

Attention Deficit/Hyperactivity Disorder (ADHD) Is Associated With Altered Heart Rate Asymmetry

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Summary

Attention deficit/hyperactivity disorder (ADHD) is associated with complex neurocardiac integrity. We aimed to study heart rate time asymmetry as a nonlinear qualitative feature of heart rate variability indicating complexity of cardiac autonomic control at rest and in response to physiological stress (orthostasis) in children suffering from ADHD. Twenty boys with ADHD and 20 healthy age-matched boys at the age of 8 to 12 years were examined. The continuous ECG was recorded in a supine position and during postural change from lying to standing (orthostasis). Time irreversibility indices – Porta's (P%), Guzik's (G%) and Ehlers' (E) – were evaluated. Our analysis showed significantly reduced heart rate asymmetry indices at rest (P%: 49.8 % vs. 52.2 %; G%: 50.2 % vs. 53.2 %; $p < 0.02$), and in response to orthostatic load (P%: 52.4 % vs. 54.5 %, G%: 52.3 % vs. 54.5 %; $p < 0.05$) associated with tachycardia in ADHD children compared to controls. Concluding, our study firstly revealed the altered heart rate asymmetry pattern in children suffering from ADHD at rest as well as in response to posture change from lying to standing (orthostasis). These findings might reflect an abnormal complex cardiac regulatory system as a potential mechanism leading to later cardiac adverse outcomes in ADHD.

Key words

ADHD • Heart rate asymmetry • Heart rate variability • Cardiac autonomic regulation • Nonlinear analysis

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Introduction

The autonomic nervous system (ANS) plays a crucial role in a wide range of mental disorders. Normally, the activities of the sympathetic and parasympathetic branches of the ANS are in dynamic balance and its proper functioning at rest as well as in response to various internal/external stimuli is important for organism flexibility, adaptability and health. In contrast, the autonomic imbalance, in which one branch of the autonomic nervous system dominates over the other, is associated with a lack of dynamic flexibility and health. This state is common to a broad range of maladaptive conditions and it is associated with the increased risk of cardiovascular adverse outcomes (Friedman 2007, Porges 2007, Thayer and Sternberg 2006).

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder from externalizing mental disorders characterized by distractibility, deficient emotional self-regulation, hyperactivity, impulsive behaviors and inattention (Furman 2005). While it is generally assumed that autonomic regulation is impaired during ADHD, the information pertaining to this dysregulation is limited. However, recent study referred to different autonomic functioning in ADHD: children with ADHD and low prosocial behavior displayed

blunted parasympathetic and sympathetic activity (i.e. hypoarousal), and children with ADHD and age-typical prosocial behavior showed elevated sympathetic activity indicating high arousal (Musser *et al.* 2013). The state “hyperarousal” in ADHD indexed by tachycardia was found also in other studies (Tonhajzerova *et al.* 2009, Imeraj *et al.* 2011). In contrast, other disorders from externalizing spectrum, such as conduct disorders, aggressive behavior or delinquency, are associated with impaired autonomic functioning characterized by sympathetic and parasympathetic underactivity in accordance with “hypoarousal” theory (Beauchaine 2001, Beauchaine *et al.* 2007, 2013, Crowell *et al.* 2006). It seems that the findings of reduced ANS activity in externalizing psychopathology may not blindly be generalized to pure ADHD without comorbidities. This question is still unresolved.

From this context, it is assumed that ADHD is associated with autonomic nervous system dysfunction, and cardiac function is extremely sensitive to autonomic regulatory outputs in the bidirectional “brain-heart” communication (Beauchaine 2001). Thus, an extensive research has been directed to identify the pathway by which this neurocardiac control is achieved (Friedman 2007, Thayer and Lane 2009). Central autonomic network (CAN), as described by Benarroch (1993), represents a highly integrated neural system through which the brain controls visceromotor, neuroendocrine and behavioral responses critical for goal directed and adaptive behavior. The primary output of the CAN mediated by the interplay of sympathetic and parasympathetic neurons innervating sinoatrial node produces the beat-to-beat heart rate oscillations – heart rate variability (HRV). However, this cardiac control system has many features of a nonlinear dynamical system: reciprocally interconnected components and many positive/negative feedback interactions resulting in healthy and adaptive complexity of heart rate dynamics (Thayer and Lane 2000, Friedman 2007). Importantly, a loss of HRV complexity – as a general feature of pathological dynamics indicating maladaptive conditions – is associated with higher risk of cardiovascular adverse outcomes (Goldberger *et al.* 2002, Bornas *et al.* 2006, Bär *et al.* 2007). Taken together, the HRV analysis should represent a noninvasive window into complex cardiac chronotropic regulation providing important information about central-peripheral interaction (Tonhajzerova *et al.* 2012b).

Recently, nonlinear methods measuring

qualitative characteristic of the cardiac time series, such as heart rate asymmetry (HRA), have been shown to be more suitable for a detailed description of heart rate autonomic control system (Javorka *et al.* 2009, Porta *et al.* 2009, Tonhajzerova *et al.* 2012a). Heart rate asymmetry is a physiological phenomenon based on the irreversible dynamics of the heart rate increments and decrements from one beat to another – HRV asymmetry originating from different structure of runs of decelerations and accelerations (Piskorski and Guzik 2011a). The analysis of time asymmetry – as the phenomenon specific for nonequilibrium systems (Hou *et al.* 2010) – checks the invariance of the statistical properties of a time series after time reversal potentially detecting a qualitative feature of cardiac complex autonomic regulation (Porta *et al.* 2008). In other words, time irreversibility analysis is capable to detect a specific class of heart rate nonlinear dynamics characterized by a temporal asymmetry (Porta *et al.* 2008) and the presence of time irreversibility in the heart rate variability results from the complexity of cardiac autonomic control in healthy conditions (Costa *et al.* 2008). Although analysis of the heart rate asymmetry has been applied to heart rate time series analysis in healthy young subjects during physical stressors – passive and active orthostasis (Casali *et al.* 2008, De La Cruz Torres and Naranjo Orellana 2010) and in the diseases such as chronic heart failure, postinfarction patients, diabetes mellitus type 1 or depression (Baumert *et al.* 2009, Porta *et al.* 2009, Guzik *et al.* 2010, 2012, Tonhajzerova *et al.* 2012a), there are not previous studies related to the heart rate time irreversibility in mental disorders from externalizing spectrum such as attention deficit/hyperactivity disorder without comorbidity.

Therefore, we addressed the hypothesis that heart rate time asymmetry as a qualitative feature of heart rate nonlinear dynamics could provide new important information about potential neurocardiac control impairment in ADHD. To the best of our knowledge, it is the first study to use heart rate time irreversibility analysis in children suffering from ADHD without comorbidities and prior pharmacotherapy.

Methods

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava in accordance with the Declaration of Helsinki (2000) of the World Medical

Association. All children/patients/guardians were carefully instructed about the study protocol and they gave informed written consent to participate in the study prior to examination.

Subjects

We have examined 20 children diagnosed with ADHD at the age 8-12 years (average age: 10.0 ± 0.3 years; BMI: 16.4 ± 0.3 kg/m²) and 20 healthy children matched to age, body mass index and education level (average age: 10.5 ± 0.4 years; BMI: 17.1 ± 0.4 kg/m²). Basic groups' characteristics are presented in Table 1.

Table 1. The characteristics of ADHD patients and control group.

	ADHD (n=20)	Controls (n=20)
Age (years)	10.0 ± 0.3	10.5 ± 0.4
SBP (mm Hg)	107 ± 1.3	108 ± 1.2
DBP (mm Hg)	62 ± 1.2	61 ± 1.1
BMI (kg/m ²)	16.4 ± 0.3	17.1 ± 0.4

Values are expressed as mean \pm SEM, nonsignificant differences were in these parameters. SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index

Following inclusion criteria were used during enrolling the patients for ADHD group. The ADHD diagnosis – combined type, severe degree of the ADHD, without any comorbidity – was ascertained by two independent specialists – child and adolescent psychiatrists according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association 2000). Consequently, the ADHD patients were ascertained not to have other psychiatric diagnoses (e.g. conduct disorders) according to diagnostic criteria of DSM-IV-TR by two independent child/adolescent psychiatrists. After this initial procedure, the ADHD diagnosis and absence of any symptoms of other psychiatric diagnoses in our studied sample were confirmed by supervised qualified specialist in child and adolescent psychiatry prior to inclusion in this study. Additionally, only the patients that have never received any treatment prior to the study were included in this study, and the HRV examination was performed prior to planned treatment by atomoxetine or methylphenidate.

For controls, the control group was recruited from healthy children of primary school with respect to age, body mass index, education level and physical

activity. Similarly, control participants did not take any medication or substances influencing cardiovascular system. Furthermore, the control participants have been never treated for any mental disorder. Importantly, only boys were recruited into the study because of the gender as one of the physiological factors influencing the HRV (Tonhajzerova *et al.* 2002).

Following strict exclusion criteria were used for both groups (ADHD patients and controls): no evidence/history of cardiovascular, respiratory, endocrinological, neurological, infectious or other disorders/factors known to affect HRV (including obesity, overweight, underweight, alcohol/drug abuse, intensive regular physical training). Moreover, smokers were excluded from this study.

Procedure

All subjects were examined in the morning between 8.00 and 12.00 a.m. after a normal breakfast in quiet room with standard conditions (temperature, minimalisation of stimuli). After 10 min of rest and stabilization of the heart rate (for an exclusion of possible stress effect), the continuous recording of the R-R intervals in a supine position followed by orthostatic stress (change of posture from lying to standing) was performed using VarCor PF6 (Dimea, Czech Republic) with sampling frequency of 1000 Hz. The time spent in each interval was 5 min.

The heart rate asymmetry analysis

The segments of 300 RR intervals without artefacts were analyzed between the first and the fifth minute of the supine position and in response to physiological stimulus (1st-5th min of standing). Following indices suitable for short-term heart rate recordings were used to measure the time irreversibility of HRV series:

1. Porta's index P% (Porta *et al.* 2008) is based on the evaluation of the percentage of negative ΔRR with respect to the total number of $\Delta RR \neq 0$;

$$P\% = \frac{N(\Delta d^-)}{N(\Delta d \neq 0)} 100$$

2. Guzik's index G% (Guzik *et al.* 2006) is based on the evaluation of the percentage of the cumulative square values of positive ΔRR to the cumulative square of all ΔRR s. Contrary to P%, the calculation of Guzik's index (G%) considers also the magnitude of the difference between two RR intervals

$$G\% = \frac{\sum_{i=1}^{N(\Delta d^+)} \Delta d(i)^2}{\sum_{i=1}^{N(\Delta d)} \Delta d(i)^2} 100$$

The range of $P\%$ and $G\%$ indexes is from 0 to 100. The number 50 represents a “cut-off point” for significant changes in these parameters. $P\%$ higher than 50 means that the negative changes (Δd^-) are larger than the positive (Δd^+) (i.e. bradycardic runs are shorter than tachycardic ones). $G\%$ higher than 50 means that the average magnitude $|\Delta d^+|$ is larger than negative one. The values below the 50 evoke the opposite reactions.

3. Ehlers' index (Ehlers *et al.* 1998) is based on the evaluation of the skewness of the distribution of ΔRR .

$$E = \frac{\sum_{i=1}^{N(\Delta d)} \Delta d(i)^3}{\left\{ \sum_{i=1}^{N(\Delta d)} \Delta d(i)^2 \right\}^{3/2}}$$

The limiting value of this index represents number 0. Ehlers' index, higher than 0, indicates, that the distribution of Δd is skewed toward positive values and *vice versa*.

The nonlinear HRV parameters show the adequate reproducibility, which underlines their suitability for the application (La Fontaine *et al.* 2010). In addition, mean RR interval (ms) – as a reciprocal value of heart rate – was calculated.

Statistical analysis

Statistical analysis was performed using the statistical software package SYSTAT 10 for Windows (SSI, Richmond, CA, USA). The non-gaussian/gaussian distribution was ascertained by Lilliefors test. Two-way ANOVA with one repeated measures factor („position“: supine vs. standing) and one grouping factor („group“: ADHD or control) was used for data analysis with gaussian distribution (all parameters). *Post-hoc* univariate F test was used for between-groups comparison. The probabilities $p < 0.05$ were considered as significant. All the data are expressed as mean \pm SEM.

Results

Between groups comparison for time irreversibility indices

ANOVA revealed a significant difference between groups in time irreversibility indices $P\%$ and $G\%$ ($F=10.972$, $p=0.002$; $F=13.354$, $p=0.001$, respectively), and in the mean RR interval ($F=8.427$, $p=0.006$).

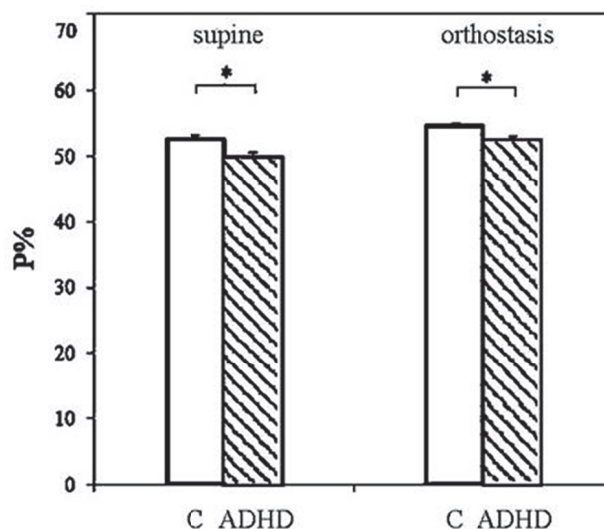


Fig. 1. Mean values of Porta index ($P\%$) in a supine position and during orthostasis. C – controls, ADHD – attention deficit/hyperactivity disorder. * $p < 0.05$

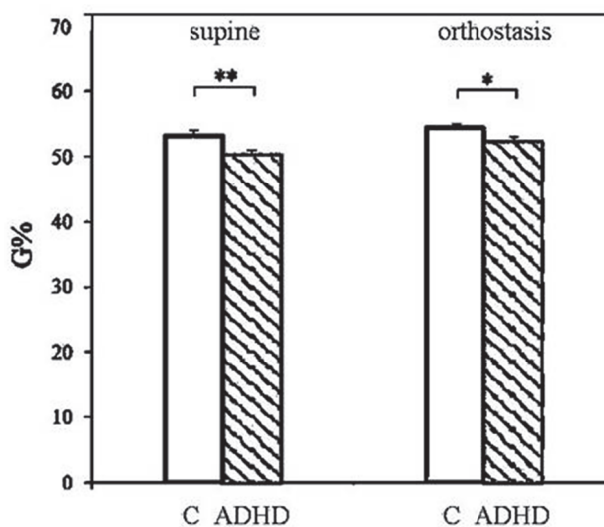


Fig. 2. Mean values of Guzik index ($G\%$) in a supine position and during orthostasis. C – controls, ADHD – attention deficit/hyperactivity disorder. * $p < 0.05$, ** $p < 0.01$

The effect of body position on time irreversibility indices

ANOVA revealed significant effect of repeated measures factor of „position“ (lying to standing – orthostatic test) for time irreversibility indices: $P\%$ ($F=12.477$, $p=0.001$), $G\%$ ($F=5.584$, $p=0.023$), and E ($F=8.053$, $p=0.007$), and for mean RR interval ($F=202.156$, $p=0.001$). No significant interactions between two factors („position“ x „group“) were found for all the parameters ($P\%$, $G\%$, E , RR interval).

Post hoc analysis

Post hoc tests revealed that both time irreversibility indices ($P\%$, $G\%$) were significantly

reduced in the ADHD compared to controls in a supine position ($F=6.387$, $p=0.016$; $F=7.613$, $p=0.009$, respectively; Fig. 1, 2). Similarly, the orthostatic load showed significantly lower heart rate asymmetry parameters P%, G% ($F=5.672$, $p=0.022$; $F=5.869$, $p=0.020$, respectively; Fig. 1, 2) in ADHD group compared to controls. No significant differences between ADHD and controls were found for Ehlers' index (E) in both positions – lying and standing ($F=3.149$, $p=0.084$; $F=1.764$, $p=0.192$, respectively). Additionally, *post hoc* analysis showed that mean RR interval was significantly shortened in the ADHD compared to controls in both positions – supine (683 ± 21 ms vs. 759 ± 20 ms; $F=5.770$, $p=0.021$) and during orthostasis (534 ± 15 ms vs. 605 ± 16 ms; $F=9.522$, $p=0.004$).

Discussion

This study examined heart rate asymmetry (HRA) as a qualitative feature of heart rate complex dynamics in children suffering from ADHD at rest and in response to physiological stress (orthostasis). Our hypothesis was confirmed. This studied group consisting of untreated children suffering from ADHD without comorbidity demonstrated reduced indices of heart rate time irreversibility (P%, G%) under resting conditions, and in response to change of posture from lying to standing – orthostatic load associated with tachycardia. These findings could indicate an abnormal complex cardiac functioning in pure ADHD children.

Heart rate asymmetry is related to nonlinear behavior of cardiac function, which is manifested by the most complex central-peripheral interrelationships resulting in the presence of asymmetric patterns (i.e. waveforms characterized by the upward side shorter or longer than the downward side) (Porta *et al.* 2008). It is reported to be the highest for healthy physiological systems under resting conditions (Costa *et al.* 2005) and to decrease with pathology, thus providing a marker for any loss of normal functionality (Karmakar *et al.* 2010, 2012). Recent studies suggest that heart rate asymmetric pattern in healthy subjects is characterized by bradycardic runs shorter than tachycardic ones (i.e. the heart rate decelerates more rapidly than it accelerates) indexed by values of P% and G% indices larger than 50 (Porta *et al.* 2008, 2009). Interestingly, other authors used the redefined Guzik's index value of symmetry equal to 50 (Karmakar *et al.* 2010). We found significantly reduced heart rate time asymmetry indices (G%, P%) in children

with ADHD compared to controls in a supine position, and these values were closer to 50 indicating heart rate symmetric pattern in the ADHD group.

Nevertheless, the physiological mechanisms responsible for heart rate irreversibility are unclear. Importantly, the heart rate asymmetry (i.e. heart rate accelerations and decelerations indexed by P%, G% and E) are influenced by the dynamic sympathovagal balance: heart rate accelerations can be caused by the increased sympathetic regulatory inputs, reduced parasympathetic drive or be an effect of both. Similarly, heart rate decelerations can be caused by a reduction in sympathetic activity, augmentation of parasympathetic tone or both altered nervous systems (Piskorski and Guzik 2011b). Further, Karmakar *et al.* (2012) showed that pharmacological autonomic modulation by atropine (parasympathetic blockade) or scopolamine (parasympathetic agitation) changes the expression of heart rate asymmetry in the following pattern: atropine reduces time irreversibility and scopolamine increases its expression. Taken together, it seems that heart rate irreversibility indices are sensitive to the sympathetic and in particular parasympathetic regulatory mechanisms which in turn modulate the electrical properties of cardiac cells (Porta *et al.* 2008, Guzik *et al.* 2013). Therefore, our findings showed the reduced heart rate time asymmetry in children suffering from ADHD compared to controls indicating an impairment of cardiac autonomic complex control in a supine position, in which the cardiac vagal activity is dominant.

Orthostatic test - the change of posture from supine to the standing position – is a well-known physiological maneuver characterized by a shifted balance of the autonomic nervous system towards progressive increase of the sympathetic activity and a concomitant decrease in the vagal activity. It is important to note that neurocardiac reactivity induced by orthostatic test is associated with autonomic regulatory subcortical centres (hypothalamus, brainstem), and at the level of the peripheral organ – heart. From this point of view, it can be used as an ideal “model” to study the complex dynamics of activated heart rate autonomic regulatory inputs. Importantly, recent studies suggest that time irreversibility indices (Porta's, Guzik's index) are sensitive to the increase in the sympathetic modulation produced by head-up tilt test (Porta *et al.* 2008) or active orthostasis in healthy subjects (Chladekova *et al.* 2011). Our findings showed the decreased heart rate asymmetry indices induced by orthostatic load indicating potential

discrete abnormalities in neurocardiac complex regulatory mechanisms in ADHD children compared to control group. Therefore, it is assumed that children with ADHD have a lower functional reserve capacity and must work harder and expend a greater portion of their autonomic reserve in order to regulate minor perturbations (Rash and Aguirre-Camacho 2012). Importantly, baroreflex sensitivity is different for blood pressure increases and reductions; thus, heart rate asymmetry could be to some extent attributed to the baroreflex characteristics (Piskorski and Guzik 2011a). From this point of view, we can speculate that baroreflex function – as a principal mechanism in cardiovascular adaptive response to posture change from lying to standing – is impaired in ADHD children. Further research based on baroreflex analysis with continuous blood pressure recording and subsequent baroreflex sensitivity is needed.

It seems that time irreversibility parameters could provide important information about complex neurocardiac control dynamics in pure ADHD, but the mechanisms involved in heart rate asymmetry are unclear and still discussed. The short-term HRV is influenced by dominant cardiac parasympathetic-linked regulatory mechanism – respiratory sinus arrhythmia (RSA) that is characterized by heart rate oscillations related to breathing pattern (heart rate increases during inspiration and decreases during expiration). It is important to note that this coupling of heart rate oscillations to the respiratory cycle can be affected by an asymmetric pattern of single breathing cycle, i.e. inspiration and expiration times are not equal and expiratory phase lasts longer in a healthy human. Thus, the RSA is considered as an important physiological mechanism contributing to the heart rate asymmetry (Piskorski and Guzik 2011a). Our previous study revealed reduced baseline cardiac vagal regulation quantified by spectral analysis of the heart rate variability at the respiratory-related high-frequency band (HF-HRV as an index of RSA) in ADHD associated with greater percentual decrease in vagal withdrawal in response to orthostatic test indicating potential subclinical abnormal dynamic activation of the autonomic nervous system in response to posture change in children with attention deficit/hyperactivity disorder (Tonhajzerova *et al.* 2009). These results are in agreement with other studies which found reduced RSA amplitude indicating cardiac vagal dysfunction in ADHD (Beauchaine 2001, Crowell *et al.* 2006, Buchhorn *et al.* 2012). According to the polyvagal theory (Porges 1995, 2009), RSA is considered as a noninvasive index of

cardiac vagal modulation as well as emotional regulation, and the ADHD is associated with emotional dysregulation (Musser *et al.* 2013). From this perspective, a potential connection between ADHD-linked emotional dysregulation (i.e. emotional lability due to emotional immaturity) and reduced cardiovagal function might represent the possible mechanisms leading to the altered heart rate asymmetry observed in our sample of child patients suffering from ADHD.

Generally, the neurophysiological mechanisms leading to heart rate asymmetry impairment as a qualitative feature of nonlinear dynamics in the complex cardiac autonomic control system related to ADHD are still unexplored. Recent neuroimaging studies suggest the involvement of developmentally abnormal brain regions including prefrontal cortex in ADHD (Cortese 2012). Consequently, the importance of the inhibitory processes by prefrontal cortex related to heart rate complex control as a sign of health was emphasized by some research groups (Friedman 2007, Thayer and Lane 2000). The central autonomic network, characterized by the reciprocally interconnected neural structures, allows the prefrontal cortex to exert an inhibitory influence on subcortical structures associated with defensive behavior and thus allows the organism to flexibly regulate its behavior in response to changing environmental demands (Thayer 2006). For example, the amygdala, which has outputs to autonomic as well as other regulatory systems, and becomes active during threat/uncertainty, is under tonic inhibitory control from the prefrontal cortex. Thus, under conditions of the threat, the prefrontal cortex becomes hypoactive which is associated with disinhibition of sympathoexcitatory circuits involved in the cardiac autonomic regulation. Importantly, proper functioning of inhibitory processes is vital to the preservation of the integrity of the system and therefore is vital to health (Tonhajzerova *et al.* 2012b).

In ADHD children, the deficit in prefrontal functioning connected to limbic system and consequent alteration of baroreflex function as well as the modifications in a network of brain regions (e.g. anterior cingulate cortex) are supposed (Börger *et al.* 1999, Pliszka *et al.* 2006). In the molecular aspect, the prefrontal cortex is powerfully modulated by catecholamines, in particular norepinephrine and dopamine, which are thought to be involved in the regulation of processes such as selective attention or arousal state (Gamo and Arnsten 2011). From this context, ADHD was found to be associated with a wide

variety (up to 158 genes) of genetic abnormalities of dopaminergic, noradrenergic, and also serotonergic transmission (receptors, transporters, pathway modulators, enzymes of the synthesis and degradation and regulators of the neurotransmitters' release) (Cristino *et al.* 2014, Lesch 2009). Specifically, the mutation of alpha2A-adrenoreceptor gene (ADRA2A) was found to impair the cognitive functions of prefrontal cortex (Franowicz *et al.* 2002), and a significant association of the 3081(A/T) polymorphism in the norepinephrine transporter (NET) gene with ADHD development was identified (Kim *et al.* 2006). Moreover, both NET -3081(A/T) and ADRA2A MspI polymorphisms were found to be associated with cardiovascular side effects of methylphenidate treatment in children suffering from ADHD (Cho *et al.* 2012). Therefore, the genetically mediated abnormalities in the neurotransmission could contribute to the discrete dysfunctions in the prefrontal cortex, limbic system, locus coeruleus-noradrenergic system and other related brain structures that are also included in the neurocardiac complex regulation (Samuels and Szabadi 2008a,b).

Furthermore, the deficits of prefrontal cortex with respect to structural and functional neuroimaging, dopaminergic and noradrenergic dysregulation are associated with a loss of inhibitory processes critical for adaptive heart rate neural regulation. Interestingly, the posterior transection of the medial prefrontal cortex significantly increased the stress-induced catecholamines release in animal model suggesting thus an inhibitory effect of prefrontal cortex on the sympathoadrenal activity (Ondicova *et al.* 2012). It seems that the prefrontal cortex dysfunction could represent one of the underlying mechanisms of the impaired catecholaminergic regulation. For example, Dvorakova *et al.* (2007) found increased urinary levels of both catecholamines (norepinephrine, epinephrine) in ADHD children, and the norepinephrine concentrations significantly correlated with the degree of hyperactivity. Other studies demonstrated the lower ratios of urinary norepinephrine to normetanephrine, and epinephrine to metanephrine after mental tasks associated with higher resting catecholamine levels indicating peripheral catecholaminergic dysregulation characterized by a potential tonic sympathoadrenal overactivation associated with maladaptive catecholamine stress reactivity in ADHD (Konrad *et al.* 2003, Pliszka *et al.* 1994). Moreover, ADHD seems to be also associated with dysregulation in other allostatic systems, such as hypothalamic-pituitary-adrenocortical axis activity

resulting in the lower resting and stressful cortisol levels in ADHD, as noted in recent studies (Ma *et al.* 2011, Pesonen *et al.* 2011). Taken together, we suggest that the potential pathomechanisms leading to the impairment of heart rate asymmetric pattern in untreated ADHD children are complex, and the alterations in heart rate irreversibility might identify potential subtle abnormalities in neurocardiac regulatory mechanisms indicating an important step towards heart-brain understanding in pure ADHD.

It should be noted that deficient cardiovascular stress reactivity was also found in adult treatment-free ADHD, and thus the impaired complex cardiac autonomic control could represent a risk factor for later cardiovascular adverse complications, such as tachycardia or hypertensive reaction observable in adult ADHD-treated patients (Hammerness *et al.* 2011, Hirvikoski *et al.* 2011). We suggest that the assessment of early and subclinical abnormal signs of complex neurocardiac regulation could represent an important contribution in clinical practice, e.g. in the cardiac function monitoring during psychopharmacological treatment.

Study limitations

This study included a homogeneous group of male patients with ADHD – combined type without any comorbidity and severe degree of the ADHD. However, the assessment of the interaction between heart rate asymmetry indices and other ADHD subtypes (predominantly inattentive type, and predominantly hyperactive/impulsive type) as well as the ADHD features/severity assessed from different rating scales could have given important information. Further research in this field is needed.

Additionally, several studies hypothesize that distinct core neurobiological deficits may underlie the developmental course of ADHD in males and females (Hermens *et al.* 2005). From this perspective, we suggest that gender could affect the heart rate asymmetry parameters in ADHD, and thus our results may only be representative for male ADHD patients. Therefore, the potentially important ADHD-linked gender differences in the heart rate asymmetry need to be identified in future studies.

Conclusion

Our study is the first to report the altered heart rate asymmetric pattern in ADHD children at rest as well

as in response to posture change from lying to standing (orthostasis). These findings might reflect a deficiency in complex cardiac regulatory system as a potential pathomechanism leading to later cardiac adverse outcomes. It seems that HRV nonlinear analysis based on heart rate irreversibility could represent a new indicator to illuminate the pathway linking complex neurocardiac integrity and attention deficit/hyperactivity disorder in

untreated children without comorbidity.

Conflict of Interest

There is no conflict of interest.

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