Running Title: REDUCED HRV IN SCHIZOPHRENIA AND BIPOLAR DISORDERS

Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls

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Abstract

Objective: Despite current diagnostic systems distinguishing schizophrenia (SZ) and bipolar disorder (BD) as separate diseases, emerging evidence suggests they share a number of clinical and epidemiological features, such as increased cardiovascular disease (CVD) risk. It is not well understood if poor cardiac autonomic nervous system regulation, which can be indexed non-invasively by the calculation of heart rate variability (HRV), contributes to these common CVD risk factors in both diseases.

Method: We calculated HRV in 47 patients with SZ, 33 patients with BD, and 212 healthy controls. Measures of symptom severity were also collected from the patient groups.

Results: HRV was significantly reduced in both these disorders in comparison to the healthy participants, however, there were no HRV differences between disorders. Importantly, these reductions were independent of the medication, age, or BMI effects. There was also preliminary evidence that patients with reduced HRV had increased overall and negative psychosis symptom severity regardless of SZ or BD diagnosis.

Conclusion: We suggest that HRV may provide a possible biomarker of CVD risk and symptom severity in severe mental illness. Thus, our results highlight the importance of cardiometabolic screening across schizophrenia and bipolar spectrum disorders.

Keywords: heart rate variability, schizophrenia, bipolar disorder, autonomic nervous system

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Significant outcomes:

- Heart rate variability (HRV), an index of cardiac autonomic system regulation, is reduced in patients with schizophrenia (SZ) and bipolar disorder (BD) compared to healthy controls.
- The SZ and BD groups demonstrate no differences in HRV, suggesting a similar cardiac autonomic nervous system profile.

Limitations:

- Lifestyle factors such as diet and physical activity may have played a role in the reported differences in HRV between the clinical and healthy groups.
- A relatively small sample size limited the ability to assess differences in HRV between SZ and BD subtypes.

Introduction

Schizophrenia (SZ) and bipolar disorders (BD) are among the most severe psychiatric disorders, each affecting ~ 1% of the population globally (1, 2). Despite current diagnostic systems (ICD-10 and DSM-5) distinguishing SZ and BD as separate disorders, emerging evidence suggests they share a number of features such as age of onset, gender distribution (3), neurocognitive dysfunction (4, 5), and medication response (6). Moreover, there is also a high genetic cross-heritability between these two disorders (7, 8) and familial co-aggregation (9). Together, the observation of these similarities have contributed to the proposal that SZ and BD are better conceptualised lying on a continuum instead of being identified as separate entities (10) (but see 11).

While the focus of the comparisons between SZ and BD has centred on these clinical, genetic, and epidemiological parallels, less attention has been paid to similarities in physical illness comorbidities. Remarkably, individuals with severe mental disorders die up to eighteen years earlier on average than the general population (12, 13). This reduced life expectancy has largely been attributed to cardiovascular diseases (CVD) (14-16), with these patients being two times more likely to exhibit CVD risk factors than the general population (17). BD and SZ both demonstrate increased levels of CVD risk factors such as rates of smoking, obesity, and metabolic syndrome (18-20)..However, there may also be some underlying common mechanisms between severe mental disorders and CVD risk factors, as recent evidence indicates genetic overlap (22). In addition to these risk factors, the regulation of efferent autonomic nervous system activity to the heart plays an important role in cardiovascular functioning and is related to cardiovascular risk. Importantly, decreased parasympathetic nervous system input to the

sinoatrial node lowers the threshold for ventricular tachycardia and may contribute to the increased risk of sudden cardiac death in severe mental disorders (23). Cardiac autonomic outflow can be non-invasively approximated via the calculation of heart rate variability (HRV) (24), which is the assessment of beat-to-beat variability of the heart period during normal sinus rhythm. Reduced HRV has been associated with an increased risk of cardiac events in both patients with a history of myocardial infarction (25, 26) and healthy individuals (27).

A growing body of evidence indicates that SZ is associated with reduced HRV (e.g., 28, 29), which may be exacerbated by antipsychotic medications (30). However, there is a dearth of research on BD in comparison. Only a handful of studies with mixed results have investigated HRV in BD, with research yet to compare BD with a representative community sample. Furthermore, the association between psychotic symptom severity and HRV is unclear. Some findings suggest that more severe psychosis is associated with reduced HRV (28) whereas others reported no distinction (29). However, these studies associate symptoms to group differences in underlying physiology (i.e., 'top-down'). To the best of our knowledge, only one other study has attempted to use the alternative 'bottom-up' approach, to investigate the clustering of HRV measures (31), with the authors concluding that specific associations between different HRV indices distinguished patients with schizophrenia and controls. To date, no study has sought to examine whether differences in underlying autonomic cardiac control may act as a biological marker that may differentiate patients with severe mental disorders according to psychosis symptom severity. Such investigation would provide further evidence for an association between parasympathetic modulation and disorder severity within psychosis spectrum disorders.

Aims of the study

Together, the aim of this study was to identify differences in HRV between patients with SZ, BD, and a healthy community sample. In light of the continuum model and observed similarities in CVD risk factors, we hypothesised that HRV would be reduced in both SZ and BD spectrum disorders in comparison to healthy controls. Relatedly, in line with our hypothesis that HRV may reflect clinically relevant processes, we also hypothesised that patients with reduced HRV would demonstrate increased psychosis symptom severity, independent of SZ/BD diagnosis.

Materials and Methods

Participants

Patients were recruited from psychiatric units at four major hospitals in the Oslo area. Healthy participants (n = 212; 56.6% males) were drawn from a randomly selected community sample using government statistical records (http://ssb.no). Patients had a DSM-IV diagnosis of a schizophrenia spectrum disorder (total n = 47; 72.5% males; schizophrenia n = 27; schizoaffective n = 4; schizophreniform disorder n = 1; other psychosis = 15) or a bipolar disorder spectrum disorder (total n = 33; 45% males; bipolar I disorder n = 22; bipolar II disorder n = 9; or bipolar disorder NOS n = 2). Available data from 67 patients revealed that only 3% were inpatients (n = 1 with schizophrenia, n = 1 with bipolar I disorder) with the remainder outpatients. Data on nicotine consumption was also collected from 49 patients indicating that 55% of the sample smoked daily.

The present study is a part of the Thematically Organised Psychosis (TOP) study and has received approval from the Regional Committee for Medical Research Ethics. After receiving information regarding the study, participants provided written informed consent. All patients underwent a structured clinical Interview for Axis I disorders (SCID) performed by trained

clinicians, a comprehensive physical examination from a physician, and completed the alcohol use disorders identification test (AUDIT) (32). Additionally, they completed the Positive and Negative Syndrome Scale (PANSS) to index current positive and negative disorder severity (33). Patients with a diagnosis of CVD (n = 5), diabetes (n = 1), or thyroid dysfunction (n = 1) were excluded from the analysis. In order to participate as a healthy control, participants or their first-degree relatives must not have had a history of any severe psychiatric disorders (e.g., schizophrenia spectrum disorders, bipolar spectrum disorders, autism spectrum disorders) based on an interview assessing severe mental illness, no self-reported chronic physical illness, and screened negative for any ongoing psychiatric disorders using the Primary Care Evaluation of Mental Disorders (34).

Physiology data collection and analysis

Interbeat intervals (IBIs) were measured from 5 minutes of pulse oximetry data collected during magnetic resonance imaging (MRI) from a photoplethysmograph placed on the right index finger (50Hz). Participants were instructed to lie still with their eyes open during the scan. The first two minutes of data were discarded for all participants to account for any differences in habituation to the imaging procedure. However, the participants had already been in the scanner for the duration of an initial localizer and structural MRI acquisition (approx. 10 min) collected in the same scanning session and thus had some time to habituate to the testing environment.

Pulse oximetry data offers a very accurate approximation of interbeat intervals (35-37). As per recommendations (24), raw IBI data were upsampled using spline interpolation to 1000Hz to refine the R-wave fiducial point for HRV calculation in ARTiiFACT (38). Artifacts were detected using an algorithm by Berntson and colleagues (39). Any detected artifacts were

manually checked, with the rater blind to participant group. Estimated IBIs using cubic spline interpolation replaced detected artifacts.

Absolute high frequency (HF; 0.15-0.4 Hz) power, which indexes cardiovagal activity (40, 41), was calculated to assess HRV using the Fast Fourier Transformation (FFT). The FFT applied a Hanning window of 256-s width with an interpolation rate of 4Hz (spline interpolation) and an overlap of 50% to the resampled and detrended data (method of least squares). Absolute HF values were log transformed to better approximate a normal distribution and fulfil assumptions for parametric statistical analysis. Additionally, respiratory frequency was collected via a strain gauge placed around the chest. Data was imported into the Sigview software package (http://sigview.com) to calculate respiratory frequency, with 23% of respiratory data discarded due to artefacts (e.g., lost signal).

Statistical analysis

All statistical tests were conducted using IBM SPSS Statistics version 22 (IBM Inc.) and the R statistical software package (42). One-way ANOVAs were performed to test for group (SZ, BD, HC) differences in age, respiratory frequency peak and body mass index (BMI). Partial eta squared (η_p^2) was calculated to determine effect sizes. Independent-samples T tests were used to examine differences in HRV according to smoking status (daily smoker vs. non daily smoker). Chi-squared tests for independence were performed to assess differences in the proportions of males and females in each group along with differences in proportions of SZ and BD patients treated with anti-cholinergic medications. A two-way ANOVA was conducted to investigate the impact of diagnosis (HC, SZ, BD), gender (male, female), and their potential interaction on absolute HF in light of documented gender differences in HRV (43). Post hoc tests of the two-

way ANOVA with Bonferroni adjustment were performed for any statistically significant main effects to assess if there were any differences between diagnosis groups and/or gender.

Due to the potential role of the prevailing heart rate (HR) on HRV (44, 45) this analysis was repeated using the absolute HF measure adjusted for HR (HF_{hradj}; division of the absolute HF signal by average R-R interval) and average HR. A Pearson correlation coefficient was also calculated to assess the relationship between absolute HF HRV and HF_{hradj}. For any non-significant results, Bayes factors were used to determine if these data indeed support a null hypothesis over the alternative theory (46). Bayes factors (*B*) provide a measure of the relative strength of evidence for the null and alternative hypotheses (47). Unlike null hypothesis significance testing, Bayes factors provide evidence for a specified null hypothesis against a specified alternative hypothesis. A *B* value less than 1/3 provides substantial evidence for the null hypothesis, over 3 provides strong evidence for the alternative hypothesis, and between 1/3 and 3 provides no strong support either way (46). For the comparison between clinical groups, the theory was modelled with a uniform distribution between 0 and 1 unit (log transformed absolute HF power). The upper bound was chosen as this was the unit change observed between the control and SZ group (.68), rounded up, as recommended by Dienes (46). The Bayes factor for the difference between controls and both SZ and BD was modelled with a uniform distribution between 0 and 2, with this upper bound chosen as it was the upper limit of the 95% CI for the difference between the control and SZ group (1.14), rounded up. The Bayes factors for the difference in symptom severity were modelled with a uniform distribution between 0 and 19 units for total difference score and 0 and 7 for the negative scale.

If, as expected, the clinical groups demonstrated no differences in absolute HF power, the groups were collapsed into a single severe mental disorder group for further analysis. A

hierarchical multiple regression was conducted to examine the associations between other covariates and absolute HF power and to assess to which degree these associations influenced any main effects of diagnosis on absolute HF. Age, BMI, and medication with a known anticholinergic effect (i.e., participants taking antipsychotics with a known anti-cholinergic effect vs. not taking antipsychotics with anti-cholinergic properties, which included all healthy participants) were entered in the first step as potential absolute HF covariates. The antipsychotics known to have anticholinergic effects included quetiapine, olanzapine, and clozapine (48). Group membership (controls vs. severe mental disorders) was entered in the second step. Assumptions of multicollinearity and influential outliers were tested via calculation of the variance inflation factor (49) and Cook's Distance (50), respectively.

Lastly, a hierarchical cluster analysis using Ward's method of minimum variance (51) with a squared Euclidean distance was performed to categorize severe mental disorder groups into high and low absolute HF HRV clusters (i.e., groups) and to compare disorder severity. Agglomeration coefficients generated by the cluster analysis, which reveal the similarity between clusters, were then compared to reveal a demarcation point between clusters, confirmed by visual inspection of the dendrogram. The resulting cluster number (i.e., low or high HRV) was then used as a between-subjects variable for between-groups independent-samples t-tests and chi-squared analyses. Unless otherwise indicated, alpha was set at $p < .05$ for all null hypothesis significance tests. Partial eta squared (η_p^2) and Cohen's *d* were calculated to determine effect sizes for ANOVAs and *t*-tests, respectively.

Results

Sample characteristics

Demographics, relevant clinical variables, and absolute HF for each group are presented in Table 1. There was no significant main effect of diagnosis on age, BMI, or respiratory peak. AUDIT scores and cigarette consumption were also not significantly different between the two patient groups. However, there was a significant difference in the proportion of males and females in each group [χ^2 (2, n = 292) = 6.23, p = .044, d = .02]. Follow-up analyses (Bonferroni adjusted threshold set at p = .017) revealed that the proportion of males was higher in the SZ group compared to the BD group [χ^2 (1, n = 80) = 5.9, p = .015, d = .02]. There was also a significant difference in the proportion of SZ (45.1%) and BD (18.2%) patients that were medicated with anti-cholinergic medications [χ^2 (1, n = 80) = 6.7, p = .01, d = .07].

Heart rate variability

Table 1 summarizes absolute HF power, HR, and respiratory peak per group. A two-way ANOVA revealed a main effect of diagnosis on absolute HF power [F(2,286) = 8.51, p < .001; η^2_p = .06] and gender [F(1,286) = 3.97, p = .047; η^2_p = .014], but no significant interaction between group and gender [F(2,286) = 1.75, p = .18; η^2_p = .012]. Post hoc analyses with Bonferroni corrections revealed the healthy control group had significantly higher absolute HF power than SZ (p = .001) and BD (p = .03). There was no difference in absolute HF power between the SZ and BD groups (p = 1). A two-way ANOVA revealed a main effect of diagnosis on HF-HRV$_{hradj}$ [F(2,286) = 12.67, p < .001; η^2_p = .081]. There was no main effect of gender [F(1,286) = 2.26, p = .13; η^2_p = .008], or significant interaction between group and gender [F(2,286) = .91, p = .4; η^2_p = .006]. Post hoc analyses with Bonferroni corrections revealed the healthy control group had significantly higher HF-HRV$_{hr\text{-}adj}$ than SZ (p < .001) and BD (p = .016). There was no difference in HF-HRV$_{adj}$ between the clinical groups (p = .75). Given the

similarities between absolute HF power and HF-$HRV_{hr\text{-}adj}$, and their high correlation [r = .86, 95 % CI (.83, .89), n = 292, $p < .001$] remaining analyses were completed with absolute HF power for consistency with prior research. A two-way ANOVA also revealed a main effect of diagnosis on average HR [$F(2,286) = 18.66$, $p < .001$; $\eta^2_p = .12$]. There was no main effect of gender [$F(1,286) = .76$, $p = .39$; $\eta^2_p = .003$], or significant interaction between group and gender [$F(2,286) = .73$, $p = .48$; $\eta^2_p = .01$]. Post hoc analyses with Bonferroni corrections revealed significantly lower average HR in HC compared to SZ ($p < .001$) and BD ($p = .01$). There was no difference in HR between the clinical groups ($p = .16$). HRV and HR displayed a significant negative relationship in healthy controls [$r = -.41$, 95 % CI (-.51, -.29), n = 212, $p < .001$], SZ [$r = -.73$, 95 % CI (-.84, -.56), n = 47, $p < .001$], and BD groups [$r = -.75$, 95 % CI (-.87, -.54), n = 33, $p < .001$]. Finally, there was no difference in absolute HF power between patients that smoked daily (mean = 5.98, SD = 1.48) compared to patients that did not [mean = 5.92, SD = 1.24; $t(40) = .14$, $p = .89$; Cohen's $d = .04$].

Bayesian analysis

Bayes factors were used to determine if these data indeed support a null hypothesis over the alternative theory for the non-significant difference in absolute HF power between the clinical groups (46). The Bayes factor was .21, which is indicative of strong evidence for the null hypothesis (i.e., no difference in absolute HF power between the SZ and BD group). The Bayes factors were 133.51 for the SZ and control comparison and 7.19 for the BD and control comparison, which provides strong evidence for the alternative hypotheses that both clinical groups have decreased absolute HF power in comparison to the control group.

The prediction of HRV via severe mental disorder diagnosis

As the Bayes factor and ANOVA results were consistent with no difference in HRV between the two clinical groups, they were collapsed into a severe mental disorder group for multiple regression. Assumptions of multicollinearity and outliers were not violated given that variance inflation factors of all variables were < 10 (49) and no values for Cook's Distance were above 1 (50). Within this collapsed clinical group, age, BMI and anti-cholinergic psychotropic medications predicted a total of 6% of the variance (adjusted R^2 = 4%) in absolute HF power, $F(3, 222) = 4.28$, $p = .006$. The addition of group membership added an additional 4% of the variance in absolute HF power for the full model fit, $F(1,221) = 10.21$, $p = .002$. A summary of the regression models is presented in Table 2.

Given the strong effect of age on absolute HF power in these models, Pearson correlation coefficients between age and absolute HF power were calculated for each group (Fig. 1). There was a significant negative correlation between age and absolute HF in the healthy controls [r = -.28, 95 % CI (-.4, -.15), n = 212, $p < .001$], a negative association on the border of significance in the BD group [r = -.34, 95 % CI (-.61, .01), n = 33, $p = .052$] and no significant relationship in the SZ group [r = .01, 95 % CI (-.28, .3), n = 47, $p = .96$]. Thus, an additional multiple regression was performed with the addition of a group x age interaction term. This did not reveal any significant differences in the age slopes between groups in the full model (β = -.33, $p = .31$) nor remove the significant main effect of diagnosis (R^2 change = .1, $p = .04$), which suggests that difference of relationship strength of age and absolute HF between groups did not influence the overall conclusion of the original models.

HRV and disorder severity

Hierarchical cluster analysis including patients only identified low (mean = 4.21, SD = .69, n = 18) and high (mean HRV = 6.51, SD = .86, n = 62) HRV groups. PANSS data was available from 14 participants in the low HRV group and 47 participants in the high HRV group. Independent samples t-tests revealed differences on the border of significance between the high and low HRV groups on overall symptom severity [t(59) = 1.7, p = .1; Cohen's d = .51] and negative symptoms severity [t(59) = 1.7, p = .1; Cohen's d = .51]. The Bayes factors were 2.5 for both comparisons, providing anecdotal evidence supporting that the low HRV group had increased overall and negative symptom severity. In other words, the data are almost 3 times more likely under the alternative hypothesis than the null for both comparisons. There were no differences on positive [t(15.35) = 1.1, p = .3; Cohen's d = .46] or general [t(14.54) = .94, p = .37; Cohen's d = .43] psychosis symptoms. Furthermore, there was no differences in the proportions of SZ and BD patients in each HRV group [χ^2(1, n = 80) = .05, p = .82; Cohen's d = .01], gender [χ^2(1, n = 80) = 1.18, p = .28; d = .03], or patients taking antipsychotics with anti-cholinergic properties [χ^2(1, n = 80) = .28, p = .87; Cohen's d = .02]. Additionally, there was no difference in age [t(78) = .26, p = .72; Cohen's d = .01] or BMI [t(58) = .3, p = .77; Cohen's d = 01] between these two groups.

Discussion

As hypothesised, this study demonstrated that SZ and BD are associated with reduced HRV in comparison to controls. Additionally the data indicated no difference in HRV between SZ and BD. Importantly, the main effects of diagnostic group did not appear to be influenced by gender, age, heart rate, or antipsychotics with anti-cholinergic properties. Consistent with observed similarities in other CVD risk factors (19), the present data is indicative of a similar

compromised cardiac autonomic profile in SZ and BD in comparison to controls. These results highlight the important need for cardiometabolic screening in severe mental disorders to reduce subsequent morbidity and mortality. Despite the current knowledge, many of these patients are not screened for cardiometabolic risk factors, with up to a third not monitored for blood pressure and triglycerides, and more than half not monitored for weight, cholesterol, and glucose levels (52, 53).

Our secondary analysis suggested that patients with reduced HRV had increased overall and negative psychosis symptom severity regardless of SZ or BD diagnosis, however, these differences were on the border of significance. Importantly, the high and low HRV groups were not significantly different in respect to age and BMI. Although this difference did not achieve statistical significance the corresponding Bayes factor indicated anecdotal evidence in favour of the alternative hypothesis. HRV offers a non-invasive index of autonomic outflow (24), which has been reported to modulate the perception of emotional cues (56-58) and social functioning (59-61). Our preliminary data is consistent with these prior findings as negative symptoms include poor rapport and diminished emotional expression. HRV may show promise as a potential biomarker to identify individuals with high negative symptom severity, which would be of substantial clinical importance given that negative symptoms predict the transition to psychosis in at-risk individuals (62, 63).

A number of neural structures have been implicated in the coordination of cardiac autonomic function including the medial prefrontal cortex and the amygdala (64). In fact, reduced activity in amygdala-prefrontal circuitry has been implicated in SZ (65) and BD (66) , which may contribute to increased CVD risk (67) and impaired social cognition (68-70). Much like severe mental illness, HRV is also highly heritable (71-73). While no specific polymorphism

has yet been identified that is associated with HRV, other CVD risk factors (e.g., lipid levels) and SZ have been reported to share a common genetic basis (22), suggesting that other CVD risk factors may also share genetic origins. Future research directly investigating the neural circuitry and genetics underlying autonomic cardiac control in severe mental disorders will provide a better understanding of why CVD risk is increased in these disorders.

There are some limitations of the study that deserve comment. Firstly, lifestyle factors such as diet and physical activity may have played a role in observed HRV differences between the clinical and healthy groups. However, there were no differences between groups in BMI, which can be used as a broad proxy for metabolic issues related to lifestyle factors. Secondly, the present study did not have the sample size required to assess potential HRV differences between SZ and BD subtypes. Thus, we were unable to identify if a particular severe mental disorder subtype exerted a unique influence on the results. Third, data relating to aggression were not available, which may have also influenced patient group reductions given the relationship between aggression and both HRV (74) and cardiovascular diseases (75). Relatedly, data relating to smoking habits were not available for control participants and only some of the patients, which may have also influenced patient group reductions in HRV. However, the available data indicated that smoking did not have an appreciable impact on HRV in patients and that the levels of smoking were comparable between the SZ and BD groups. Moreover, prior research has demonstrated HRV reductions in severe mental illness compared to healthy controls even after accounting for smoking habits (74, 76). Finally, although participants had some time to habituate to the testing environment, the collection of IBI intervals during MRI data collection may have been stressful for some participants, but not others. Respiration rate, which can be used as a proxy for state anxiety, was not different between diagnostic groups. Although there was a

difference in average HR between the HC group and the two clinical groups it is problematic to disentangle state and trait HR effects given evidence that these groups have an increased resting average HR compared to a healthy individuals (28).

In summary, our data suggests that both SZ and BD are characterised by reduced HRV compared to healthy controls, and indicate similar levels of HRV across bipolar and schizophrenia spectrum disorders. These findings provide further physiological evidence for shared features between SZ and BD that may contribute to the increased risk of cardiovascular disease in severe mental illness. Larger studies are needed to test if this finding is consistent across SZ and BD subtypes and if reduced HRV predicts future CVD in patients with severe mental illness.

Declarations of interest

OAA received speaker's honorarium from GSK, Lundbeck, and Otsuka. The other authors have nothing to declare.

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Figure 1 caption.

The relationship between HRV and age (years) in healthy controls (HC), patients with schizophrenia spectrum disorder (SZ), and patients with bipolar spectrum disorders (BD). Black line of best fit represents all groups combined. HF HRV = Absolute high frequency heart rate variability, log transformed.

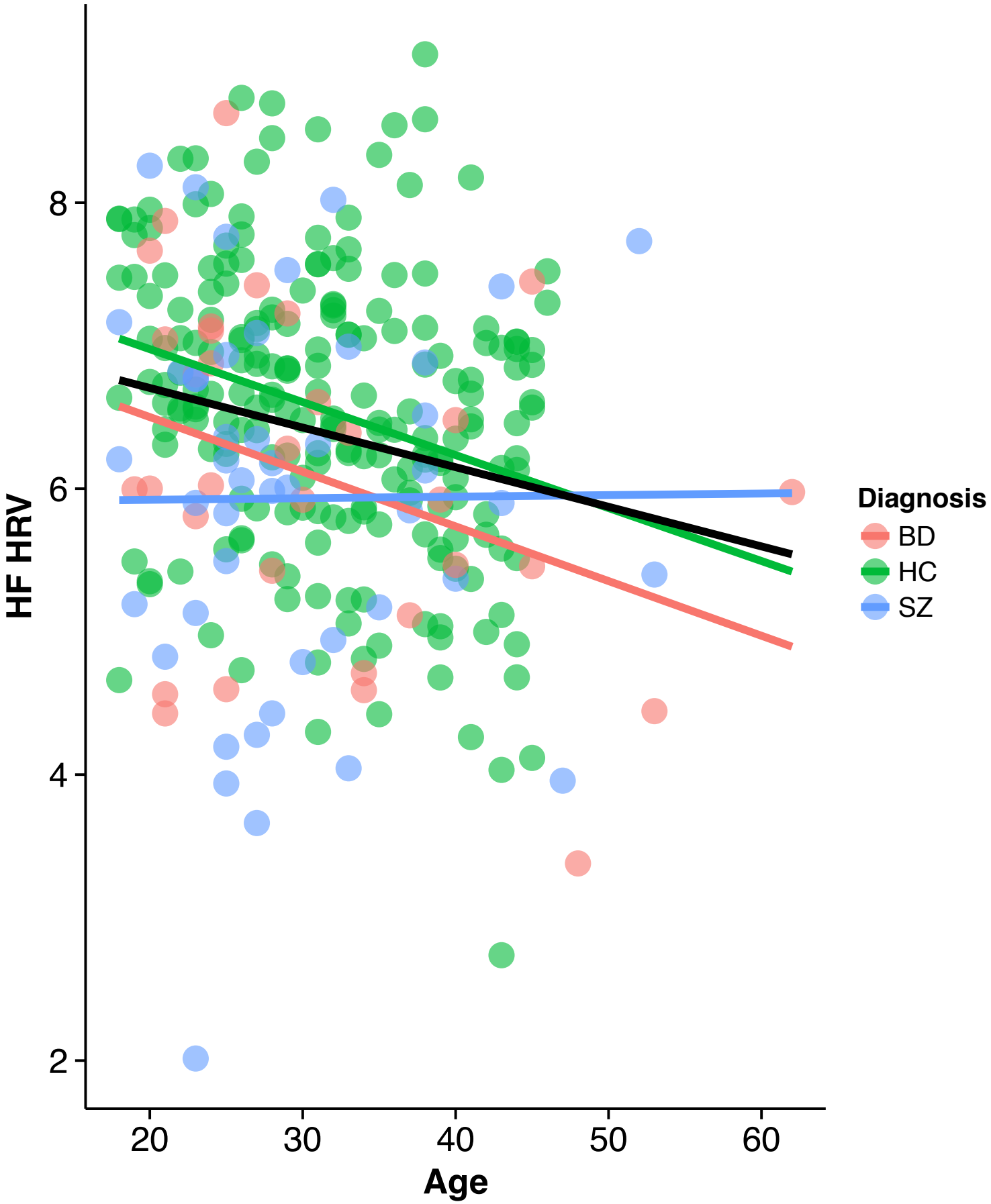
HF HRV
8
6
4
2
20
30
40
50
60
Age
Diagnosis
BD
HC
SZ

Table 1. Demographics, clinical variables, and HRV.

Group	HC (n = 212)	SZ (n = 47)	BD (n = 33)	F (df)	*p*	η_p^2
Age	31.69 (7.66)	29.78 (8.4)	30.88 (10.64)	1.42 (2,289)	.25	0.01
BMI[a]	24.46 (3.58)	25.24 (3.31)	24.08 (3.58)	.9 (2,223)	.41	0.01
HRV	6.54 (1.02)	5.97 (1.29)	6.08 (1.19)	8.51 (2,286)	< .001	0.06
Heart rate (bpm)	64.08 (9.86)	75.03 (13.25)	69.88 (11.6)	23.01 (2,289)	< .001	0.14
Respiratory peak (Hz)[b]	0.3 (0.05)	0.3 (0.06)	0.28 (0.07)	.79 (2,220)	.47	0.01
PANSS total[c]	-	57.81 (19.1)	43 (8.26)	15.64(1,65)	< .001	0.19
Positive symptoms[c]	-	12.97 (4.98)	9.03 (2.63)	15.31(1,65)	< .001	0.19
Negative symptoms[c]	-	15.05 (7.08)	9.5 (2.98)	16.12(1,65)	< .001	0.2
General symptoms[c]	-	29.78 (9)	24.47 (5.01)	8.41(1,65)	< .01	0.11
AUDIT score[d]	-	6.25 (6.44)	8.46 (6.28)	2.02(1,65)	.16	0.03
Cigarettes per day[e]		7.32 (8.34)	6.75 (8.5)	.05 (1,39)	.83	< .01

Note. Values are means with standard deviations in parenthesis or number of participants (%). HC = Healthy controls SZ = Schizophrenia spectrum disorders; BD = Bipolar spectrum disorders; BMI = Body mass index; bpm = beats per minute; PANSS total = Positive and negative syndrome scale summed score; Negative symptoms = Summed score of negative symptom subscale; Positive symptoms = Summed score of positive symptom subscale; HRV = Heart rate variability, log transformed absolute high frequency power; AUDIT = Alcohol use disorders identification test. [a]HC group n = 166, SZ group n = 32, BD group n = 28. [b]HC group n = 152, SZ group n = 37, BD group n = 24. [c]SZ group n = 37, BD group n = 30. [d]SZ group n = 29, BD group n = 30. [e] SZ group n = 25, BD group n = 16.

Table 2. Multiple regression analyses for variables predicting HRV

Variable	*B*	*SE B*	*β*	*p*
Step 1				
Age	-0.03	0.01	-.23	0.001
Medication with anti-cholinergic effects	0.25	0.24	.07	0.3
BMI	-0.01	0.02	-.02	0.8
Step 2				
Age	-0.03	0.01	-.23	< 0.001
Medication with anti-cholinergic effects	-0.27	0.29	-.08	0.34
BMI	-0.01	0.02	-0.01	0.86
Group	0.64	0.2	.25	0.002

Note. *B* = Unstandardized coefficients; *SE B* = Standard error of unstandardized coeficents; β = standardized coefficents.