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Effect of gender-related depression on heart rate variability during an autonomic nervous test

Danni Kuang[a], Liqian Cui[b], Shiyuan Kuang[c], Rongqian Yang[a,d,e,1,*], Xiuwen Chen[f], Lei Zhang[g], Ruixue Lv[g], Shanxing Ou[h], Chuanxu Song[g]

[a] Department of Biomedical Engineering, South China University of Technology, Guangzhou, China
[b] The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[c] The Affiliate Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), China
[d] Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, China
[e] Department of Therapeutic Radiology, Yale University, New Haven, CT 06520, USA
[f] Medical Devices Research & Testing Center, South China University of Technology, Guangzhou, China
[g] Shenzhen Sayes Medical Technology Co., Ltd., Shenzhen, China
[h] General Hospital of Guangzhou Military Command of PLA, Guangzhou, China

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ABSTRACT

Patients with depression have lower heart rate variability (HRV) compared with controls. However, studies have indicated HRV difference between male and female controls. The gender effect might be interactive with the depression effect on the HRV, resulting in a low accuracy of recognising the patients with depression from the controls. Our study explores the effect of gender-related depression on HRV. Four ANS tests including resting, deep breathing, Valsalva, and orthostatic test are employed as stimuli. HRV were collected from 182 subjects comprising 91 depressive patients (33 females/58 males) and 91 controls (33 females/58 males) in the four tests. Time and frequency domains and nonlinear parameters are employed to quantify HRV. Two-way ANOVA is applied to evaluate the effect of gender-related depression. Most HRV parameters of the patients significantly differ from those of the controls, but some parameters indicate different depression effect between the males and females in the deep breathing and Valsalva test. Some HRV parameters illustrate significant difference between the male and female controls. Therefore, the effect of depression on HRV of each gender should be investigated.

1. Introduction

Depression is one of the most prevalent psychiatric disorders. It is associated with autonomic nervous system (ANS) dysfunction (Akar et al., 2016; Bob et al., 2008; Wang et al., 2013). Heart rate variability (HRV) has been widely used to evaluate the ANS modulation of depression. HRV remarkably differs between patients with depression and controls. Parasympathetic modulation decreases in patients with depression and they have low HRV parameters, such as the standard deviation of the successive difference in RR intervals (RMSSD), high frequency energy (HF) and Valsalva ratio (Agelink et al., 2002; Dubey and Sawane, 2017; Kg et al., 2006; Tonhajzerova et al., 2011; Udupa et al., 2007). However, other studies have revealed that sympathetic modulation increases (Koschke et al., 2009; Udupa et al., 2007). The severity of depression is negatively related to HRV parameters. The more severe the depression is, the lower the HRV will be, indicating low parasympathetic modulation. HRV parameters have been regarded as important markers in recognising patients with depression (Kuang et al., 2017; Roh et al., 2014; Zhang et al., 2011). However, previous studies showed that depression is approximately twice as common in females as it is in males (Möllerleimkühler, 2007; Nolenhoeksema, 2001); various factors, such as reproductive factors, behavioural genetics and symptom presentation, may contribute to gender differences in depression (Nolenhoeksema, 2001). One issue is that whether such gender differences become manifested in HRV and inhibit the predictive value of HRV for depression recognition. Gender-related differences in HRV of controls have been observed. Males have lower HF and greater respiratory sinus arrhythmia, approximate entropy (ApEn), low frequency energy (LF) and ratio of low–high frequency energy (LF/HF) than females probably because of oestrogen secretion by females (Antelmi et al., 2004; Liao et al., 1995; Sloan et al., 2008; Snieder et al., 2007; Thayer et al., 2016). Evidently, the effects of gender and

* Corresponding author at: Department of Biomedical Engineering, South China University of Technology, Guangzhou, China.
E-mail addresses: bmeyrq@foxmail.com, bmeyrq@foxmail.com (R. Yang).
[1] Present address: No. 382, East Road of Outer Ring, Guangzhou College Town, Panyu District, Guangzhou City, China.

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depression are reflected on HRV parameters, which may interfere depression recognition.

The effects of gender-related depression on HRV should be examined. Previous studies showed that sympathetic modulation in male controls is stronger than that in female controls, but such differences disappear between male and female patients with depression, indicating that differences between controls and patients of females are greater than those of males. In particular, the alternation of the ANS modulation of female patients with depression may vary from that of male patients with depression compared with that of controls (Voss et al., 2011). These observations are shown in blood pressure variability (BPV), but the gender-related effect of depression on HRV is not observed at rest test. Studying the effect of depression on HRV only at rest test is insufficient. Alternated ANS activity can be stronger when patients with depression are exposed to stress conditions. Deep breathing test, Valsalva test and orthostatic test are also standard tests for evaluating ANS modulation (Boulton et al., 2005; Chen et al., 2017; Rechlin et al., 1995; Udupa et al., 2007; Zygmunt and Stanczyk, 2010), and they can induce various ANS activities.

In this study, a series of tests, namely, resting test, deep breathing test, Valsalva test and orthostatic test, is performed to stimulate the ANS. First, the effect of gender-related depression on HRV is explored. Secondly, HRV differences between male and female patients with depression and controls are surveyed. Thirdly, gender-related differences in HRV of the controls are investigated. The complete test lasts 10 min. Time and frequency domains and nonlinear measurements are performed to quantify HRV. Two-way ANOVA is applied to study the gender-related depression effect and the single-factor effect on HRV.

2. Methods

2.1. Subjects

A total of 182 subjects comprising 91 patients with depression (33 females/58 males) and 91 healthy people (33 females/58 males) are included, but pregnant and postpartum females are excluded. Patients with depression were diagnosed by psychiatrists. The mean age of males is 29.8 ± 10.0 years, and their body mass index (BMI) is 22.6 ± 3.1 kg/m^2. The mean age of females is 29.4 ± 8.9 years, and their BMI is 21.5 ± 3.0 kg/m^2. Hamilton depression rating scale (HAMD) (Hamilton, 1960) is used to evaluate the severity of depression. The HAMD scores of male and female patients with depression are 20.6 ± 6.0 and 23.3 ± 6.0, respectively. Patients with depression are reported with no history of cardiovascular diseases, diabetes, neurological diseases or other psychiatric diseases. Subjects with physical comorbidities are excluded. All of the patients never received antidepressant drugs. Male controls are 26.3 ± 4.2 years old, and their BMI is 22.3 ± 2.7 kg/m^2. Female controls are 25.9 ± 5.5 years old, and their BMI is 19.6 ± 1.8 kg/m^2. None of the controls are reported with a history of psychiatric diseases, cardiovascular diseases, neurological diseases or other diseases. All of the subjects are confirmed to not take caffeine-containing and alcoholic drinks and instructed to avoid undergoing strenuous exercises within 24 h prior to the test.

2.2. Data acquisition

Resting, deep breathing, Valsalva and orthostatic tests are standard for evaluating ANS modulation. Deep breathing induces parasympathetic activity, and orthostatic test is related to sympathetic activation and decreased parasympathetic modulation (Duclasoares et al., 2010; Udupa et al., 2007). Valsalva manoeuvre is associated with an increased sympathetic activity (Duclasoares et al., 2010; Udupa et al., 2007). Conversely, Zygmunt and Stanczyk (2010) considered that this manoeuvre is related to parasympathetic modulation. Other studies have demonstrated that heart rate responses to Valsalva manoeuvre are controlled by parasympathetic and sympathetic modulation but dominantly by parasympathetic modulation (Ewing, 1978; Rothschild et al., 1987). Valsalva manoeuvre induces ANS activity. In a Valsalva manoeuvre test, subjects are asked to maintain their mercury manometer at 40 mmHg for 15 s with the help of a mouthpiece. In this study, this manoeuvre is simplified for convenient application. The simplified manoeuvre can stimulate ANS. The 10 min test involving four stages is implemented as follows. (1) In the resting stage, subjects sit and breathe normally for 4 min. (2) In the deep breathing stage, subjects inhale and hold their breath for 5 s. Then, they closely exhale and hold their breath for 5 s. This procedure is repeated six times within 1 min. (3) In the Valsalva stage, subjects inhale and hold their breath for 15 s. They then exhale and relax for another 15 s. This procedure is repeated three times within 1.5 min. (4) In the orthostatic stage, subjects stand up and breathe normally for 2 min. They undergo relaxation and adjustment for 0.50 min before the next stage begins. All of the subjects are arranged into a quiet room, and the tests start when the subjects are relaxed. Data are recorded during working hours (9:00–12:00 a.m. and 14:00–18:00 p.m.). Electrocardiography (ECG) signals are obtained during the 10 min test by using three-limb ECG leads (ECG-B; SAYES, Shenzhen, China) sampled at 500 Hz. Then, R-wave peaks are extracted from the ECG signals, and the HRV is calculated.

2.3. HRV parameters

Time and frequency domains and nonlinear dynamic measurements are commonly used to analyse HRV (Camm et al., 1996). The most commonly used parameters of time domain measurement are the mean values of HRV (MEAN), the standard deviation of average normal intervals (SDNN), RMSSD and the percentage of RR intervals greater than 50 ms (PNN50). The frequency domain parameters of HRV mainly include LF (0.04–0.15 Hz), HF (0.15–0.4 Hz) and LF/HF. RMSSD and PNN50 can reflect parasympathetic modulation, whereas SDNN reflects sympathetic and parasympathetic modulation. LF is sensitive to sympathetic and parasympathetic activities, and HF can reflect parasympathetic activities (Camm et al., 1996). Continuous wavelet transform is applied to calculate frequency energy.

The nonlinear characteristic of HRV is associated with ANS regulations (Cam et al., 1996). Diverse nonlinear measurements, such as ApEn, sample entropy (SamEn), multiscale entropy (MSE) and detrended fluctuation analysis (DFA), are performed to determine the complexity or regularity of HRV. ApEn is used to evaluate the irregularity of dynamical systems (Pincus, 1991) and strongly associated with indices describing vagal modulation (Beckers et al., 2006). However, studies have shown inconsistent outcomes when ApEn is used. Thus, an improved method, namely, SamEn, is introduced on the basis of ApEn (Richman and Moorman, 2000). High entropy indicates high complexity or less regularity. HRV irregularity is associated with ANS modulation (Kapidžić et al., 2014; Weippert et al., 2014; Zhao et al., 2015). Costa suggested that quantifying the complexity of physiologic dynamics can be under multiple scales and introduced MSE on the basis of SamEn (Costa et al., 2005). In this study, MSEs under three scales, including Scale 1 (MSE_1), Scale 2 (MSE_2) and Scale 3 (MSE_3), are calculated. The length of the compared runs is $m = 2$, and the filter limitation is $r = 25\%$ (Costa et al., 2005). In DFA, the properties of a time series are determined using a fractal framework, and this procedure is applied to survey the correlation of heart rate fluctuation during sleep and the nonlinear properties of HRV in controls (Beckers et al., 2006; Pikkujämsä et al., 2001). DFA has a clinical advantage for predicting diseases, such as ventricular dysfunction, on the basis of short-range scaling exponent (α_1) (Peña et al., 2009). α_1 and long-range scaling exponent (α_2) are commonly used. α_1 is related to sympathetic activity, whereas α_2 is linked to sympathetic and parasympathetic activities (Beckers et al., 2006). In our study, α_1 is the slope of 4–11 points plotted by $F(n) \sim n$, where n represents the size of the observation window, and F denotes the average root mean square fluctuation; α_2 is

the slope of 12–64 points (Peña et al., 2009).

2.4. Statistical analysis

This research involves two factors, namely, *Depression* and *Gender*. *Depression* has two categories, namely, subjects with and without depression. *Gender* has two categories, namely, males and females. In two-way ANOVA, the effect of two different factors (*Depression* and *Gender*) on one continuous dependent variable (HRV parameters) is evaluated. The main effect of *Depression* and *Gender* on HRV parameters and the interaction between them on HRV parameters are evaluated. The main effect is defined as an integrated effect of *Depression* on HRV parameters, which disregard the levels of *Gender* and vice versa. Interaction describes the nonadditivity of the simultaneous effect of *Depression* and *Gender* on HRV parameters. The interaction between *Depression* and *Gender* indicates that the effect of one of the factors on HRV parameters depends on the levels of the other factors. The interaction of *Depression* and *Gender* on HRV is utilised to explore the effect of gender-related depression on HRV. Simple effect measures the effect of *Depression* on HRV parameters with restricted levels of *Gender* and vice versa. This simple effect is examined through univariate ANOVA. This study includes two steps. Firstly, two-way ANOVA is implemented to analyse the main effect and interaction of *Depression* and *Gender* on HRV parameters in the four tests. Secondly, univariate ANOVA is implemented to analyse the effect of *Depression* with the restricted levels of *Gender* and vice versa. The confidence level is 95%, and the significant difference is $p \leq 0.05$.

3. Results

The mean and standard deviations of time and frequency domains and the nonlinear HRV parameters are shown in Tables 1 and 2. The main effect of *Depression* and *Gender* and their interaction on HRV parameters are illustrated in Table 1. The simple effect of *Depression* and *Gender* is depicted in Table 2. The significant parameters during the four ANS tests are listed in Table 3.

In Table 1, the main effect of *Depression* is greatly significant on most HRV parameters, that is, most HRV parameters of patients with depression indicate highly significant differences compared with the controls that do not consider gender. The main effect of *Gender* is significant on some HRV parameters, that is, some HRV parameters of males significantly differ from those of females regardless of the presence or absence of depression. The significant interaction of *Depression* and *Gender* is not observed in all of the HRV parameters in the resting and orthostatic tests. In the deep breathing test, the significant interaction of *Depression* and *Gender* is found in LF/HF, MSE_1 and α_2 (Table 1). The simple effect of *Depression* (Table 2) during the deep breathing test indicates that the male patients with depression show lower LF/HF and higher MSE_1 and α_2 than the male controls do. Nevertheless, significant differences are not observed in females. The simple effect of *Gender* (Table 2) also reveals that LF/HF and α_2 show no difference between male and female controls. Nevertheless, significant differences are found between male and female patients. In the Valsalva test, the interaction of *Depression* and *Gender* on α_2 is revealed. The simple effect of *Depression* (Table 2) in the Valsalva test shows that α_2 of patients with depression is significantly lower than that of the female controls, but such finding is not observed in males. The simple effect of *Gender* demonstrates that differences are observed between male and female patients but not between male and female controls.

In Table 2, the following parameters show significant differences between male and female controls: LF/HF in resting and orthostatic tests, LF in deep breathing and Valsalva tests, α_1 in resting test and MSE_1 in deep breathing tests. In terms of the simple effect of *Depression* on males and females, most HRV parameters reveal significant differences between patients with depression and controls in males and females, indicating that male and female patients with depression have lower HRV than that of the controls.

4. Discussion

This study explores the effect of gender-related depression on HRV, differences in HRV between patients with depression and controls and gender differences in HRV in controls. Our findings show that the effect of depression on HRV is different between males and females in deep breathing and Valsalva test, whereas its effects are the same in the resting and orthostatic test. The HRV of male and female patients with depression is lower than that of the controls. Some HRV parameters indicate variation between male and female controls.

During the resting test, the MEAN, SDNN, RMSSD, PNN50, HF and α_1 of patients with depression are lower than those of the controls in our study. RMSSD, PNN50 and HF reflect parasympathetic activities, thus suggesting parasympathetic dysfunction in patients with depression, in accordance with Agelink et al. (2002). LF reflects sympathetic and parasympathetic modulation, and LF/HF measures sympathovagal balance. Higher LF and LF/HF indicate an increased sympathetic activity in patients with depression at rest (Udupa et al., 2007; Wang et al., 2013). However, such findings are not observed in patients with depression under the resting test in our study, so they do not support the increased sympathetic activity in patients with depression. In terms of nonlinear parameters, the lower MSE_1 and the higher α_1 in patients with depression suggest that they have lower complexity and decreased parasympathetic activity at rest. However, a contradictory result is observed in the deep breathing test. MSE_1 of the male patients is higher than that of the male controls, which indicating that male patients have greater increased parasympathetic modulation than male controls when their ANS is exposed to deep breathing stress. Table 3 demonstrates that time domain parameters are consistently differentiated in the controls and the male and female patients, whereas frequency domain and nonlinear parameters show inconsistency during the four ANS tests. It seems that time domain parameters are more valuable than frequency domain and nonlinear parameters, but correlation between parameters should be considered and further surveyed. These three approaches are used to evaluate HRV from various aspects, and combining them is effective when machine learning algorithm is used to recognise depression (Kuang et al., 2017). Amongst the ANS tests, deep breathing test is likely the most useful, whereas orthostatic test is statistically the most useless (Table 3). However, contradictory results were observed in our previous research involving feature selection algorithm (Kuang et al., 2017) possibly because the parameters of deep breathing test are relatively related to each other; as such, correlation-based feature selection algorithm filters out many parameters (Hall, 1999). The parameters of orthostatic test are reversed. Thus, the overall and precise conclusion about more valuable ANS tests should be carefully interpreted.

Gender-related differences in HRV of the controls have been studied through time and frequency domain measurements (Koenig and Thayer, 2016). In time domain measurements, some studies have revealed no gender difference in RMSSD, PNN50 and SDNN at rest (Beckers et al., 2006; Cowan et al., 1994; Pikkujämsä et al., 2001). In our study, none of the time domain parameters indicate the difference between male and female controls. Consistent with our study, most studies have revealed higher LF (Beckers et al., 2006; Liao et al., 1995; Sloan et al., 2008; Thayer et al., 2016) and higher LF/HF in males than in females, suggesting that males have greater sympathetic modulation or lower parasympathetic modulation than females at rest (Liao et al., 1995; Sloan et al., 2008; Sookan and Mckune, 2012; Thayer et al., 2016). Some studies have indicated higher HF in females than in males (Antelmi et al., 2004; Sookan and Mckune, 2012), whereas other studies have shown no remarkable difference in HF (Beckers et al., 2006; Pikkujämsä et al., 2001; Sloan et al., 2008). This difference in ANS between genders has some remarkable explanations. Estrogen plays an important role in ANS activity by facilitating vagal modulation and

Table 1
The main effect of factors *Depression* and *Gender* as well as interaction between them.

Parameters	Controls $N = 91$	Patients $N = 91$	Males $N = 116$	Females $N = 66$	*P*-value P_D /Power	P_G /Power	P_I /Power
Resting test							
MEAN (ms)	820 ± 107	740 ± 106	786 ± 112	769 ± 117	0.000/0.999	0.306/0.175	0.265/0.199
SDNN (ms)	47.55 ± 17.87	38.20 ± 16.84	44.28 ± 19.07	40.41 ± 15.58	0.000/0.975	0.147/0.305	0.123/0.338
RMSSD (ms)	36.56 ± 18.77	26.06 ± 14.51	31.11 ± 18.12	31.66 ± 16.59	0.000/0.993	0.833/0.055	0.147/0.305
PNN50 (%)	18.06 ± 17.16	8.36 ± 11.31	12.52 ± 15.03	14.42 ± 15.76	0.000/0.998	0.394/0.136	0.074/0.432
LF (10^3 ms^2)	2.00 ± 2.23	1.55 ± 1.41	1.98 ± 2.11	1.41 ± 1.31	0.077/0.423	0.047/0.513	0.488/0.106
HF (10^3 ms^2)	2.49 ± 3.35	1.36 ± 1.65	1.95 ± 2.98	1.88 ± 2.11	0.004/0.827	0.865/0.053	0.554/0.091
LF/HF (N/A)	1.50 ± 2.18	1.80 ± 1.47	1.88 ± 2.13	1.25 ± 1.17	0.207/0.242	0.029/0.592	0.484/0.107
MSE_1 (N/A)	1.39 ± 0.25	1.26 ± 0.19	1.30 ± 0.24	1.37 ± 0.21	0.000/0.974	0.033/0.571	0.595/0.083
MSE_2 (N/A)	1.49 ± 0.23	1.43 ± 0.23	1.43 ± 0.24	1.50 ± 0.21	0.068/0.447	0.057/0.479	0.664/0.072
MSE_3 (N/A)	1.43 ± 0.22	1.39 ± 0.25	1.41 ± 0.25	1.41 ± 0.21	0.379/0.142	0.954/0.050	0.397/0.135
α_1 (N/A)	1.01 ± 0.21	1.13 ± 0.25	1.12 ± 0.23	1.00 ± 0.24	0.001/0.904	0.001/0.919	0.703/0.067
α_2 (N/A)	0.89 ± 0.21	0.93 ± 0.20	0.89 ± 0.22	0.95 ± 0.17	0.330/0.163	0.065/0.454	0.950/0.050
Deep breathing test							
MEAN (ms)	800 ± 96	720 ± 98	761 ± 102	758 ± 100	0.000/1.000	0.877/0.053	0.962/0.050
SDNN (ms)	89.74 ± 27.70	64.50 ± 28.58	80.26 ± 32.45	71.60 ± 26.96	0.000/1.000	0.046/0.515	0.881/0.053
RMSSD (ms)	53.94 ± 23.75	36.26 ± 20.06	47.28 ± 25.29	41.26 ± 20.05	0.000/0.999	0.076/0.426	0.806/0.057
PNN50 (%)	26.63 ± 13.49	14.96 ± 12.63	21.79 ± 14.75	19.04 ± 13.37	0.000/1.000	0.175/0.273	0.872/0.053
LF(10^3 ms^2)	20.13 ± 11.84	11.35 ± 10.28	16.89 ± 12.37	13.71 ± 10.19	0.000/0.998	0.063/0.461	0.297/0.180
HF (10^3 ms^2)	3.86 ± 4.68	2.16 ± 2.62	3.43 ± 4.37	2.28 ± 2.67	0.005/0.809	0.049/0.505	0.788/0.058
LF/HF (N/A)	8.02 ± 4.83	6.79 ± 4.03	6.86 ± 4.41	8.35 ± 4.46	0.217/0.234	0.028/0.597	0.035/0.559
MSE_1 (N/A)	0.81 ± 0.20	0.85 ± 0.25	0.81 ± 0.21	0.87 ± 0.24	0.577/0.086	0.071/0.440	0.047/0.513
MSE_2 (N/A)	1.19 ± 0.73	1.14 ± 0.44	1.20 ± 0.69	1.11 ± 0.40	0.437/0.121	0.344/0.156	0.478/0.109
MSE_3 (N/A)	2.37 ± 2.29	1.70 ± 1.60	2.20 ± 2.11	1.75 ± 1.77	0.033/0.569	0.138/0.316	0.855/0.054
α_1 (N/A)	1.50 ± 0.16	1.54 ± 0.17	1.50 ± 0.16	1.55 ± 0.16	0.059/0.474	0.073/0.435	0.059/0.474
α_2 (N/A)	0.37 ± 0.29	0.44 ± 0.36	0.43 ± 0.35	0.34 ± 0.29	0.403/0.133	0.068/0.447	0.039/0.544
Valsalva test							
MEAN (ms)	817 ± 95	735 ± 102	783 ± 107	764 ± 106	0.000/1.000	0.229/0.224	0.648/0.074
SDNN (ms)	74.80 ± 24.96	58.76 ± 22.64	69.90 ± 26.35	61.29 ± 21.81	0.000/0.992	0.019/0.653	0.993/0.050
RMSSD (ms)	37.59 ± 16.68	28.26 ± 13.88	34.53 ± 16.53	30.11 ± 14.72	0.000/0.988	0.062/0.464	0.323/0.167
PNN50 (%)	13.87 ± 9.82	8.51 ± 8.01	11.81 ± 9.11	10.10 ± 9.68	0.000/0.990	0.215/0.236	0.128/0.331
LF (10^3 ms^2)	7.44 ± 5.84	5.43 ± 4.53	7.31 ± 5.91	4.90 ± 3.58	0.010/0.731	0.003/0.859	0.875/0.053
HF (10^3 ms^2)	2.19 ± 2.28	1.45 ± 1.58	2.02 ± 2.28	1.46 ± 1.28	0.009/0.747	0.065/0.454	0.522/0.098
LF/HF (N/A)	4.73 ± 3.77	4.99 ± 3.28	5.11 ± 3.65	4.43 ± 3.28	0.418/0.127	0.215/0.236	0.242/0.215
MSE_1 (N/A)	0.82 ± 0.21	0.80 ± 0.22	0.80 ± 0.21	0.83 ± 0.21	0.351/0.153	0.258/0.204	0.699/0.067
MSE_2 (N/A)	1.14 ± 0.33	1.09 ± 0.34	1.12 ± 0.33	1.12 ± 0.34	0.246/0.212	0.886/0.052	0.435/0.122
MSE_3 (N/A)	1.67 ± 1.19	1.61 ± 1.05	1.66 ± 1.17	1.61 ± 1.05	0.492/0.105	0.786/0.058	0.225/0.227
α_1 (N/A)	1.54 ± 0.20	1.58 ± 0.18	1.57 ± 0.18	1.55 ± 0.21	0.092/0.393	0.554/0.091	0.368/0.146
α_2 (N/A)	0.74 ± 0.23	0.77 ± 0.25	0.71 ± 0.24	0.83 ± 0.24	0.160/0.289	0.001/0.905	0.050/0.502
Orthostatic test							
MEAN (ms)	749 ± 109	677 ± 94	715 ± 110	709 ± 104	0.000/0.998	0.679/0.070	0.240/0.216
SDNN (ms)	41.94 ± 19.28	32.60 ± 15.76	38.16 ± 18.62	35.71 ± 17.39	0.000/0.943	0.370/0.146	0.640/0.075
RMSSD (ms)	22.46 ± 13.70	15.67 ± 10.34	19.02 ± 13.07	19.15 ± 11.76	0.000/0.973	0.945/0.051	0.293/0.182
PNN50 (%)	5.95 ± 11.27	2.36 ± 5.62	4.10 ± 8.60	4.23 ± 9.89	0.003/0.839	0.925/0.051	0.198/0.251
LF (10^3 ms^2)	1.85 ± 3.52	1.24 ± 1.63	1.80 ± 3.36	1.10 ± 0.89	0.220/0.232	0.098/0.380	0.467/0.112
HF (10^3 ms^2)	0.95 ± 1.3	0.60 ± 1.29	0.85 ± 1.56	0.66 ± 0.71	0.078/0.423	0.352/0.153	0.820/0.056
LF/HF (N/A)	3.18 ± 3.71	3.54 ± 2.83	3.64 ± 3.75	2.86 ± 2.23	0.273/0.194	0.125/0.336	0.172/0.276
MSE_1 (N/A)	1.10 ± 0.35	1.01 ± 0.31	1.04 ± 0.34	1.08 ± 0.33	0.034/0.565	0.412/0.129	0.428/0.124
MSE_2 (N/A)	1.37 ± 0.79	1.25 ± 0.40	1.34 ± 0.72	1.25 ± 0.40	0.302/0.178	0.343/0.157	0.555/0.090
MSE_3 (N/A)	1.57 ± 1.13	1.49 ± 1.15	1.60 ± 1.16	1.41 ± 1.09	0.699/0.067	0.270/0.196	0.837/0.055
α_1 (N/A)	1.40 ± 0.29	1.43 ± 0.28	1.43 ± 0.26	1.39 ± 0.32	0.289/0.185	0.273/0.194	0.324/0.166
α_2 (N/A)	0.78 ± 0.32	0.92 ± 0.35	0.85 ± 0.36	0.84 ± 0.32	0.012/0.710	0.782/0.059	0.570/0.088

P_D—the main effect of factor *Depression;* P_G—the main effect of factor *Gender;* P_I—the interaction between *Depression* and *Gender*, Power—statistical power.

attenuating sympathetic modulation, resulting in higher HF and lower LF and LF/HF in females than in males (Liu, 2003; Neves et al., 2007). Functional nerve growth gene carried by males only is associated with low vagal activity, leading to lower HF and RMSSD in males than in females (Chang et al., 2014b). Brain-derived neurotrophic factor affects the ANS in a gender-specific manner; consequently, the effects of some genes on the ANS are different between male and female subjects (Chang et al., 2014a). The HPA axis responses of males are different from those of females when these subjects are exposed to psychological stress stimulation (Seeman et al., 2001; Uhart et al., 2006). In contrast to the ANS, the HPA axis is a hormonal system, indicating that HPA axis responses are slower than nervous system responses, but studies have indicated the inter-relation between the two systems following a coordinated and temporal sequence (Cacioppo et al., 1995; Rotenberg and McGrath, 2016). When the ANS is exposed to deep breathing, Valsalva, and orthostatic tests, LF, HF and LF/HF are influenced not only by ANS but also by external elements, such as respiratory rate during deep breathing and Valsalva test. In this study, the respiratory rate is controlled consistently in all subjects in deep breathing and Valsalva test. Variations in LF, HF and LF/HF almost result from different ANS adjustments to stress. In particular, HRV differences between female and male controls indicate variations in the reaction of the ANS to stress. In terms of nonlinear parameters, lower α_1 during resting test and higher MSE_1 during deep breathing test are observed in the female controls than in the male controls, consistent with references (Beckers et al., 2006; Kapidžić et al., 2014; Pikkujämsä et al., 2001). These findings on nonlinear parameters suggest that the HRV irregularity of female controls is greater than that of male controls, suggesting more parasympathetic activities but lower sympathetic modulation in the former than in the latter.

Table 2
The simple effect of factors *Depression* and *Gender*.

Parameters	Males		Females		*P*-value			
	Controls $N = 58$	Patients $N = 58$	Controls $N = 33$	Patients $N = 33$	P_{Mcp} /Power	P_{Fcp} /Power	P_{Cmf} /Power	P_{Pmf} /Power
Resting test								
MEAN (ms)	820 ± 104	752 ± 109	821 ± 114	717 ± 96	0.001/0.925	0.000/0.977	0.948/0.050	0.131/0.326
SDNN (ms)	47.46 ± 19.39	41.10 ± 18.37	47.71 ± 15.10	33.11 ± 12.44	0.048/0.507	0.001/0.928	0.948/0.050	0.035/0.561
RMSSD (ms)	35.00 ± 19.37	27.23 ± 16.01	39.31 ± 17.60	24.01 ± 11.34	0.014/0.699	0.000/0.958	0.240/0.216	0.380/0.141
PNN50 (%)	15.91 ± 16.71	9.12 ± 12.38	21.82 ± 17.54	7.02 ± 9.16	0.012/0.712	0.000/0.985	0.062/0.462	0.506/0.102
LF (10^3 ms^2)	2.14 ± 2.57	1.83 ± 1.53	1.77 ± 1.48	1.06 ± 1.00	0.371/0.145	0.123/0.337	0.356/0.151	0.058/0.475
HF (10 ms^2)	2.43 ± 3.77	1.47 ± 1.80	2.60 ± 2.49	1.16 ± 1.34	0.055/0.485	0.029/0.590	0.765/0.060	0.590/0.084
LF/HF (N/A)	1.80 ± 2.64	1.96 ± 1.47	0.97 ± 0.73	1.53 ± 1.45	0.640/0.075	0.220/0.232	0.041/0.533	0.289/0.185
MSE_1 (N/A)	1.36 ± 0.27	1.24 ± 0.19	1.45 ± 0.20	1.30 ± 0.20	0.005/0.799	0.006/0.792	0.059/0.471	0.254/0.206
MSE_2 (N/A)	1.46 ± 0.25	1.41 ± 0.22	1.54 ± 0.18	1.46 ± 0.23	0.246/0.212	0.157/0.293	0.098/0.381	0.296/0.181
MSE_3 (N/A)	1.45 ± 0.23	1.38 ± 0.26	1.41 ± 0.19	1.41 ± 0.23	0.153/0.298	0.983/0.050	0.523/0.098	0.577/0.086
α_1 (N/A)	1.05 ± 0.22	1.18 ± 0.23	0.95 ± 0.20	1.05 ± 0.26	0.003/0.857	0.071/0.440	0.035/0.559	0.009/0.753
α_2 (N/A)	0.87 ± 0.22	0.91 ± 0.21	0.93 ± 0.17	0.96 ± 0.16	0.389/0.138	0.568/0.088	0.177/0.271	0.207/0.243
Deep breathing test								
MEAN (ms)	800 ± 87	721 ± 102	799 ± 111	718 ± 93	0.000/0.992	0.001/917	0.940/0.051	0.887/0.052
SDNN (ms)	93.12 ± 29.60	67.41 ± 30.20	83.80 ± 23.22	59.39 ± 25.10	0.000/0.998	0.001/0.941	0.129/0.330	0.190/0.258
RMSSD (ms)	56.42 ± 25.41	38.14 ± 21.78	49.57 ± 20.13	32.95 ± 16.41	0.000/0.994	0.002/0.866	0.153/0.297	0.279/0.191
PNN50 (%)	27.74 ± 13.21	15.84 ± 13.86	24.67 ± 13.96	13.41 ± 10.13	0.000/0.998	0.001/0.936	0.283/0.188	0.397/0.135
LF (10^3 ms^2)	21.93 ± 12.52	11.86 ± 10.76	16.97 ± 9.96	10.45 ± 9.48	0.000/0.998	0.017/0.667	0.041/0.536	0.560/0.089
HF (10^3 ms^2)	4.34 ± 5.32	2.52 ± 2.93	3.03 ± 3.15	1.53 ± 1.84	0.010/0.731	0.108/0.362	0.113/0.354	0.227/0.226
LF/HF (N/A)	7.99 ± 4.91	5.74 ± 3.55	8.06 ± 4.76	8.65 ± 4.19	0.006/0.792	0.581/0.085	0.945/0.051	0.002/0.862
MSE_1 (N/A)	0.77 ± 0.19	0.85 ± 0.23	0.90 ± 0.20	0.85 ± 0.28	0.035/0.562	0.367/0.147	0.008/0.767	0.896/0.052
MSE_2 (N/A)	1.20 ± 0.86	1.19 ± 0.47	1.18 ± 0.41	1.04 ± 0.39	0.955/0.050	0.352/0.153	0.867/0.053	0.242/0.215
MSE_3 (N/A)	2.55 ± 2.41	1.85 ± 1.70	2.05 ± 2.05	1.45 ± 1.39	0.055/0.486	0.220/0.231	0.239/0.217	0.357/0.151
α_1 (N/A)	1.50 ± 0.16	1.50 ± 0.17	1.50 ± 0.15	1.59 ± 0.16	1.000/0.050	0.018/0.660	0.945/0.051	0.009/0.742
α_2 (N/A)	0.36 ± 0.27	0.51 ± 0.40	0.37 ± 0.32	0.31 ± 0.26	0.016/0.674	0.438/0.121	0.863/0.053	0.006/0.787
Valsalva test								
MEAN (ms)	821 ± 96	745 ± 104	810 ± 95	719 ± ± 97	0.000/0.986	0.000/0.959	0.597/0.082	0.241/0.216
SDNN (ms)	77.91 ± 27.86	61.89 ± 22.24	69.33 ± 17.94	53.25 ± 22.61	0.000/0.953	0.006/0.786	0.097/0.382	0.095/0.386
RMSSD (ms)	38.35 ± 17.25	30.70 ± 14.97	36.26 ± 15.79	23.96 ± 10.62	0.008/0.766	0.001/0.903	0.531/0.096	0.044/0.524
PNN50 (%)	13.73 ± 9.20	9.90 ± 8.69	14.12 ± 10.98	6.08 ± 6.04	0.022/0.634	0.000/0.954	0.839/0.055	0.051/0.497
LF (10^3 ms^2)	8.27 ± 6.71	6.35 ± 4.86	5.99 ± 3.47	3.82 ± 3.40	0.045/0.519	0.087/0.402	0.042/0.530	0.024/0.617
HF (10^3 ms^2)	2.32 ± 2.65	1.72 ± 1.81	1.96 ± 1.43	0.97 ± 0.89	0.099/0.379	0.041/0.533	0.392/0.137	0.079/0.419
LF/HF (N/A)	5.20 ± 4.41	5.01 ± 2.71	3.89 ± 2.03	4.97 ± 4.14	0.764/0.060	0.215/0.235	0.089/0.398	0.960/0.050
MSE_1 (N/A)	0.81 ± 0.22	0.79 ± 0.21	0.86 ± 0.18	0.81 ± 0.24	0.650/0.074	0.409/0.131	0.283/0.188	0.598/0.082
MSE_2 (N/A)	1.13 ± 0.31	1.11 ± 0.35	1.17 ± 0.38	1.07 ± 0.30	0.753/0.061	0.225/0.228	0.513/0.100	0.652/0.073
MSE_3 (N/A)	1.61 ± 1.08	1.71 ± 1.26	1.78 ± 1.38	1.45 ± 0.50	0.662/0.072	0.234/0.221	0.505/0.102	0.294/0.182
α_1 (N/A)	1.56 ± 0.19	1.58 ± 0.17	1.51 ± 0.21	1.59 ± 0.20	0.510/0.101	0.106/0.366	0.292/0.183	0.828/0.055
α_2 (N/A)	0.72 ± 0.23	0.70 ± 0.24	0.77 ± 0.23	0.89 ± 0.23	0.639/0.075	0.035/0.559	0.355/0.152	0.000/0.959
Orthostatic test								
MEAN (ms)	745 ± 114	686 ± 98	757 ± 100	661 ± 84	0.002/0.876	0.000/0.969	0.589/0.084	0.261/0.202
SDNN (ms)	42.36 ± 19.77	33.95 ± 16.52	41.19 ± 18.67	30.23 ± 14.27	0.011/0.722	0.013/0.708	0.761/0.061	0.334/0.161
RMSSD (ms)	21.70 ± 13.95	16.34 ± 11.65	23.81 ± 13.37	14.49 ± 7.56	0.019/0.656	0.002/0.871	0.428/0.124	0.487/0.107
PNN50 (%)	5.25 ± 10.05	2.95 ± 6.75	7.16 ± 13.23	1.31 ± 2.42	0.166/0.282	0.008/0.756	0.328/0.164	0.398/0.134
LF (10^3 ms^2)	2.21 ± 4.35	1.39 ± 1.89	1.20 ± 0.77	0.99 ± 1.00	0.105/0.367	0.754/0.061	0.092/0.391	0.510/0.101
HF (10^3 ms^2)	1.00 ± 1.56	0.69 ± 1.57	0.86 ± 0.81	0.45 ± 0.53	0.201/0.248	0.211/0.239	0.618/0.079	0.412/0.129
LF/HF (N/A)	3.71 ± 4.39	3.57 ± 3.02	2.24 ± 1.75	3.49 ± 2.50	0.823/0.056	0.124/0.337	0.041/0.535	0.903/0.052
MSE_1 (N/A)	1.07 ± 0.36	1.01 ± 0.30	1.16 ± 0.31	1.01 ± 0.33	0.267/0.198	0.068/0.446	0.255/0.206	0.984/0.050
MSE_2 (N/A)	1.42 ± 0.94	1.26 ± 0.38	1.27 ± 0.38	1.23 ± 0.43	0.179/0.269	0.781/0.059	0.277/0.192	0.800/0.057
MSE_3 (N/A)	1.66 ± 1.14	1.55 ± 1.19	1.42 ± 1.11	1.39 ± 1.10	0.623/0.078	0.909/0.051	0.355/0.152	0.525/0.097
α_1 (N/A)	1.43 ± 0.26	1.44 ± 0.26	1.34 ± 0.34	1.43 ± 0.31	0.951/0.050	0.200/0.249	0.141/0.312	0.938/0.051
α_2 (N/A)	0.77 ± 0.29	0.93 ± 0.40	0.79 ± 0.37	0.89 ± 0.25	0.011/0.725	0.222/0.230	0.836/0.055	0.550/0.091

P_{Mcp}—the significance test between the male controls and patients with depression; P_{Fcp}—the significance test between the female controls and patients with depression; P_{Cmf}—the significance test between the male and female controls; P_{Pmf}—the significance test between the male and female patients with depression. P_{Mcp} and P_{Fcp} indicate the simple effect of *Depression* on heart rate variability of the males and females respectively. P_{Cmf} and P_{Pmf} indicate the simple effect of *Gender* on heart rate variability of the controls and patients with depression respectively, Power—statistical power.

Table 3
The significant parameters during the resting, deep breathing, Valsalva, and orthostatic test.

Measurements	Subjects	Resting	Deep breathing	Valsalva	Orthostatic
Time domain	Male controls vs male patients	All	All	All	MEAN, SDNN, RMSSD
	Female controls vs female patients	All	All	All	All
	Controls vs patients	All	All	All	All
Frequency domain	Male controls vs male patients	None	All	LF	None
	Female controls vs female patients	HF	LF	HF	None
	Controls vs patients	HF	LF, HF	LF, HF	None
Nonlinear	Male controls vs male patients	MSE_1, α_1	MSE_1, α_2	None	α_2
	Female controls vs female patients	MSE_1	α_1	α_2	None
	Controls vs patients	MSE_1, α_1	MSE_3	None	MSE_1, α_2

The effect of gender-related depression on HRV is explored on the basis of the effects of *Depression* and *Gender* interaction on HRV through two-way ANOVA. Our results indicate the same effect of depression on HRV between males and females at rest. Voss et al. (2011) also surveyed the effect of gender-related depression and analysed the integrating effect of the interaction between *Depression* and *Gender* on all HRV parameters in rest through multivariate ANOVA. They found no remarkable integrated interaction in rest. However, when subjects are exposed to deep breathing and Valsalva stress, the effect of gender-related depression of LF/HF, MSE_1 and α_2 on HRV is observed, suggesting that the reactive mechanism of ANS to stress is different between male and female patients with depression. Voss et al. (2011) further revealed that *Depression* and *Gender* remarkably have an integrating interaction effect on BPV and that ANS is altered differently in male and female patients with depression compared with that of the controls; furthermore, ANS of females may be altered to a greater extent than that of males (Voss et al., 2011). Gender effect can interfere with the interpretation of the difference between controls and patients with depression. Thus, gender effect should be considered when frequency domain and nonlinear parameters are used to analyse the HRV of patients and controls. Gender difference is vital in studies on the physiological characteristic of patients with depression. The effect of depression on HRV of each gender should be investigated. For instance, considering the effect of gender, a high accuracy is achieved when depression is examined using HRV. Gender can be regarded as a feature to establish models, or models can be established with each gender. Gender difference can be utilised to study the high incidence of depression in females, and gender bias should be further explored in clinical and public health.

Limitations should be noted. Firstly, additional subjects should be included in future studies. Secondly, if numerous subjects are classified by other factors, such as age and depression severity, then results become more accurate. In our study, age and depression severity are not explored because of sample size. The age of subjects is between 20 and 40 years, and the severity of depression shows no significant difference between male and female patients according HAMD scores. Moreover, other factors, such as smoking status, alcohol use and habitual physical activity, greatly influence the modulation of ANS (Blom et al., 2009; Malpas et al., 1991; Niedermaier et al., 1993). These factors should be considered in establishing models in future studies.

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Conflict of interest

The authors declare no conflict of interest in this study.

Contributors

Danni Kuang contributed to data processing, manuscript preparation and modification. Rongqian Yang, Shanxing Ou, and Chuanxu Song were involved in study design and manuscript modification. Liqian Cui and Shiyuan Kuang participated in subject selection and data acquisition. Xiuwen Chen, Lei Zhang and Ruixue Lv participated in data processing.

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