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ORIGINAL CONTRIBUTION

Diurnal variations in arousal: a naturalistic heart rate study in children with ADHD

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Abstract Previous studies suggest an altered circadian regulation of arousal in children with attention-deficit hyperactivity disorder (ADHD) as measured by activity, circadian preference, and sleep-wake patterns. Although heart rate is an important measure to evaluate arousal profiles, to date it is unknown whether 24-h heart rate patterns differentiate between children with and without ADHD. In this study, 24-h heart rate data were collected in 30 non-medicated children with ADHD (aged 6–11) and 30 sex-, class-, and age-matched normal controls in their naturalistic home and school setting, during 5 days. Simultaneously, 24-h activity patterns were registered. Confounding effects of demographic variables (e.g., age, sex, BMI, pubertal stage) and comorbid internalizing and externalizing problems on heart rate levels were additionally assessed. Longitudinal analysis showed that heart rate levels were overall higher in the ADHD group ($p < 0.01$)—with the largest effects during afternoon and night—in a model controlling for age. Other factors did not significantly contribute to variations in heart rate levels. Compared to controls, children with ADHD showed higher activity levels during daytime (especially early afternoon), but not during nighttime ($p < 0.05$). Post hoc analyses showed that environmental effects might influence daytime variations. Findings suggest an autonomic imbalance in children with ADHD as compared to controls, with higher heart rate levels in the ADHD group. Nighttime tachycardia in this group could not be explained by nighttime activity levels or comorbid externalizing/internalizing problems. Further research on autonomic functioning in ADHD is recommended because of the major impact of higher resting heart rate on health outcomes.

Keywords ADHD · Arousal · Circadian · Heart rate · Activity

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common child psychiatric diagnoses typified by inattention problems, hyperactivity, and impulsivity (American Psychiatry Association) [4]. Several theoretical models have explained the behavioral symptoms in this developmental disorder in terms of arousal regulation deficits [51, 52, 68]. As arousal is closely related to sleep-wake regulation [50], it is not surprising that arousal is characterized by a circadian rhythm [54]. To date, several research domains have pointed to differential circadian arousal patterns in ADHD. There is evidence that subjects with ADHD show a higher "eveningness" preference [12, 47, 55], more sleep-wake disturbances [10, 14, 27, 37, 40], and more hyperactivity problems in the afternoon [3, 44, 60, 67]. As findings on this research topic are inconsistent [13, 17, 23, 36], further clarification of time of day effects in arousal is critical to fully understand underlying mechanisms involved in arousal and behavioral symptoms of ADHD.

One of the major systems involved in arousal regulation is the autonomic nervous system [41, 50, 54]. Heart rate has been considered as a reliable, non-invasive measure for the autonomic activity of an individual [35, 49], which is especially related to emotional and motivational aspects of arousal [6, 22, 38]. Heart rate reflects the balance between the activity of the two branches of the autonomic nervous system, the sympathetic and parasympathetic division [38], which are associated with stress and rest states, respectively [20, 29]. This parasympathetic branch, more specifically the ventral vagal complex, is also involved in emotion and behavior regulation processes such as attention, motor activity, emotion, and social engagement [42, 43].

To date, however, it is unknown whether circadian regulation of the autonomic nervous system is different in children with ADHD as no evaluation of 24-h heart rate patterns is available. One study with a shorter-term evaluation (3 periods of 5 min) suggested that children with ADHD have elevated heart rate levels compared to controls [59]. This finding was associated with changes in cardiac autonomic regulation, i.e., decreased cardiac vagal modulation in supine position and altered ability of dynamic activation of the autonomic nervous system in response to orthostasis.

The main aim of this paper is to investigate whether 24-h heart rate patterns under natural environmental conditions are different in non-medicated children with ADHD as compared to normal control children. We have a particular interest in resting heart rate, i.e., nighttime levels, as this measure can be used as an indicator of autonomic balance and vagal tone [57]. Based on a short-term evaluation study [59], we expect elevated heart rate levels, i.e., a decreased vagal tone, in children with ADHD as compared to normal controls. In line with previously reported circadian alterations in arousal, we further hypothesize that group differences in heart rate are particularly expressed at specific times of day.

Additionally, we take into account several possible confounders of heart rate levels. First, demographic variables such as age and sex, but also pubertal stage (Tanner) and body mass index (BMI) could influence heart rate levels [5, 64]. In this context, also average use of caffeine and presence of nightmares were questioned. Second, both externalizing problems such as oppositional defiant disorder (ODD) and conduct disorder (CD) and internalizing problems such as anxiety and depression have been related to different autonomic functioning, i.e., lower and higher resting heart rate levels, respectively [20, 32, 35, 39]. Third, activity is hypothesized to influence heart rate levels. We simultaneously assess 24-h activity patterns in order to explore possible confounding effects on heart rate patterns and to guide interpretations on the behavioral level. We suggest a close relation between activity and heart rate levels, and expect higher activity levels in children with ADHD as compared to normal controls, especially during afternoon hours.

Method

Subjects

Thirty children diagnosed with ADHD (24 boys and 6 girls), aged 6–11, were recruited from a child psychiatric outpatient unit. As controls, we selected 30 age- and sex-matched healthy, normally developing children within the same class as the child with ADHD. Control children had no formal psychiatric or medical diagnosis, and were all medication-free. Children with ADHD had a formal diagnosis of ADHD combined type—both inattention and hyperactivity/impulsivity problems—based on a child and adolescent psychiatric evaluation during which also a structured interview was used to assess symptoms of ADHD in accordance with the Diagnosis and Statistical Manual of Mental Disorders criteria [Diagnostic Interview Schedule for Children, parent version (PDISC-IV)] [53]. Exclusion criteria included an IQ < 80 as measured by the Wechsler Intelligence Scale for Children, third edition (WISC-III-R) [66], pervasive developmental disorders, neurological disorders such as epilepsy, chronic medical conditions such as hypertension, diabetes mellitus, and asthma, and any medical treatment (e.g., atomoxetine or psychotropic medications) except for methylphenidate. Twenty-six children with ADHD took methylphenidate (17 short- and 9 long-acting formulations), but all children were free from treatment at least 72 h prior to participation in the study. None of the participating children used alcohol or nicotine. Current behavioral and emotional problems were screened in both groups using the Child Behavior Checklist (CBCL) [1, 62] and the Teacher Report Form (TRF) [2, 63].

Procedure

The Ethical Committee of Ghent University Hospital, Belgium, approved this study. Children with ADHD were recruited from the child psychiatric outpatient unit of the Ghent University Hospital (Belgium). After parents of children with ADHD provided written consent, the school and teacher of the child with ADHD were contacted to seek their collaboration in the study. Teachers primarily selected three sex-and age-matched normally developing classmates without formal psychiatric or medical diagnosis. If all parents of the control group provided written consent, one control child was selected randomly to participate in the study.

Observations were carried out in the naturalistic home and school environment of the children during five consecutive days (3 school days and 2 weekend days). To randomize the order of weekdays and weekend days, 16 paired (ADHD and control classmate) observations were randomly carried out from Tuesday evening until Sunday evening, and 14 paired observations from Friday evening until Wednesday evening. During schooldays, the child with ADHD and its matched control were exposed to similar contextual conditions. School started between 8:20 and 8:45 a.m., and finished between 3:30 and 4:00 p.m., with recess/lunch periods between 10:00 and 10:30 a.m., between noon and 1:30 p.m., and between 2:30 and 3:00 p.m. In general, academic lessons (mathematics and language lessons) were mostly planned in the morning (70 vs. 30% in the afternoon), whereas non-academic lessons (music and arts) were mostly scheduled in the afternoon (90 vs. 10% in the morning).

On the start day of the study, all persons involved attended a meeting during which the course of the study was briefly recapitulated. Length, weight, and Tanner pubertal stage of all children were assessed. Parents reported on children's caffeine use and the presence of nightmares. A detailed explanation on activity and heart rate devices was given. Parents were instructed how children should wear the Actiwatch and practiced how to attach the Actiheart and replace monitoring electrodes. Children received a small reward for their participation.

Measures

Demographic variables

Because of their possible influence on heart rate levels, age, sex, Tanner pubertal stage, and BMI were taken into account [5, 64]. Additionally, average caffeine use and the presence of nightmares in all children were questioned.

CBCL/TRF

The CBCL [1, 62] screens for emotional and behavioral problems in children aged 4–18. The CBCL was completed by parents, and a parallel version, the TRF [2, 63], was completed by classroom teachers of all children. The CBCL and TRF contain items rated on a 3-point Likert scale yielding three broadband scales: internalizing, externalizing, and total problems. Both questionnaires have good reliability and validity.

The prevalence of comorbid psychiatric problems was high in our sample of children with ADHD. As both externalizing problems (such as ODD and CD) and internalizing problems (such as anxiety and depression) have been related to lower [20, 32, 35, 39] and higher [20, 35] heart rate levels, respectively, the possible influence of externalizing and internalizing problems (as measured by the CBCL) on heart rate levels was taken into account.

Actiheart: 24-h heart rate patterns

Heart rate was measured with the Actiheart (Cambridge Neurotechnology Ltd, Cambridge, UK), a small single-piece device with a combined heart rate and movement sensor, designed to clip on to two standard ECG electrodes (3 M Ag/AgCl 2223, Germany), positioned at the level of the third intercostal space [16]. More detailed technical information on this device has been reported by Brage et al. [11].

In this circadian study, the epoch length was set to 1 min to make longer-term evaluation possible. Through an interface, the data were loaded into a software program (Actiheart software, version 2.4, Cambridge Neurotechnology Ltd, Cambridge, UK) and cleaned before further analysis so that bathing and swimming periods were excluded from the analysis. For data analysis, heart rate counts were averaged per hour.

Actigraph: 24-h activity patterns

An actigraph is an acceleration-sensitive, watch-like device typically worn on the non-dominant wrist (Actiwatch, Cambridge Neurotechnology Ltd, Cambridge, UK). For the purpose of this study, an epoch length of 1 min was set. Each time an actigraph is moved compared to a reference signal a voltage is generated. The number of movements during a 1 min interval is accumulated and saved before resetting the counter to zero, providing a measure of activity frequency (counts/min). Through an interface, the actigraph data were loaded into a software program (Sleep Analysis, version 7, Cambridge Neurotechnology Ltd, Cambridge, UK) for further analysis. For the purpose of this study, actigraph data were evaluated in terms of absolute intensity by calculating activity counts per hour.

Statistical analyses

Demographic variables (age, sex, BMI, pubertal stage, caffeine use, and presence of nightmares) and scores on the

CBCL and TRF were compared between ADHD and control group using analysis of variance (ANOVA) or chi-square tests as appropriate.

Mixed model analysis was conducted with SAS PROC MIXED (SAS, version 9.2) to test whether 24-h heart rate and activity data differed between ADHD and control group. This method is preferred above repeated measures ANOVA for the study of longitudinal data [9, 24]. Likelihood ratio tests were used to define the best fitting mixed model for heart rate and activity separately. Different plausible covariance-pattern models, namely heterogeneous compound symmetry, heterogeneous autoregressive, and unstructured covariance patterns were fitted, with or without inclusion of random intercept effects for subject and for day of evaluation within subject in the model. Main predictors of heart rate and activity were diagnostic group (ADHD vs. control), time of day (24 hourly data points), day of evaluation (day 1–5), and weekday versus weekend day. An interaction term was included for group × time of day to detect differential group effects across time. The heart rate model statement was expanded with other possible confounders of heart rate levels. In the first step, demographic variables (age, sex, pubertal stage, BMI, caffeine use, nightmares) were entered. In the second step, comorbid psychiatric problems (internalizing, externalizing) were entered. Predictors that did not significantly contribute to variations in heart rate were stepwise excluded from the model (significance level at 0.10).

In order to interpret effects obtained with the mixed model, several contrast analyses were additionally performed. First, polynomial time-related contrasts (i.e., linear, quadratic, and cubic effects) were defined for time and for group × time effects. Second, groups were contrasted to evaluate differences in heart rate and activity levels at each time point. To help interpret clinical relevance of statistically significant effects, effect sizes (ES) were calculated as the standardized mean difference between groups (Cohen delta or $d = M_1 - M_2/\mathrm{SD}_{\mathrm{pooled}}$), which is independent of sample size. ES are defined as small (0.2), moderate (0.5), and large (0.8). Finally, post hoc analyses were performed to address time-to-time (i.e., peak-to-through) changes across ADHD and control individuals during school days, when contextual influences were similar for both groups. ES was calculated as partial eta squared (η_p^2) to take into account associations between repeated measurement data (time_x vs. time_{x+1}). ES are defined as small (0.01), moderate (0.06), and large (0.14). Comparison of the school versus home assessment was used to explore whether time-to-time effects could be related to environmental school influences.

Results

Demographic variables and current emotional and behavioral problems

Age, sex, BMI, pubertal stage, caffeine use, and presence of nightmares did not differ between groups (see Table 1). Children with ADHD showed higher ratings on all scales of CBCL and TRF (except for somatic complaints) compared to normal controls (see Table 1).

24-h heart rate patterns

Considering heart rate, a model with an unstructured covariance pattern including a random intercept for subject fitted best the data. This model revealed a significant effect of diagnostic group [$F(1,7030) = 7.81$; $p < 0.01$], time of day [$F(23,7030) = 135.54$; $p < 0.0001$], but no effect of diagnostic group × time of day [$F(23,7030) < 1$; ns], in a model controlling for day of evaluation [$F(4,7030) = 2.61$; $p < 0.05$], weekday versus weekend day [$F(1,7030) < 1$; ns], and age [$F(1,7030) = 11.40$; $p < 0.001$]. Sex, BMI, pubertal stage, caffeine use, presence of nightmares, and comorbid externalizing and internalizing problems were excluded from the final model, as these factors did not significantly contribute to variations in heart rate levels.

Polynomial contrasts of the time effect showed a large significant quadratic effect [$t(7030) = -43.36$; $p < 0.001$], next to (smaller) significant linear [$t(7030) = 17.45$; $p < 0.001$] and cubic [$t(7030) = -18.43$; $p < 0.001$] effects. These effects were reflected in the solutions of fixed effects; heart rate levels were significantly higher during daytime than during nighttime in both groups, with an increase in heart rate levels from early morning to noon (steep from 6–8 a.m. and more gradual to noon) and a gradual decrease from noon to evening and night.

Overall, heart rate levels were significantly higher in the ADHD group compared to the normal control group. However, polynomial contrasts of the group × time effect showed a significant cubic effect [$t(7030) = 2.33$; $p < 0.05$], reflecting that group differences were particularly expressed at specific times of the day. Contrast analyses confirmed that children with ADHD showed higher heart rate levels as compared to controls, but that these effects were larger during nighttime and afternoon (moderate ES) than during morning hours (small ES) (see Table 2). A visual representation of group differences in heart rate levels, averaged across 5 days, is presented in Fig. 1.

Table 1 Test statistics of demographic variables and problem ratings on the CBCL and the TRF

	ADHD M (SD)/*n* (%)	Control M (SD)/*n* (%)	$F(1,59)/\chi^2(1)$
Age	8.97 (1.50)	8.80 (1.54)	$F(1,59) < 1$, ns
Sex (*n*)			
Male	24 (80)	24 (80)	$\chi^2(1) < 1$, ns
Female	6 (20)	6 (20)	$\chi^2(1) < 1$, ns
Pubertal stage			
Pre-pubertal pubic hair stage (*n*)			
Male	23 (96)	24 (100)	$\chi^2(1) < 1$, ns
Female	5 (83)	5 (83)	$\chi^2(1) < 1$, ns
Pre-pubertal genital stage (*n*)			
Male	24 (100)	24 m (100)	$\chi^2(1) < 1$, ns
Pre-pubertal breast stage (*n*)			
Female	5 (83)	5 (83)	$\chi^2(1) < 1$, ns
BMI	16.12 (1.54)	15.88 (1.62)	$F(1,59) < 1$, ns
Caffeine use (*n*)	10 (33)	11 (37)	$\chi^2(1) < 1$, ns
Presence of nightmares (*n*)	3 (10)	1 (3)	$\chi^2(1) = 1.41$, ns
CBCL internalizing	62.77 (8.24)	46.23 (9.25)	53.48***
CBCL externalizing	66.63 (7.70)	44.67 (8.52)	109.74***
CBCL total	68.90 (6.40)	42.60 (9.54)	156.82***
TRF internalizing	52.80 (6.62)	46.10 (6.31)	16.12***
TRF externalizing	58.87 (9.10)	46.20 (5.34)	43.21***
TRF total	59.63 (5.96)	42.70 (5.90)	122.33***

ADHD attention-deficit hyperactivity disorder, *M* mean, *SD* standard deviation, *n* number in sample, % percentage of sample, *BMI* body mass index, *CBCL* child behavior checklist, *TRF* teacher report form

*** $p < 0.001$

24-h activity patterns

Considering activity, a model with a heterogeneous autoregressive symmetry pattern and a random intercept for subject and for day within subject effect fitted the data best. This model showed a significant effect of diagnostic group [$F(1,6854) = 4.33$; $p < 0.05$], time of day [$F(23,6854) = 148.23$; $p < 0.0001$] and a significant interaction effect of diagnostic group × time of day [$F(23,6854)$; $p < 0.05$], in a model controlling for day of evaluation [$F(4,235) <1$; ns] and weekday versus weekend days [$F(1,6854) <1$; ns].

Polynomial contrasts of the time effect showed a large significant quadratic effect [$t(6854) = -45.88$; $p < 0.001$], next to (smaller) significant linear [$t(6854) = 12.66$; $p < 0.001$] and cubic [$t(6854) = -11.91$; $p < 0.001$] effects. These effects were reflected in the solutions of fixed effects; activity levels were significantly lower during night than during day hours in both groups, with an increase in activity levels from early morning to noon and a decrease from noon to nighttime levels.

Polynomial contrasts of the group x time effect showed a significant quadratic effect [$t(6854) = 2.83$; $p < 0.01$], reflecting group differences at specific times of the day, but not during others. During day hours, more specifically between 9 and 10 a.m. and between 11 a.m. and 4 p.m., activity levels were significantly higher in the ADHD compared to the normal control group, but no group differences were observed during evening and night hours. Contrast analyses confirmed moderate to large group effects between 11 a.m. and 4 p.m., small to moderate effects in the morning, but no evidence for group differences during evening and night (see Table 2). A visual representation of group differences in activity levels, averaged across 5 days, is presented in Fig. 1.

Possible contextual influence on diurnal variations in activity and heart rate

Mixed model analyses described above did not reveal evidence for significant different effects of weekday and weekend days on activity and heart rate variations. This was confirmed by analyses for weekday and weekend days separately yielding results comparable to our pervious findings [polynomial effects for group × time: heart rate (weekday: $p < 0.05$; weekend day: $p < 0.05$) and activity

Table 2 Mean difference, pooled standard deviation, and effect size (Cohen d) for ADHD and control group at each time point, averaged across all days

	Heart rate (beats per min)			Activity (counts per min)		
	M_{diff}	SD_{pooled}	ES (weekdays/weekend days)	M_{diff}	SD_{pooled}	ES (weekdays/weekend days)
0 a.m.	3.45	8.15	0.42 (0.73**/0.25)	10.56	72.42	0.15 (0.17/0.18)
1 a.m.	4.10	7.48	0.55* (0.60*/0.79**)	0.34	137.19	0.003 (0.009/0.004)
2 a.m.	6.30	9.32	0.68** (0.69**/0.70**)	1.76	137.19	0.01 (0.05/0.02)
3 a.m.	5.48	8.35	0.66* (0.73**/0.70**)	0.43	137.19	0.003 (0.05/0.002)
4 a.m.	4.35	7.33	0.59* (0.63*/0.86***)	0.75	137.19	0.005 (0.15/0.004)
5 a.m.	3.92	7.17	0.55* (0.67**/0.74**)	1.88	137.19	0.01 (0.11/0.006)
6 a.m.	4.14	7.55	0.55* (0.54*/0.73**)	12.11	72.26	0.17 (0.17/0.04)
7 a.m.	2.55	8.61	0.30 (0.40/0.28)	19.01	115.35	0.16 (0.27/0.008)
8 a.m.	1.95	9.99	0.20 (0.13/0.30)	50.85	146.33	0.35 (0.45°/0.12)
9 a.m.	4.51	9.83	0.46° (0.56*/0.24)	82.69	150.02	0.55* (0.67**/0.15)
10 a.m.	1.76	10.39	0.17 (0.12/0.15)	34.05	153.20	0.22 (0.10/0.23)
11 a.m.	3.18	10.35	0.31 (0.22/0.26)	139.42	137.80	1.01*** (0.82**/0.56*)
0 p.m.	6.20	10.60	0.59* (0.32/0.77**)	118.26	201.95	0.59* (0.45°/0.46°)
1 p.m.	6.39	10.63	0.60* (0.53*/0.57*)	152.79	177.00	0.86*** (0.52*/0.80**)
2 p.m.	7.20	10.50	0.69** (0.31/0.88***)	133.63	160.94	0.83** (0.52*/0.71**)
3 p.m.	6.86	10.56	0.65* (0.43°/0.73**)	87.66	170.69	0.51* (0.40/0.35)
4 p.m.	7.01	11.90	0.59* (0.19/0.80**)	37.42	200.72	0.19 (0.16/0.45°)
5 p.m.	5.26	10.44	0.50° (0.36/0.50*)	31.16	183.07	0.17 (0.04/0.30)
6 p.m.	5.57	10.90	0.51* (0.49°/0.37)	29.84	183.06	0.16 (0.12/0.12)
7 p.m.	5.08	10.40	0.49° (0.66**/0.30)	34.61	149.66	0.23 (0.39/0.02)
8 p.m.	5.31	10.48	0.51* (1.01***/0.23)	23.12	132.61	0.17 (0.10/0.16)
9 p.m.	5.36	9.34	0.57* (1.04***/0.35)	12.33	117.20	0.11 (0.20/0.02)
10 p.m.	3.83	9.00	0.43° (0.83**/0.19)	21.07	102.27	0.21 (0.17/0.31)
11 p.m.	3.49	8.28	0.42 (0.81**/0.25)	17.83	84.78	0.21 (0.40/0.23)

M_{diff} mean difference between groups, SD_{pooled} pooled standard deviation, *ES* effect size (Cohen d)

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ° $p < 0.10$

(weekday: $p < 0.01$; weekend day: $p < 0.01$)]. A visual representation of group differences in heart rate and activity levels, averaged across weekdays and weekend days separately, is presented in Fig. 2.

However, variations in ES comparing groups at each time point across weekday and weekend days suggest that more subtle weekday/weekend effects may be present (see Table 2); for example, large group effects at 9 a.m. on weekdays but not on weekend days. Compared to the overall large time of day effect, small effects produced by school schedules (i.e., classroom and playground transitions) may be superimposed on the overall activity and heart rate pattern of children with and without ADHD. Therefore, contrast analyses were performed to estimate effect size of the peak-to-through differences during school hours (i.e., between 8 a.m. and 4 p.m.) in both groups (see Table 3). In general, subsequent time-to-time changes in activity were very large between 8 a.m. and 1 p.m. for both groups. Only for 10–11 a.m., children with ADHD showed no significant drop in activity levels in their transition from playtime to class condition. Time-to-time changes in heart rate reflect similar patterns as described for activity except for the noon to 1 p.m. change. Similar analyses for weekend days could not reveal these large time-to-time changes in the morning (see Table 3). In the afternoon, both groups showed smaller time-to-time variations in activity and heart rate during weekdays and weekend days.

Discussion

To the best of our knowledge, this is the first study investigating alterations in diurnal arousal patterns in children with ADHD by 24-h registration of heart rate combined with activity.

The main aim of this study was to assess whether 24-h heart rate patterns in non-medicated children with ADHD, registered during 5 days, under natural environmental conditions, were different as compared to normal controls. Although a typical circadian heart rate pattern with low

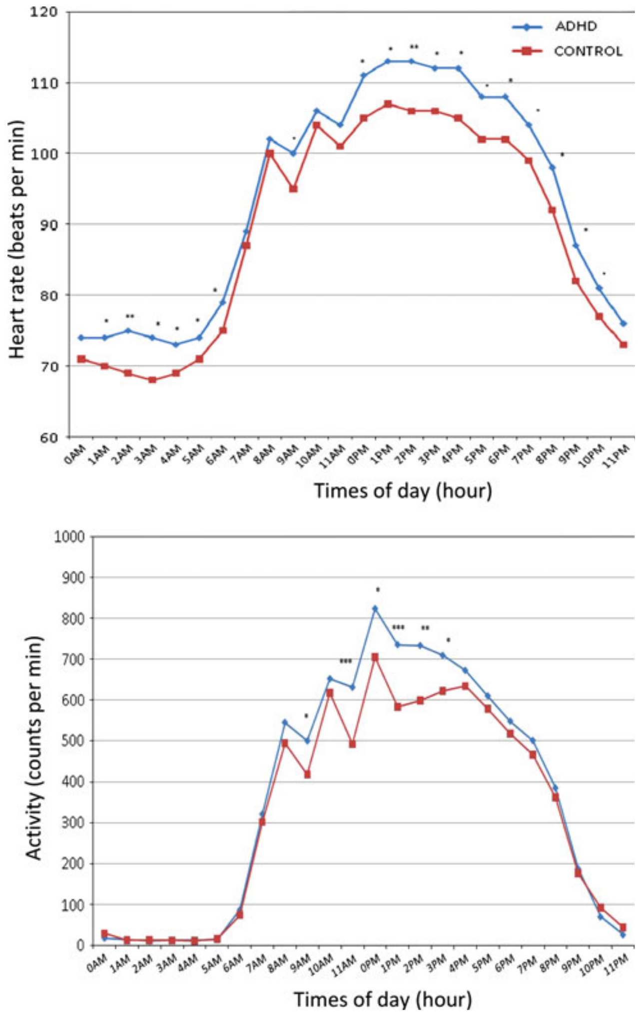

Fig. 1 24-h heart rate (*top*) and activity (*bottom*) pattern in children with ADHD and controls, averaged over 5 days. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{\circ}p < 0.10$

levels during night and high levels during day hours was revealed [49, 65], we found no significant interaction effect of time of day × group. Heart rate levels in children with ADHD were overall significantly higher than in control children, independent of comorbid internalizing and externalizing problems. However, additional contrast analyses revealed that these group effects were larger at specific times of day, namely afternoon and nighttime hours. Especially the increase in nighttime levels, i.e., resting heart rate, seems important as this measure refers to a lower vagal tone [56, 57]. Our results are in line with Tonhajzerova et al. [59], who found during their short-term evaluation that non-medicated children with ADHD had tachycardia compared to normal controls in both supine position and orthostasis. These results reflected an autonomic imbalance—low parasympathetic activity and a relative sympathetic dominance—indicated by low heart rate variability, which the authors hypothesized to be a marker for prefrontal hypo-activity. Thayer and Sternberg [58] described the prefrontal cortex to be part of the central autonomic network (CAN), an entity that controls both visceromotor and behavioral responses that are critical for goal-directed behavior and adaptability. As such they suggested that deficits in the prefrontal cortex may lead to a relative sympathetic dominance as the frontal cortex normally exerts tonic inhibition on brainstem sympathoexcitatory circuits. In ADHD, such a prefrontal hypofunction has been shown with respect to structural and functional neuroimaging, dopaminergic and noradrenergic activity, and neuropsychological executive functioning [8, 25, 26, 61].

Additionally, this study simultaneously registered activity to adjust for locomotor-driven increases in heart rate. Analyses showed a diurnal pattern with low levels during night and high levels during day hours (especially afternoon) in line with previous reports [19, 46]. This diurnal pattern seems to be influenced by environmental conditions and activities. For example, both groups showed a significant peak at 10 a.m. and at 12 a.m. during school days—but not weekend days—reflecting recess and lunchtime periods. This finding suggests that school-related context factors (i.e., classroom and playground transitions) may be responsible for peak-to-through variations in activity levels, especially in the morning. In the afternoon, activity levels in both groups were higher than at 9 a.m. and at 11 a.m. class conditions. Although this could be due to the planning of more academic lessons in the morning and less academic lessons in the afternoon, a similar morning-afternoon effect was observed during weekend days. This finding indicates that morning to afternoon variations in activity are, at least partly, independent of class schedules in children with and without ADHD. However, a significant interaction effect of diagnostic group x time of day was observed. Compared to control children, children with ADHD had higher activity levels during daytime, especially during noon and early afternoon hours, but surprisingly, not during night. Boonstra et al. [10] described a similar pattern in adults with ADHD, i.e., high but stable activity levels during day hours, but no evidence of significant difference at night. Daytime activity levels in children with ADHD may be more variable as differential effects between children with ADHD and control children were described to be particularly expressed when a highly demanding environment and afternoon hours overlap [44, 60]. In the morning, children with ADHD showed no significant drop in activity from the 10 a.m. playtime to the 11 a.m. class condition compared to their normal classmates. Such settling-down problems after recess periods in ADHD have previously been described [3]. As this study did not systematically assess environmental factors, it is not sure

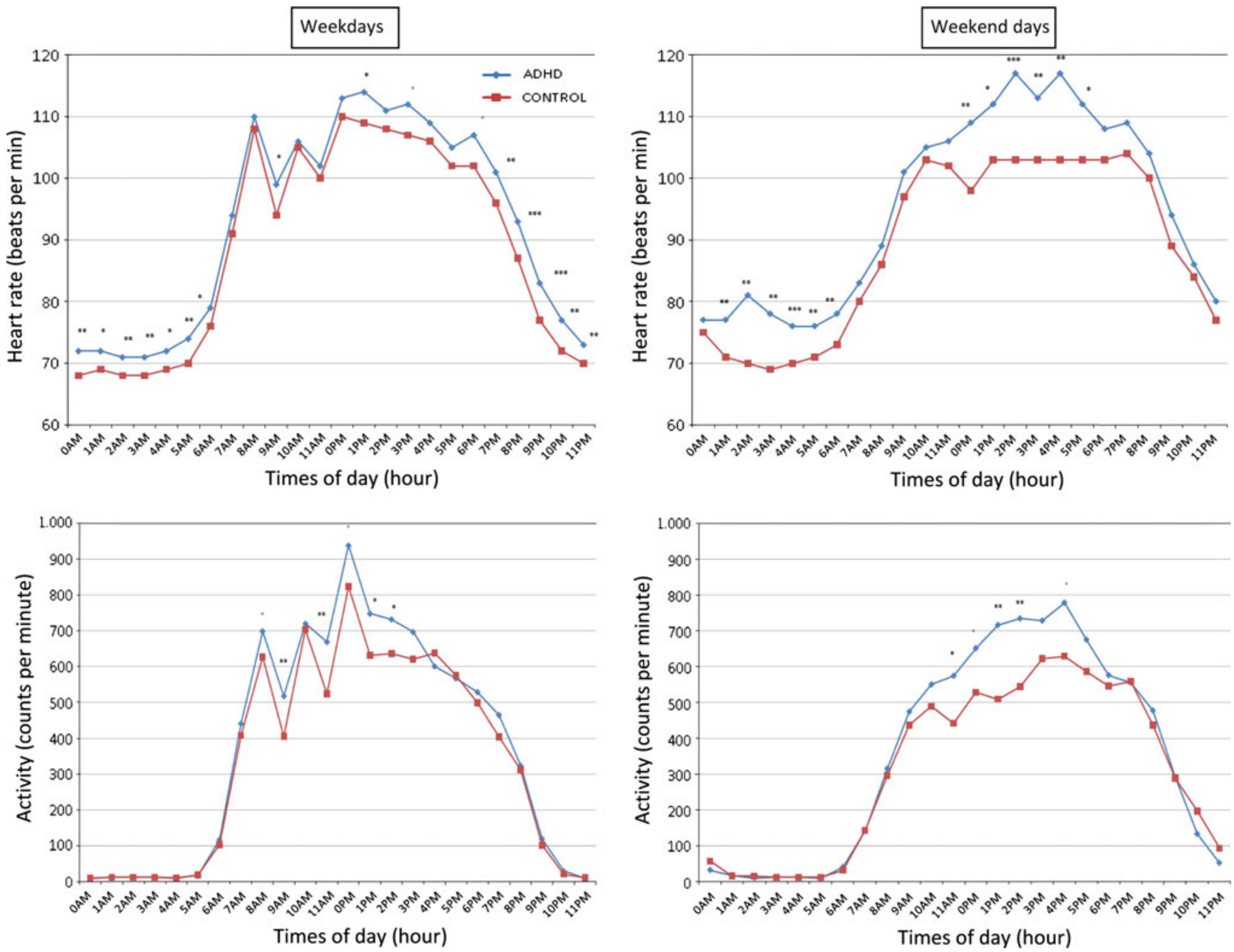

Fig. 2 24-h heart rate (*top*) and activity (*bottom*) pattern in children with ADHD and controls, averaged over weekdays (*left*) and weekend days (*right*). ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, °$p < 0.10$

whether the interaction effect in activity levels refers to a true ‘circadian’ alteration. Especially the fact that no group difference was observed during nighttime in this study could point towards an important role of environmental conditions to express arousal-related fluctuations in ADHD behavior. In addition, group differences were only detected between 8 a.m. and 4 p.m., indicating the possible involvement of school tasks that were similar for each ADHD and control dyad during this period. Alternatively, it is unlikely that only environmental factors would be responsible for these differences as weekday and weekend days revealed comparable findings considering the expression of ADHD hyperactivity.

In relation to heart rate, we hypothesized that elevated heart rate levels could be driven by higher locomotor activity in the ADHD group. Even though this could be true considering day hours, no such confounding effect of activity on heart rate levels could be retained during night. Nighttime activity levels were not significantly different between groups and could therefore not be responsible for higher nighttime heart rate levels. Although we expected a close relation between heart rate and activity levels, statistically, more ‘continue’ problems with the inhibition of sympathetic activity did not coincide with the ‘specific time of day’ problems with the inhibition of behavior. In his polyvagal theory, Porges [42] described two vagal systems: one system associated with the regulation of visceral functions (e.g., heart rate), the other with processes of attention, motor activity, emotion, and social engagement. Although heart rate and activity vary constantly to adapt to changing environmental demands [57], these two systems employ different adaptation strategies [42].

There are a number of issues to consider in evaluating this research as besides activity, also other factors could have elevated heart rate levels in ADHD. First, higher stress levels are expected to elevate heart rate levels so that differential results in ADHD may be due to secondary conditions rather than to ADHD itself. Next to the

Table 3 Effect size (η_p^2) of time-to-time activity and heart rate variations in children with ADHD and controls between 8 a.m. and 4 p.m. during school days and weekend days

	School days				Weekend days			
	ADHD activity	Control activity	ADHD heart rate	Control heart rate	ADHD activity	Control activity	ADHD heart rate	Control heart rate
8 a.m.–9 a.m.	0.31**	0.43***	0.62***	0.61***	0.53***	0.28**	0.57***	0.45***
9 a.m.–10 a.m.	0.41***	0.55***	0.52***	0.62***	0.11°	0.04	0.15*	0.18*
10 a.m.–11 a.m.	0.05	0.41***	0.20*	0.40***	0.004	0.02	0	0.01
11 a.m.–0 p.m.	0.46***	0.56***	0.59***	0.59***	0.16	0.11°	0.04	0.004
0 p.m.–1 p.m.	0.31**	0.24**	0.01	0.09	0.007	0.01	0.35**	0.09
1 p.m.–2 p.m.	0.007	0	0.14	0.02	0.001	0.03	0.09	0.009
2 p.m.–3 p.m.	0.03	0.006	0.03	0.03	0.003	0.09	0.01	0.06
3 p.m.–4 p.m.	0.16*	0.004	0.15*	0.01	0.007	0	0.03	0.02

ADHD attention-deficit hyperactivity disorder

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ° $p < 0.10$

prefrontal cortex, also limbic structures are part of the CAN and a close association between these regions and baroreflex functions has been described [56]. It has been suggested that anomalies in heart rate could be an early peripheral marker of latent asymptomatic and undiagnosed comorbid emotional disorders which may be the result of accumulated stress [59]. In our study, we looked at confounding effects of psychiatric comorbid problems as physiological dysregulation of the autonomic nervous system has been related to psychiatric disorders other than ADHD [20, 32, 39]. However, we found no evidence that comorbid externalizing and internalizing problems contributed significantly to variations in heart rate levels.

Second, pubertal stage and sex have been reported to influence heart rate levels [5, 64]. Most children in our sample were pre-pubertal without evidence for differences between the ADHD and control group. However, differences for boys and girls in onset of puberty is expected to be about 2 years so that sex differences may be present in our sample but could not be detected due to the small number of girls ($n = 6$) per group in the study. Additional analyses of boys only ($n = 24$ per group) revealed similar results to those obtained for the whole sample.

Third, the confounding effect of stimulant medication must be considered as significant increases in heart rate, especially during the first 6 months of treatment, have been reported [18]. Although all participants were free from medication at least 72 h prior to participation, to date, it is not sure whether fast-release preparations of methylphenidate could still have influenced cardiovascular functioning. In this study, day-to-day variability in heart rate levels, however, showed no decrease in the effect pattern from day one to day five. Additional analyses showed that midnight heart rate levels were significantly higher on day five than on day one ($p < 0.01$), reducing the possibility that our findings can be explained by longer-term effects of stimulant medication.

Fourth, confounders such as caffeine use and the presence of nightmares may have influenced daytime and nighttime heart rate levels. These factors, however, were not significantly different between groups and did not significantly contribute to heart rate variations. None of the children in our sample used nicotine, alcohol, or illicit drugs.

Finally, regular physical training is known to lower resting heart rate levels. However, we did not systematically assess the amount of sport activities and outdoor play in our sample. Therefore, we cannot exclude the possibility that such activities could have affected heart rate in our control more than in our ADHD group.

In the light of these considerations, our finding of elevated heart rate levels, i.e., hyperarousal, may suggest the necessity to critically re-evaluate the arousal concept in ADHD. Theoretical frameworks [51, 68] have mostly defined ADHD in terms of hypo-arousal deficits, largely ignoring circadian changes in arousal. In our study, we found time-of-day effects to be important as higher heart rate levels in ADHD were particularly expressed during night and afternoon hours. To our knowledge, nighttime heart rate levels have not been assessed yet in children with ADHD. During daytime periods however, low resting heart rate has consistently been reported in aggressive and antisocial behavior [32, 39]. This finding may not blindly be generalized to ADHD as studies in this population revealed inconsistent results with most of them describing no difference in resting heart rate [28, 30]. Next to possible confounding effects of time of day, these baseline levels may be influenced by varying levels of anticipatory stress as 'resting' assessments were mostly carried out prior to a laboratory experiment investigating the environmental effects on arousal. Environmental influences may be superimposed on the diurnal pattern as was suggested by more variable effect sizes during daytime in our study. A wealth of studies in subjects with ADHD reported hypo-aroused heart rate responses in relation to for example stress [30] and reward [15, 28]. It is difficult however, to compare these findings to those of our study as we did not investigate heart rate in response to such stimuli, under strict laboratory conditions. Nevertheless, we carefully explain our findings in the light of hypo-aroused responsiveness in ADHD. First, it seems that smaller group differences in morning hours may reflect a deviation from the overall higher arousal level, i.e., 'relative hypo-arousal', in children with ADHD during moments of higher academic demands. This effect was however, also present throughout weekend days during which cognitive involvement is less plausible. Second, in relation to activity, blunted heart rate responses were reported during peak exercise in ADHD [34]. For a larger min–max difference in activity in children with ADHD (i.e., 812 counts/min for ADHD and 694 for control; $p < 0.01$), our findings reveal a comparable min–max difference in heart rate (i.e., 40 bpm for ADHD and 39 for control; ns), possibly indicating a lower dynamic autonomic potential in children with ADHD than could be expected based on their activity pattern. Alternatively, hyperaroused response patterns have been proposed in ADHD as sustained by higher heart rate levels in response to for example reward [33]. Hyperarousal deficits have additionally been supported by the use of α_2 adrenergic agonists such as clonidine for the effective treatment of ADHD symptoms [48]. These drugs, originally developed for the treatment of hypertension, decrease the firing of noradrenalin neurons in the locus coeruleus, resulting in decreased arousal [7]. A similar action of atomoxetine, a noradrenalin re-uptake inhibitor used to treat ADHD, has been described. Li et al. [31] found an autonomic shift from tachycardia to bradycardia (decrease of sympathetic and increase of parasympathetic tone) after drug administration in rats. This contrasts with the action of methylphenidate, a dopaminergic agent that is known to increase arousal states in ADHD. Altogether, these findings point to the involvement of time- and context-related aspects in the dynamic modulation of arousal deficits in ADHD, which should be taken into account in future research evaluating deviations from 'optimal' arousal levels (hypo- and hyperarousal) in ADHD.

In summary, we suggest an autonomic imbalance with overall higher heart rate levels—particularly expressed during night and afternoon hours—in our sample of non-medicated children with ADHD. This finding seems independent from activity levels or comorbid psychiatric problems. However, further research is needed to validate our results in a larger sample with heart rate variability as a measure for autonomic function and to assess longer-term effects of these findings in children with ADHD. Higher resting heart rate may have a major impact on health outcomes as an association with higher morbidity and mortality from both cardiovascular and non-cardiovascular diseases has been described [21, 45]. In addition, the long-term use of psychostimulants must be questioned if overall heart rate levels are 'truly' increased in children with ADHD.

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References

1. Achenbach TM (2001) Child Behavior Checklist for ages 4–18 (CBCL/4–18). University of Vermont, Burlington
2. Achenbach TM (2001) Teacher report form (TRF). University of Vermont, Burlington
3. Antrop I, Roeyers H, De Baecke L (2005) Effects of time of day on classroom behaviour in children with ADHD. Sch Psychol Int 26:29–43
4. American Psychiatry Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Press, Washington, DC
5. Archbold KH, Johnson NL, Goodwin JL, Rosen CL, Quan SF (2010) Normative heart rate parameters during sleep for children aged 6 to 11 years. J Clin Sleep Med 6:47–50
6. Arnett PA, Newman JP (2000) Gray's three-arousal model: an empirical investigation. Pers Individ Differ 28:1171–1189
7. Arnsten AF, Steere JC, Hunt RD (1996) The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention-deficit hyperactivity disorder. Arch Gen Psychiatry 53:448–455
8. Arnsten AFT (1998) Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn Sci 2:436–447
9. Bagiella E, Sloan RP, Heitjan DF (2000) Mixed-effects models in psychophysiology. Psychophysiology 37:13–20
10. Boonstra AM, Kooij JJS, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJW (2007) Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 30:433–442
11. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ (2005) Reliability and validity of the combined heart rate and movement sensor actiheart. Eur J Clin Nutr 59:561–570
12. Caci H, Bouchez J, Bayle FJ (2009) Inattentive symptoms of ADHD are related to evening orientation. J Atten Disord 13:36–41
13. Corkum P, Tannock R, Moldofsky H, Hogg-Johnson S, Humphries T (2001) Actigraphy and parental ratings of sleep in children with attention-deficit-hyperactivity disorder (ADHD). Sleep 24:303–312

14. Cortese S, Faraone SV, Konofal E, Lecendreux M (2009) Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 48:894–908
15. Crone EA, Jennings JR, van der Molen MW (2003) Sensitivity to interference and response contingencies in attention-deficit/hyperactivity disorder. J Child Psychol Psychiatry Allied Discip 44:214–226
16. Crouter SE, Churilla JR, Bassett DR (2008) Accuracy of the actiheart for the assessment of energy expenditure in adults. Eur J Clin Nutr 62:704–711
17. Dagan Y, Zeevi-Luria S, Sever Y, Hallis D, Yovel I, Sadeh A, Dolev E (1997) Sleep quality in children with attention deficit hyperactivity disorder: an actigraphic study. Psychiatry Clin Neurosci 51:383–386
18. Daniels SR (2009) Cardiovascular effects of methylphenidate. J Pediatr 155:A3
19. Deforche B, De Bourdeaudhuij I, D'Hondt E, Cardon G (2009) Objectively measured physical activity, physical activity related personality and body mass index in 6-to 10-yr-old children: a cross-sectional study. Int J Behav Nutr Phys Act 6:25
20. Dietrich A, Riese H, Sondeijker F, Greaves-Lord K, Van Roon AM, Ormel J, Neeleman J, Rosmalen JGM (2007) Externalizing and internalizing problems in relation to autonomic function: a population-based study in preadolescents. J Am Acad Child Adolesc Psychiatry 46:378–386
21. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, Stamler J (1999) Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality—the Chicago Heart Association Detection Project in Industry. Am J Epidemiol 149:853–862
22. Groeppel-Klein A (2005) Arousal and consumer in-store behavior. Brain Res Bull 67:428–437
23. Gruber R, Sadeh A, Raviv A (2000) Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 39:495–501
24. Gueorguieva R, Krystal JH (2004) Move over ANOVA—progress in analyzing repeated-measures data and its reflection in papers published in the archives of general psychiatry. Arch Gen Psychiatry 61:310–317
25. Halperin JM, Schulz KP (2006) Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull 132:560–581
26. Himelstein J, Newcorn JH, Halperin JM (2000) The neurobiology of attention-deficit hyperactivity disorder. Front Biosci 5:461–478
27. Hvolby A, Jorgensen J, Bilenberg N (2008) Actigraphic and parental reports of sleep difficulties in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 162:323–329
28. Iaboni F, Douglas VI, Ditto B (1997) Psychophysiological response of ADHD children to reward and extinction. Psychophysiology 34:116–123
29. Jose AD (1966) Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man. Am J Cardiol 18:476–478
30. Lackschewitz H, Huther G, Kroner-Herwig B (2008) Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). Psychoneuroendocrinology 33:612–624
31. Li WY, Strang SE, Brown DR, Smith R, Silcox DL, Li SG, Baldridge BR, Nesselroade KP, Randall DC (2010) Atomoxetine changes rat's HR response to stress from tachycardia to bradycardia via alterations in autonomic function. Auton Neurosc 154:48–53
32. Lorber MF (2004) Psychophysiology of aggression, psychopathy, and conduct problems: a meta-analysis. Psychol Bull 130:531–552
33. Luman M, Oosterlaan J, Knol DL, Sergeant JA (2008) Decision-making in ADHD: sensitive to frequency but blind to the magnitude of penalty? J Child Psychol Psychiatry 49:712–722
34. Mahon AD, Stephens BR, Cole AS (2008) Exercise responses in boys with attention deficit/hyperactivity disorder effects of stimulant medication. J Atten Disord 12:170–176
35. Mezzacappa E, Tremblay RE, Kindlon D, Saul JP, Arseneault L, Seguin J, Pihl RO, Earls F (1997) Anxiety, antisocial behavior, and heart rate regulation in adolescent males. J Child Psychol Psychiatry 38:457–469
36. Mick E, Biederman J, Jetton J, Faraone SV (2000) Sleep disturbances associated with attention deficit hyperactivity disorder: the impact of psychiatric comorbidity and pharmacotherapy. J Child Adolesc Psychopharmacol 10:223–231
37. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, Rutherford J, Mehl RC, Wang M, Tuell A, Hume BC, Gozal D (2003) Sleep and neurobehavioral characteristics of 5-to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. Pediatrics 111:554–563
38. Oldehinkel AJ, Verhulst FC, Ormel J (2008) Low heart rate: a marker of stress resilience. The TRAILS study. Biol Psychiatry 63:1141–1146
39. Ortiz J, Raine A (2004) Heart rate level and antisocial behavior in children and adolescents: a meta-analysis. J Am Acad Child Adolesc Psychiatry 43:154–162
40. Owens J, Sangal RB, Sutton VK, Bakken R, Allen AJ, Kelsey D (2009) Subjective and objective measures of sleep in children with attention-deficit/hyperactivity disorder. Sleep Med 10:446–456
41. Pfaff D, Banavar JR (2007) A theoretical framework for CNS arousal. Bioessays 29:803–810
42. Porges SW (1995) Orienting in a defensive world: mammalian modifications of our evolutionary heritage. A polyvagal theory. Psychophysiology 32:301–318
43. Porges SW (2007) The polyvagal perspective. Biol Psychol 74:116–143
44. Porrino LJ, Rapoport JL, Behar D, Sceery W, Ismond DR, Bunney WE (1983) A naturalistic assessment of the motor-activity of hyperactive boys. 1. Comparison with normal controls. Arch Gen Psychiatry 40:681–687
45. Reunanen A, Karjalainen J, Ristola P, Heliovaara M, Knekt P, Aromaa A (2000) Heart rate and mortality. J Intern Med 247:231–239
46. Riddoch CJ, Mattocks C, Deere K, Saunders J, Kirkby J, Tilling K, Leary SD, Blair SN, Ness AR (2007) Objective measurement of levels and patterns of physical activity. Arch Dis Child 92:963–969
47. Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD (2007) Seasonality and circadian preference in adult attention-deficit/hyperactivity disorder: clinical and neuropsychological correlates. Compr Psychiatry 48:562–571
48. Scahill L (2009) Alpha-2 adrenergic agonists in children with inattention, hyperactivity and impulsiveness. CNS Drugs 23:43–49
49. Scheer F, Kalsbeek A, Buijs RM (2003) Cardiovascular control by the suprachiasmatic nucleus: neural and neuroendocrine mechanisms in human and rat. Biol Chem 384:697–709
50. Schwartz JR, Roth T (2008) Neurophysiology of sleep and wakefulness: basic science and clinical implications. Curr Neuropharmacol 6:367–378
51. Sergeant J, Van der Meere J (1990) Convergence of approaches in localizing the hyperactivity deficit. In: Lahey BB, Kazdin AE

(eds) Advances in clinical child psychology. Plenum, New York, pp 207–246
52. Sergeant J, Van der Meere J (1988) What happens after a hyperactive child commits an error? Psychiatry Res 24:157–164
53. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000) NIMH Diagnostic Interview for Children version: description, differences from previous versions and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 39:28–38
54. Silver R, LeSauter J (2008) Circadian and homeostatic factors in arousal. Ann NY Acad Sci USA 1129:263–274
55. Susman EJ, Dockray S, Schiefelbein VL, Herwehe S, Heaton JA, Dorn LD (2007) Morningness/eveningness, morning-to-afternoon cortisol ratio, and antisocial behavior problems during puberty. Dev Psychol 43:811–822
56. Thayer JF, Brosschot JF (2005) Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 30:1050–1058
57. Thayer JF, Lane RD (2007) The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 74:224–242
58. Thayer JF, Sternberg E (2006) Beyond heart rate variability—vagal regulation of allostatic systems. Ann NY Acad Sci USA 1088:361–372
59. Tonhajzerova I, Ondrejka I, Adamik P, Hruby R, Javorka M, Trunkvalterova Z, Mokra D, Javorka K (2009) Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder (ADHD). Indian J Med Res 130:44–50
60. Tsujii N, Okada A, Kaku R, Kuriki N, Hanada K, Matsuo J, Kusube T, Hitomi K (2007) Association between activity level and situational factors in children with attention deficit/hyperactivity disorder in elementary school. Psychiatry Clin Neurosci 61:181–185
61. Valera EM, Faraone SV, Murray KE, Seidman LJ (2007) Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry 61:1361–1369
62. Verhulst F, van der Ende J, Koot H (1997) Handleiding voor de Child Behavior Checklist (CBCL). Sophia Kinderziekenhuis/academisch Ziekenhuis Rotterdam/Erasmus Universiteit Antwerpen, Rotterdam
63. Verhulst F, van der Ende J, Koot H (1997) Handleiding voor de Teacher Report Form (TRF). Sophia Kinderziekenhuis/academisch Ziekenhuis Rotterdam/Erasmus Universiteit Antwerpen, Rotterdam
64. Wallis LA, Healy M, Undy MB, Maconochie I (2005) Age related reference ranges for respiration rate and heart rate from 4 to 16 years. Arch Dis Child 90:1117–1121
65. Waterhouse J, Atkinson G, Reilly T, Jones H, Edwards B (2007) Chronophysiology of the cardiovascular system. Biol Rhythm Res 38:181–194
66. Wechsler D (1991) Wechsler intelligence scale for children. In: Psychological Coroporation, San Antonio
67. Zagar R, Bowers ND (1983) The effect of time of day on problem-solving and classroom-behavior. Psychol Schools 20:337–345
68. Zentall SS, Zentall TR (1983) Optimal stimulation—a model of disordered activity and performance in normal and deviant children. Psychol Bull 94:446–471