Author’s response to reviews

Title: A systematic review for the antidepressant effects of sleep deprivation with repetitive transcranial magnetic stimulation

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Author’s response to reviews:

Qiwen Mu, M.D., Ph.D.
Sept. 18, 2015
RE: BPSY-D-15-00120

Dear Editor and Reviewers,

Thank you for giving us a chance to revise our manuscript, and also thanks a lot for the
constructive suggestions which would help us improve the quality of the paper both in expressions and in depth. Based on the reviewers’ comments and suggestions, we have revised our manuscript. Here we submit a revised version of our manuscript with the title “A systematic review for the antidepressant effects of sleep deprivation with repetitive transcranial magnetic stimulation”. In this response letter, we have addressed the referees’ comments point-by-point. Please feel free to contact us if there are any other issues need us to address.

Sincerely yours,

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The following is a point-by-point response to the reviewers’ comments. All the revised contents have been highlighted by using "track changes" in the “Revised Manuscript with Track Changes”.

Section Editor:

The reviewers have raised important points. Please address all comments from the reviewers. In particular, be sure to address reviewer 1’s concerns and remove one of the studies that appears to be a conference abstract or explain why if must remain if indeed it is a separate study to the 2014 one that reviewer 1 has noted in their comments. Please ensure that you raise these concerns and discuss them in the limitations section of your manuscript. Please also ensure that you provide more detail of each author's contribution to the work.

Response: Thanks very much for the Section Editor’s comments. We have followed the reviewers’ suggestions and fully addressed their concerns. Also, we have discussed the reviewers’ concerns in the limitations section of our manuscript (Page 20, Line 23 to Page 21, Line 7). More details of each author's contribution to the work have been figured out in the revised manuscript (Page 22, Line 15 to Page 23, Line 2).

Page 20, Line 23 to Page 21, Line 7: Certain limitations exist in this systematic review. First, the outcome measures in Kreuzer’s study were calculated according to the original materials provided [32], which might lead to errors with the measurements. Second, potential publication bias might be an influence factor for the power of this systematic review. Third, the included RCTs did not report the methods of allocation concealment, which induced an unclear risk of bias for the study. Finally, the present review contained only three articles from two research
groups so that the total sample size was too small to accurately predict the effect of rTMS on SD. More RCTs with larger sample sizes are warranted.

Page 22, Line 15 to Page 23, Line 2: QT conceived and designed the study, participated in the literature searches and drafted the manuscript. GML participated in the design of the study and the literature search. AGW conceived and designed the study and screened the articles. TL contributed to the acquisition and selection of data, and helped to draft the manuscript. SGF performed the analysis. ZWG helped to extract the data and perform the analysis. HPC contributed to the quality assessment of the included studies. BH helped to analyze the characteristics of the included studies and helped to assess the studies’ quality. MAM contributed to the draft and the revision of the manuscript. JO helped to draft the manuscript. GQX revised the manuscript. QWM conceived of the study and revised the manuscript. All authors read and approved the final manuscript.

Reviewer #1: Although this paper is generally well presented, there are a few important concerns which must be addressed, and I really question the utility of undertaking a meta-analysis on so few studies, which come from only 2 research teams.

The Illic 2010 reference, one of the 4 studies included in the meta-analysis, is only an abstract which was presented at a conference. This explains why important information is missing about this study, as shown in Tables 1, 2 and Figure 2. I also don't see how this study fit the inclusion criteria as listed on page 8 and 9, as they don't have most of the details from the published abstract. For example there was no mention in the abstract that DSM criteria or MINI was used.

I am thus assuming the authors could not get further information about the study from Illic et al when they tried to contact them? It is very surprising if this work was presented at a conference meeting in 2010 and has not yet been published. Could it be that there were problems with the work, such that it could not be published?

Actually, what I strongly suspect is that the Illic 2010 study is actually exactly the same as the Kristic et al., 2014 study. The author lists overlap, the study design presented in Table 1 and 2 is identical, with the inclusion of 2 more participants only. Thus I do not believe these constitute independent studies and both cannot be included. If I am incorrect, and there were undertaken at different times with different participants, I still don't believe that Illic et al 2010 can be included if the results of this study have not be published (in more than a conference abstract presentation with no figures/tables and insufficient study details).

The issue with the Illic 2010 study, described above, combined with the skewed data from Eichhammer et al., 2002, mean only 2 studies can be included in the meta-analysis. Is this worthwhile? Would it just be better to describe the results from the 3 independent studies (Eichhammer et al., 2002; Kreuzer et al., 2012; Kristic et al., 2014) and discuss how they differ and what the overall findings might be?
The authors can no longer conclude anything about PSD vs TSD, nor the rTMS parameters which were most effective (1 vs 10 Hz as they have said) because the Illic 2010 results should not be included.

The data shown in Figure 4, 5 and 7 is no longer valid and needs to be removed.

Response: The reviewer is right. Because we had not been able to reach the authors of the Illic 2010 study, we could not identify whether it had been published or not. Now it has been proved that the Illic 2010 study is actually the same as the Kristic et al., 2014 study. We are so sorry for this technical error. In the revised manuscript, we have taken the reviewer’s suggestion and removed the Illic 2010 study from the data synthesis. The results of the remaining 3 independent studies (Eichhammer et al., 2002; Kreuzer et al., 2012; and Kristic et al., 2014) were just described and discussed how they differ and what the overall findings might be. The subgroup analyses were removed, as well as Figure 3, 4, 5, 6 and 7. The revised contents were highlighted by using “track changes” in the “Revised Manuscript with Track Changes” file.

Other more minor points:

1. Table 1 should detail the actually diagnostic criteria and tools used to assess depression.

   Response: The reviewer’s suggestion is well taken. We have added the diagnostic criteria and tools for depression in Table 1 (Page 14).

2. Figure 3: the authors state that the weight is a reflection of sample size, but this doesn't match with the numbers shown in Table 1. From Table 1 the larger sample is Kreuzer study, so shouldn't this have the greatest weight?

   Response: The reviewer is right. We feel sorry that we did not notice that problem. According to the reviewer’s suggestion above, we have just described the remaining 3 independent studies and removed the Figure 3.

3. There are a number of references which appear to be "Letters to Editor" or "Editorials". The authors should be quoting the original research articles, not commentaries or personal opinions. For example Epperson et al., 2014 - but I also wonder about reference 3, 16, 19, 54 and maybe others (I didn't check them all). There also appears to be an issue with the page numbers for ref 30.

   Response: Thanks very much for the reviewer’s suggestion. We have checked all the references and removed the inappropriate references from the manuscript. The citation of Epperson et al., 2014 and the reference 3 and 16 were removed. Although the reference 19 is a “Letter to Editor”, it is a classic literature, and the transcranial magnetic stimulation (TMS) is first referred in that article. Therefore, we did not remove reference 19 (now it is reference
11 in the revised manuscript), but we have added another reference to show additional
evidence (Reference 12). The reference 54 (now it is reference 51 in the revised manuscript)
is an abstract about rTMS. We listed it here because we had retrieved it through the database.
It is an evidence for the search strategy, so we kept this reference in the reference list, but
made a minor modification for the citation so that it can be figured out that it is an abstract
within a journal supplement. Also, we have checked the reference 30 (now it is reference 23)
for several times and found that the page numbers was indeed page 13-18, and according to
the norm of BMC Psychiatry, it was presented as page 13-8. Apart from these references,
we have also revised some other mistakes in the reference list, such as reference 47
(reference 40 in the revised manuscript).

4. The introduction is good but a bit long. Paragraph 2 could be removed for example, as not
directly relevant here.

Response: Thanks for the reviewer’s advice. We have shortened the introduction and
removed the unnecessary content from the manuscript.

5. There are numerous limitations which need to be discussed at the end of the manuscript,
including the fact that there are so few studies and appear to be from only 2 research groups,
as well as positive publication bias which doesn't not seem to be mentioned.

Response: Thanks for the reviewer’s suggestions. We have added the limitations as the
reviewer suggested. The revised limitations are as follows (Page 20, Line 23 to Page 21, Line
7):

Certain limitations exist in this systematic review. First, the outcome measures in Kreuzer’s
study were calculated according to the original materials provided [32], which might lead to
errors with the measurements. Second, potential publication bias might be an influence factor
for the power of this systematic review. Third, the included RCTs did not report the methods
of allocation concealment, which induced an unclear risk of bias for the study. Finally, the
present review contained only three articles from two research groups so that the total sample
size was too small to accurately predict the effect of rTMS on SD. More RCTs with larger
sample sizes are warranted.

Reviewer #2: The article is based on therapy for depression, which is a very important area of
research. It will be helpful for the fellow scientists and physicians. But I have some suggestions
regarding it.

Response: Thanks for the reviewer’s positive comment and helpful suggestions. We have
addressed the reviewer’s comments point-by-point as follows.
1. The abstract is well written but need to be more sophisticated. Introduction is appreciable and self-explanatory.

Response: Thanks for the reviewer’s comment and advice. We have revised the abstract to make it more sophisticated (Page 3-4).

2. The methodology section stated that there were no specific protocols. But for significant publication response, you need to have a protocol.

Response: Yes, the reviewer is right. In fact, we do have a kind of protocol in use, but it was not published, so we stated it in our manuscript that there were no specific protocols. To avoid confusion, we have deleted that sentence.

3. You need to show justification for the used timeline, 1985 to 2015.

Response: The reviewer’s suggestion is well taken. We have addressed the justification for the used timeline (1985 to 2015) in the search strategy (Page 7, Line 21):

Because rTMS was first proposed in 1985, the searches were limited to human studies published between January 1985 and March 2015.

4. In selection criteria, You could also exclude any pseudo-depression, history of hysteria or mania, alcoholics, ACTH hormonal abnormality, any hormonal impairment, congenital anomalies, and intake of any anti-depressants. Please clarify your second exclusion criteria.

Response: Thanks very much for the reviewer’s advice. We have added the contents in the selection criteria as suggested (Page 8, Line 10-13). Also, the second exclusion criterion has been clarified as: “Same study subjects were enrolled in other reports.” (Page 9, Line 4).

5. At the end of the assessment of bias, the articles with unclear bias could be eliminated.

Response: Thanks for the reviewer’s advice. We have re-described the assessment results of bias (Page 12, Line 1-11) and also have redrawn the risk of bias graph (Figure 2). The articles with unclear bias have been eliminated.

Page 12, Line 1-11:

3.2 Risk of bias in the included studies

Figure 2 shows the risk of bias assessments for the included studies. All the trials had reported the random sequence generation, but were determined with an unclear risk of allocation concealment. Only one study reported the blinding procedure of the participants and personnel in detail [40]: “All of the patients were naive to both TMS and partial SD; and thus, it was not likely that they could recognize the treatment modality”. The other two studies had unclear or
high risk of bias with respect to the procedures of the participants and personnel. One study had a high risk of incomplete outcome data [39]. The blinding of outcome assessment and selective reporting in the included trials were all of low risk. No other biases had been reported in the three included studies.

6. In outcome measures, please elaborate the calculation procedure of HRSD scores.

Response: The reviewer’s suggestion is well taken. We have elaborated the calculation procedure of HRSD scores in Page 10, Line 13-16:

The HRSD scores were calculated based on a multiple item questionnaire which was designed for an indication of depression, mainly including mood, feelings of guilt, suicide, insomnia, work and activities, retardation, agitation, anxiety, hypochondriasis, weight loss, somatic symptoms, and insight [45].

7. Didn't you need to contact with the corresponding authors of the selected articles? If yes, please mention it within the methodology.

Response: Yes, the reviewer is right. We did have contacted with the corresponding authors of the selected articles and we have mentioned that in the methodology (Page 10, Line 22-23):

The authors of the included articles were contacted for more detailed information about their studies.

8. Please elaborate the use of CGI scale and BfS scale and add a reference to it.

Response: The reviewer’s suggestion is well taken. We have elaborated the use of CGI scale and BfS scale and add references to them in Page 11, Line 3-9:

CGI is a 7-point scale commonly used in psychiatry, measuring the illness severity, global improvement or change, and the therapeutic response from subjective aspects, as it requires the surveyor to compare the subjects with typical patients in clinics [41]. CGI is usually used to measure depressive symptoms [46, 47]. BfS is a self-rating scale for the measurement of subjective well-being conditions. It is especially suitable to assess the rapid mood changes [48, 49].

9. The result section is in an organized manner. But, you need to focus all the significant outcomes and compare those with previous articles in the discussion. The discussion needs to have more comparison with previous articles.

Response: The reviewer’s suggestion is well taken. We have added more comparisons between the outcomes in our manuscript and those in previous articles. The addition is presented in the discussion as follows (Page 19, Line 5-13):
Although numerous systematic reviews and/or meta-analyses have been published and proved that rTMS was an effective treatment for depressive patients [52-56], there were few reviews addressing the combined therapy of rTMS with other antidepressant treatments. Only one recent meta-analysis conducted by Liu et al. [57] had reported an augmentative effect of rTMS on medication treatment for medication-resistant depression patients. Nevertheless, the study of Liu et al. did not concentrate on the combined use of rTMS and SD. In this work, we reviewed the literature on the effects of SD and rTMS co-therapy for depression and attempted to determine whether rTMS could augment the antidepressive effect of SD.

10. In conclusion, you stated <...including those who are medication-resistant >. Please mention the type/name of the medications to which they were resistant.

Response: The reviewer is right. We should have mentioned the type/name of the medications to support the statement “including those who are medication-resistant”. In the revised manuscript, we have rewritten the conclusion (Page 21, Line 9-17):

From this systematic review, an overview of the research for the combined use of rTMS and SD is presented. Only three studies are now available in the databases. Two of them showed augmentative effects of rTMS on SD in depressive patients; while the other one showed non-significant effects. The few publications limited a conclusive evidence for the therapeutic effects of SD and rTMS co-therapy in patients with depression. However, these studies provide a direction for future research of rTMS-SD co-therapy for depression. Further well-designed studies with a larger number of patients are highly warranted to confirm whether there is an augmentative antidepressant effect of rTMS on SD.

11. Try to add some more references. The referencing is good. Please double-check the reference no 7, 13, 27, 42, 47, and 54 which was found invalid by BMC online editorial manager system.

Response: Thanks very much for the reviewer’s reminding. We have double-checked the references, and we are puzzled about that these references were listed as invalid by BMC online editorial manager system. The reference 7, 13, 27, 42, and 47 (In the revised manuscript, it is reference 64, 6, 20, 35, and 40, respectively.) can be retrieved from PubMed, with the PMID: 24974667, 19014078, 20524444, 25313818, and 9881538, respectively. The reference 54 (Now it is reference 51) can be retrieved from the Cochrane Library.

Reviewer #3: Consider revising:

1. Further data need to be added to support the authors’ conclusions.

Response: Thanks very much for the reviewer’s suggestion. Indeed, the conclusions we made needed more data to support it. Because of the limited data available currently, we redefined
our conclusions. Also, in the Discussion section, we added the limitation about this issue. The revised conclusions (Page 21, Line 9-17) and the added limitation (Page 21, Line 4-7) are as follows:

Page 21, Line 9-17: From this systematic review, an overview of the research for the combined use of rTMS and SD is presented. Only three studies are now available in the databases. Two of them showed augmentative effects of rTMS on SD in depressive patients; while the other one showed non-significant effects. The few publications limited the further analysis for the therapeutic effects of SD and rTMS co-therapy in patients with depression. However, they provide a direction for future research of therapies for depression. Further well-designed studies with a large number of patients are highly warranted to confirm whether there is an augmentative antidepressant effect of rTMS on SD.

Page 21, Line 4-7: Finally, the present review contained only three articles from two research groups so that the total sample size was too small to accurately predict the effect of rTMS on SD. More RCTs with larger sample sizes are warranted.

2. Better justification is needed for the arguments based on existing data; or the clarity and/or coherence of the paper needs to be improved.

Response: The reviewer is right. We have changed the interpretation of the existing data to make a better justification for the arguments. Revisions have been made throughout the full text.

3. The interpretation seems slightly overly expressed. Since the studies included are very few, there should be no use of overly positive statements.

Response: We totally agree with the reviewer’s opinion. We have changed the interpretation of the data and avoided the overly positive expressions. The revised interpretation can be seen in the Abstract (Page 4, Line 4-7) and the Conclusions (Page 21, Line 9-17).

Page 4, Line 4-7: Conclusions: From this study, an overview of the publications concerning the combined use of rTMS and SD is presented, which provides a direction for future research of therapies for depression. More studies are needed to confirm whether there is an augmentative antidepressant effect of rTMS on SD.

Page 21, Line 9-17: From this systematic review, an overview of the research for the combined use of rTMS and SD is presented. Only three studies are now available in the databases. Two of them showed augmentative effects of rTMS on SD in depressive patients; while the other one showed non-significant effects. The few publications limited the further analysis for the therapeutic effects of SD and rTMS co-therapy in patients with depression. However, they provide a direction for future research of therapies for depression. Further
well-designed studies with a large number of patients are highly warranted to confirm whether there is an augmentative antidepressant effect of rTMS on SD.