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Associations between symptoms of depression and heart rate variability: An exploratory study

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Abstract

Major depressive disorder (MDD) is associated with decreased heart rate variability (HRV), a predictor of cardiovascular morbidity by many, but not all studies. This inconsistency could be due to the association of HRV with specific depressive symptoms. Here, we investigated the association of HRV parameters with components of depressive symptoms from 120 MDD patients, at baseline of a published trial comparing the effect of sertraline to transcranial direct current stimulation. We used Principal Component Analysis to extract components of the Hamilton Rating Scale for Depression (HAM-D-17), the Montgomery Asberg Depression Rating Scale (MADRS) and the Beck Inventory for Depressive Symptomatology (BDI). We constructed one equation of multiple linear

regression for each HRV parameter as the dependent variable, and the components of depressive symptoms of the three scales as the independent ones, adjusted for age and gender. A component of HAM-D-17 predicted LF/HF (low frequency/high frequency) and a component of MADRS predicted LF (low frequency). "Guilt" and "loss of interest/pleasure in activities" were present in the components of both scales, and the MADRS component also included "psychomotor retardation". These results suggest that melancholic features might be relevant for the association between MDD and HRV. Considering multiple comparisons, these results are preliminary.

Keywords: depressive symptoms; major depressive disorder; heart rate; melancholic features; melancholia; cardiovascular disease.

1. Introduction*

Major depressive disorder (MDD) is associated with cardiovascular disease (CVD) (Kemp et al., 2015; Kemp and Quintana, 2013). One potential explanation for this association is autonomic nervous system dysfunction (Carney et al., 1995), particularly in more severe (Kemp et al., 2014c; Stein et al., 2000), and melancholic cases (Kemp et al., 2014c), which may increase risk for developing CVD, and worsen prognosis for those with preexisting CVD (Lichtman et al., 2014). Heart rate variability (HRV), an index of beat-to-beat variations in heart rate, may reflect the health of the autonomic nervous system such that high HRV reflects healthy cardiac function, while low HRV reflects autonomic inflexibility, which may, over time, increase the risk for CVD (Kemp and Quintana, 2013; Kemp et al., 2012). Low HRV has even been shown to predict future adverse cardiovascular events in those without any prior history of CVD (Hillebrand et al., 2013).

More than two decades ago, it was reported that patients with depression display decreased HRV (Carney et al., 1995); since that time, two meta-analyses have reported that depression is associated with reductions in HRV, findings associated with a modest effect size (Kemp et al., 2010; Rottenberg et al., 2007). However, contradictory data have been reported, leading some to suggest that HRV reductions in depression are driven primarily by antidepressants (Kemp et al., 2014a; Licht et al., 2008; O'Regan et al., 2015). A possible explanation for these inconsistencies might be the complexity of the depressive syndrome, which is comprised of multiple symptoms from different domains; some specific symptoms may be associated with low HRV, while others may have no relationship with HRV (Rottenberg et al., 2007). Consequently, when all the symptoms are evaluated simultaneously, the associations of specific symptoms with low HRV may not be identified.

In prior study (Brunoni et al., 2013a), we demonstrated that depressed subjects display lower HRV values compared to healthy controls. These patients were assessed at baseline in a double blind clinical trial (Brunoni et al., 2013b). Patients displayed reductions in various measures of HRV including the Root Mean Square of the Successive Differences (RMSSD; $t_{117} = 2.86$; $p = 0.005$; Cohen's $d = 0.35$) and High Frequency (HF) HRV ($t_{117} = 3.77$; $p < 0.001$; Cohen's $d = 0.45$) (Brunoni et al., 2013a). In the present study, we

* MDD: major depressive disorder; CVD: cardiovascular disease; HRV: heart rate variability; tDCS: transcranial direct current stimulation; RMSSD: root mean square of the successive differences; FFT: Fast Fourier Transform; LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency; HAM-D-17: Hamilton Rating Scale for Depression, 17-item version; MADRS: Montgomery Asberg Depression Rating Scale; BDI: Beck Depression Inventory.

investigated whether distinct components of depressive symptoms, in these same patients, are differentially associated with changes in HRV.

2. Methods

2.1 Subjects

We evaluated data from 120 patients collected during a baseline assessment for previously published, double-blind, randomized, controlled clinical trial, designed to assess the combined safety and efficacy of tDCS vs. a common pharmacological treatment (sertraline hydrochloride, 50 mg/d) for MDD (Brunoni et al., 2013a). Patients were antidepressant-free, with moderate to severe, nonpsychotic, unipolar MDD, with low risk for cardiovascular disease. Patients were excluded if they had other Axis I disorders, including alcohol dependence or harmful substance use (although comorbid anxiety disorders were allowed); any Axis II disorders; previous neurological conditions (epilepsy, traumatic brain injury, stroke, etc.); any severe, life-threatening Axis III disorders; and specific contraindications for tDCS (e.g., metallic plates in the head).

The study was approved (registration number: 041/16) by the Ethics Committee of the University Hospital of the University of Sao Paulo, in accordance with the Helsinki Declaration.

2.2 Procedures

2.2.1 Depression scales

Trained researchers assessed depression severity at baseline before starting antidepressant treatment. These scales included the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17) (Hamilton, 1960) and the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). All patients also completed the Beck Depression Inventory (BDI) (Beck et al., 1961).

2.2.2 HRV recording

To assess HRV, electrocardiography was recorded in a quiet, temperature-controlled room set at 22^{O}C. A digital electrocardiograph Wincardio (Micromed, Brasilia, Brazil), with a sampling rate of 250 Hz, was used to acquire the records. The electrodes were placed on the limbs, and the signals were recorded for 15 minutes. We used Wincardio 4.4 to generate the beat-to-beat R-R interval series from the higher R-wave amplitude lead (usually D2). The artifacts and ectopic beats were corrected by the spline cubic interpolation.

The following variables were extracted:

(a) for the time-domain, we used RMSSD (root mean square of the successive differences), which reflects the variance between successive beat-to-beat intervals with higher values reflecting higher variability. RMSSD is the most appropriate time-domain measure for short-duration ECG recordings (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). .

(b) for the frequency-domain, a Fast Fourier Transform (FFT) method was used. Oscillatory components present in the time series were labeled as LF (low frequency, with frequencies of 0.04 to 0.15 Hz) and HF (high frequency, with frequencies of 0.15 to 0.4 Hz) bands. After extracting these parameters, we also calculated the LF/HF ratio, another commonly reported measure in the frequency-domain.

2.3 Statistical analysis

In order to investigate the association of HRV with specific components of depressive symptoms, we first extracted principal components from each scale (HAM-D-17, MADRS and BDI) using Principal Components Analysis, including Varimax rotation and Kaiser normalization. We established the number of components by a visual analysis of scree plots of each scale (Figures 1, 2 and 3). Scores of each component are their factorial scores. We constructed equations using multiple linear regression analysis, including all components of depressive symptoms from the three scales, gender and age as independent variables and one parameter of HRV as the dependent variable. We used a stepwise backward procedure to achieve the final model, maintaining variables with $p < 0.10$. We chose the backward procedure given that it tends to be less prone to selection bias due to collinearity among the predictors compared to the forward procedure (Hutmacher and Kowalski, 2015). We ran this procedure for each parameter of HRV including RMSSD, LF, HF and LF/HF ratio. We had considered performing a multivariate analysis including all the HRV parameters together. However, we chose to analyze each HRV parameter individually, considering that most of these parameters reflect distinct aspects of the autonomic system. For example, LF may reflect baroreflex modulation (Goldstein et al., 2011), while HF reflects parasympathetic activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

We maintained the significance level at $p<0.05$ and did not correct for multiple comparisons; thus, the study should be considered a exploratory.

3. Results

3.1 Participant characteristics

Sociodemographic and clinical characteristics of the sample are displayed in **Table 1**. Briefly, our sample comprised 82 women and 38 men (mean age = 42 years, SD=12; education = 13.7 years, SD = 4) with depression of moderate severity (HAM-D-17 mean score = 21.8; SD=4). For technical reasons, HRV data were not collected from all participants; HRV measures were obtained from a total of 118 patients.

3.2 Components of depressive symptoms

Based on the Scree plot we found six components in the HAM-D-17, two components in the MADRS and three in the BDI. The components of the HAM-D-17 were: a) Component 1 (“sleep”): item 4 (early insomnia), item 5 (middle insomnia) and item 6 (late insomnia); b) Component 2 (“somatic anxiety”): item 11 (somatic anxiety) and item 15 (hypochondria); c) Component 3 (“weight”): item 12 (somatic symptoms) and item 16 (loss of weight); d) Component 4 (“core symptoms”): item 1 (depressed mood), item 2 (feelings of guilt), item 3 (suicidal thoughts) and item 7 (work and activities); e) Component 5 (“somatic agitation”): inverse relationship between item 9 (agitation) and item 13 (general somatic symptoms); f) Component 6 (“genital”): item 14 (genital symptoms).

The components of the MADRS were: a) Component 1 (“mood”): item 1 (apparent sadness), item 2 (reported sadness), item 3 (inner tension) and item 9 (pessimistic thoughts); b) Component 2 (“anhedonia- retardation”): item 6 (concentration difficulties), item 7 (lassitude), item 8 (inability to feel) and item 9 (pessimistic thoughts).

Finally, the components of the BDI were: a) Component 1 (“mood-anhedonia”): item 1 (sadness), item 2 (pessimism), item 3 (failure), item 4 (loss of pleasure), item 12 (loss of interest), item 13 (indecisiveness), item 15 (loss of energy), item 17 (irritability);

b) Component 2 ("negative self-image"): item 3 (failure), item 5 (guilty feelings), item 6 (punishment feelings), item 7 (self-dislike), item 8 (self-criticalness), item 9 (suicidal thoughts or wishes), item 10 (crying), item 11 (agitation) and item 14 (worthlessness); c) Component 3 ("general physical"): item 16 (changes in sleeping pattern), item 18 (changes in appetite), item 20 (tiredness or fatigue) and item 21 (loss of interest in sex).

3.3 Association between depressive symptom components and HRV parameters

After controlling for age and gender, multiple linear regression analysis revealed that LF was predicted by component 4 of the HAM-D-17 (i.e. "core symptoms" including: depressed mood, feelings of guilt, suicidal thoughts and lack of disposition for work and other activities), and LF/HF ratio by component 2 of the MADRS (i.e. "anhedonia-retardation" including lack of concentration, lassitude, and pessimistic thoughts). The BDI did not predict any HRV parameter **(Table 2).**

4. Discussion

Here we show that depressive symptoms in the HAM-D-17 (i.e. component "core symptoms" including depressed mood, feelings of guilt, suicidal thoughts and lack of disposition for work and other activities) predict the LF HRV component, while depressive symptoms in the MADRS (i.e. component "anhedonia- retardation" including lack of concentration, lassitude, inability to feel, and pessimistic thoughts) predict the LF/HF ratio. These results support the concept that HRV is associated with some depressive symptoms, but not with all (Rottenberg et al., 2007).

4.1 Components of depressive symptoms, melancholic features and HRV

HRV was associated with components of symptoms including "loss of interest/pleasure" and "guilt"; symptoms considered to be melancholic by the Manual of Diagnostic and Statistics of Mental Disorders of the American Psychiatric Association (DSM – 5). Reinforcing their potential relevance, "loss of interest/pleasure" and "guilt" were present in the component from HAM-D-17 as well as the component from MADRS. Furthermore, the MADRS component associated with HRV also include the symptom "psychomotor retardation", another characteristic of melancholia. In line with our findings, melancholic features have previously been related to HRV parameters and poor cardiovascular prognosis. For example, anhedonia (loss of interest/pleasure) has been reported to be a predictor of cardiovascular events (Leroy et al., 2010) and to be associated with increased sympathetic sensitivity during pregnancy (Pearson et al., 2012); guilt, in normal volunteers has been associated with prolonged cardiac sympathetic arousal as measured by pre-ejection period (PEP) (Fourie et al., 2011). Another melancholic symptom, late insomnia, assessed by daily diary measures of late insomnia has been reported to have an inverse association with Cardiac Vagal Control, which is based on HF HRV (Rottenberg et al., 2007).

Considering diagnosis instead of symptoms, an earlier study reported that melancholic depressed patients, had higher HR, but not HF HRV (respiratory sinus arrhythmia) relative to non-depressed controls (Moser et al., 1998). The increase in heart rate found in their melancholic patients, was explained as a possible reflex of increased sympathetic autonomic system or an increased autonomous heart rate (Moser et al., 1998). Similarly, a recent study investigating the impact of melancholia over HR and HRV, compared to non-melancholia and control, found that melancholic patients had increased HR relative to non-melancholic ones and healthy controls (Kemp et al., 2014c); while measures of HF HRV in

melancholic patients were decreased relative to healthy controls, but not to non-melancholic patients (Kemp et al., 2014c). An explanation for these findings could be that vagal function (reflected by HF HRV) distinguishes melancholic patients from healthy controls, while non-vagal components of heart rate may distinguish disorder subtypes (i.e. melancholia versus non-melancholia) (Kemp et al., 2014c).

Considering the cross-sectional nature of our study, it is not possible to know whether depressive symptoms lead to changes in HRV/dysfunctional autonomic function, or changes in HRV/dysfunctional autonomic function leads to depression. Traditionally, depression has been considered the predictor for changes in HRV/dysfunctional autonomic function. However, HRV at baseline, have predicted incident depressive symptoms at follow-up, indicating that both directions may exist (i.e. melancholic symptoms were not analyzed separately) (Jandackova et al., 2016).

4.2 Components of depressive symptoms, non-melancholic features and HRV

Of relevance, considering non-melancholic symptoms, the HAM-D-17 component that predicted LF, included suicidal thoughts. Prior study has revealed associations between suicidality and respiratory sinus arrhythmia (Rottenberg et al., 2002). Suicidality has been related to the capacity of dealing with stress. Depressed women with suicidal attempt, while submitted to the Trier Social Stress Test, showed lower HF HRV compared to depressed women without suicidal attempt, indicating reduced capacity to regulate response to stress in those with suicidal attempt (Wilson et al., 2016). Also, an absence of SSRIs' effect on vagal system under stress, while starting antidepressant treatment in adolescents, may be an explanation for suicidality in this population (Kemp et al., 2014b). On this matter, stress has been shown to increase HR and decrease HF HRV, effects that may be influenced by escitalopram, depending on the age of patients (Kemp et al., 2014b). In adults aged 25 years and above, escitalopram has increased HF HRV at rest, but not at stress and decreased HR at rest and attenuated the increase on HR under stress; effects that had not occurred in those under 25 years. Thus, in young patients, SSRIs would not lead to a benefit on dealing with stress by attenuating the reduction of vagally mediated response to stress, assessed by the absence of attenuating the increase in HR under stress (Kemp et al., 2014b). Considering the association between reduced vagal response and suicide attempt mentioned above (Wilson et al., 2016), such lack of preserving the vagally mediated response to stress could be related to the increase in suicidality in depressed young patients starting a SSRI treatment. Our results showing the association between LF HRV and suicidal ideation support that this relationship might also be mediated by non-vagal mechanisms. Little is known regarding the direction of this relationship, if increased suicidality leads to changes in HRV/autonomic system or a dysfunctional HRV/ autonomic system leads to an increase in suicidality. Lower cardiovascular fitness at age of 18 years has been prospectively associated with an increased risk of suicide attempt or death by suicide in adulthood (Aberg et al., 2014), suggesting that the direction might be the autonomic system acting on suicidality. Additionally, the association between high resting HR and suicide may also be explained by sharing biological mechanisms, such as genetic factors or neural determinants (Lemogne et al., 2011).

Contrasting with our findings regarding the inclusion of suicidal thoughts -a psychological symptom- in one of the components of depressive symptoms related to HRV, de Jonge et al. found an association of low HRV parameters (SDNN, LF, and HF) with a group of somatic depressive symptoms (sleeping difficulties, fatigue and appetite problems), but not with cognitive ones (de Jonge et al., 2007). This contrast may be explained by the fact that, although being psychological, suicidal thoughts was in a HAM-

D-17 component including the core symptoms of depression (i.e. depressed mood and anhedonia) and melancholic features (i.e. anhedonia and feelings of guilt) (de Jonge et al., 2007). Intriguingly, the associations with LF were in the opposite directions, in our study higher scores on the component 2 of MADRS predicted higher LF, whereas in the de Jonge et al. study, somatic symptoms were associated with low LF (de Jonge et al., 2007). Such discrepancy may be explained if we consider that LF may reflect a mix of sympathetic and parasympathetic activity (Bassett, 2016). In line with this view, the relationship of depression with LF has diverged among the studies; it has been reported to be associated with low LF (Yeh et al., 2016), and with high LF (Wang et al., 2013).

In our sample, the depressive components that predicted HRV did not include anxiety related and sleep related symptoms. Besides late insomnia, as commented above (Rottenberg et al., 2007), HRV has been related to other sleep symptoms. Increased scores on subjective sleep quality assessed with the Pittsburgh Sleep Quality Index were positively correlated with increased LF/HF ratio in subjects with MDD (Yang et al., 2011). Regarding anxiety symptomatology, anxiety has been associated with decreased baroreflex sensitivity, which is a reflex of lower parasympathetic activity and a predictor of cardiovascular mortality (Virtanen et al., 2003). This contrast with our results suggests that differences in methods, samples, presence of moderators and other factors including comorbidities (i.e. potential confounders) may influence the results. A topic that deserves future studies.

4.3 Components of depressive symptoms not relevant for HRV

In our patients, most components of depressive symptoms were not associated with HRV. Previously, studies have reported an absence of relationship between some depressive symptoms and HRV. For example, as mentioned above, psychological symptoms were not associated with HRV (de Jonge et al., 2007). A cross sectional study to determine whether psychological factors (somatization, depression, anxiety, hostility and phobicity) were associated with HRV, blood pressure variability and baroreflex sensitivity, also found that psychological factors were non-related to HRV (Virtanen et al., 2003). No association between HRV and irritability has been found in patients with MDD (Verhoeven et al., 2011). As mentioned above, considering that it is an initial study, our positive and negative results deserve future confirmation.

4.4 Clinical and physiological signification of LF and LF/HF ratio

Various studies have suggested that LF should not be considered as an indicator of sympathetic activity and LF/HF ratio should not be considered as an indicator of sympathovagal balance. Factors supporting these criticisms include the influence of LF peak by factors other than sympathetic and parasympathetic system; the existence of conditions that may provoke simultaneous increases in sympathetic and parasympathetic activity or simultaneous decreases in both systems (i.e. not always an increase in one and decrease in the other autonomic system); and the relationship between HRV and sympathetic and parasympathetic activity is not necessarily linear (Billman, 2013). As mentioned above, LF may represent a mix of sympathetic and parasympathetic activity (Bassett, 2016). Additionally, studies in humans and animals have indicated that LF and LF/HF ratio may be an index of baroreflex function, which in turn could affect cardiac autonomic function (Goldstein et al., 2011). Additionally, as pointed out by Reyes del Paso et al. (2013), HRV parameters may reflect diverse information about autonomic regulation and be influenced by distinct factors, for example, HF is influenced by respiratory activity; and LF is influenced by blood pressure control mechanisms (Reyes del Paso et al., 2013). Therefore, it might be too early to conclusively designate physiological meanings to LF and LF/HF ratio. Notwithstanding, studies continue to support the association of LF/HF

ratio with depression (Kemp et al., 2012; Kemp et al., 2010) and its value as indicator of cardiac morbidity (Davydov et al., 2007). For example, LF/HF ratio was the most important predictor of the magnitude of flow-mediated dilation of the brachial artery (i.e. an indicator of endothelial function) in 47 patients with ischemic heart disease (Watanabe et al., 2013). Increased values of LF/HF ratio have been associated with complications in patients with myocardial infarction (Ablonskytė-Dūdonienė et al., 2013) and also with tricyclic intoxication (Dinleyici et al., 2013).

4.5 Contribution of the study

Our findings showing that not all depressive symptoms, but only some components, are relevant for the relationship with HRV, may be fundamental to the possibility of reverting the HRV/autonomic system dysfunction by achieving remission of these components and not the current concept of depression remission. For example, the previous reported study with our sample, applying the wide used concept of remission based on HAM-D-17 scores < 7, revealed that the association of MDD was independent of the state of depression (remission versus non-remission) (Brunoni et al., 2013a). However, remitted patients, according to that criteria, may still have residual symptoms of a component that is significantly relevant for the relationship with HRV. Consequently, it is possible that the reversion of changes in HRV/autonomic system associated with depression could require the remission of the specific components of depressive symptoms that are related to HRV.

4.6 Limitations

Some limitations of our study should be considered. We used three scales of depression instead of only one, and performed several comparisons without correcting the level of significance, thus our results should be considered preliminary. Although preliminary, it is worth noting that the melancholic symptoms "loss of interest" and "guilt" were present in both components that predicted HRV, one from HAM-D-17 and one from MADRS.

4.7 Conclusions

Our results support the concept that there might exist an association between HRV and some component of depressive symptoms, but not all symptoms. In particular, increased LF and LH/HF were predicted by a component of depressive symptoms from HAM-D-17 and one from MADRS, both characterized by melancholic symptoms and sharing the symptoms "loss of interest/pleasure" and "guilt". If confirmed, our data support the view that the presence of melancholic features might place depression as a distinct identifiable mood disorder (Parker et al., 2010).

Future research should consider the relevance of melancholic features and their remission on the relationship between HRV parameters and depression.

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Conflicts of interest

LB reports personal fees from Libbs Laboratory and from Apsen Laboratory, outside the submitted work.

The other authors have no conflicts of interest to disclose.

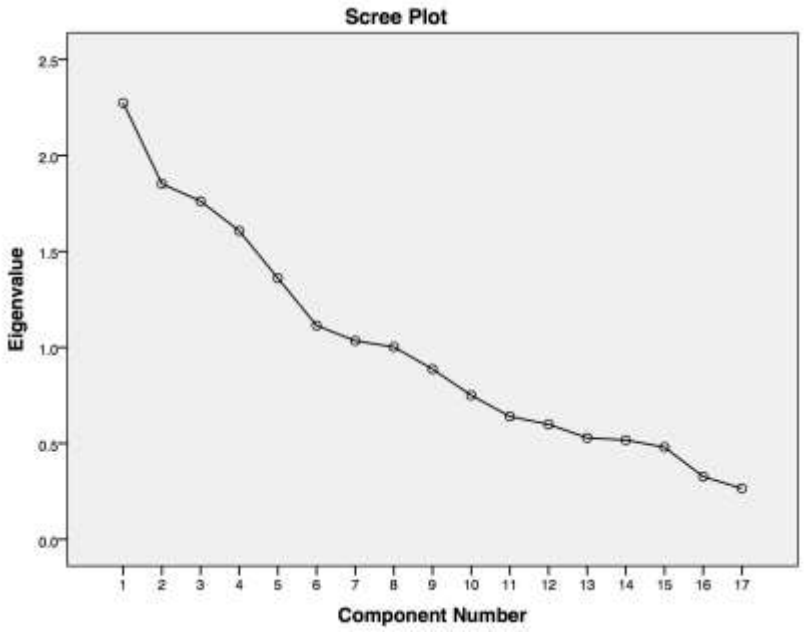

Figure 1. Scree plot HAM-D-17

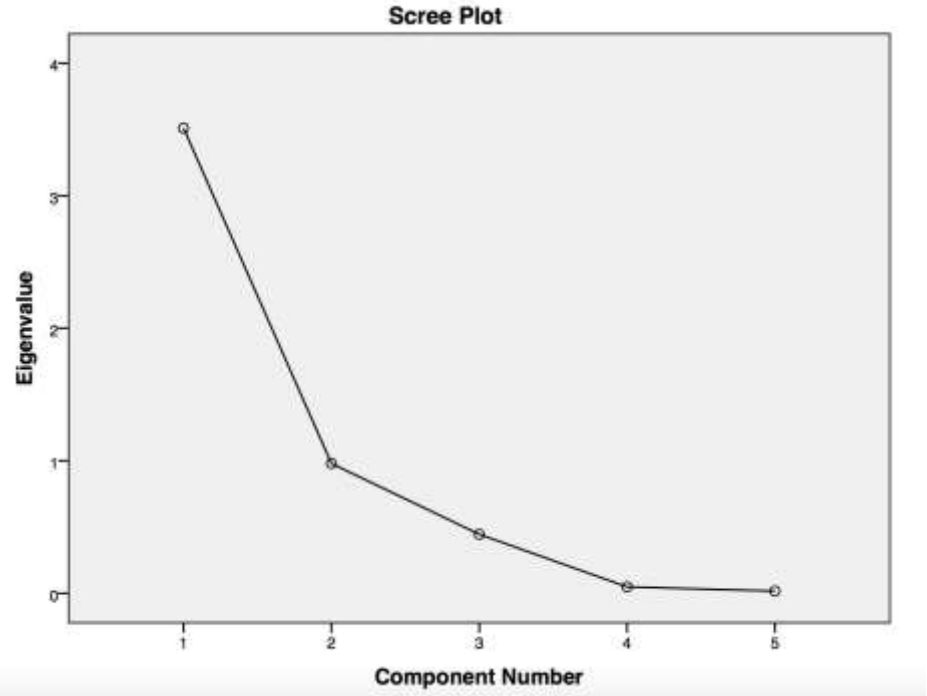

Figure 2. Scree plot MADRS

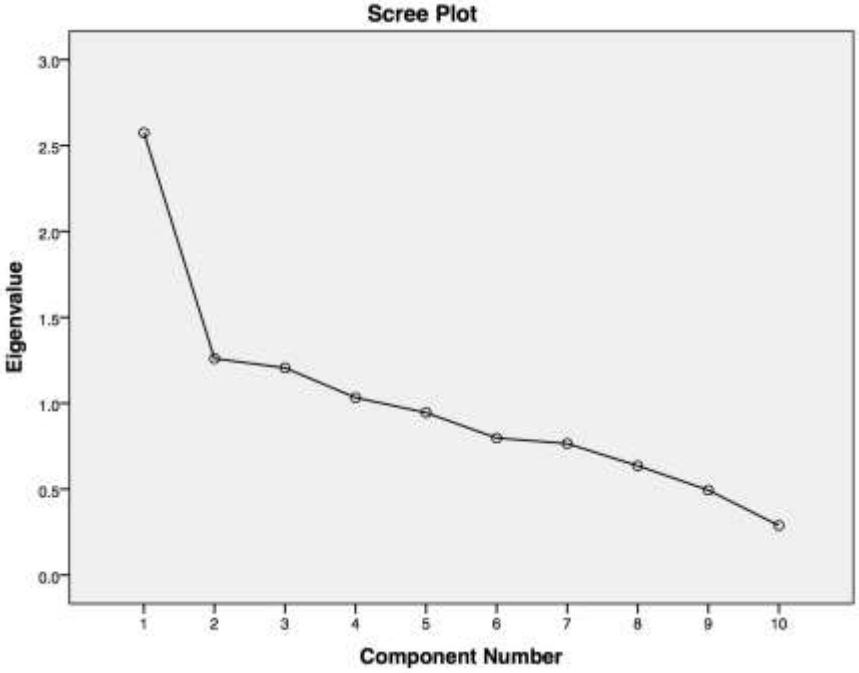

Figure 3. Scree plot, BDI

Table 1. Sociodemographic characteristics of the sample

Numerical variables	**Mean**	**+ SD**
Age, years	42	12
Years of schooling	13.7	4
Baseline scores		
MADRS	30.6	6
HAM-D-17	21.8	4
BDI	32.7	9
Clinical Global Impression	4.4	1
Categorical variables	***n***	**%**
Women	82	68
Depression subtypes		
Atypical	63	52
Melancholic	31	26
Treatment-resistant depression		
≤ 1 failed trial	67	56
> 2 failed trials	26	21
Clinical comorbidities		
Current smokers	21	17
Hypothyroidism	16	13
Hypertension	27	22
Psychiatric comorbidities		
General Anxiety Disorder	60	50
Social Phobia	15	12
Panic Disorder	17	14
Dysthymia	31	26

HAM-D-17:17-item version of Hamilton Rating Scale for Depression; MADRS: Montgomery-Åsberg Depression Rating Scale; BDI: Beck Depression Inventory.

Table 2. Relationship between a parameter of HRV and components of depressive symptoms: multiple linear regression analysis, adjusted

Dependent variable (Parameters of HRV)	Independent variables (Components of depressive symptoms)	β	CI 95%	*p*
RMSSD	Constant		5.53 – 6.59	<0.001
	HAM-D-17 Component 4	-0.17	-1.11 – 0.04	0.073
	MADRS Component 2	0.14	-0.08 – 1.08	0.093
LF	Constant		22.80 – 31.73	<0.001
	HAM-D-17 Component 4	-0.18	-9.37– 0.45	0.075
	MADRS Component 2	**0.22**	**0.66 – 10.55**	**0.029**
HF	Constant		19.60 – 29.76	<0.001
	HAM-D-17 Component 4	-0.19	-11.14 – 0.04	0.058
	MADRS Component 2	0.16	-0.66 – 10.55	0.080
LF/HF	Constant		1.19 – 1.40	<0.001
	HAM-D-17 Component 4	**0.21**	**0.01 – 0.23**	**0.021**

HRV: heart rate variability; HAM-D-17:17-item version of Hamilton Rating Scale for Depression; MADRS: Montgomery-Åsberg Depression Rating Scale; RMSSD: square root of the mean of squares of diferences between sucessive NN intervals. HF: high frequency; LF: low frequency; LF/HF: ratio between LF and HF; CI 95%: confidence interval of 95%
An equation of multiple linear regression analysis was built for each parameter of heart rate variability as the dependent variable and the 11 components of the depression scales as the independent ones. The equations were adjusted for age and gender. A Final model was achieved using stepwise procedure maintaining variables with significance below 0.10.
MADRS Component 2: item 6 (concentration difficulties), item 7 (lassitude), item 8 (inability to feel) and item 9 (pessimistic thoughts).
HAM-D-17 Component 4: item 1 (depressed mood), item 2 (feelings of guilt), item 3 (suicidal thoughts) and item 7 (work and activities).

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HIGHLIGHTS

- Heart rate variability may be related with some, but not all, depressive symptoms.
- Melancholic symptoms may be essential for the relation with heart rate variability.
- Studying remission of specific depressive symptoms and heart rate variability is needed.