Author's response to reviews

Title: Transcranial bright light treatment via the ear canals in seasonal affective disorder: a randomized, double-blind dose-response study

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Author's response to reviews: see over
Dear Dr. Ritter,

Thank you and the reviewers for your valuable comments and the opportunity to resubmit our manuscript entitled MS: 2097859221117993 – “Transcranial bright light treatment via ear canals in seasonal affective disorder: a randomized, double-blind dose-response study”.

We have addressed all the reviewers’ questions and comments in numerical order. Text changes are indicated by underlined text within the manuscript. The revised version of the manuscript has been reviewed and edited by a native English speaker for language and grammar.

We hope that the revised manuscript meets the standards for publication in BMC Psychiatry. We look forward to hearing from you.

Yours sincerely,

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Reviewer 1:

The authors' clarifications have been very helpful in evaluating the work. Previous work published by the same group (Can transcranial brain-targeted bright light treatment via ear canals be effective in relieving symptoms in seasonal affective disorder? - A pilot study. Med Hypotheses 2012, 78:511-515) suggests that TBL may ameliorate SAD symptoms, but was not placebo controlled. A similar argument as presented in the present manuscript based on response rates was provided in that study as well, negating a placebo effect; however, without a placebo control the argument still remains only a speculation. Without the addition of a placebo control, which would demonstrate that TBL improves SAD symptoms the negative findings of a dose response in the present study are only of marginal significance over the previously published work.

Major:

1. The authors have still not clarified whether the participants and physicians were blinded to receiving active treatment, not just the intensity. If they were, then that may serve to mitigate the concerns of a placebo effect. If this was the case, please clarify and report in the manuscript.

   *In this blinded study setting, both the researchers and subjects were blinded to receiving active treatment. We have added the following sentence to the methods section of the manuscript: “Both the research team and the patients were blind to the group assignment and receiving active treatment”. (Please see page 8, line 176)*

2. While the authors’ argument negating a placebo effect appears reasonable, it is nonetheless very concerning and troubling that the response rates based on SIGH-SAD and HAMA were 35-45% and 47-62%, which fall within the range of placebo response in previous studies, as mentioned by the authors in their response. Please discuss.

   *In a meta-analysis on earlier antidepressant studies the size of placebo effect was found to be 29.7% (Walsh et al. 2002) and accounted for 68% of the effect in the treatment group (Rief et al., 2009). It is assumed that sham devices have higher response rates than placebo pills in the treatment of depression (Kaptchuk et al., 2000). However, repetitive transcranial magnetic stimulation (rTMS) as a non-pharmacological and transcranially administered treatment has shown to have a lower placebo response than pharmacological therapy in major depression (Brunoni et al., 2009). In addition the subjects in this study were severely depressed, which decreases the effect of placebo (Kirsch et al., 2008). Thus it is not likely that the placebo response of transcranial bright light would be higher than the response seen in earlier antidepressant studies. The theoretical values for the size of the placebo effect (accounts for 68% of the effect in the treatment group) in this study (24-53%) would be in line with the size of the placebo reported in earlier studies with pharmaceuticals and conventional bright light.*


We have added the following sentence to the revised manuscript: “In a meta-analysis on earlier antidepressant studies the size of the placebo effect was found to be 29.7% (Walsh et al. 2002) and account for 68% of the effect in the treatment group (Rief et al., 2009). It is assumed that sham devices have higher response rates than placebo pills in the treatment of depression (Kaptchuk et al., 2000). However, repetitive transcranial magnetic stimulation (rTMS) as a non-pharmacological and transcranially administered treatment has been found to elicit even lower placebo response than pharmacological therapy in major depression (Brunoni et al., 2009). In addition, the subjects in this study were severely depressed, which decreases the effect of placebo (Kirsch et al., 2008). Assuming that the placebo response of transcranial bright light is in line with the placebo effect found in earlier antidepressant studies, it is not likely that the alleviation of the symptoms in this study would be entirely explained by means of placebo effect.” (See page 15, lines 357)

3. Please clarify the rationale for using the different doses. Since it appears that the major objective of the current study was to establish a dose response curve, the doses do not appear to be very different. Why did the authors not test a wider range of intensities?

In this study, the intensities of 1, 4 and 9 lumen (2400-21500lux) were utilized. As the reviewer suggested, it might have been beneficial to measure the effect of transcranial bright light also with lower light intensities. Since the initial hypothesis of this study was that the lowest dose used in this study (1 lumen) remains under the saturation threshold, doses with lower intensity than 1 lumen were not added to the study setting.

4. The authors should include the following point in their revised manuscript as presented in their response “However, based on the literature on the wavelength-dependent effects of light in humans, we chose to use a blue-enriched light source as this corresponds with the known maximum sensitivity of light-sensitive melanopsin in the retina. Assuming that the potentially light-sensitive proteins like melanopsin found outside of the retina (The Human protein Atlas, 2014) have similar features to the ones located in the retina, it is not unreasonable to assume that the extra-retinal potentially light sensitive proteins might also be sensitive to shorter wavelengths.”

We have added the following sentence to the discussion: “Based on the literature on the wavelength-dependent effects of light in humans, a blue-enriched light source was used in this study. It is not unreasonable to assume that the recently found extra-retinal proteins such as melanopsin (Human protein atlas, 2014) have similar
features as the ones located in the retina and thus are also sensitive to shorter wavelengths.” (Please see page 16, lines 386)

The Human Protein Atlas 2014 [http://www.proteinatlas.org/ENSG00000122375/tissue]
[http://www.proteinatlas.org/ENSG00000054277/tissue]

5. The authors should elaborate their discussion section on cognitive performance to clarify that the improvement in reaction time is not likely an acute effect, as suggested by the negative findings by Bromundt et al., 2014, but instead likely associated with an improvement in depressive symptomatology.

As suggested by the reviewer, we have added the following sentence to the revised manuscript: “The earlier findings on effect of TBL on cognitive performance in healthy subjects (Tulppo et al., 2014; Jurvelin et al., 2012) were also observed after treatment period of several weeks. In a recent study TBL was not found to have an acute effect on reaction time (Bromundt et al., 2014) suggesting that the improved cognitive performance found in this study is instead due to cumulative effect or associated with an improvement in depressive symptomatology.” (Please see page 14, line 325)

Minor:


We have checked and corrected the mistakes in reference list.

Reviewer 2:

The comments and reactions of the authors on my review are rather disappointing and at some points they are satisfying. I have still problems with the following two points

1. Especially the reaction on the major problem of this study: the lack of a placebo condition. This problem should be mentioned in the discussion with more emphasis. The results can be totally explained by means of placebo effects. Placebo effects can be very strong. For example, in a meta analysis of 96 studies Rief et al. (2009) found that 68 % of the effects of antidepressants can be explained as a placebo effect. At least this possibility should be mentioned in the discussion, only a warning to interpret the results with caution is not enough.
As reviewer 2 suggested, we have added the following sentence to the abstract and discussion section regarding placebo condition: “Further studies on the effects of transcranial bright light with an adequate placebo condition are needed” (Please see page 3, line 60 and page 18, line 428). In addition, we have added the reference of Rief et al. 2009 to the revised manuscript (page 15, line 359). Please see the answer 2 to the reviewer 1 as well.


2. In the abstract, the results based on the SIGH-SAD should be mentioned. The reason therefore is that this instrument is used as a ‘golden standard’ in SAD research, so comparisons with other studies is easy, and patients are include based on the scores of this instrument.

We have added the results from SIGH-SAD and HAM-A to the abstract, as suggested by the reviewer. (Please see page 2, line 49).