Author's response to reviews

Title: Altered cardiac autonomic nervous function in depression

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Author's response to reviews: see over
Melissa Norton

Editor-in-Chief of Journal of BMC Psychiatry

Dear Dr Norton

The authors thank the reviewers for their comments on our manuscript entitled: “Altered cardiac autonomic nervous function in depression” We have addressed the reviewers’ comments, provided below.

Answer questions: highlighted in red in the manuscript.

Dr Jess Fiedorowicz comments:

Major Compulsory Revisions

1) The following concern was brought up on prior review: “There is considerable potential for selection bias in this sample. Those with depression are a very select group. They have required hospitalization, yet were not suicidal and haven’t been on medications for six months. They are without anxiety and without any risk factors for vascular disease (both of which are highly common among individuals with depression). While the authors have included these exclusion criteria because of impact on these outcome measures, they have created a group with major depression that is difficult to imagine and unlikely to be representative.” The authors should minimally include this limitation in their discussion.

While we acknowledge certain limitations of these data, patients were eligible for recruitment to the study using strict selection criteria applied to minimise confounding factors in the relationship between HRV and depression. We have however, updated the Discussion section of the manuscript to address the limitations of this select sample with respect to generalisability (pg 15-16).
2) Prior reviewers asked about treatment. The added statement adds a treatment: “Selective serotonin-reuptake inhibitors (SSRIs) were routinely used to treat to patients with major depression.” though does not characterize the treatment observed in this sample. What % were treated with SSRIs and what % with other agents?

All participants were treated with SSRIs (40mg/d paroxetine [n=15], 20mg/d escitalopram [n=18], 100mg/d sertraline [n=20]). We have updated the text accordingly (pg 10).

3) The authors do not appear to control for multiple comparisons and the subsequent potential for Type I error needs to be discussed as a limitation.

Thank you for this suggestion, we have revised the contents of the strengths and limitations section on page 16.

4) The following statement does not appear accurate and appears to be mis-cited (citing a depression paper): “At present, the domain parameters of HRV is as a reliable indicator of the risk for malignant ventricular arrhythmias and sudden cardiac death than ventricular late potentials, left ventricular ejection fraction, QT dispersion and the level of cardiac function [23].”

Thank you to the reviewer for picking this up, this is the incorrect reference and has been updated accordingly: (38): Rodrigues TR, Miranda RC, Lichter AP, Lobo NC, Figueroa CS, da Consolação Moreira M. Heart rate variability in myocardial infarction with and without malignant arrhythmias: comparison with heart transplant recipients and normal subjects. Pacing Clin Electrophysiol. 1996,19:1857-1862.

5) The measures of autonomic function are indirect measures and this limitation should be acknowledged. The discussion of limitations as a whole could be better developed.

Overall, we have considered the reviewer’s comments and have further developed the Limitations section of the Discussion (pg 16).
6) A table comparing sociodemographic and clinical characteristics of cases and controls would be of value.

Thank you, we have added this table (table 1).

Table 1 Demographic data between the control and depression groups (n=53), means and Standard Error of the Mean (SEM) unless indicated

<table>
<thead>
<tr>
<th>Items</th>
<th>Control</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>42.1±11.61</td>
<td>40.9±10.5</td>
</tr>
<tr>
<td>(Ranges)</td>
<td>20-63</td>
<td>20-65</td>
</tr>
<tr>
<td>Gender (male/female) (n)</td>
<td>27/26 (51%/49%)</td>
<td>25/28 (47%/53%)</td>
</tr>
<tr>
<td>Resting SBP (mm Hg)</td>
<td>125±20</td>
<td>130±22</td>
</tr>
<tr>
<td>Resting DBP (mm Hg)</td>
<td>74±9</td>
<td>70±10</td>
</tr>
<tr>
<td>Smokers/non-smokers (n)</td>
<td>24/29 (45%/55%)</td>
<td>28/25 (53%/47%)</td>
</tr>
</tbody>
</table>

No significant differences in the demographic variables (age, sex, blood pressure, smoking) between the control and depression groups, were observed.

Minor Essential Revisions

1) Abbreviations vary through the manuscript (e.g. SDNNR and SDNN). Please review all abbreviations for consistency of use.

Thank you, we have revised the contents to ensure consistency.

2) The final sentence of the abstract conclusions extends beyond the scope of this paper. The manuscript does not assess induced arrhythmia or cardiac events.

We have revised the contents of the abstract.

3) Were the assessments of arrhythmias on EKG conducted blind to group status.

Please indicate if so or add to limitations if not.

Yes, arrhythmias assessments were conducted by technicians who were blinded to the status of the participant. We have added this content on pg 7.

4) The prevalence of paroxysmal ventricular tachycardia appears high. Could the authors clarify the threshold by which this diagnosis was made?

In China, we use repeated ECG readings (3+) to diagnose paroxysmal tachycardia.
We have updated the Methods section to include this classification.

Discretionary Revisions:
1) Background, sentence 2, please rewrite.
We have revised the contents of the Background section.

2 Reviewer: Juan Sztajzel
1. The authors noted that all patients were treated with selective serotonin reuptake inhibitors (SSRIs), but they did not give any information in how far these agents, which are known to have an effect on cardiac rhythm, were responsible for the observed HRV changes.
As all participants were receiving medication, we would not expect this to impact to overall between group differences observed. However, we do acknowledge that SSRI have been shown to impact on cardiac rhythm, thus it is possible that using a sample comprising those on anti depressants may have diluted or alternatively, magnified our findings, compared with a sample from the general population, or using depressed individuals who were not on medication. We have expanded the Discussion section to include this (pg 16).

2. In table 2 the authors exposed the frequency domain indices, but again the units are not clear. Their results for the LF and HF indices are expressed in ms units, but they appear to be more like normalized units (nu). What do the authors think?
The absolute values are expressed in ms$^2$. We have revised the contents of the Methods and table 2, 3 to ensure this is clear.

3. Reviewer: Elisabetta Patron
Reviewer's report:
Minor Essential Revisions
1) On page 10 the authors stated: “the practical clinical outcome of these data showed increased sympathetic nerve and reduced parasympathetic nerve
activities, suggesting dysregulation of sympathetic and parasympathetic coordination in depression.”

LF index reflect both parasympathetic and sympathetic activity, therefore if LF index is elevated it does not mean necessarily that sympathetic activity is increased. Moreover LF activity reflects baroreflex activity and is highly influenced by position of the subject during recording. The same is for LF/HF ratio, if LF reflects both parasympathetic and sympathetic activity LF/HF ratio may reflect a change in parasympathetic vagus nerve activity, and may be influenced by far more factors. Therefore the interpretation of the result on these two indices (LF and LF/HF) should be explained with more caution.

Indeed, low-frequency power (LF, 0.04–0.15 Hz, ms$^2$) is a combination of sympathetic and parasympathetic activity; with high-frequency power (HF, 0.15-0.4 Hz, ms$^2$): describing parasympathetic tone. The ratio of low-high frequency power (LF/HF) reflects the balance of sympathetic and parasympathetic innervations. We hypothesise that the decreased HF and increased LF and ratio of LF/HF observed in our study (using frequency domain analysis) suggests reduced parasympathetic nerve activities and the unbalance of sympathetic and parasympathetic innervations, which may reflect dysregulation of sympathetic and parasympathetic coordination in depression. We have updated pg 8 to include greater detail in the methods, time domain and frequency domain indices absolute measures of HRV, p8 and pg 13, and the Discussion.

2) In Table 2 the authors report Frequency domain indexes (i.e. LF, HF and LF/HF) in ms, but in the text they stated they calculated and reported Frequency domain indexes as absolute values, expressed in ms2. Also the authors stated they calculate normalized indexes, but from the result section and from Table 2 it is not clear if the absolutes values or the normalized indexes were used for the analysis, the authors should disambiguate this issue.

Frequency domain indexes were treated as absolute values in our manuscript, expressed in ms$^2$, because absolute values have been shown to be more sensitive than the normalized indexes in the analyse of 24h HRV. We have added to and revised the contents in the
Methods and Table 2, 3 to clarify this.

3) The authors report correlation between depressive severity index and LF/HF and between depressive severity index and SDNN. For completeness, the authors should report information on correlations between all HRV indexes (both time and frequency domain) and depression severity index.

We specifically chose to report domain parameters SDNN and LF/HF. SDNN reflects total variability in the period of recording, therefore SDNN has been shown to be the most significant prognostic value among time domain parameters (Sredniawa B, Musialik-Lydka A, Herdyńska-Was M, Pasyk S The assessment and clinical significance of heart rate variability Pol Merkur Lekarski. 1999 Dec;7(42):283-8). The value of LF/HF came from the ratio of absolute values of the LF and HF power for each patient, it is as an indicator of the sympathovagal balance of the autonomic nervous system, (Wang HM, Huang SC, SDNN/RMSSD as a Surrogate for LF/HF: A Revised Investigation. Modelling and Simulation in Engineering 2012, inpress). The aim of our study was to investigate any correlations between the extent of autonomic nervous system dysfunction and severity of depression.

We have added and revised the contents of the Methods.

Discretionary Revisions
1) In the background and/or discussion session the authors could refer to the wide literature associating depression to reduced HRV in patients with cardiovascular disease (among which: Bigger et al., 1993; Carney et al., 2001; Rich et al., 1988; Gehi et al., 2005; Stein et al., 2000; Martens et al., 2008; Patron et al., 2012) and refer to the review of Carney and colleagues (2002) on Depression as a risk factor for cardiac mortality and morbidity.

Thank you for these suggestions, we have added References (1), (5), (16), (17), (18), (19), (33), (39).

Yours sincerely
Michael Berk  cont’d…

Michael Berk  
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