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Gender-dependent impact of major depression on autonomic cardiovascular modulation

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ABSTRACT

Depression has been shown to increase the risk for cardiovascular disease (CVD) more strongly in women than in men. Although the underlying mechanisms are unknown, a putative role of increased sympathetic modulation has been suggested for the association of CVD and depression. The aim of this study was to investigate possible gender-associated differences of autonomic function in healthy volunteers and patients suffering from major depressive disorder (MDD).

Linear as well as non-linear measures of heart rate variability (HRV), blood pressure variability (BPV) and baroreflex sensitivity (BRS) were obtained in each 18 male and 18 female unmedicated patients and respective control subjects.

Gender differences were detectable in healthy subjects showing predominant sympathetic modulation in males. This was most obvious in BPV analysis. These gender differences were abolished in patients suffering from MDD, mainly due to altered autonomic modulation in female patients.

Our results indicate that BPV is more sensitive to reveal depression-associated changes of autonomic function as compared to HRV. Moreover, female patients contribute most to the overall difference between patients and controls. The shift in the balance of autonomic function in women might account for the increased prevalence of CVD in these patients.

1. Introduction

Major depression has been shown to exhibit a mild, yet detectable and putatively clinically relevant influence on autonomic modulation of the heart (Koschke et al., 2009; Rottenberg, 2007). Heart rate variability (HRV) is a well-established method to estimate mainly the influence of vagal modulation on the heart. Here, recorded heart rate time series may be processed in a linear or non-linear fashion in order to gain insights into the variability or complexity of the underlying modulating systems. Healthy physiological function is characterized by a complex interaction of multiple control mechanisms (e.g., on the heart rate) that enable individuals to adapt to unpredictable changes of everyday life. Therefore, linear calculations using rather simple measures (e.g., standard deviation) to describe the variability in a series of heart beats are not sufficient to explain such complex systems. As already implied by its name, 'non-linear dynamics' can describe complex systems in which output is not proportional to input due to many interacting regulatory mechanisms. One way to measure system complexity is to calculate the so-called entropy (Pincus, 1991). Here, non-linear entropy is a measure of the amount of information needed to predict future states of the system. The more complex the dynamics are, the larger is the entropy. Larger entropy physiologically means that the system might be more responsive to different strains.

The principle approach of data processing can be transferred to other biosignals such as the systolic and the diastolic blood pressures leading to the calculation of blood pressure variability (BPV) (Voss et al., 2006; Voss et al., 2009), mainly indicating sympathetic modulation (Grassi et al., 2010). This close association of sympathetic

Abbreviations: ANOVA, analysis of variance; BBI, beat-to-beat interval; BDI, Beck's depression inventory; BPV, blood pressure variability; BRS, baroreflex sensitivity; bslope, bradycardic slope; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSM-IV, Diagnostic and statistical manual of mental disorders, 4th edition; ECG, electrocardiogram; GIF, graphics interchange format; HAMD, Hamilton depression rating scale; Hc, compression entropy; HF, high frequency component of HRV; HRV, heart rate variability; ln, natural logarithm; LF, low frequency component of HRV; MANOVA, multivariate analysis of variance; MDD, major depressive disorder; MSNA, muscle sympathetic nerve activity; n.a., not applicable; NN, normal-to-normal (heart beat); phvar, probability of high variability; plvar, probability of low variability; PPA, Poincaré plot analysis; RMSSD, square root of the mean squared differences of successive NN intervals; RR-inteval, R-wave to R-wave interval (ECG); SBP, systolic blood pressure; SCID, structured clinical interview for DSM disorders; SD, standard deviation; SPSS, statistical package for the social sciences; STAI, state-trait anxiety inventory; tslope, tachycardic slope.

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activity and BPV has first been shown in animal experiments (Oosting et al., 1997), and has later been confirmed in humans *inter alia* by a direct microneurographic approach (Dell'Oro et al., 2003; Grassi, 2009). Furthermore, baroreflex sensitivity (BRS) characterizes the interplay between heart rate and blood pressure regulation, thereby mainly reflecting vagal modulation (Gerritsen et al., 2000; La Rovere et al., 1995). Watkins and Grossman (Watkins and Grossman, 1999) further suggested that low BRS may be a marker of increased risk of cardiac events associated with depression.

Previous research has provided a plethora of evidence of an autonomic imbalance in patients suffering from MDD. Changes were observed both in the sympathetic (Barton et al., 2007; Esler et al., 1982; Scalco et al., 2009; Veith et al., 1994) and in the parasympathetic division (Boettger et al., 2009; Koschke et al., 2009; Quick et al., 2010; Ruhland et al., 2008). Thus, previous studies provided support for the hypothesis of an overactive sympathetic branch (e.g., Barton et al., 2007), accompanied by decreased vagal modulation. The latter was predominately demonstrated for the heart rate component (Agelink et al., 2002; Agelink et al., 2004; Boettger et al., 2008). Since such a shift might eventually increase the risk for life-threatening arrhythmias, previous and current work aims to identify additional factors in order to implement risk stratification strategies in depressed patients. One major question in this respect is whether gender differences regarding autonomic balance can be observed in patients with MDD, particularly since the clinical presentation and the incidence of MDD varies between sexes (Moller-Leimkuhler, 2007). Major depression is twice as common in women as in men (Kessler et al., 1993; Weissman et al., 1993).

Several studies have shown gender-related differences in healthy, middle-aged subjects regarding sympathetic and parasympathetic modulation (Bigger et al., 1995; Gerritsen et al., 2000; Hogarth et al., 2007), while others were unable to demonstrate differences (Fu et al., 2005; Ng et al., 1994). Most studies presented evidence for increased heart rate variability and parasympathetic modulation in women, mainly using the high frequency power of the frequency domain or respiratory sinus arrhythmia (Bigger et al., 1995; Kuo et al., 1999; Ryan et al., 1994; Snieder et al., 2007). Likewise, lower central sympathetic output to the periphery and lower vasoconstrictor responses were demonstrated in women by the assessment of muscle sympathetic nerve activity (MSNA) to cold pressor and isometric handgrip tests (Hogarth et al., 2007). In contrast, systolic and diastolic BPV, and particularly their LF components, have been shown to be higher in women than in men (Laitinen et al., 1999). Some discrepancies of previous studies might be caused by the number of included participants and respective statistical power or by age-related changes of autonomic function influencing putative differences between genders (Kuo et al., 1999). In addition, insights into autonomic regulation and the characterization of HRV, BPV and BRS parameters have progressed over the years. For instance, the LF parameter of the frequency domain of HRV was initially interpreted as a marker for sympathetic modulation, while more recent studies have indicated that it most likely reflects baroreflex function.

Moreover, differences in HRV between men and women have rarely been assessed using non-linear methods (Ryan et al., 1994; Snieder et al., 2007; Stein et al., 2009), although more information can be derived from these more novel methods. Furthermore, the influence of gender on BPV has not been a subject of extensive investigation to date.

Therefore, we aimed to test two hypotheses in our study. Firstly, we wanted to demonstrate differences in autonomic function between depressed subjects and healthy controls by means of the analysis of HRV as well as by BPV and BRS. Secondly, we aimed to investigate to what extent MDD influences differences of autonomic function in male and female subjects. This was achieved by obtaining measures of HRV, BPV and BRS from 36 patients and 36 matched controls.

Table 1
Demographic and clinical data of participants.

	Controls		Patients	
	Female	Male	Female	Male
N	18	18	18	18
Age (years; mean ± SD)	30 ± 5	34 ± 7	31 ± 6	35 ± 8
Body mass index (kg/m²)	23.7 ± 4.9	22.9 ± 3.7	24.1 ± 5.6	22.3 ± 6.6
Smoker/nonsmoker	0/18	2/16	1/17	3/15
Duration of disease (years)	N.a.	N.a.	5.6 ± 8.7	5.0 ± 6.1
HAMD	N.a.	N.a.	23 (11–33)	20 (6–44)
BDI	N.a.	N.a.	25 (12–41)	22 (4–31)
STAI (X1)	N.a.	N.a.	51 (32–67)	59 (30–77)
STAI (X2)	N.a.	N.a.	56 (39–70)	58 (36–76)

HAMD — Hamilton depression rating scale; BDI — Beck's depression inventory; STAI — state–trait anxiety inventory; and N.a. not applicable. There were no significant differences between controls and patients. Data are presented as mean ± SD.

2. Materials and methods

2.1. Participants

Thirty-six Caucasian patients (18 male/18 female) suffering from an acute recurrent episode of MDD and 36 controls matched with respect to age, weight and gender were investigated. Table 1 depicts demographic and clinical data for both groups. In particular, participants were matched for age, since this has been shown to influence most of the parameters assessed in this study (Boettger et al., 2010). Patients admitted to our inpatient ward were diagnosed by a staff psychiatrist. All patients fulfilled DSM-IV criteria for MDD and had not taken antidepressants for at least 8 weeks prior to hospital admission. Diagnosis was confirmed by means of a structured clinical interview for DSM-IV axis I disorders (SCID, (First, 2005)). Control subjects were recruited from hospital employees (n = 2), medical students (n = 9) and the general community (n = 25) by local newspaper and flyer advertisement. Patients with any sign of mood-congruent or incongruent delusions as well as any suspicion of hallucinations were not included into the study. Similarly, control subjects did not take any medication. Significant medical or psychiatric diseases (additional to MDD in patients) were examined by thorough clinical investigation and SCID (also in controls).

In order to assess the severity of depressive symptoms, the Hamilton depression rating scale (HAMD, (Hamilton, 1960)) and the Beck's Depression Inventory (BDI, (Beck et al., 1961)) were applied. For the assessment of anxiety, all participants were subjected to the State–Trait Anxiety Inventory for Adults (STAI, (Spielberger et al., 1979)).

This study is in accordance with the Declaration of Helsinki. Participants were thoroughly informed about the nature and aims of the examinations and were included in the study only after giving written informed consent to a protocol approved by the local Ethics Committee of the Medical Faculty of the Friedrich-Schiller-University Jena. Patients were especially informed that the rejection of participation in the study would not affect future treatment.

2.2. Data acquisition and preprocessing

Examinations were performed in a quiet room which was kept comfortably warm (22–24 °C) between 1 and 6 p.m. Subjects were asked to relax, breath regularly and move as little as possible. Respiratory rate was obtained for all participants.

The electrocardiogram (high resolution, 1000 Hz) was recorded for 30 min from two separate adhesive monitoring electrodes (Task Force Monitor®, CNSystems, Medizintechnik GmbH, Austria), which were placed on the chest wall to assure maximal R-wave amplitude.