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Heart rate time irreversibility is impaired in adolescent major depression

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ABSTRACT

We aimed to study heart rate time irreversibility — a nonlinear qualitative characteristics of heart rate variability indicating complexity of cardiac autonomic control at rest and in response to physiological stress (orthostasis) in never-treated major depressive disorder (MDD) adolescent female patients.

Methods: We studied 20 MDD girls and 20 healthy age-matched girls at the age of 15 to 18 years. The ECG was recorded in supine position and in response to position change from lying to standing (orthostasis). Time irreversibility analysis was performed using Porta's (P%), Guzik's (G%) and Ehlers' (E) index. The depressive disorder severity was evaluated using Montgomery–Asberg Depression Rating Scale (MADRS) and Children's Depression Inventory (CDI).

Results: Resting heart rate time irreversibility indices (logG%, logP%, Ehlers' index) were significantly reduced in MDD female patients without significant differences in response to orthostasis in MDD girls compared to controls. No significant correlations between time irreversibility and MDD severity were observed.

Conclusion: This study revealed the impaired heart rate asymmetry pattern indicating an altered complexity of cardiac autonomic regulation in adolescent female patients suffering from MDD.

1. Introduction

Autonomic nervous system imbalance is a common finding in maladaptive conditions and pathological states including major depressive disorder (MDD) (Friedman, 2007; Porges, 2007; Thayer and Sternberg, 2006) where abnormal control of organs is commonly present: *e.g.* gastric dysmotility caused by increased sympathetic modulation (Quick et al., 2010). Moreover, a reduced parasympathetic regulation has been shown by pupillometric analysis (Bär et al., 2004).

Cardiac activity is extremely sensitive to autonomic regulatory inputs. The interplay of sympathetic and parasympathetic outputs of the central autonomic network, as described by Benarroch (1993), coming into sinoatrial node produces the complex beat-to-beat heart rate oscillations. The spontaneous oscillations of heart rate — heart rate variability (HRV) is determined by dynamic interaction of acceleratory sympathetic nervous system and deceleratory parasympathetic nervous system indicating a healthy and adaptive organism. A lack of sensitive complex neurocardiac control could represent a potential pathomechanism contributing to higher risk of adverse cardiovascular outcomes associated with major depression (Carney and Freedland, 2009). Moreover, adolescence could be a critical and vulnerable age-period to a potential depression-induced impairment of sensitive neurocardiac control due to developmental and brain maturational changes (Thayer et al., 2009; Yang et al., 2007). This makes adolescence an interesting age-period for studying complex cardiac functioning in depression as an important population target for prevention of potential cardiac complications (Bosch et al., 2009; Byrne et al., 2010; Galambos et al., 2004).

Short-term HRV reflects the autonomic control of the heart rate. HRV is routinely analysed by linear (time and frequency domain) analysis quantifying predominantly the magnitude of heart rate fluctuations (Task Force, 1996). However, these methods ignore the complexity and nonlinearity of a control system underlying heart rate oscillations. The central cardiac control network has many features of a nonlinear dynamic system with reciprocally interconnected components and many positive/negative feedback interactions (Friedman, 2007; Thayer and Lane, 2000). A healthy complex system results in complex heart rate oscillations. Therefore, the complexity of heart rate oscillations indicates better adaptability and flexibility of a

Abbreviations: ANOVA, Analysis of variance; ANS, Autonomic nervous system; CDI, Children's Depression Inventory; E, Ehlers' index; G%, Guzik's index; HRV, Heart rate variability; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, Major depressive disorder; P%, Porta's index; RSA, Respiratory sinus arrhythmia.

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healthy biological system. By contrast, a loss of complexity is proposed as a general feature of pathological dynamics indicating rigidity and insufficient cardiovascular system adaptation to various conditions (Bär et al., 2007; Friedman, 2007). The linear methods of HRV analysis are not sufficient to characterise the complex heart rate dynamics. Therefore, new nonlinear methods quantifying the qualitative features (including heart rate complexity, time asymmetry, recurrences in heart rate dynamics) of complex dynamics are increasingly used in HRV analysis (Voss et al., 2009).

The majority of studies indicate altered heart rate complexity of HRV analysis in depressed patients using various nonlinear parameters (Baumert et al., 2009; Berger et al., 2011; Boettger et al., 2008; Schulz et al., 2010; Tonhajzerova et al., 2010; Voss et al., 2011). Recently, the phenomenon of heart rate *time asymmetry* specific for nonequilibrium systems (Hou et al., 2010) has gained more attention. Time irreversibility analysis checks the invariance of the statistical properties of a time series after time reversal. In other words, time irreversibility analysis is capable of detecting a specific class of heart rate nonlinear dynamics characterised 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 the time irreversibility has been applied to HRV analysis in healthy subjects (De La Cruz Torres and Naranjo Orellana, 2010) or in the somatic diseases such as chronic heart failure, postinfarction patients and diabetes mellitus type 1 (Guzik et al., 2010; Guzik et al., 2012; Porta et al., 2009), there are no previous studies related to the heart rate time irreversibility in adult as well as adolescent major depression.

Furthermore, the autonomic nervous system is the principal rapidly reacting system that controls heart rate in various physiological manoeuvres (*e.g.* orthostasis). The orthostatic test measures the dynamic baroreflex-mediated changes of the autonomic nervous system developing immediately after the onset of posture change from lying to standing in the form of a vagal withdrawal associated with sympathetic activation. It is conceivable that potential depression-related abnormalities of the neurocardiac reflex control could be detectable predominantly in response to stress (Byrne et al., 2010).

We addressed the hypothesis that heart rate time asymmetry as one of the recently described features of nonlinear dynamics could provide new information about a potential neurocardiac control impairment in adolescent major depression at rest and in response to orthostatic stress. To the best of our knowledge, it is the first study to use heart rate time irreversibility in adolescent MDD.

2. Methods

2.1. Subjects

The short-term ECG recordings obtained in the same patient cohort as used in our previous study (Tonhajzerova et al., 2010) were used for nonlinear analysis of the heart rate time irreversibility. As we reported previously (Tonhajzerova et al., 2010), the MDD group (n = 20) and control group (n = 20) were matched with respect to average age (16.6 ± 0.2 and 16.5 ± 0.2 years, respectively) and the body mass index (20.4 ± 0.3 and 20.5 ± 0.2 kg/m^2, respectively). Only girls were recruited into the study because of gender being one of the physiological factors influencing the HRV (Tonhajzerova et al., 2002) and a recent study referred to the gender-dependent impact of major depression on autonomic cardiovascular modulation (Voss et al., 2011).

The patients suffering from major depressive disorder were recruited from the patients admitted to our inpatient child and adolescent psychiatric ward. These patients were firstly seeking the help of a psychiatrist because of their symptoms or on recommendation of their general practitioner. The diagnosis of MDD, single episode without psychotic symptoms (*e.g.* mood congruent or incongruent delusions, hallucinations) and other psychiatric disorders (*e.g.* ADHD, conduct disorders, anxiety disorder), was classified by thorough clinical investigations based on unstructured diagnostic interview by a staff child/adolescent psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). Consecutively, the diagnosis was confirmed by a supervised qualified specialist in child and adolescent psychiatry prior to inclusion in this study. The mean duration of episode was 8.1 ± 0.5 weeks (from 4 to 11 weeks). Patients included in this study have never received any psychotropic medication before the study. To assess the severity of depressive symptoms, the Montgomery–Asberg Depression Rating Scale (MADRS) and Children's Depression Inventory (CDI) were applied. The rating of MADRS was based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The specialist (psychiatrist) decided whether the rating lies on the definite scale steps (0, 2, 4, 6) or between them (1, 3, 5). The total possible score is 60, where higher scores indicate greater depressive symptomatology (Montgomery and Asberg, 1979). The CDI is a widely used 27-item self-report instrument designed to assess the symptoms of depression in children and adolescents. Items are scored on a 0 (absence of symptom) to 2 (definite symptom) scale. A total score (range 0–54, higher scores indicate greater depression severity) is calculated by summing all items (Kovacs, 1992). In the MDD group the average MADRS was 38.6 ± 2.6 and the average CDI was 33.9 ± 1.8. Both scales are suitable for adolescent age and they have acceptable reliability and validity.

Control subjects were strictly recruited from high school students with respect to age, body mass index and educational level. Similarly, control participants did not take any medication. The exclusion criteria for both MDD and control groups were: a history of cardiovascular, respiratory, endocrinological, neurological, infectious or other disorders known to affect HRV (including obesity, overweight, underweight, alcohol, drug abuse, smoking). Furthermore, the control participants have never been treated for any mental disorder. All subjects were instructed not to use substances which influence activities of the cardiovascular system (caffeine, alcohol) for at least 12 h before the recording. In addition, we have not obtained specific data for female participants such as the hormonal state associated with menstrual cycle phase.

This 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. All subjects and their parents were carefully instructed about the study protocol and they gave written informed consent to participate in the study prior to examination.

2.2. Study protocol

As we reported previously (Tonhajzerova et al., 2010), the examinations were performed in a quiet room with standard temperature (23 °C) and minimalisation of stimuli in the morning between 8.00 and 11.30 a.m. after a normal breakfast 2 h prior to the examination. The subjects were asked to empty bowel and bladder before the examination and they were instructed to lie back comfortably and not to speak or move unless necessary. After the first period (15 min of rest) required for stabilisation of the heart rate and for an exclusion of a potential stress effect the subjects remained in a supine position. Then, continuous recording of RR interval at rest and during standing was performed using VarCorPF6 (Dimea, Czech Republic) with sampling frequency of 1000 Hz. The applied system was developed and validated according to methodological recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) (Salinger and Gwozdziewicz, 2008) and it was used in our previous studies (*e.g.* Javorka et al., 2008; Tonhajzerova et al., 2010).