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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-hour heart rate patterns differentiate between children with and without ADHD.

In this study, 24-hour 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 five days. Simultaneously, 24-hour 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 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 may 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

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, 2000) [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-hour heart rate patterns is available. One study with a shorter-term evaluation (three 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-hour 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-hour 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 for DSM-IV, parent version (DISC-IV)) [53]. Exclusion criteria included an IQ less than 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. 26 children with ADHD took methylphenidate (17 short- and 9 long-acting formulation), but all children were free from treatment at least 72 hours 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

This study was approved by the Ethical Committee of Ghent University Hospital, Belgium. Children with ADHD were recruited from the child psychiatric outpatient unit of the University Hospital Ghent (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 (three school days and two weekend days). To random 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 AM and finished between 3:30 and 4:00 PM, with recess/lunch periods between 10:00 and 10:30 AM, between noon and 1:30 PM, and between 2:30 and 3:00 PM. In general, academic lessons (mathematics, language arts) 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 body BMI were taken into account [5, 64]. Additionally, average caffeine use and the presences of nightmares in all children was questioned.

CBCL/TRF

The CBCL [1, 62] screens for emotional and behavioral problems in children aged 4 to 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-hour 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 (3M 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-hour activity patterns

An actigraph is an acceleration-sensitive, watch-like device typically worn on the non-dominant wrist (Actiwatch, Cambridge Neurotechnology Ltd, Cambridge, United Kingdom). 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 per minute). 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 usus, 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-hour 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 versus control), time of day (24 hourly data points), day of evaluation (day one to five), and weekday versus weekend day. An interaction term was included for group x 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 x 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 $d = M_1 - M_2 / SD_{pooled}$), 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 were 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).

INSERT TABLE 1 ABOUT HERE

24-hour 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 x 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 AM to 8 AM 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 x 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 Figure 1.

INSERT TABLE 2 ABOUT HERE

INSERT FIGURE 1 ABOUT HERE

24-hour 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 x 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 8 and 9 AM and between 11 AM and 4 PM, 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 AM and 4 PM, 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 Figure 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 previous findings (polynomial effects for group x time: heart rate (weekday: $p < 0.05$; weekend day: $p < 0.05$) and activity (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 Figure 2.

INSERT FIGURE 2 ABOUT HERE

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 AM 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 AM and 4 PM) in both groups (see Table 3). In general, subsequent time-to-time changes in activity were very large between 8 AM and 1 PM for both groups. Only for 10 to 11 AM, 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 2 PM 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.

INSERT TABLE 3 ABOUT HERE

DISCUSSION

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

The main aim of this study was to assess whether 24-hour heart rate patterns in non-medicated children with ADHD, registered during five days, under natural environmental conditions, were different as compared to normal controls. Although a typical circadian heart rate pattern with low levels during night and high levels during day hours was revealed [49, 65], we found no significant interaction effect of time of day x 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 10AM and at 12 AM 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 AM and at 11 AM class conditions. Though 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 AM

playtime to the 11 AM 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 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 AM and 4 PM, 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 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 hours 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 5 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 day- 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]. Also 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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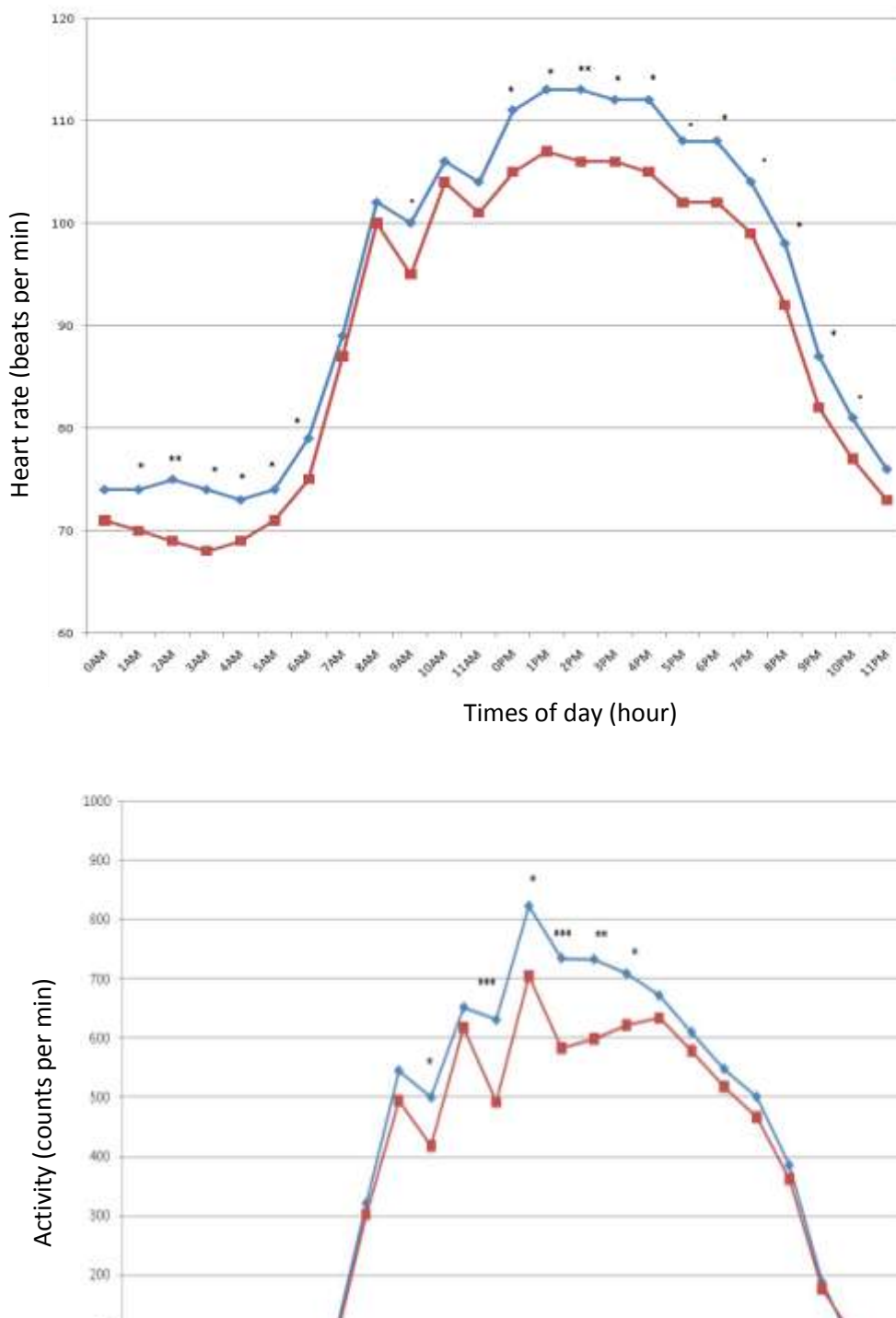
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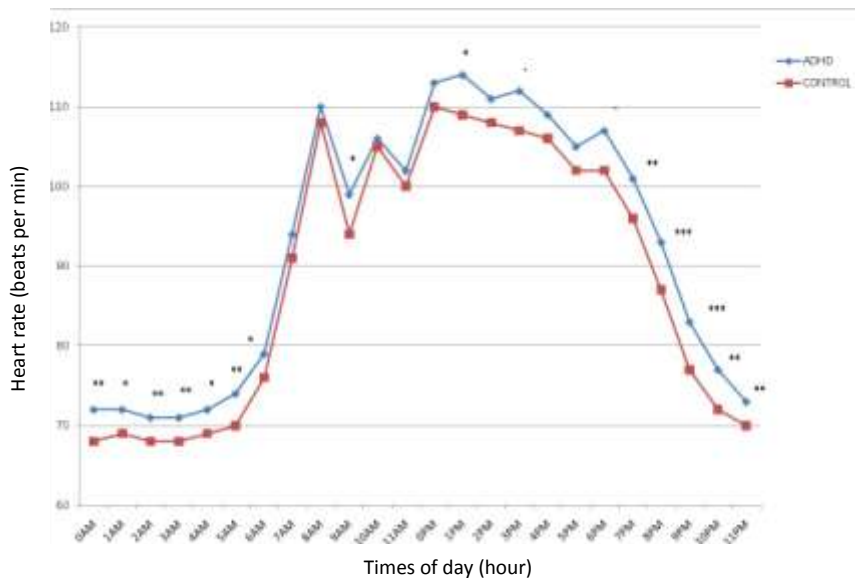
Figure 1 24-hour heart rate (top) and activity (bottom) pattern in children with ADHD and controls, averaged over five days



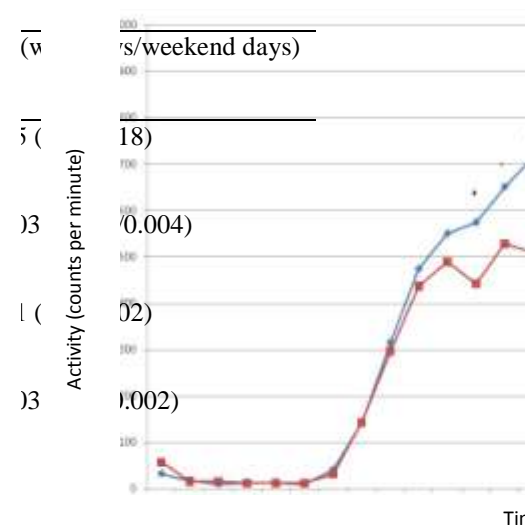
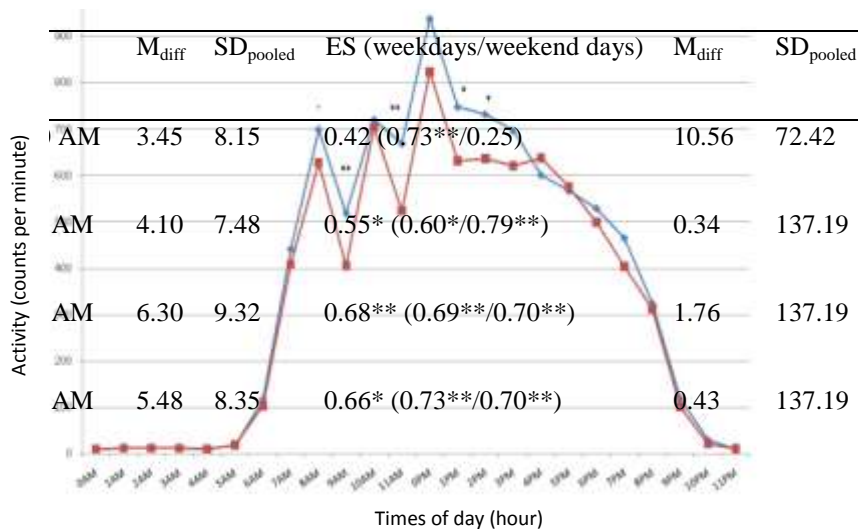
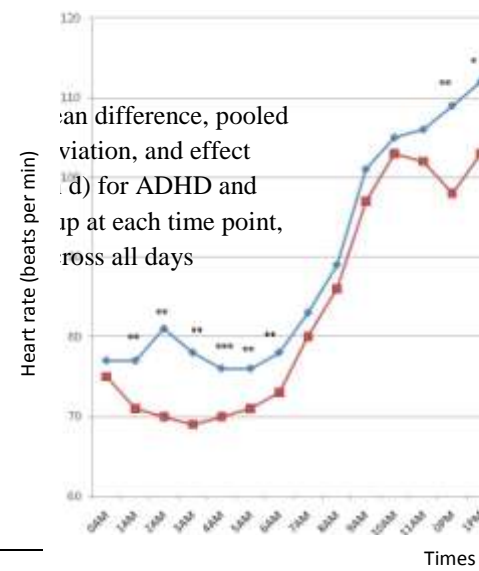
Times of day (hour)

Note. ***p < 0.001, **p < 0.01, *p < 0.05, °p < 0.10

Figure 2 24-hour heart rate (top) and activity (bottom) pattern in children with ADHD and controls, averaged over weekdays (left) and weekend days (right)



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Note. ***p < 0.001, **p < 0.01, *p <

0.05, °p < 0.10

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

Heart rate			Activity		
	M _{diff}	SD _{pooled}	ES (weekdays/weekend days)	M _{diff}	SD _{pooled} ES (weekdays/weekend days)
11 PM	3.49	8.28	0.42 (0.81**/0.25)	17.83	84.78 0.21 (0.40/0.23)

Note. 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

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

	ADHD	Control	
	M (SD) / n (%)	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)	24 m (80), 6 f (20)	24 m (80), 6 f (20)	$\chi^2(1)$ < 1, ns
Pubertal stage			
- Pre-pubertal pubic hair stage (n)	23 m (96), 5 f (83)	24 m (100), 5 f (83)	$\chi^2(1)$ < 1, ns
- Pre-pubertal genital stage (n)	24 m (100)	24 m (100)	$\chi^2(1)$ < 1, ns
- Pre-pubertal breast stage (n)	5 f (83)	5 f (83)	$\chi^2(1)$ < 1, ns
BMI	16.12 (1.54)	15.88 (1.62)	F(1,59) < 1, ns
Caffeine usus (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***

Note. ADHD = attention-deficit hyperactivity disorder; M = mean; SD = standard deviation; n = number in sample; % = percentage of sample; m = males; f = females; BMI = body mass index; CBCL = child behavior checklist; TRF = teacher report form

***p < 0.001

Table 3 Effect size (η_p^2) of time-to-time activity and heart rate variations in children with ADHD and controls between 8AM and 4 PM 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 AM – 9 AM	0.31**	0.43***	0.62***	0.61***	0.53***	0.28**	0.57***	0.45***
9 AM – 10 AM	0.41***	0.55***	0.52***	0.62***	0.11°	0.04	0.15*	0.18*
10 AM – 11 AM	0.05	0.41***	0.20*	0.40***	0.004	0.02	0	0.01
11 AM – 0 PM	0.46***	0.56***	0.59***	0.59***	0.16	0.11°	0.04	0.004
0 PM – 1 PM	0.31**	0.24**	0.01	0.09	0.007	0.01	0.35**	0.09

1 PM –	0.007	0	0.14	0.02	0.001	0.03	0.09	0.009
2 PM								
2 PM –	0.03	0.006	0.03	0.03	0.003	0.09	0.01	0.06
3 PM								
3 PM –	0.16*	0.004	0.15*	0.01	0.007	0	0.03	0.02
4 PM								

Note. ADHD = attention-deficit hyperactivity disorder

***p < 0.001; **p < 0.01; *p < 0.05; °p < 0.10