Journal of Psychiatric Research 84 (2017) 169–173

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Short communication

State-related differences in heart rate variability in bipolar disorder

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ARTICLE INFO

Article history:
Received 7 July 2016
Received in revised form
9 September 2016
Accepted 7 October 2016

Keywords:
Bipolar disorder
Heart rate variability
HRV
Affective state
State-dependent marker

ABSTRACT

Heart rate variability (HRV) is a validated measure of sympato-vagal balance in the autonomic nervous system. HRV appears decreased in patients with bipolar disorder (BD) compared with healthy individuals, but the extent of state-related alterations has been sparingly investigated. The present study examined differences in HRV between affective states in BD.

A heart rate and movement sensor weighing 8 g collected average acceleration, heart rate and the two slowest and fastest heart beats (of the most recent 16 beats) every 30 s over a period of at least three consecutive weekdays and nights in a prospective longitudinal design from a total of 31 different affective states in 16 outpatients with BD. A proxy measure of HRV was calculated as the difference between the second-shortest and the second-longest inter-beat-interval collected during each of the epochs. Analyses were based on over 100.000 HRV data-points.

In unadjusted analyses and in analyses adjusted for age, gender and heart rate, during a manic state HRV was increased by 18% compared with a depressed state ($e^B = 1.18$, 95% CI: 1.16–1.20, $p < 0.001$) and increased by 17% compared with a euthymic state ($e^B = 1.17$, 95% CI: 1.15–1.19, $p < 0.001$), whereas there was no difference between a depressive state and a euthymic state ($e^B = 0.98$, 95% CI: 0.96–1.00, $p = 0.12$). Further inclusion of BMI as a covariate did not alter any of the associations.

HRV appears to be altered in a state-dependent manner in bipolar disorder and could represent a candidate state marker. Further studies with larger sample sizes are warranted.

1. Introduction

The autonomic nervous system links the central nervous system and the cardiovascular system (Benarroch, 2014; Lown and Verrier, 1976). Heart rate variability (HRV) reflects the oscillation in the time intervals between consecutive heartbeats, and is proposed as a measure of balance in the activity of the autonomic nervous system (Berntson et al., 2008; Billman, 2011; Electrophysiology, 1996). A reduced HRV has been found to predict an adverse prognosis in the general population, and is a strong and independent predictor of mortality after an acute myocardial infarction (Algra et al., 1993; Kleiger et al., 1987; Rennie et al., 2003). The autonomic nervous system control centres within the central nervous system (the central autonomic network) (Benarroch, 1993, 2014). Several lines of evidence indicate autonomic dysfunction and central autonomic network disturbances in bipolar disorder (Levy, 2013; Outhred et al., 2014; Wang et al., 2016), and HRV has been found reduced during different affective states in patients with bipolar disorder compared with healthy control subjects in individual studies (Bassett et al., 2016; Chang et al., 2014, 2015; Cohen et al., 2003; Gruber et al., 2015; Henry et al., 2010; Lee et al., 2012; Levy, 2014; Moon et al., 2013; Quintana et al., 2016; Voggt et al., 2015). In the first focused systematic review and meta-analysis of HRV in bipolar disorder, we recently found support for a reduced HRV in patients with bipolar disorder compared with healthy control individuals although several methodological issues in individual studies limiting the evidence were identified (Faurholt-Jepsen et al., under review for publication). Recent extended case-series have suggested intra-individual changes in HRV between affective states in bipolar disorder (Lanata et al., 2015; Valenza et al., 2013, 2014a, 2014b, 2015). Thus, HRV may represent a potential objective candidate marker differentiating between patients with bipolar disorder and healthy control individuals, but it has only been sparingly investigated whether HRV could serve as an objective state marker discriminating between affective states in bipolar disorder (Alvares et al., 2015; Bassett, 2016).

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http://dx.doi.org/10.1016/j.jpsychires.2016.10.005
0022-3956/

Using repeated measurements per patient, the present longitudinal study measured the levels of heart rate and movement during free-living using a small combined heart rate and movement sensor across affective states in outpatients with bipolar disorder in naturalistic settings.

Data on activity energy expenditure and acceleration from the present study have been published elsewhere (Faurholt-Jepsen et al., 2016a), thus data in the present paper represent secondary analyses. The objective of the present paper was to investigate differences in HRV between affective states in patients with bipolar disorder.

2. Material and methods

2.1. Participants

The patients were recruited from The Copenhagen Clinic for Affective Disorders, Denmark from October 2013 to December 2014. Inclusion criteria were: bipolar disorder diagnosis according to ICD-10 using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1990). Exclusion criteria were: pregnancy; lack of Danish language skills; severe physical illness; and schizophrenia, schizotypal or delusional disorders according to the SCAN interview. The patients participated in the study for 12 weeks during their course of treatment at the clinic and received various types, combinations and doses of psychopharmacological treatment during the study period. For each patient the heart rate was monitored during different affective states. At the first day of each monitoring period the affective state and the severity of depressive and manic symptoms were assessed according to a clinical ICD-10 diagnosis in combination with clinical ratings using the Hamilton Depression Rating Scale 17-item (HDRS-17) (Hamilton, 1967) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively (see Statistical methods).

2.2. Heart rate monitoring

HRV data were collected using a combined heart rate and movement sensor (Actiheart, Cambridge Neurotechnology Ltd, Papworth, UK). The reliability and validity of the sensor compared with ECG have been described elsewhere (Brage et al., 2005). The sensor weighs 8 g and is capable of monitoring heart rate (bpm) and acceleration (m/s^2) during everyday life settings for periods of up to 11 days (Brage et al., 2007). The sensor was mounted on the thorax at the apex of the sternum and lateral to the left in a horizontal line using two ECG electrodes (Unomedical, Mona Vale, Australia) (Brage et al., 2006) during as many different affective states as possible for each patient. The sensor was set up for collecting average acceleration and heart rate as well as to the two slowest and the two fastest heart beats (of the most recent 16 beats) every 30 s over a period of at least three consecutive weekdays and nights. The sensor data were downloaded to a computer and a proxy measure of HRV was calculated as the difference between the second-shortest and the second-longest inter-beat-interval collected during each of the 30-s epoch; this measure is about a third of the standard deviation for the underlying beat duration distribution (correlation of $r = 0.85$) in 2000 simulated 16-beat datasets across the physiological range of resting HRV (Umetani et al., 1998) (Supplementary Materials). Since HRV is best reflected during resting states (Electrophysiology, 1996; Rennie et al., 2003), the measure of HRV used in the present analyses were restricted to data collected from midnight to 6 a.m. and when acceleration was zero. Few patients briefly took off the sensor during the monitoring period, and these time segments were also excluded from the analyses. Histograms of all included heart beats were reviewed and no discernable artefacts found.

2.3. Statistical methods

A priori a depressive state was defined as an ICD-10 diagnosis of bipolar disorder current episode depression combined with a HDRS-17 score $\geq$13 and a YMRS score $\leq$13; a manic or mixed state was defined as an ICD-10 diagnosis of bipolar disorder current episode hypomania, mania or mixed state combined with a YMRS score $\geq$13; a euthymic state was consequently defined as remission or partial remission combined with a HDRS-17 score <13 and a YMRS score <13. For each analysis on repeated measures of the level of HRV a two-level linear mixed effects regression model was considered. This model allows for both intra-individual variation and inter-individual variation of the dependent variables. The first level represented the repeated measurements of HRV within-individuals. The second level represented the between-individuals variation of HRV. All considered models included a patient specific random effect and all other covariates were specified as fixed effects. Firstly, models considering differences in HRV according to the patients' affective states (depressive, manic/mixed or euthymic) were conducted. Secondly, models considering differences in HRV according to the severity of depressive and manic symptoms reflected by scores on the HDRS-17 and YMRS, respectively were conducted. Models were conducted unadjusted and further in separate models adjusted for age, gender, heart rate and BMI as possible confounding factors. Model assumptions were checked visually by means of residuals and QQ plots, and logarithm transformations were done where appropriate. Results are expressed using the parameter estimate for slope by B or when based on log-transformed values by the back-transformed values of the natural logarithm of B (e^B). Thus, results are expressed as ratios in analyses on differences between groups and as fractional changes in analyses on continuous variables. The significance level of the p-values in the statistical models was set to 0.05 (two-tailed). The statistical software program STATA version 13 (StataCorp LP, College Station, TX, USA) was used for the analyses.

2.4. Ethical considerations

The study was approved by the Regional Ethics Committee in the Capital Region of Denmark (H-2-2011-056) and the Danish Data protection agency (2013-41-1710).

3. Results

HRV data were collected from 16 outpatients with bipolar disorder, and of these 14 patients provided HRV data during a euthymic state (mean HDRS-17 = 9.4 (SD 3.0) and mean YMRS = 3.8 (SD 3.3)), 11 patients during a depressive state (mean HDRS-17 = 18.3 (SD 3.2) and mean YMRS = 2.9 (SD 3.5)), and seven patients during a manic or mixed state (mean HDRS-17 = 9.2 (SD 2.9) and mean YMRS = 15.7 (SD 2.1)). Eight patients provided data during one affective state, four patients during two affective states and five patients during three affective states. Patients had a median age of 31.3 years (SD 10.1), 48.9% were of male gender and overall patients had an illness duration of 9.1 years (SD 4.8). The majority of patients were prescribed anticonvulsants (68.7%) and antipsychotics (61.3%). Further clinical characteristics are presented in Table 1.

3.1. HRV differences between affective states

In both the unadjusted models and the models adjusted for age, gender and heart rate, HRV was increased by 18% in manic states