Author's response to reviews

Title: Altered cardiac autonomic nervous function in depression

Authors:

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Version: 2 Date: 12 April 2013

Author's response to reviews: see over
Melissa Norton

Editor-in-Chief of Journal of BMC Psychiatry

Dear Melissa

Many thanks for your great assistance, the following responses to reviewers' comments have been addressed.

Answer questions: highlighted in red in the manuscript.

Dr Jess Fiedorowicz comments:

Reviewer's report
Title: Altered cardiac autonomic nervous function in depression
Version: 3 Date: 23 November 2012
Reviewer: Jess Fiedorowicz
Reviewer's report:
Major Compulsory Revisions
1) 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.

In our study, exclusion criteria in those patients with depression are need. They were required hospitalization for treatment (Selective serotonin-reuptake inhibitors (SSRIs) were routinely used to treat to patients) and checking the Heart Rate Variability (24h), not found in patients with suicide behavior, without prominent anxiety in according with HAMA score <14 points, Comorbid medical conditions including diabetes mellitus, hypertension and coronary disease were also excluded.

We have revised the contents in the pg 5, the paragraph of Subjects, line 9-14.
2) The depression severity index can be better described in the methods. 
The depression severity index: Summing the scale items to produce a raw score by the method of Zhou [14], further SDS can be derived by utilizing the formula “ZSDS Index=Raw Score/80”. 
The contents in the pg 7, the paragraph of methods, the depression severity index, line 1-3.

3) The authors report excluding baseline EKG abnormality yet are studying arrhythmias. This is confusing. 
They should be excluded comorbid coronary disease. 
The contents in the pg 5, the paragraph of Subjects, line 13-14.

4) A one hour time range is included for the 24 ambulatory EKG. 
The data was collected between 8:00 am to 8:00 am the next morning. 
We have revised the contents in the pg 6, the paragraph of Dynamic electrocardiogram Collection, line 1-2.

5) The methods report participants could not be on antihypertensives but later mention holding beta-blockers. 
They were not allowed to take agents, such as Beta Blockers. 
The contents in the pg 6, the paragraph of Experiment Processes, line 1, 2, 4.

6) The interpretation of time domain HRV measures is over-simplified. 
Exactly, we have revised and added the contents in the pg 7-8, the paragraph of “Time domain and frequency domain indices absolute measures of HRV”, line 6-16.

7) There is no mention of how arrhythmias were classified, nor any inter-rater reliability or blinding in this assessment. 
The arrhythmias were classified by percentage, the contents in the pg 8, the paragraph of Statistical Analyses, line 2.

Minor Essential Revisions
1) The manuscript will require some copyediting. There are also some sections where citations seem appropriate (e.g. first sentence of background).
Michael Berk  cont’d…

We have revised the contents in the pg 4, the paragraph of background, line 1-3.

Particular sections that could be reworded to improve clarity of presentation include:

a) Abstract, conclusion section
   We have revised the contents in the pg 3, Abstract, conclusion section.

b) Latter portion of background
   We have revised the contents in the pg 4, Latter portion of background, line 4-7. Discussion, paragraph 8
   We have revised the contents in the pg 14, Discussion paragraph 7, line 4,5,7,8,9.

2) Figure 3 connects the lines across discrete categories of arrhythmias. A bar graph might be a clearer way to present these results which are not changing over time or by some continuous measure.
   Exactly, Figure 3 has been changed to bar graph.

3) Methods, Subjects, paragraph 2. I presume the authors mean HAMA > 14 to exclude.
   Exactly, we have revised the contents in the pg 5, Methods, Subjects, paragraph 1, line 11.

4) The rationale for 15 minutes of rest is not clear prior to 24 hour ambulatory monitoring.
   The data was collected between 8:00 am to 8:00 am the next morning.
   We have revised the contents in the pg 6, the paragraph of Dynamic electrocardiogram Collection, line 1-2.

5) The authors should specify whether relative or absolute measures are used on frequency domain indices.
   The absolute values are expressed in ms$^2$ on frequency domain indices. in the pg 8, the paragraph of Time domain and frequency domain indices absolute measures of HRV line 6-7.
Michael Berk cont’d…

6) Results, analysis of correlation. It is unclear what negative correlation is being referred to in the last sentence.

Pearson relativity analysis shows a negative correlation between the depressive severity index and the value of SDNNR. We have revised the contents in the pg 11, the paragraph of the analysis of the correlation, line 7-8.

8) Results, rates of arrhythmia. The figure but not the text makes clear which specific arrhythmias were significant.
We have revised in the figure3.

9) Discussion, paragraph 6. The relevance of the first portion of this paragraph is less clear.
We have revised in the Discussion, in the pg 13, paragraph 5, line 6-10.

10) Written informed consent is mentioned twice in methods.
We have revised to once in the methods, consent, in the pg 6, line 1.

Reviewer: Juan Sztajzel

The study is interesting. The authors posed an important question which was adequately described and analyzed.

Specific comments:

Methods Section:
1. The authors should give some information on the antidepressive treatment that the study individuals were taking. Indeed, antidepressive drugs (selective serotonin reuptake inhibitors or tricyclic antidepressants) may have an effect on heart rate. Thus, this may have had some impact on the 24-hour Holter recordings.
The patients all were required hospitalization for treatment (Selective serotonin-reuptake inhibitors (SSRIs) were routinely used to treat to patients).
We have revised and added the contents in the pg 5, the paragraph of Subjects, line 9-10.

Results section:
1. The authors should give more details on the chapter « The rates of arrhythmia in depression ». What does it mean to have higher rates of premature atrial or ventricular beats? They
should show some quantitative data of the arrhythmias retrieved from the Holter recordings.
For instance, did the study individuals have 10 or 100 premature beats per hour?
Exactly, there were higher incidence (%) of premature atrial or ventricular beats in depressive group. Incidence (%) of the arrhythmias was used in our article according to some references, For instance, Djillali Annane et.al. Incidence and Prognosis of Sustained Arrhythmias in Critically Ill Patients. American Journal of Respiratory and Critical Care Medicine, Vol. 178, No. 1 (2008), pp. 20-25.

Discussion and conclusion:
The authors found that HRV was diminished in depressive individuals, associating an increase of the sympathetic tone and a reduction of the parasympathetic tone with an increased incidence of arrhythmias.

1. What is the practical clinical outcome of these data?
We found that individuals with depression are at greater risk induced arrhythmia and adverse cardiovascular events because of the imbalance of the autonomic nervous system. We have revised and added the contents in the pg 15, the paragraph of Discussion and conclusions, line 4-5.

2. Are these individuals at higher risk of having a major cardiac event?
Yes, they are at greater risk induced arrhythmia and adverse cardiovascular events. We have revised and added the contents in the pg 15, the paragraph of Discussion and conclusions, line 4-5.

3. What would be the impact of this finding on any further treatment in these individuals? 4. Would they need to take any betablockers?
Patients treated with antidepressants and betablockers for future treatment.
We have added the contents in the pg 15, the paragraph of Discussion and conclusions, line 6-7.

Reviewer: Elisabetta Patron
Reviewer's report:
Major Compulsory Revisions
1) The authors should propose a justification for their choices of HRV indices,
Michael Berk  cont’d…

since there are other possibilities that they did not use. In particular, there is no
general accordance on the interpretation of SDANN index, which the authors
reported as a sensitive indicator of sympathetic nerve function. Because of HRV is a
physiological phenomenon by the sinus cardiac cycle fluctuates around its mean heart rate, is
a quantitative non-invasive and highly reproducible index of cardiac autonomic function, and
also is an important indicator of balance sympathetic and parasympathetic tone. It reflects the
autonomic nerve system of heart function by the dynamic controlling effect. Please see the
paragraph of methods, time domain and frequency domain indices absolute measures of HRV,
p7, line 1-5.

We have added the contents of the interpretation of SDANN index in the pg 7, the paragraph
of methods, time domain and frequency domain indices absolute measures of HRV, p7, line
9-12.

2) It is unclear how LF power and HF power were obtained. According to the
Method section they should have calculated LF power and HF power, that are
usually expressed in ms$^2$, but in Table 2 they are expressed in ms (please see
Task Force, 1996). The authors should explain precisely how frequency domain indexes were
obtained.
We have added and revised the contents in the pg 8, the paragraph of Methods, time domain
and frequency domain indices absolute measures of HRV, line 7.

3) pg 12 the authors stated that there is a “linear and positive relation between
depression severity and the level of cardiac autonomic dysfunction”, but both the correlations
reported are not significant (p>0.05). If the correlations are not
significant the discussion must be changed. Moreover, I’d like to see the
correlations (r’s and p’s) between all HRV indexes and depression level.
Exactly, we have revised the contents in the pg 11, the paragraph of the analysis of the
correlation, line 3-4, 7-8.

Discretionary Revisions
Michael Berk cont’d…

1) There are circadian variations in HRV, and most can be attributed to sleep or variation in activity, since the authors recorded 24h HRV, they ought add information on sleep time and, if possible, on daytime activity.

Exactly, that will be our further study.

Yours sincerely

Michael Berk
Professor of Psychiatry, Deakin University