and a negative relationship was noted between SlE and φ (F = 3.686, p = 0.030; Table 6).

Table 6. Association of sleep efficiency with 24 h rest–activity rhythm characteristics.

Parameter	SlE < 85%	85 ≤ SlE < 94%	SlE ≥ 95%	F	p	η^2
N	29	27	23			
MESOR, a.u.	10.38 ± 1.83	10.85 ± 2.10	9.74 ± 1.74	1.641	0.201	0.045
A, a.u.	7.76 ± 1.72	7.54 ± 2.53	7.10 ± 1.76	0.483	0.619	0.014
φ, hh:mm	15:13 ± 01:14 [C]	14:50 ± 00:52	14:26 ± 01:03 [c]	**3.686**	**0.030**	**0.095**
M10, a.u.	17.26 ± 3.18	17.84 ± 3.24	16.68 ± 3.29	0.626	0.538	0.018
M10t, hh:mm	15:40 ± 01:15 [C]	15:14 ± 01:29	14:50 ± 01:37 [c]	2.331	0.105	0.062
L5, a.u.	0.57 ± 0.16	0.67 ± 0.32	0.55 ± 0.19	1.491	0.232	0.041
L5t, hh:mm	03:22 ± 01:23	03:27 ± 01:04	02:52 ± 01:16	2.302	0.108	0.062
IS, a.u.	0.52 ± 0.10	0.50 ± 0.11	0.51 ± 0.12	0.078	0.925	0.002
IV, a.u.	0.93 ± 0.18	0.93 ± 0.24	0.90 ± 0.14	0.283	0.754	0.008
AcoB, a.u.	14.86 ± 2.33	15.34 ± 2.60	14.22 ± 2.75	0.922	0.402	0.025
AciB, a.u.	1.52 ± 0.60	1.85 ± 1.27	1.57 ± 1.01	0.590	0.557	0.017

Abbreviations as in Table 1. For details see footnote to Table 2.

We conducted a multiple regression analysis to identify associations among subjective and objective indices, adjusted for related factors (sex, age, BMIc). In total, seven significant relationships were identified (Table 7). There was a significant association of MSFsc with M10t (B = 0.252, p = 0.015), L5t (B = 0.338, p = 0.005), and IS (B = −0.021, p = 0.017) and of SlD with M10t (B = −0.257, p = 0.003), L5t (B = −0.340, p = 0.001), and IS (B = 0.042, p = 0.003). There was a significant association of SJL (B = 0.320, p = 0.032) and PSQI global scores (B = 0.990, p = 0.013) with AciB and of SlE with φ (B = −0.043, p = 0.007; Table 7).

Table 7. Associations among sleep–wake rhythm and 24 h rest–activity rhythm characteristics.

Model #	Dependent Variable	Predictors	B	β	p	ΔR^2
1	MSFsc	M10t	0.252	0.278	0.015	0.077
2	MSFsc	L5t	0.338	0.316	0.005	0.100
3	MSFsc	IS	−0.021	−0.245	0.017	0.060
4	SJL	AciB	0.320	0.241	0.032	0.145
5	SlD	M10t	−0.257	−0.322	0.003	0.080
6	SlD	L5t	−0.340	−0.361	0.001	0.105
7	SlD	IS	0.042	0.313	0.003	0.093
8	SlE	φ	−0.043	−0.308	0.007	0.095
9	PSQI	AciB	0.990	0.293	0.013	0.169

A series of multiple regression analyses were performed using ‘sleep–wake rhythm characteristics (MSF_{SC}, SJL, SlD, SlE, PSQI)’ as dependent variables and ‘24 h rest–activity rhythm characteristics (MESOR, A, φ, M10(t), 2 + ln(L5), L5t, IS, IV, AcoB, 1 + ln(AciB))’ as independent variables (predictors) adjusted for ‘age’, ‘sex’, and ‘BMIc’; a stepwise inclusion procedure was used; B: non-standardized regression coefficient; β: standardized regression coefficient; p: significance of B; ΔR^2: portion of the variance accounted for by separate predictors in the model.

4. Discussion

This study assessed the relationship between the wrist actimetry-derived 24 h rhythm of motor activity indices and the sleep–wake rhythm characteristics obtained by a questionnaire survey. Parametric (MESOR, A, and φ) and nonparametric (IS, IV, L5, L5t, M10, M10t, AcoB, and AciB) indices were used as the objective indicators of the 24 h rhythm of motor activity. The indicators obtained using the MCTQ (MSFsc, SJL, SlD, SlE) and PSQI global score were used as the subjective indicators of the sleep–wake rhythm and sleep quality. In general, a closer relationship was noted between the nonparametric indicators of the 24 h rhythm of motor activity and the sleep–wake rhythm characteristics. According to our data, the IS, L5t, and M10t were predictors of the MSFsc and SlD, and the AciB was a predictor of SJL and the PSQI global score (Figure 3). Of the parametric indicators, only φ showed a significant association with the SlE. Based on this, it can be concluded that the nonparametric indicators of the 24 h rhythm of motor activity are more suitable for assessing the state of the circadian system. Therefore, in the further development of the circadian misalignment concept and its contribution to various pathologies, it is necessary to take this circumstance into account.

In previous studies, nonparametric indicators of the 24 h rhythm of motor activity were actively used to assess the state of the circadian system in patients with chronic diseases. It has been shown that women with breast cancer have significantly higher values of IV [43] and low values of the IS [44], M10 [43,44], and L5 [43]. Low IS values are associated with elevated blood pressure and a higher incidence of arterial hypertension [45]. High IV values were observed in individuals with bipolar disorders [46]. Low IS values and high IV values are associated with increased mortality [47]. The parametric indicators of the 24 h rest–activity rhythm have been used relatively less frequently. A decrease in the MESOR and A values was observed in women with breast cancer [43,44] and in people suffering from a binge eating disorder [48]. In [49], it was suggested that when approximating a time series of motor activity using the Cosinor method, a significant part of the trait variability was considered as unexplained. However, from our point of view, a more fundamental reason for the low sensitivity of the parametric indicators is that the 24 h rest–activity rhythm itself is a complex integral indicator, which, along with the circadian system, is associated with a number of other external and internal factors. As an output, activity is non-sinusoidal and incorporates napping components that vary in timing and duration among individuals. Therefore, in order to increase the sensitivity of the wrist actimetry method in assessing the state of the circadian system, it is necessary to take into account the contribution of these concomitant factors by improving the design of the study and the method of processing the time series. First, it is necessary to use wrist actimetry in combination with other methods, for example, the 24 h rhythm of the wrist temperature. This direction is being successfully developed by scientists under the leadership of Madrid J.A. et al. [26]. Secondly, it is necessary to improve the data processing algorithm in order to reduce the variability of the indicator introduced by the concomitant factors and to increase the variability associated with the function of the circadian system.

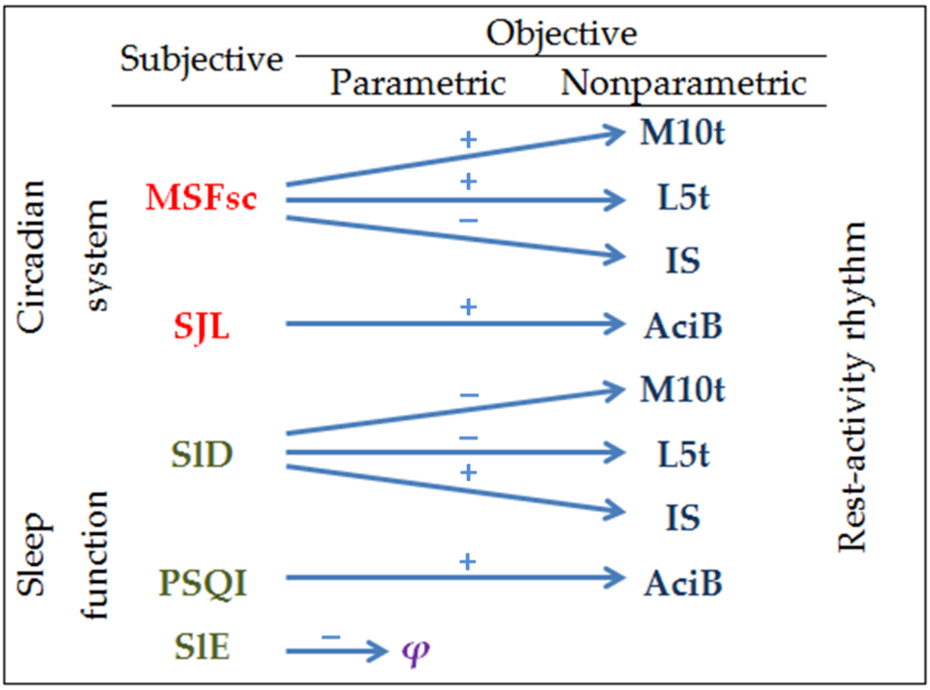

Figure 3. Associations among subjective and objective indices.

One way to solve the second problem is to use combined indicators based on parametric and nonparametric indices. Consider, for example, the phase of entrainment (MSFsc). It is logical to assume the existence of a close relationship between the MSFsc and φ. However, we did not find such a relationship. At the same time, there was a significant association of the MSFsc with the L5t and M10t. It is important to emphasize that, despite the difference in the calculation method, the M10t in its meaning is an analogue of φ, although it differs from it by more than 1.5 h (Table 1). Therefore, it is obvious that by introducing a correction factor when calculating φ, it is possible to increase the accuracy of calculating the phase of the 24 h rest–activity rhythm. In addition, we have shown a significant association of the SlD with the L5t and M10t; so, when calculating the phase of the 24 h rest–activity rhythm, it is also necessary to correct for the duration of sleep.

The situation is somewhat more complicated with the SJL indicator, which reflects the state of circadian misalignment. It is known that there is a positive relationship between the MSFsc and SJL [3], indicating that persons with a late chronotype are more prone to circadian misalignment. Of the previously proposed wrist actimetry-derived indices, the IS is more suitable for use as an objective indicator reflecting the state of circadian misalignment [24]. In this study, we noted a negative relationship between the MSFsc and the IS, indicating that the stability of the 24 h rest–activity rhythm is reduced in individuals with a late chronotype. Similar results were previously obtained by other authors in healthy individuals [24] and in patients with spinal cord injury [50]. However, neither ANCOVA nor multiple regression analysis allowed us to identify a significant association between SJL and the IS, only post hoc comparison showed a significant decrease in the IS in individuals with SJL $\geq$ 2 h. Unfortunately, there is no information about the nature of the relationship between SJL and the IS in the available literature. There are only indirect data confirming our conclusion. One work [45] showed that the IS is a stronger predictor of blood pressure disorders in adults than SJL. This indicates that the IS describes the state of circadian misalignment somewhat differently than SJL. In the future, it will be necessary to study in more detail the factors affecting the nature of the relationship between SJL and the IS, which will allow us to create a combined objective indicator that more accurately describes the state of circadian misalignment.

Previously, the relationship between SJL and the PSQI global score has been repeatedly noted [51,52], indicating that one of the signs accompanying circadian misalignment is a deterioration in sleep quality. In our study, there was a significant relationship between SJL and the AciB, an indicator reflecting the level of motor activity in bed at night. The AciB can be considered as an objective indicator reflecting the quality of sleep: the higher the level of motor activity at night, the worse the sleep quality. This is evidenced by the significant relationship between the AciB and the PSQI global score. The indicator AciB is an analogue of the previously described nonparametric indicator L5. However, this indicator does not reliably describe sleep quality, since we did not find a significant association between the L5 and the PSQI global score. In the future, when creating an objective indicator characterizing the state of circadian misalignment, one should correct for sleep quality, for example, using the AciB index.

The presented study has a number of limitations. We used an insufficiently large sample size. In addition, the work used actimeters of an outdated model that did not automatically calculate the characteristics of the sleep function, such as the sleep onset and offset, sleep inertia and latency, and sleep efficiency and duration. Therefore, the conclusions presented in this paper should be considered as preliminary, requiring careful rechecking.

5. Conclusions

The presented data indicate that the nonparametric indices of the 24 h rest–activity rhythm are more closely related to the subjective characteristics of the sleep–wake rhythm and sleep quality obtained by the questionnaire survey. These results should be taken into account when further improving objective methods for assessing the state of circadian misalignment in order to assess its contribution to chronic diseases.

Author Contributions: Conceptualization, M.B. and D.G.; methodology, T.T. and L.B.; software, M.B.; validation, M.B., T.T. and L.B.; formal analysis, L.B.; investigation, M.B., T.T., L.B. and D.G.; data curation, M.B.; writing—original draft preparation, M.B. and T.T.; writing—review and editing, M.B. and D.G.; visualization, M.B.; supervision, M.B. and D.G.; funding acquisition, D.G. All authors have read and agreed to the published version of the manuscript.

Funding: The research was carried out within the framework of the research project of the Institute of Physiology of the Federal Research Centre Komi Scientific Centre of the Ural Branch of the Russian Academy of Sciences FUUU-2022-0066 (No. 1021051201895-9) and was partially funded by the grant of the Government of Tyumen District, Decree of 20.11.2020 No. 928-rp.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Institute of Physiology of the Komi Scientific Center of the Ural Branch of the Russian Academy of Sciences (Protocol # 3, 26 March 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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