Published in final edited form as:
J Psychiatr Res. 2017 January ; 84: 169–173. doi:10.1016/j.jpsychires.2016.10.005.

State-related differences in heart rate variability in bipolar disorder

Maria Faurholt-Jepsen[1,*], **Søren Brage**[2], **Lars Vedel Kessing**[1], and **Klaus Munkholm**[1]

[1]Psychiatric Center Copenhagen, Rigshospitalet, Denmark

[2]MRC Epidemiology Unit, Cambridge, United Kingdom

Abstract

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

Methods—A small heart rate and movement sensor weighing 8 grams collected summary data every 30 seconds over a period of minimum 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 mean of the second-shortest and the second-longest inter-beat-interval collected during each of the 30-seconds epoch. Analyses were based on over 100.000 HRV data-points.

Results—In unadjusted as well as 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.

Conclusions—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.

Keywords

Bipolar disorder; Heart rate variability; HRV; affective state; state-dependent marker

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

[*]Corresponding author: Maria Faurholt-Jepsen, Psychiatric Center Copenhagen, Rigshospitalet, Blegdamsvej 9, DK- 2100 Copenhagen, Denmark, Telephone: +45 3864 7073, maria@faurholt-jepsen.dk.

Conflicts of interest

MFJ has been a consultant for Eli Lilly and Lundbeck. LVK has within the recent three years been a consultant for Lundbeck and Astra Zeneca. SB and KM have no conflicts of interest.

Europe PMC Funders Author Manuscripts

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). Several lines of evidence indicate autonomous dysfunction in bipolar disorder (Levy, 2013; 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 (Chang et al., 2014, 2015; Clarke, 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., 2015; 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.). Few papers have suggested intra-individual changes in HRV between affective states and suggested that HRV may represent a state biomarker, but data across affective states were presented separately for each individual (Lanata et al., 2015; Valenza et al., 2013, 2014a, 2014b, 2015). An inverse association between HRV and the severity of depressive and manic symptoms have been found in some studies (Chang et al., 2015; Henry et al., 2010; Lee et al., 2012). However, no previous study has investigated differences in HRV between affective states using a study design with repeated measurements and compared data from groups of patients. Thus, HRV may represent a potential objective candidate marker differentiating between patients with bipolar disorder and healthy control individuals, but it has been sparingly investigated whether HRV could serve as an objective state marker discriminating between affective states in bipolar disorder.

Using repeated measurements, 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., 2016), 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.

Material and Methods

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).

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 only 8 grams 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 averageacceleration and heart rate as well as the two slowest and the two fastest heart beats (of the most recent 16 beats) every 30 seconds 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-seconds epochs; 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 (REFERENCE). 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 am 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.

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 ≥13 and a YMRS score ≤ 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 ≥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.

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).

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.

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 compared with depressive states (adjusted model: *e^B=1.18, 95% CI: 1.15-1.20, p<0.001*). In both the unadjusted models and the models adjusted for age, gender and heart rate, HRV was increased by 17% in manic states compared with euthymic states (adjusted model: *e^B=1.17, 95% CI: 1.15-1.19, p<0.001*). There was no difference between depressive states and euthymic states (e^B=0.98, 95% CI: 0.96-1.00, p=0.12). Including BMI as a covariate did not alter these estimates and was therefore not included in the final adjusted analyses presented. Further analyses on differences in HRV between affective states are presented in Table 2.

Exploratory analyses including only individual patients presenting with all three affective states (mania, depression, euthymia) during the follow-up period showed that HRV was reduced during a depressive state compared with a manic as well as a euthymic state (p<0.001).

HRV alterations in relation to the severity of depressive and manic symptoms

In both the unadjusted models and the models adjusted for age, gender and heart rate, there was a negative correlation between HRV and the severity of depressive symptoms measured using the HDRS-17 (adjusted model: e^B *=0.99, 95% CI: 0.99-0.99, p<0.001*), meaning that for every increase of ten points on the HDRS-17 HRV was reduced by 10%. Further, in the unadjusted models and the models adjusted for age, gender and heart rate, there was a positive correlation between HRV and YMRS score (adjusted model: e^B*=1.02, 95% CI: 1.02-1.02, p<0.001*). Considering BMI as a covariate did not alter the estimates, and was therefore not included in the final adjusted analyses presented.

Discussion

HRV has been proposed to be reduced during different affective states in patients with bipolar disorder compared with healthy control individuals, but the extent of state-related alterations in HRV has been sparingly investigated. This study investigated differences in HRV between affective states in a group of patients with bipolar disorder, and found that HRV was increased during manic states compared with depressive and euthymic states using a longitudinal study design with repeated measurements per patient and employing analyses comparing HRV between groups of patients during different affective states. In line with findings from a previous study (Chang et al., 2015), we found an inverse association between HRV and the severity of depressive symptoms and further a positive association between HRV and the severity of manic symptoms. A recent meta-analysis by the authors (Faurholt-Jepsen et al.) suggested that HRV may represent an objective diagnostic candidate marker differentiating between patient with bipolar disorder and healthy control individuals. Findings from the present study support findings from previous papers (Lanata et al., 2015; Valenza et al., 2013, 2014a, 2014b, 2015) suggesting that HRV may also be altered during different affective states in a state-dependent manner and that it could potentially represent a state marker in bipolar disorder.

Limitations

Several limitations to the present study should be mentioned. Firstly, a small number of patients were included and interpretation of the findings should be made with caution. However, the individual patients were assessed several times during follow-up and included at the beginning of their course of treatment presenting with rather severe levels of affective symptoms during follow-up, thus allowing analysis of within-patient changes in HRV. Secondly, while patients received various types, doses and combinations of psychopharmacological medication during the study, medication was not included as a covariate in the analyses due to the many various possible combinations of medications. Since medication may influence HRV, this could have influenced the results. Along this line, future studies including more patients during different affective states should consider adjusting the analyses for other possible confounding factors such as smoking, alcohol consumption and coffee intake. Thirdly, data on HRV were collected over prolonged time-periods sampled during 30-seconds epochs and thus not representing beat-by-beat data. However, sensor data were collected consecutively over a minimum of three days, using a sensor that has been found reliable and valid for the measurement of movement and heart

rate compared with ECG (Brage et al., 2005), and more than 100.000 data-points were included in the analyses. Further, the proxy measure of HRV was calculated as the mean difference between the second-shortest and the second-longest inter-beat-interval collected during the 30-seconds epoch, thus potentially more prone to movement artefacts. However, we used the simultaneous movement (accelerometer) registration and limited data collected during nighttime to only include data collected during rest (where acceleration was zero). Potential diurnal variation in HRV is thus not reflected in the present study. Fourthly, depressive and manic states were defined as a combination of ICD-10 and pre-defined cut-off scores on the HDRS-17 and YMRS. The cut-off scores were chosen to achieve a high specificity of a current depressive and manic state, and consequently a euthymic state included patients in full and partial remission. Lastly, the study lack healthy control individuals and comparison of HRV between patients and healthy control individuals cannot be made from the results in the present study.

Conclusions and future perspectives

This study on differences in HRV between affective states in bipolar disorder suggests that HRV may be altered in a state-dependent manner and thus could represent a candidate state marker. Future longitudinal studies investigating differences in HRV between affective states should include a larger sample size of patients with bipolar disorder experiencing different affective states. Investigating HRV in healthy relatives at risk of bipolar disorder could provide important information as to whether alterations in HRV are a cause or consequence of bipolar disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Source of Funding and acknowledgement

No funding was provided for the present study. We wish to thank the patients for participating in the study.

References

Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. Contribution of the 24 hour electrocardiogram to the prediction of sudden coronary death. Br Heart J. 1993; 70:421–427. [PubMed: 8260272]

Benarroch EE. Central Autonomic NetworkAutonomic Neurology. Benarroch E, editorOxford University Press; 2014. 3–14.

Berntson GG, Norman GJ, Hawkley LC, Cacioppo JT. Cardiac Autonomic Balance vs. Cardiac Regulatory Capacity. Psychophysiology. 2008; 45:643–652. [PubMed: 18282204]

Billman GE. Heart Rate Variability – A Historical Perspective. Front Physiol. 2011; 2

Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. Eur J Clin Nutr. 2005; 59:561–570. [PubMed: 15714212]

Brage S, Brage N, Ekelund U, Luan J, Franks P, Froberg K, Wareham N. Effect of combined movement and heart rate monitor placement on physical activity estimates during treadmill locomotion and free-living. Eur J Appl Physiol. 2006; 96:517–524. [PubMed: 16344938]

Brage S, Ekelund U, Brage N, Hennings MA, Froberg K, Franks PW, Wareham NJ. Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity. J Appl Physiol Bethesda Md 1985. 2007; 103:682–692.

Europe PMC Funders Author Manuscripts

Chang H-A, Chang C-C, Tzeng N-S, Kuo TBJ, Lu R-B, Huang S-Y. Heart rate variability in unmedicated patients with bipolar disorder in the manic phase. Psychiatry Clin Neurosci. 2014; 68:674–682. [PubMed: 24612182]

Chang H-A, Chang C-C, Kuo TBJ, Huang S-Y. Distinguishing bipolar II depression from unipolar major depressive disorder: Differences in heart rate variability. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry. 2015:1–10.

Clarke R. A study of heart rate variability in bipolar affective disorder I and recurrent major depressive disorder, during remission and over the bedtime period. Australian and New Zealand Journal of Psychiatry. 2015:1–122. [PubMed: 25870440]

Cohen H, Kaplan Z, Kotler M, Mittelman I, Osher Y, Bersudsky Y. Impaired heart rate variability in euthymic bipolar patients. Bipolar Disord. 2003; 5:138–143. [PubMed: 12680904]

Electrophysiology, T.F. of the E.S. of C. the N.A.S. of P. Heart Rate Variability Standards of Measurement, Physiological Interpretation, and Clinical Use. Circulation. 1996; 93:1043–1065. [PubMed: 8598068]

Faurholt-Jepsen M, Brage S, Vinberg M, Kessing LV. State-related differences in the level of psychomotor activity in patients with bipolar disorder – Continuous heart rate and movement monitoring. Psychiatry Res. 2016; 237:166–174. [PubMed: 26832835]

Faurholt-Jepsen M, Brage S, Kessing LV, Munkholm K. Heart rate variability in bipolar disorder: a systematic review and meta-analysis. 2016 Submitt. Publ.

Gruber J, Mennin DS, Fields A, Purcell A, Murray G. Heart rate variability as a potential indicator of positive valence system disturbance: A proof of concept investigation. Int J Psychophysiol. 2015 Nov; 2015(2 Pt 2):240–8.

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967; 6:278–296. [PubMed: 6080235]

Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W. Heart rate variability in bipolar mania and schizophrenia. J Psychiatr Res. 2010; 44:168–176. [PubMed: 19700172]

Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol. 1987; 59:256–262. [PubMed: 3812275]

Lanata A, Valenza G, Nardelli M, Gentili C, Scilingo EP. Complexity Index From a Personalized Wearable Monitoring System for Assessing Remission in Mental Health. IEEE J Biomed Health Inform. 2015; 19:132–139. [PubMed: 25291802]

Lee J-S, Kim B, Hong Y, Joo YH. Heart rate variability in the subsyndromal depressive phase of bipolar disorder. Psychiatry Clin Neurosci. 2012; 66:361–366. [PubMed: 22624742]

Levy B. Autonomic nervous system arousal and cognitive functioning in bipolar disorder. Bipolar Disord. 2013; 15:70–79. [PubMed: 23237079]

Levy B. Illness severity, trait anxiety, cognitive impairment and heart rate variability in bipolar disorder. Psychiatry Res. 2014; 220:890–895. [PubMed: 25219620]

Lown B, Verrier RL. Neural Activity and Ventricular Fibrillation. N Engl J Med. 1976; 294:1165–1170. [PubMed: 57572]

Moon E, Lee S-H, Kim D-H, Hwang B. Comparative Study of Heart Rate Variability in Patients with Schizophrenia, Bipolar Disorder, Post-traumatic Stress Disorder, or Major Depressive Disorder. Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol. 2013; 11:137–143.

Quintana DS, Westlye LT, Kaufmann T, Rustan ØG, Brandt CL, Haatveit B, Steen NE, Andreassen OA. Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls. Acta Psychiatr Scand. 2015 n/a-n/a.

Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of Moderate and Vigorous Physical Activity on Heart Rate Variability in a British Study of Civil Servants. Am J Epidemiol. 2003; 158:135–143. [PubMed: 12851226]

Stegle O, Fallert SV, MacKay DJC, Brage S. Gaussian process robust regression for noisy heart rate data. IEEE Trans Biomed Eng. 2008; 55:2143–2151. [PubMed: 18713683]

Valenza G, Gentili C, Lanatà A, Scilingo EP. Mood recognition in bipolar patients through the PSYCHE platform: preliminary evaluations and perspectives. Artif Intell Med. 2013; 57:49–58. [PubMed: 23332576]

Valenza G, Nardelli M, Bertschy G, Lanata A, Barbieri R, Scilingo EP. Maximal-radius multiscale entropy of cardiovascular variability: A promising biomarker of pathological mood states in bipolar disorders. 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2014a. 6663–6666.

Valenza G, Nardelli M, Lanatà A, Gentili C, Bertschy G, Paradiso R, Scilingo EP. Wearable monitoring for mood recognition in bipolar disorder based on history-dependent long-term heart rate variability analysis. IEEE J Biomed Health Inform. 2014b; 18:1625–1635. [PubMed: 24240031]

Valenza G, Citi L, Gentili C, Lanata A, Scilingo EP, Barbieri R. Characterization of depressive States in bipolar patients using wearable textile technology and instantaneous heart rate variability assessment. IEEE J Biomed Health Inform. 2015; 19:263–274. [PubMed: 25561449]

Voggt A, Berger M, Obermeier M, Löw A, Seemueller F, Riedel M, Moeller HJ, Zimmermann R, Kirchberg F, Von Schacky C, et al. Heart rate variability and Omega-3 Index in euthymic patients with bipolar disorders. Eur Psychiatry J Assoc Eur Psychiatr. 2015; 30:228–232.

Wang X, Cao P, Xu L, Cai L, Zhang L, Feng R, Jiang H, Chen W. Sympathetic skin response and R–R interval variation in the assessment of clinical remission of bipolar disorder. Psychiatry Res. 2016; 237:279–281. [PubMed: 26803363]

Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 1990; 47:589–593. [PubMed: 2190539]

Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978; 133:429–435. [PubMed: 728692]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 1
Background characteristics of patients with bipolar disorder, n = 16.

Age, years	31.3 (10.1)
Gender, % male (n)	48.9 (8)
BMI, kg/m^2	25.6 (5.3)
Depressive episodes, number	4 [2–15]
Hypomanic/Manic episodes, number	4 [3–6]
Illness duration, years	9.1 (4.8)
Hospitalizations, number	1 [0–2]
Psychopharmacological medication	
Anticonvulsants, % (n)	68.7 (11)
Antipsychotics, % (n)	61.3 (10)
Lithium, % (n)	22.8 (4)
Antidepressants, % (n)	12.7 (2)
HDRS-17, total score	
Euthymic state	9.4 (3.0)
Depressive state	18.3 (3.2)
Manic state	9.2 (2.9)
YMRS, total score	
Euthymic state	3.8 (3.3)
Depressive state	2.9 (3.5)
Manic state	15.7 (2.1)

Data are expressed as mean (SD), median [IQR] or proportions (n) unless stated otherwise. BMI: Body Mass Index; HDRS-17: Hamilton Depression Rating Scale 17-items; YMRS: Young Mania Rating Scale; Euthymic state: HDRS-17 < 13 and YMRS<13; Depressive state: HDRS-17 ≥ 13 and YMRS≤13; Manic state: YMRS≥13.

Europe PMC Funders Author Manuscripts

Table 2

Differences in Heart Rate Variability (HRV) between affective states in bipolar disorder, N = 31.

	Unadjusted analysis			Model 1			Model 2			Model 3		
	e^B	95% CI	P	e^B	95% CI	P	e^B	95% CI	P	e^B	95% CI	P
HRV												
Mania vs. Depression	1.19	1.17–1.20	<0.001	1.20	1.17–1.22	<0.001	1.20	1.18–1.23	<0.001	1.18	1.16–1.20	<0.001
Mania vs. Euthymia	1.17	1.15–1.19	<0.001	1.19	1.16–1.21	<0.001	1.19	1.16–1.21	<0.001	1.19	1.16–1.21	<0.001
Depression vs. Euthymia	0.98	0.96–1.00	0.15	0.98	0.96–1.00	0.12	0.98	0.96–1.00	0.12	0.98	0.96–1.00	0.12

Model 1: Analyses adjusted for age; Model 2: Analyses adjusted for age and gender; Model 3: Analyses adjusted for age, gender and heart rate (bpm). Considering BMI as a covariate did not alter the HRV estimates and was excluded from the final adjusted analyses. e^B: Logarithm transformed parameter estimates are expressed as ratios between groups. 95% CI: 95% confidence intervals.