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Merikanto, Ilona

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Advanced phases and reduced amplitudes are suggested to characterize the daily rest-activity cycles in depressed adolescent boys

Ilona Merikanto[1,2], Timo Partonen[1], Tiina Paunio[3,4], Anu E. Castaneda[5], Mauri Marttunen[1,4], Anna S. Urrila[1,4*]

[1]National Institute for Health and Welfare, Department of Public Health Solutions, Mental Health Unit, Helsinki, Finland

[2]Orton Orthopaedics Hospital, Helsinki, Finland

[3]National Institute for Health and Welfare, Department of Health, Genetics and Biomarkers Unit, Helsinki, Finland

[4]University of Helsinki and Helsinki University Hospital, Department of Psychiatry, Helsinki, Finland

[5]National Institute for Health and Welfare, Department of Welfare, Equality and Inclusion Unit, Helsinki, Finland

***Corresponding author:**

Anna S. Urrila, National Institute for Health and Welfare, Department of Health, Mental Health Unit, P.O. Box 30, 00271 Helsinki, Finland, **Tel.:** +358-40-351 8547, **E-mail:** anna.urrila@helsinki.fi

ABSTRACT

Self-reported eveningness has been previously associated with depressed mood among adults and adolescents. Here we study how circadian indicators based on actigraphic data differ between depressed and healthy adolescent boys. Our sample consisted of 17 medication-free adolescent boys, aged 14.5 to 17.5 years, of which eight had depressive disorder and were currently depressed and nine were healthy comparison participants. Psychiatric assessment was conducted by diagnostic interviews and complemented with observer-rating and self-rating scales. Actigraphic data were collected with wrist actigraphs for a minimum period of 25 consecutive days (range of 25 to 44 days). The behavioral trait of morningness-eveningness was measured with the 19-item Horne-Östberg Morningness-Eveningness Questionnaire. Based on the self-report the depressed boys were more prone to eveningness than healthy controls, but based on the actigraphic data they had earlier phases especially on school days and lower activity levels especially on weekends. On weekends the depressed boys showed a greater shift towards later-timed phases than healthy controls. Our results confirm a mismatch of the subjective morningness-eveningness preference (late-preference) and the objective rest-activity rhythm (early-prone) during school days in depressed adolescent boys.

Key words: actigraphy, adolescence, circadian, depression, diurnal, youth

Introduction

Individuals differ in their daily timing of physiological functions and activity patterns, which determines the individual chronotype of the person. Individual chronotypes can be classified into an earlier-timed Morning-type, an Intermediate-type, or a later-timed Evening-type (Horne and Östberg, 1976) on a dimensional trait of morningness-eveningness behavior (Duffy et al., 1999, 2001). Age and physiological development influence this circadian preference. During adolescence, there is a higher tendency towards eveningness than towards earlier-timed daily rhythms, whereas tendency towards morningness appears to increase with aging (Broms et al., 2014; Merikanto et al., 2012; Roenneberg et al., 2004).

Disturbances of the circadian system have been suggested to play an important role in the pathogenesis of affective disorders (Wulff et al., 2010). Eveningness and tendency towards depression have been associated together in population-based, representative epidemiological studies among both young adults and adults (Chelminski et al., 1999; Drennan et al., 1991; Merikanto et al., 2013, 2015, 2016). The evening chronotype has been regarded as a vulnerability marker to emotional difficulties among adolescents also under experimental conditions (Dagys et al., 2012). It has been postulated that the normal phase delay occurring in adolescence is amplified along with depression (Urrila et al., 2015).

Spontaneous rest-activity cycles, reflecting the circadian rhythms, can be recorded for extended time periods with wrist actigraphy. Actigraphy has been regarded more reliable in detecting the circadian rhythms than daily sleep logs which rely on self-disclosure, and more reliable than observations which capture only short periods of time such as polysomnographic recordings (Ancoli-Israel et al., 2003). Earlier findings of actigraphy studies among adolescents with depressive disorder have pointed at blunted circadian rhythms, being characterized by lower

activity levels and lower circadian amplitudes as compared to healthy controls (Armitage et al., 2004; Finazzi et al, 2010; Teicher et al.,2013), and potentially at a delayed sleep phase (Robillard et al., 2013). Findings seem, however, to depend on age, gender, and features of depression: these findings have been more marked in adolescents as compared to children (Teicher et al., 1993), girls may show this effect at an earlier age than boys (Armitage et al., 2004), and a delayed sleep phase seems more common among bipolar vs. unipolar depression (Robillard et al., 2013) as well as with a longer duration of illness (Grierson et al., 2016; Naismith et al., 2012).

Here, we studied how the daily rest-activity cycles differ between healthy and depressed non-medicated adolescent boys, aged 14-17 years, by collecting and analyzing actigraphic data from a period consisting of at least 25 consecutive days. Based on earlier reports, we hypothesized that depressed adolescent boys would show lower activity levels and delayed phases as compared to healthy controls.

Materials and methods

Participants

The sample consisted of eight depressed adolescent boys as cases and nine healthy comparison participants as controls. The patients were outpatients originally recruited from the Helsinki University Central Hospital, Department of Adolescent Psychiatry outpatient units for a project on sleep in adolescent depression (n=10). The healthy controls were recruited via advertisements in a newspaper for the hospital staff (n=10). One patient from the original sample did not meet the diagnostic criteria for depressive disorder and was thus excluded from the analyses. Further, a sufficient amount of actigraphic data were not received from one participant in the healthy

control group and for one participant in the patient group due to poor compliance to the study protocol, leaving a total of 17 participants for analysis.

All subjects underwent thorough clinical examination, which included a psychiatric interview, routine morning blood samples, and structural brain MRI taken at the Helsinki University Central Hospital. For all participants, exclusion criteria included current use of any medication, chronic somatic illness, mental retardation, age of over 17.5 or under 14.5 years, substance abuse or dependence, any contraindication for brain magnetic resonance imaging, and insufficient skills of the Finnish language. In the patient group, a principal DSM-IV axis I diagnosis other than depressive disorder led to exclusion.

Both the participants and their parents or legal guardians gave a written informed consent for study participation. The study protocol was approved by the ethics committee of the Helsinki University Central Hospital (24.8.2011; 137/13/03/03/2011 §183).

Psychiatric assessment

The participants were assessed for the current and lifetime episodes of DSM-IV axis I disorders with the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997). All the interviews were performed by the same clinician (A.S.U.), and the diagnoses were confirmed in consensus meetings with a senior clinician (M.M.). The DSM-IV axis I diagnoses for the patients are shown in Table 1. The global assessment of functioning scale (GAF, with the numeric range of 0 to 100) was used according to the DSM-IV guidelines to assess the overall psychosocial functioning as part of the DSM-IV axial diagnostic procedure (American Psychiatric Association, 1994).

The severity of depressive symptoms was further assessed with the 21-item Beck Depression Inventory (BDI-21) (Beck et al., 1961), and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), both of which have been successfully applied to adolescent samples (Brooks and Kutcher, 2001; Clarke et al., 2005; Emslie et al., 2007; Marton et al., 1991; Mufson et al., 2004; Urrila et al., 2012). The participants also filled in the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the Pediatric Daytime Sleepiness Scale (PDSS) (Drake et al., 2003), and the Athens Insomnia Scale (AIS) (Soldatos et al., 2000) to complement the psychiatric assessment. The detailed characteristics are shown in Table 2.

Self-reported circadian preference

Circadian phase preference was measured with the Morningness-Eveningness Questionnaire (MEQ) (Horne and Östberg, 1976). MEQ scores have a range from 16 to 68, and lower scores indicate more preference to evening activities. The scores of 41 and below indicate “evening types”, scores between 42 and 58 “intermediate types”, and scores of 59 and above “morning types”.

Actigraphy

The participants were instructed to wear wrist actigraphs (Actiwatch-Plus®, Cambridge Neurotechnology Ltd, Cambridge, UK) on their non-dominant wrist for four consecutive weeks. Actigraphic data were collected in 60-second epochs over the recording period. For all the participants and all the variables, the primary period for analysis consisted of 23 consecutive days, being equal to the fast Fourier transformation period of 32,768 minutes, and starting on Monday whenever possible. As exceptions, for one patient the analyzed period started on Thursday, and for one healthy control on Friday.

The data were analyzed using the software provided by the manufacturer (Actiwatch Activity & Sleep Analysis, version 5.43), and the following variables were calculated: 1) variables measuring the level of rest-activity: amplitude (the range of activity levels across the 24-hour period), relative amplitude (M10 minus L5 divided by M10 plus L5), activity during the five hours of lowest activity (L5), activity during the 10 most active hours (M10), and average activity counts (separately during school days and weekends); 2) variables measuring the phase of the rest-activity rhythm: the onset of five hours of lowest activity (L5 onset), the onset of 10 most active hours (M10 onset), and cosine peak (separately during school days and weekends, indicating the timing of peak activity during the circadian period); 3) variables measuring the period of the rest-activity rhythm: period (the first peak of the daily rest-activity cycles in fast Fourier transformation, FFT, with the one-hour display), and peak correlation (indicating the length of the circadian period, with the one-minute resolution); 4) variables measuring the stability of the rest-activity rhythm: interdaily stability, and intradaily variability.

In addition to the main analyses, additional confirmatory non-parametric circadian rhythm analyses (NPCRA) were made to benefit from the maximum length of each actigraphic recording, which ranged between 25 to 44 days among the participants (see Supplementary Tables 1 and 2).

Statistical analyses

Statistical analyses were performed with the SPSS version 21 (IBM, Chicago, IL). Descriptive characteristics were compared between the patients and healthy controls with chi-squared tests for the categorical variables, and with the one-way analysis of variance (ANOVA) for the scale variables (Please see Table 2 for detailed description of the descriptive characteristics). The mean values of the circadian estimates were compared between the patients and healthy controls by

using the one-way ANOVA. Linear regression analyses were performed to estimate the association of the group status (the depressed vs. healthy participants) with the circadian variables. First, the crude (univariate) associations were analyzed. Second, the models were controlled for the age at the start of the recording, body-mass index (BMI; kg/m^2), and serum testosterone level. BMI was included in the covariates, as it is associated with depressive symptoms, late bedtimes and sleep problems in adolescents (Arora et al., 2015; Golley et al., 2013; Sjöberg et al., 2005; Snell et al., 2007). Age and testosterone level were included in the covariates, as age and rise in testosterone levels may associate with depression and circadian rhythms in adolescents (Angold et al., 1998, 1999; Crowley et al. 2014). Finally, the models were controlled for the age at the start of the recording, BMI, testosterone level, and chronotype. The self-reported chronotype and objectively measured rest-activity cycles are not completely interchangeable: the first describes the circadian preference in the timing of daily activities and behaviors, whereas the latter shows the actualized individual sleep-wake rhythm. Therefore, the self-reported chronotype was included in the covariates, as it is associated with depressive symptoms (Merikanto et al., 2013, 2015). In these analyses, the healthy controls were the reference category. A value of $p<0.05$ was generally considered as statistically significant. To assess the statistical strength of the results, a Bonferroni correction was applied when multiple variables were assessed to test a single hypothesis.

Results

Sample characteristics

The participants were on average 16.0 years old (with a standard deviation of 0.9) at the start of the actigraphic recordings. Of the patients, seven suffered from their first depressive episode, and one from his second depressive episode (Table 1). The severity of depression was moderate on

average, and the mean (± s.d.) length of the current depressive episode was 53 (± 52) weeks. None of the patients suffered from bipolar disorder or manifested psychotic features. No clear atypical or melancholic features of depressive disorder were evident among the patients. Two patients presented with comorbid DSM-IV axis I disorders: one with anxiety disorder, and one with disruptive behavior disorder. No DSM-IV axis I diagnoses were found among the healthy controls. As expected, the patients had higher scores on the BDI-21, HDRS, and AIS, and lower scores on the GAF than healthy controls, while there were no differences in the age, BMI, testosterone level, BAI, AUDIT, or PDSS scores (Table 2).

All adolescents were free of psychotropic and other medication during the whole study period. The depressed adolescents received treatment as usual at the adolescent psychiatric outpatient unit (individual and family appointments), but none of them received formal psychotherapy. No structural pathologies were found in their brain anatomy according to magnetic resonance imaging, and the absence of somatic conditions was confirmed based on the clinical assessment and routine blood samples. All subjects consumed daily less than three cups of coffee or the equivalent amount of other caffeinated products.

During the study, the participants were attending, depending on their age, either the compulsory basic comprehensive school (eighth or ninth grade), general upper secondary school (first or second grade), or vocational school (first or second grade). The majority of the participants lived with both of their parents. In both the patient and the healthy control groups, one participant lived with a single parent, and additionally, in the patient group, one participant lived in a children's home, and one participant lived every alternate week with his mother and father.

Circadian phase preference

There were no Morning-types in the sample, so it consisted of only two chronotypes, the Intermediate-type and the Evening-type. The Evening-type was significantly more common among the patients (71% within the group) than among healthy controls (22% within the group). In line with this, the MEQ score was significantly lower among the patients than healthy controls, indicating a greater preference towards the eveningness among the patients (Table 2).

Actigraphy

Level of rest-activity. The average activity counts on weekends was lower among the patients than healthy controls in all the regression models by both FFT and NPCRA period (Table 4 and Supplementary Table 2) and in ANOVA by using the maximum recording period of NPCRA (Supplementary Table 1). The number of average activity counts on school days was lower among the patients than healthy controls in the full regression model 3 when the maximum recording period of NPCRA was analyzed (Supplementary Table 2). The activity during the 10 most active hours (M10) was lower among the patients than healthy controls in the full regression model 3 by FFT period (Table 4) and in all the regression analysis models analyzed using the maximum recording period of NPCRA (Supplementary table 2). The amplitude was lower among the patients in the full regression model 3 by FFT period (Table 4). Using a Bonferroni corrected p-value of $p<0.0083$, only the average activity on weekends remained statistically significant (in tables 4 and supplementary table 2 regarding regression models 3, where $p=0.002$ and $p=0.003$ respectively). No statistically significant findings were seen in the relative amplitude and the activity during the five hours of lowest activity (L5).

Phase of the rest-activity rhythm. The onset of 10 most active hours (M10 onset) and school day cosine peak were earlier among the patients than healthy controls in ANOVA, and in all the

regression models analyzed, both by FFT and NPCRA period (Tables 3 and 4; Supplementary Tables 1 and 2). These results were most robust in the full model 3 by FFT period after controlling for the age at the start of the actigraphic recordings, BMI, testosterone level, and chronotype (Table 4). Using a Bonferroni corrected p-value of $p<0.0125$, most of these results remained statistically significant ($p<0.01$): the cosine peak in ANOVA (table 3), and both the cosine peak and the M10 onset in all the regression models (in tables 4 and supplementary table 2). No statistically significant findings were seen in the L5 onset and the cosine peak weekends.

Period of the rest-activity rhythm. The analysis of peak correlation in the full regression model 3 by FFT period, adjusted with self-reported chronotype, indicated an earlier activity peak among the patients than healthy controls (Table 4). No statistically significant findings were seen in the period.

Stability of the rest-activity rhythm. No statistically significant findings were observed in inter-daily stability or intra-daily variability in any of the analyses.

Discussion

To summarize, we found advanced phases, reduced activity amplitudes, and shorter periods of rest-activity cycles among depressed adolescent boys as compared to healthy controls.

Our findings on lower activity levels and reduced amplitudes among depressed adolescent boys as compared to healthy controls are in line with our hypothesis and in agreement with previous studies pointing towards weakened circadian rhythms among depressed adolescents (Armitage et al., 2004; Teicher et al., 1993). Compared to earlier studies with shorter actigraphy measurement periods (five consecutive days in Armitage et al., 2004; 72 hours in Teicher et al., 1993), our longer

measurement period enabled us, however, also to separate school days and weekdays and extend previous findings.

In our sample, the most active 10 hours of the day overlapped with the period spent at school (usually between 8 a.m. and 16 p.m. in Finland) more clearly among the patients (10 most active hours starting from 9:30 a.m.) than among the healthy controls (starting at 11:47 a.m.) who were thus more active also in the evenings. Concerning the earlier-timed activity in particular during school days, it is plausible that the patients were trying to manage with school, but were missing some extra-curricular activities. The healthy controls also had higher activity levels especially during weekends than patients, which might indicate having more social contacts and hobbies.

Our findings herein provide support for the hypothesis of circadian rhythms dysregulation in depression, which proposes that a breakdown in circadian rhythms is linked to and might even cause depression (Goodwin et al., 1982). Our results indicated a discrepancy between the subjectively reported preference to daily activities (later in depressed adolescent boys) and the objectively measured phase of rest-activity rhythms (earlier in depressed adolescent boys vs. healthy controls). This mismatch might pose a disadvantage for depressed adolescents. Our results are in line with the view that depressive episodes advance the timing of the rest-activity cycles in relation to the remaining circadian rhythms, thus suggesting a weakening of the coupling to the principal pacemaker (Daimon et al., 1992). However, the findings remain conflicting to date, some studies suggesting a delayed objectively measured phase (Lewy, 2010; Robillard et al., 2014; Xian et al., 2015). Further, healthy evening-typed persons (“night owls”) as compared with morning-typed persons (“morning larks”), all aged 19 to 64 years, had a higher ratio of phase advancing to phase delaying by light exposure, indicating a longer circadian period in evening-typed persons (Emens et al., 2009).

The analysis of peak correlation, yielding the circadian period length, indicated a shorter period among the patients than healthy controls, but only when the analysis was adjusted with the self-reported circadian preference. Interestingly, the shift towards more later-timed peaks in activity during weekends than on school days was greater in the patients than healthy controls. This shift was almost three hours towards the evening among the patients, while it was just one hour towards the evening among the healthy controls. It is likely that the timing of the highest activity peaks on weekends reflects more closely the natural chronotype of the patients than the timing of the peak activity on school days, which is dictated by school schedule and might be especially challenging for depressed individuals.

The strengths of this study include the homogeneous nature of the sample in terms of age and gender, the lack of psychotropic and other medication use among all participants, the detailed psychiatric evaluation, the low amount of comorbid psychiatric disorders, and the long actigraphy recording period.

Limitations of the study include most notably the small sample size, which allows us to make only preliminary conclusions on the results, and which limits more specific subgroup analyses. As the sample size in this study is rather small and we included multiple variables for testing each of the two *a priori* hypotheses, our study should be regarded as exploratory and the results as preliminary. Our statistically strongest results survived, however, a conservative Bonferroni-correction for multiple testing: the depressed boys showed consistently advanced phases (as measured by M10 onset and cosine peak on weekdays) in all regression analyses with both the FFT and the NPCRA period even at a significance level of $p<0.01$ (Table 4 and supplementary table 2). Our finding on a reduced amplitude and in particular that of a shorter period should, however, be

more cautiously assessed, since they were statistically much weaker. Further studies with larger sample sizes are therefore needed to confirm and extend our results.

A further limitation of our study is that we assessed only the rest-activity cycles, not other circadian measures such as cortisol, melatonin, or temperature rhythms. In addition, it would be important in the future to include repeated mood assessments along the actigraphy recording period. It could also be argued that including only patients without psychotropic treatments can present a selection bias, but then again psychotropic medication can affect the actualized sleep rhythm (Ferguson, 2001; Armitage et al., 1997; Golub et al. 2016) and thus might skew the effect between depression and circadian rhythm. Excluding female participants from the sample, on the one hand, limits the generalizability of the findings to depressed adolescent girls, but on the other hand, also excluded the potential confounding effects of the menstrual cycle phase on the measurement of circadian rhythms (Dzaja et al., 2005). Depressed adolescent girls and boys have also been reported to differ in their circadian rest-activity cycles and should thus be studied separately (Armitage et al., 2004). Furthermore, Morning-types were not represented in our sample, which thus limits the comparisons made between different circadian preference types.

To conclude, our results suggest that depressed adolescent boys report higher tendency towards eveningness, but have earlier phases especially on school days, as well as lower activity levels especially on weekends, and possibly generally shorter circadian periods than healthy controls. Our results confirm earlier findings on disrupted circadian rhythms in depressed adolescent boys. The conflicting results between subjective and objective measures of circadian rhythms may point towards a wearing mismatch of subjective circadian phase preference (late-preference) and actualized objectively measured rest-activity (early-prone) in depressed adolescent boys. Paying attention to increasing the total daytime activity (e.g., by means of favoring sports or other

activities), to the regularity of rest-activity cycles (e.g., by means of regular sleep schedules or meals), to suitable exposure to time-givers (e.g., by means of light exposures), and to the appropriate timing of these events are potential measures to synchronize the external and internal clocks in depressed adolescents, and to avoid mismatch and misalignment. Further research efforts are required to address the benefits and disadvantages of these interventions in the treatment of adolescent depression.

Declaration of Interest statement

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Advanced phases, reduced amplitudes, and shorter periods are suggested to characterize the daily rest-activity cycles in depressed adolescent boys

Table 1. DSM-IV axis I diagnoses of the cases.

Subject	**Dg1**	**Dg2**
1	296.21 Major Depressive Disorder: single episode; mild	
2	296.22 Major Depressive Disorder: single episode; moderate	
3	296.21 Major Depressive Disorder: single episode; mild	
4	296.32 Major Depressive Disorder: recurrent; moderate	
5	296.22 Major Depressive Disorder: single episode; moderate	
6	311.00 Depressive Disorder NOS	300.00 Anxiety Disorder NOS
7	296.22 Major Depressive Disorder: single episode; moderate	312.90 Disruptive Behavior Disorder NOS
8	311.00 Depressive Disorder NOS	

Dg1 = principal DSM-IV axis I diagnosis, Dg2 = comorbid axis I diagnosis (when applicable). NOS = not otherwise specified.

Table 2. Descriptive information by subgroup.

		Controls (N=9)	Patients (N=8)
Age at ACG start (years)		16.0 ± 0.7	16.0 ± 1.1
BMI		20.6 ± 1.8	21.4 ± 3.9
Chronotype *	Evening-type (%)	22.2	71.4
	Intermediate-type (%)	77.8	28.6
MEQ*		45.2 ± 7.1	35.7 ± 7.0
Serum testosterone level		19.4 ± 3.6	20.4 ± 4.1
BDI-21**		2.6 ± 4.2	16.9 ± 12.0
HDRS****		0.3 ± 0.7	12.9 ± 4.4
BAI		3.2 ± 4.3	8.4 ± 5.8
AUDIT		4.6 ± 4.6	1.6 ± 1.6
PDSS		13.0 ± 5.1	17.9 ± 5.0
GAF****		81.1 ± 4.9	50.6 ± 6.2
AIS**		2.0 ± 2.3	9.4 ± 6.2

ACG = actigraphy; BMI = body mass index; MEQ = Morningness-Eveningness Questionnaire; BDI-21 = 21-item Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; BAI = Beck Anxiety Inventory; AUDIT = Alcohol Use Disorder Identification Test; PDSS = Pediatric Daytime Sleepiness Scale; GAF = Global Assessment of Functioning; AIS = the Athens Insomnia Scale. Values are expressed as mean ± s.d., except for chronotype (%). *p <0.05; **p <0.01; ***p <0.001; ****p <0.0001 in one-way ANOVA (scale variables) or chi-squared test (categorical variables).

Table 3. Results from ANOVA by using the FFT period (23 days).

	Patients (n=8)		Controls (n=9)	
	Mean ± SD	**95% Confidence interval for Mean (lower – upper)**	**Mean ± SD**	**95% Confidence interval for Mean (lower – upper)**
Level of rest-activity				
Amplitude	18731 ± 4745	14764 – 22698	22236 ± 5361	18116 – 26356
Relative amplitude	0.87 ± 0.06	0.83 – 0.92	0.87 ± 0.09	0.80 – 0.94
L5	1318 ± 589	825 - 1810	1674 ± 1417	584 – 2763
M10	20049 ± 4884	15965 - 24132	23851 ± 5446	19665 – 28037
Average school days	217.9 ± 55.6	171.4 - 264.4	250.0 ± 59.8	204.0 - 295.9
Average weekends	156.9 ± 51.0	114.3 - 199.5	205.9 ± 54.4	164.1 - 247.7
Phase of the rest-activity rhythm				
L5 onset	1:52:30 ± 0:38:27	1:20:21 - 2:24:38	2:00:00 ± 00:42:25	1:27:23 - 2:32:36
M10 onset	9:30:00 ± 2:08:17*	7:42:45 - 11:17:14	11:46:40 ± 1:18:06*	10:46:37 - 12:46:42
Cosine peak school days	14:19:45 ± 1:40:35**	12:55:38 - 15:43:51	16:28:13 ± 1:13:26**	15:31:45 - 17:24:40
Cosine peak weekends	16:54:45 ± 1:02:02	16:02:53 -17:46:36	17:20:26 ± 0:51:37	16:40:45 - 18:00:07
Period of the rest-activity rhythm				
Period 1st peak	23:41 ± 0.04	23:37 - 23:44	21:07 ± 7:39	15:14 - 27:00
Peak correlation	24:00:45 ± 0:03:34	23:57:45 - 24:03:45	24:03:53 ± 0:04:30	24:00:25 - 24:07:21
Stability of the rest-activity rhythm				
Intra-daily variability	0.77 ± 0.13	0.66 – 0.87	0.81 ± 0.16	0.69 – 0.94
Inter-daily stability	0.40 ± 0.11	0.31 – 0.48	0.41 ± 0.09	0.34 – 0.47

*p <0.05; **p <0.01

Advanced phases, reduced amplitudes, and shorter periods are suggested to characterize the daily rest-activity cycles in depressed adolescent boys

Table 3. Results from ANOVA by using the FFT period (23 days).

	Patients (n=8)		**Controls (n=9)**	
	Mean ± SD	**95% Confidence interval for Mean (lower – upper)**	**Mean ± SD**	**95% Confidence interval for Mean (lower – upper)**
Level of rest-activity				
Amplitude	18731 ± 4745	14764 – 22698	22236 ± 5361	18116 – 26356
Relative amplitude	0.87 ± 0.06	0.83 – 0.92	0.87 ± 0.09	0.80 – 0.94
L5	1318 ± 589	825 - 1810	1674 ± 1417	584 – 2763
M10	20049 ± 4884	15965 - 24132	23851 ± 5446	19665 – 28037
Average school days	217.9 ± 55.6	171.4 - 264.4	250.0 ± 59.8	204.0 - 295.9
Average weekends	156.9 ± 51.0	114.3 - 199.5	205.9 ± 54.4	164.1 - 247.7
Phase of the rest-activity rhythm				
L5 onset	1:52:30 ± 0:38:27	1:20:21 - 2:24:38	2:00:00 ± 00:42:25	1:27:23 - 2:32:36
M10 onset	9:30:00 ± 2:08:17*	7:42:45 - 11:17:14	11:46:40 ± 1:18:06*	10:46:37 - 12:46:42
Cosine peak school days	14:19:45 ± 1:40:35**	12:55:38 - 15:43:51	16:28:13 ± 1:13:26**	15:31:45 - 17:24:40
Cosine peak weekends	16:54:45 ± 1:02:02	16:02:53 -17:46:36	17:20:26 ± 0:51:37	16:40:45 - 18:00:07
Period of the rest-activity rhythm				
Period 1st peak	23:41 ± 0.04	23:37 - 23:44	21:07 ± 7:39	15:14 - 27:00
Peak correlation	24:00:45 ± 0:03:34	23:57:45 - 24:03:45	24:03:53 ± 0:04:30	24:00:25 - 24:07:21
Stability of the rest-activity rhythm				
Intra-daily variability	0.77 ± 0.13	0.66 – 0.87	0.81 ± 0.16	0.69 – 0.94
Inter-daily stability	0.40 ± 0.11	0.31 – 0.48	0.41 ± 0.09	0.34 – 0.47

*p <0.05; **p <0.01

Table 4. Results from linear regression by using the FFT period (23 days).

	Model 1		**Model 2**		**Model 3**	
	B	**95% CI (lower – upper)**	**B**	**95% CI (lower – upper)**	**B**	**95% CI (lower – upper)**
Level of rest-activity						
Amplitude	-3505.0	-8052.0 – 1042.0	-3505.0	-8052.0 – 1042.0	-4705.9*	-9030.8 – -381.0
Relative amplitude	0.002	-0.07 – 0.07	0.002	-0.07 – 0.07	0.004	-0.07 – 0.08
L5	-356.4	-1350.0 – 637.2	-356.4	-1350.0– 637.2	-487.8	-1521.9 –546.2
M10	-3802.6	-8446.8– 841.6	-3802.6	-8446.8 – 841.6	-5135.0 *	-9446.4 – -823.6
Average school days	-32.04	-83.82 – 19.74	-32.04	-83.82 – 19.74	-46.57	-94.98 – 1.84
Average weekends	-49.04*	-96.29 – -1.78	-49.04*	-96.29 – -1.78	-64.88**	-106.04 – -23.72
Phase of the rest-activity rhythm						
L5 onset	-450.0	-2630.3 – 1730.3	-450.0	-2630.3 – 1730.3	-514.3	-2842.1 –1813.6
M10 onset	-8200.0**	-13812.5 – -2587.5	-8200.0**	-13812.5 – -2587.5	-9485.7***	-14995.3 – -3976.1
Cosine peak school days	-7708.3**	-12387.5 – -3029.1	-7708.3**	-12387.5 – -3029.1	-8404.8***	-13238.7 – -3570.9
Cosine peak weekends	-1541.7	-4586.2 – 1502.9	-1541.7	-4586.2 – 1502.9	-1595.2	-4848.5 – 1658.0
Period of the rest-activity rhythm						
Peak correlation	-188.3	-408.5 – 31.8	-188.3	-408.5 – 31.8	-241.9 *	-455.5 – -28.4
Period 1st peak	9228.3	-8772.1 – 27228.8	9228.3	-8772.1 – 27228.8	9247.6	-9995.6 – 28490.8
Stability of the rest-activity rhythm						
Inter-daily stability	-0.01	-0.10 – 0.08	-0.01	-0.10 – 0.08	-0.03	-0.12 – 0.07
Intra-daily variability	-0.04	-0.20 – 0.09	-0.04	-0.20 – 0.09	-0.03	-0.16 – 0.11

Model 1 crude (univariate); model 2 controlled for age at ACG, BMI, and testosterone level; model 3 controlled for age at ACG, BMI, testosterone level, and chronotype. Healthy controls as the reference category. CI = Confidence interval for mean. *p <0.05; **p <0.01; ***p <0.001.

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Supplementary Table 1. Results from ANOVA by using the maximum NPCRA period (25-44 days).

	Patients (n=8)		**Controls (n=9)**	
	Mean ± SD	**95% Confidence interval for Mean (lower – upper)**	**Mean ± SD**	**95% Confidence interval for Mean (lower – upper)**
Level of rest-activity				
Amplitude	19704 ± 5447	15150 – 24258	22386 ± 5200	18389 – 26383
Relative amplitude	0.87 ± 0.06	0.82 – 0.92	0.87 ± 0.08	0.81 – 0.94
L5	1336 ± 647	795 - 1877	1661 ± 1261	692 – 2630
M10	19497 ± 4158	16021 - 22973	24001 ± 5344	19893 – 28109
Average school days	217.1 ± 54.1	171.8 - 262.3	250.0 ± 58.0	205.4 - 294.6
Average weekends	155.2 ± 45.5*	117.2 - 193.2	208.3 ± 55.4*	165.2 – 250.8
Phase of the rest-activity rhythm				
L5 onset	1:52:30 ± 0:38:27	1:20:21 - 2:24:38	2:06:40 ± 00:36:03	1:38:57 - 2:34:22
M10 onset	9:37:30 ± 2:11:59*	7:47:09 - 11:27:50	11:46:40 ± 1:18:06*	10:46:37 - 12:46:42
Cosine peak school days	14:36:37 ± 1:43:12*	13:10:20 - 16:02:54	16:29:53 ± 1:14:56*	15:32:16 - 17:27:29
Cosine peak weekends	16:49:07 ± 1:03:07	15:56:20 -17:41:54	17:29:20 ± 0:43:39	18:02:53 - 18:02:53
Period of the rest-activity rhythm				
Peak correlation	24:01:15 ± 0:02:57	23:58:46 - 24:03:43	24:04:00 ± 0:04:03	24:00:52 - 24:07:07
Stability of the rest-activity rhythm				
Inter-daily stability	0.37 ± 0.10	0.29 – 0.45	0.40 ± 0.08	0.34 – 0.47
Intra-daily variability	0.75 ± 0.13	0.64 – 0.85	0.80 ± 0.12	0.66 – 0.93

*p <0.05

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Supplementary Table 2. Results from linear regression by using the maximum NPCRA period (25-44 days).

	Model 1		**Model 2**		**Model 3**	
	B	**95% CI (lower – upper)**	**B**	**95% CI (lower – upper)**	**B**	**95% CI (lower – upper)**
Level of rest-activity						
Amplitude	-2682.0	-7438.6 – 2074.6	-2682.0	-7438.6 – 2074.6	-3722.7	-8430.1– 984.6
Relative amplitude	-0.002	-0.12– 0.05	-0.002	-0.07 – 0.06	0.001	-0.07 – 0.07
L5	-325.3	-1239.1 – 588.6	-325.3	-1239.1– 588.6	-468.9	-1409.0 – 471.3
M10	-4503.5*	-8821.9 – -185.2	-4503.5*	-8821.9 – -185.2	-5573.8**	-9745.3 – -1402.4
Average school days	-32.96	-83.27 – 17.35	-32.96	-83.27– 17.35	-48.49*	-93.98 – -3.01
Average weekends	-53.08*	-98.70 – -7.46	-53.08*	-98.70 – -7.46	-67.12**	-108.42 – -25.82
Phase of the rest-activity rhythm						
L5 onset	-850.0	-2846.4 – 1146.4	-850.0	-2846.4 – 1146.4	-914.3	-3045.2 – 1216.6
M10 onset	-7750.0**	-13476.8 – -2023.2	-7750.0**	-13476.8 – -2023.2	-8971.4**	-14662.4 – -3280.4
Cosine peak school days	-6795.8**	-11587.0 – -2004.7	-6795.8**	-11587.0 – -2004.7	-7519.1**	-12463.6 – -2574.6
Cosine peak weekends	-2412.5	-5291.3 – 466.3	-2412.5	-5291.3 – 466.3	-2685.7	-5721.6 – 350.1
Period of the rest-activity rhythm						
Peak correlation	-165.0	-357.8 – 27.8	-165.0	-357.8 – 27.8	-145.7	-348.7 – 57.3
Stability of the rest-activity rhythm						
Inter-daily stability	-0.04	-0.18 – 0.09	-0.04	-0.12 – 0.05	-0.05	-0.13 – 0.04
Intra-daily variability	-0.05	-0.18– 0.09	-0.05	-0.18– 0.09	-0.04	-0.18 – 0.11

Model 1 crude (univariate); model 2 controlled for age at ACG, BMI, and testosterone level; model 3 controlled for age at ACG, BMI, testosterone level, and chronotype. Healthy controls as the reference category. CI = Confidence interval for mean. *p <0.05; **p <0.01.