

Comparative Study of Heart Rate Variability in Patients with Schizophrenia, Bipolar Disorder, Post-traumatic Stress Disorder, or Major Depressive Disorder

Eunok Moon¹, Seung-Hwan Lee^{1,2}, Do-Hyung Kim², Boram Hwang²

¹Clinical Emotion and Cognition Research Laboratory, ²Department of Psychiatry, Inje University Ilsan Paik Hospital, Goyang, Korea

Objective: Heart rate variability (HRV) changes as a function of psychiatric illness. This study aimed to evaluate HRV among patients with various psychiatric disorders.

Methods: The present study recruited patients with schizophrenia (n=35), bipolar disorder (n=41), post-traumatic stress disorder (PTSD; n=34), or major depressive disorder (n=34) as well as healthy controls (n=27). The time-domain analysis (the standard deviation of all RR intervals [SDNN] and the square root of the mean squared differences of successive normal sinus intervals [RMSSD]), the frequency-domain analysis (very low frequency, low frequency [LF], high frequency [HF], and total power [TP]), and a non-linear complexity measure the approximate entropy were computed.

Results: SDNN and HF were significantly reduced in patients with schizophrenia compared with healthy controls. SDNN, RMSSD, TP, LF, and HF were significantly reduced in bipolar patients compared with healthy controls. HF was significantly reduced in PTSD patients compared with healthy controls.

Conclusion: Our findings indicate that HRV is not sufficiently powerful to discriminate among various psychiatric illnesses. However, our results suggest that HRV, particularly HF, could be used as a tool for discriminating between psychiatric patients and healthy controls.

KEY WORDS: Heart rate variability; Schizophrenia; Bipolar disorder; Post traumatic stress disorder; Major depressive disorder.

INTRODUCTION

Autonomic nervous system (ANS) functioning depends on a balance between the activities of the sympathetic and parasympathetic nervous systems in the human body. Under resting conditions, parasympathetic activity is dominant, whereas sympathetic activity is dominant under anxious and physically active conditions. To maintain this balance, the parasympathetic system needs to be very sensitive and respond quickly to external and internal environmental changes. This balance can be measured using heart rate variability (HRV).

HRV is analyzed using time-domain analysis, frequency-domain analysis, and a non-linear complexity measure. In the time-domain analysis, the standard deviation of all RR intervals (SDNN) and the square root of the mean squared differences of successive normal sinus in-

tervals (RMSSD) are computed according to standardized procedures.^{1,2)} SDNN is therefore a measure of heart rate change and reflects total variability during the recording period. RMSSD is sensitive to high-frequency period fluctuations in the respiratory frequency range and is used as an index of vagal cardiac control.³⁾ In the frequency-domain analysis, the power spectra of three frequency bands are calculated: very low frequency (VLF; 0.005-0.040 Hz), low frequency (LF; 0.04-0.15 Hz), high frequency (HF; 0.15-0.40 Hz), and total power (TP), including VLF, LF, and HF.¹⁾ For the non-linear complexity measure, the approximate entropy (ApEn) is calculated.⁴⁾ The ApEn is a parameter that was developed to quantify the degree of regularity versus unpredictability in a higher dimensional attractor reconstructed from a time series, such as the instantaneous heart rate time series.^{5,6)} A lower ApEn value reflects a higher degree of regularity, and the higher the entropy value, the more unpredictable the time series.^{5,6)}

Sympathetic activity acts at a lower frequency (LF: 0.04-0.15 Hz)⁷⁾ of heart rate, and parasympathetic activity produces changes in heart rate at a relatively higher fre-

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Address for correspondence: Seung-Hwan Lee, PhD
Department of Psychiatry, Inje University Ilsan Paik Hospital, 170
Juhwa-ro, Ilsanseo-gu, Goyang 411-706, Korea
Tel: +82-31-910-7260, Fax: +82-31-910-7268
E-mail: lshpss@paik.ac.kr

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quency (HF: 0.15-0.4 Hz) than does sympathetic activity. ANS activity can be mapped by variations in the high-frequency bandwidth of the heart rate (i.e., parasympathetic activity), and HRV is therefore often used as a convenient and non-invasive index of ANS activity. High-frequency HRV (HF-HRV) is widely accepted as representing the flexibility of vagal (parasympathetic) tone and the general capacity of the ANS to respond to changing environmental conditions in an adaptive way.⁸⁾ Thus, HRV may reflect the pathophysiology of various psychiatric disorders.

Although many researchers have conducted HRV studies with patients with major depressive disorder (MDD), the results of these studies are in conflict.⁹⁻¹²⁾ Most found reduced vagal modulation in patients with MDD,¹³⁻¹⁶⁾ whereas others did not find differences in HRV between patients and controls.^{11,17,18)} Antidepressant medication is assumed to have mixed effects on HRV. Research papers on this issue illustrate that changes in autonomic functioning depend on the type of antidepressant. Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors tend to reduce HRV,^{14,19,20)} whereas selective serotonin reuptake inhibitors (SSRIs) increase HRV.^{19,21)}

Lower HF-HRV has been reported in conditions characterized by deficient emotional regulation, such as high trait anxiety²²⁾ and negative affect.²³⁾ This diminished HF-HRV is observed across anxiety disorders (e.g., panic, generalized anxiety, social anxiety, and obsessive-compulsive disorder) relative to healthy controls.²⁴⁾ Further, patients with post-traumatic stress disorder (PTSD) have reduced HRV modulation.²⁵⁻²⁸⁾

An increasing number of reports have also observed HRV dysfunction in schizophrenia.²⁹⁻³¹⁾ Two studies reported that drug-naïve patients with schizophrenia exhibit decreased HF-HRV power compared with healthy subjects but no differences in LF power were observed.^{29,31)} These data suggest that schizophrenia is characterized by a decrease in parasympathetic activity independent of medication effects. Decreased vagal tone in patients with schizophrenia is significantly correlated with symptom severity.^{32,33)}

One report examined HRV in a population of subjects with euthymic bipolar disorder and reported a decrease in SDNN, a decrease in the LF/HF ratio, and an increase in HF power compared with healthy subjects,³⁴⁾ indicating an increase in vagal tone. Henry *et al.*³⁵⁾ reported that patients in the manic phase of bipolar disorder exhibit a significant decrease in HRV compared with age- and sex-matched healthy subjects. An increase in the ratio of

sympathetic to parasympathetic activity is associated with more severe manic symptoms and unusual thought content.

Although studies comparing HRV in patients with specific psychiatric disorders with control subjects have been conducted, we know of no previous studies evaluating and comparing the HRV of patients with various psychiatric disorders (i.e., MDD, anxiety disorder, bipolar disorder, schizophrenia) with that of healthy controls. Comparing the HRV pattern associated with various psychiatric illnesses under the same examination conditions could provide clinicians with useful information about disease characteristics. The aim of our study was to assess the pattern of resting-state HRV response demonstrated by patients with various psychiatric disorders. We aimed to determine if HRV could be used as a way to discriminate among various psychiatric disorders.

METHODS

Subjects

A total of 171 subjects between the ages of 18 and 60 years participated in this study. The sample included patients with schizophrenia (n=35), bipolar disorder (n=41), PTSD (n=34), and MDD (n=34) as well as healthy controls (n=27). All of the patients met criteria for Axis I diagnoses in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994). Healthy control subjects were recruited from the local community via newspaper advertisements. After initial screening to rule out Axis I disorders, potential healthy controls were interviewed using the Structured Clinical Interview for DSM-IV Axis II Disorders³⁶⁾ and were excluded if they had any kind of personality disorder.

All patients with MDD and PTSD were being treated with SSRIs (i.e., fluoxetine, escitalopram, or paroxetine). Patients with schizophrenia were being treated with atypical antipsychotic medication (i.e., olanzapine, risperidone, quetiapine, or aripiprazole). Patients with bipolar disorder were being treated with mood stabilizing agents (i.e., lithium, valproate, or lamotrigine) with or without atypical antipsychotics. None of the subjects had a history of neurological disorder, substance abuse, mental retardation, or brain trauma. Written informed consent was obtained from all subjects, and the study protocol was approved by the Ethics Committee of Inje University Ilsan Paik Hospital.

Heart Rate Variability

HRV measurements were taken 0 to 7 days after starting medication. Smoking and coffee consumption were prohibited for at least 6 h before measurement. After each subject was allowed to adapt to the experimental conditions for approximately 10 min, 5-min single-channel (3-lead) electrocardiogram (ECG) recordings were performed in the seated position at complete rest using the HRV analyzer (SA-3000P) from Medicore Co., Ltd (Seoul, Korea). The ECG signal was amplified and digitized, and the RR interval time series was generated using the automatic scheme to detect the R peak in the ECG using previously published methods.¹⁾

Statistical Analysis

A chi-square test for group differences according to sex and one-way analyses of variance (ANOVAs) were used to examine differences in demographic variables using SPSS 18.0 for Windows. A multivariate ANOVA was used with age and sex as covariates to analyze HRV items.

As a *post hoc* analysis, between-group estimated marginal means were compared with confidence interval adjustment using the Bonferroni method. Spearman's correlation analysis was used to analyze relationships between HRV items and symptom severity for each psychiatric disorder.

RESULTS

Demographic Variables

Demographic characteristics are presented in Table 1. The sex and age distributions of the groups significantly differed as subjects were recruited from a hospital setting.

HRV Variables

All HRV variables are presented in Table 2.

SDNN

We found a significant main effect of SDNN ($F[4, 165]=3.55, p=0.008$). *Post hoc* analysis revealed two sig-

Table 1. Demographic characteristics and symptoms ratings

	Schizophrenia (n=35)	Bipolar disorder (n=41)	PTSD (n=34)	MDD (n=34)	Healthycontrol (n=27)	F value
Sex (male/female)	17/18	11/30	19/15	6/28	6/21	0.002*
Age (yr)	33.89 (12.03)	36.20 (12.43)	40.82 (14.64)	57.82 (15.86) [†]	34.30 (11.09)	18.93 [†]
Illness duration (yr)	6.02 (6.24)	5.28 (5.87)	0.87 (1.14)	2.98 (3.45)		8.596 [†]
PANSS score						
Positive	25.14 (8.66)	25.81 (7.60)				
Negative	21.06 (8.24)	14.76 (4.94)				
General	49.86 (10.76)	48.71 (6.97)				
Total	96.06 (19.17)	89.30 (15.22)				
YMRS score		19.15 (8.58)				
HAMA score			24.09 (7.35)			
HAMD score				25.76 (7.04)		

Values are presented as number only or mean (standard deviation).

*Chi Square p value; [†] $p<0.05$, [‡] $p<0.001$.

PTSD, post-traumatic stress disorder; MDD, major depressive disorder; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.

Table 2. Estimated mean values and standard error of HRV items

HRV Items	Schizophrenia (n=35)	Bipolar disorder (n=41)	PTSD (n=34)	MDD (n=34)	Healthy control (n=27)	F value
SDNN	30.05 (1.95)	28.80(1.78)	31.21 (1.96)	33.71 (2.23)	38.57 (2.22)	3.55*
RMSSD	23.99 (2.08)	20.30 (1.89)	22.36 (2.09)	25.99 (2.37)	30.27 (2.35)	3.17 [†]
VLF	335.96 (62.76)	363.65 (57.27)	404.21 (63.10)	421.23 (71.54)	501.26 (71.13)	0.92
LF	228.63 (39.43)	163.04 (35.99)	178.86 (39.65)	239.35 (44.95)	335.48 (44.70)	2.72 [†]
HF	197.24 (31.82)	121.35 (29.04)	157.56 (31.99)	159.16 (36.27)	332.83 (36.07)	5.86 [†]
TP	761.08 (104.47)	651.42 (95.33)	735.71 (105.03)	843.67 (119.02)	1174.69 (118.41)	3.38 [†]
LF/HF	1.55 (0.31)	2.00 (0.28)	2.47 (0.31)	1.88 (0.35)	1.56 (0.35)	1.423
ApEn	1.19 (0.02)	1.17 (0.02)	1.15 (0.02)	1.11 (0.02)	1.13 (0.02)	1.64

Values are presented as mean (standard deviation).

Multivariate ANCOVA was conducted with age and sex as covariates. [†] $p<0.05$, * $p<0.01$, [‡] $p<0.001$.

PTSD, post traumatic stress disorder; MDD, major depressive disorder; SDNN, standard deviation of all RR intervals; RMSSD, square root of the mean squared differences of successive normal sinus intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; TP, total power; ApEn, approximate entropy.

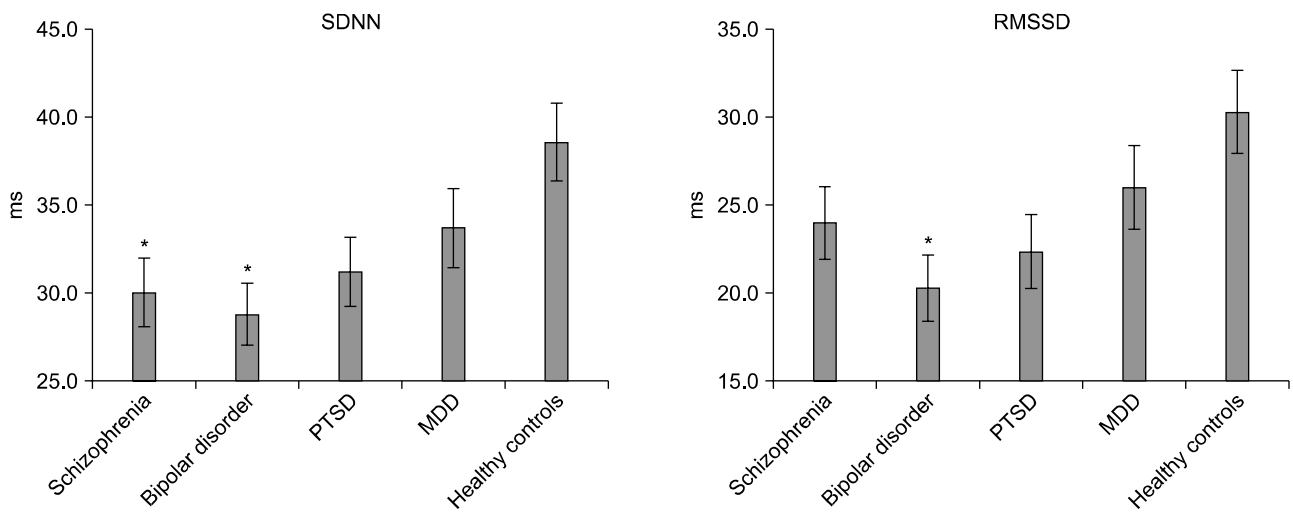


Fig. 1. Time domain analysis of heart rate variability (HRV) index. The standard deviation of all RR intervals (SDNN) of schizophrenia and bipolar disorder were significantly reduced compared to healthy controls. The square root of the mean squared differences of successive normal sinus intervals (RMSSD) of bipolar disorder was significantly reduced compared to healthy controls. *Significant differences compared to healthy controls ($p < 0.05$). PTSD, post-traumatic stress disorder; MDD, major depressive disorder.

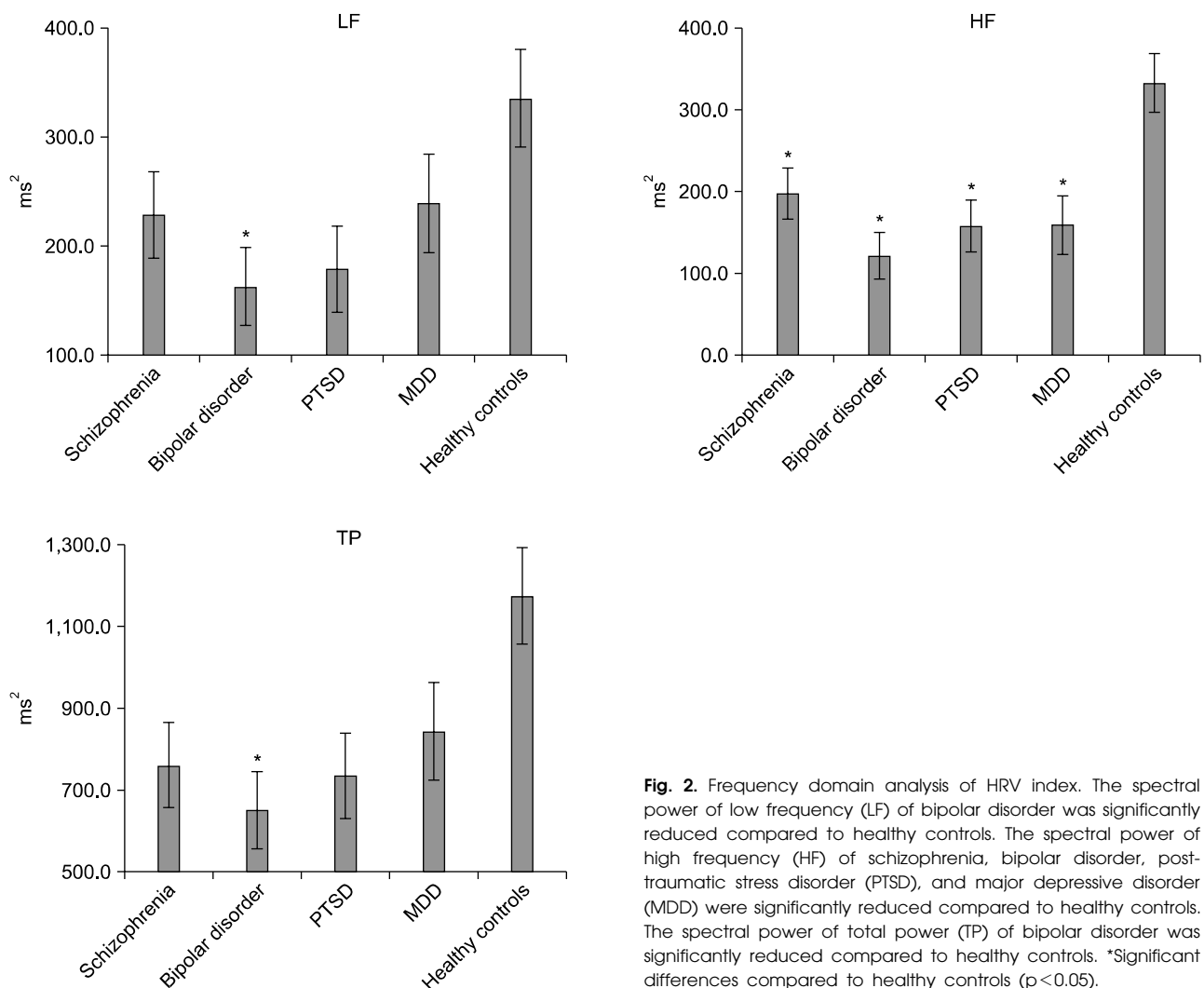


Fig. 2. Frequency domain analysis of HRV index. The spectral power of low frequency (LF) of bipolar disorder was significantly reduced compared to healthy controls. The spectral power of high frequency (HF) of schizophrenia, bipolar disorder, post-traumatic stress disorder (PTSD), and major depressive disorder (MDD) were significantly reduced compared to healthy controls. The spectral power of total power (TP) of bipolar disorder was significantly reduced compared to healthy controls. *Significant differences compared to healthy controls ($p < 0.05$).

nificant differences in between-group comparisons: patients with schizophrenia versus healthy controls (estimated mean±standard error; 30.05±1.95 vs. 38.57±2.22, corrected $p=0.040$) and patients with bipolar disorder versus healthy controls (28.80±1.78 vs. 38.57±2.22, corrected $p=0.006$) (Fig. 1).

RMSSD

We found a significant main effect of RMSSD ($F[4, 165]=3.17, p=0.015$). *Post hoc* analysis revealed a significant difference in the between-group comparisons: patients with bipolar disorder versus healthy controls (20.30±1.89 vs. 30.27±2.35, corrected $p=0.009$) (Fig. 1).

VLF

No significant main effect was observed.

LF

We observed a significant main effect of LF ($F[4, 165]=2.72, p=0.031$). *Post hoc* analysis revealed a significant difference in between-group comparisons: patients with bipolar disorder versus healthy controls (163.04±35.99 vs. 335.48±44.70, corrected $p=0.025$) (Fig. 2).

HF

A significant main effect of HF was observed ($F[4, 165]=5.86, p<0.000$). *Post hoc* analysis revealed four significant differences in the between-group comparisons: patients with schizophrenia versus healthy controls (197.24±31.82 vs. 332.83±36.07, corrected $p=0.048$), patients with bipolar disorder versus healthy controls (121.35±29.04 vs. 332.83±36.07, corrected $p<0.001$), patients with PTSD versus healthy controls (157.56±31.99 vs. 332.83±36.07, corrected $p=0.004$), and patients with MDD versus healthy controls (159.16±36.27 vs. 332.83±36.07, corrected $p=0.014$) (Fig. 2).

TP

We found a significant main effect of TP ($F[4, 165]=3.38, p=0.011$). *Post hoc* analysis revealed a significant difference in the between-group comparisons: patients with bipolar disorder versus healthy controls (651.42±95.33 vs. 1174.69±118.41, corrected $p=0.006$) (Fig. 2).

LH/HF

No significant main effect was observed.

ApEn

No significant main effect was observed.

DISCUSSION

This study compared the HRV of patients with several psychiatric disorders (i.e., schizophrenia, bipolar disorder, PTSD, and MDD) with that of healthy controls. We found that SDNN and HF were significantly reduced in patients with schizophrenia compared with healthy controls. Patients with bipolar disorder showed the most decreased HRV function, and they also had significantly reduced SDNN, RMSSD, TP, LF, and HF compared with healthy controls. HF was significantly reduced in patients with PTSD compared with healthy controls.

HF was significantly reduced in patients with schizophrenia compared with healthy controls; however, no significant difference was observed in LF. The present results are consistent with previous studies. Bär *et al.*²⁹⁾ and Valkonen-Korhonen *et al.*³¹⁾ revealed that HF was decreased in patients with schizophrenia patients compared with healthy controls, whereas LF was not. These data suggest that patients with schizophrenia have dysfunctional parasympathetic functioning and relatively preserved sympathetic functioning compared with healthy controls. RMSSD dysfunction also occurs in patients with schizophrenia.³⁶⁾ RMSSD is supposedly related to parasympathetic activity, providing another measure of vagal tone. Therefore, decreased RMSSD in patients with schizophrenia suggests that this disorder is characterized by dysfunctional parasympathetic activity.

Patients with bipolar disorder demonstrated the most decreased HRV function, and they had significantly reduced SDNN, RMSSD, TP, LF, and HF compared with healthy controls. Previous studies are consistent with the present findings. Cohen *et al.*³⁴⁾ examined HRV in euthymic bipolar subjects and reported a decrease in SDNN, a decrease in the LF/HF ratio, and an increase in HF power compared with healthy subjects. Additionally, Migliorini *et al.*³⁷⁾ reported that patients with bipolar disorder had significantly decreased RMSSD and SDNN. According to Henry *et al.*,³⁵⁾ patients in the manic phase of bipolar disorder exhibit a significant decrease in HRV compared with age- and sex-matched healthy subjects. An increase in the ratio of sympathetic to parasympathetic activity is associated with more severe manic symptoms and unusual thought content, indicating that HRV alterations in bipolar disorder may be state-dependent. In our study, patients with bipolar disorder showed the most significant HRV

dysregulation compared with patients with other kinds of psychiatric illnesses. Extreme affective lability, which is experienced by patients with bipolar disorder, may have contributed to the significant HRV dysregulation in these patients. From this perspective, the finding of decreased HRV during emotional regulation in subjects with high neuroticism reported by Di Simplicio *et al.*³⁸⁾ supports our results. Further research on this issue is required.

HF was significantly reduced in patients with PTSD compared with healthy controls. The present results support previous studies.³⁹⁾ According to Hauschildt *et al.*,⁴⁰⁾ the PTSD group had lower HRV than did non-trauma-exposed controls at baseline and throughout different affective conditions, implying decreased parasympathetic activity and inflexible response regulation. These results show that PTSD is related to the magnitude of the decrease in parasympathetic cardiac control during stress.

The patients with MDD in our study had no significant main change in HRV. However, in other studies, patients with MDD with and without comorbid anxiety had reduced HRV. Those with comorbid anxiety disorder showed the greatest reductions.⁴¹⁾ In another study, depression was also associated with reduced HRV, which decreases with the increasing severity of depression.¹⁰⁾

A recent study reported that vagal nerve stimulation (VNS) successfully improves depressive symptoms in treatment-resistant depression,⁴²⁾ suggesting a strong relationship between sympathovagal dysregulation and depressive symptoms.

In sum, our results suggest that, among various psychiatric illnesses (i.e., schizophrenia, bipolar disorder, MDD, and PTSD), patient with bipolar disorder have the most decreased HRV function compared with healthy controls.

This study has several limitations. First, we did not exclude the medication effect. As antidepressants have different effects on HRV function,^{14,19-21)} medication effects should be carefully controlled in future studies. Second, the age effect could not be strictly controlled, and HRV is known to be influenced by age and sex differences.^{43,44)} Indeed, elderly individuals tend towards a reduced HF-HRV index compared with younger people. Moreover, men with depressive symptoms have reduced parasympathetic activity compared with control subjects, whereas no differences between depressed women and controls have been reported.⁴⁴⁾ Because the demographic characteristics of patients with various psychiatric disorders (e.g., schizophrenia, bipolar disorder, PTSD, and MDD) differ, the recruitment of separate groups of healthy controls that are well matched to individuals with

each psychiatric disorder is necessary to clarify the HRV data.

Despite these limitations, our study has value because we explored the HRV indices of those with various psychiatric disorders using the same study protocol. Our results do not support the use of HRV for discriminating among psychiatric illnesses. However, our results suggest that HRV, particularly HF-HRV, is a sensitive variable and can be used as a supplementary tool for discriminating between patients with psychiatric illnesses and healthy controls.

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