Author's response to reviews

Title: Transcranial bright light treatment via ear canals in seasonal affective disorder: a randomized, controlled, 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, controlled, 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:

1. The study is described as a “randomized, controlled double-blind dose-response study” (pg. 5 last paragraph). This statement is very misleading as it is not clear what was controlled in this study. The light treatments occurred at home under unsupervised uncontrolled conditions. It is also not clear what aspect was double-blind as there is no placebo control. It appears that the authors are referring to the patients and physicians being blinded to the intensity condition as the double-blind state of the study. It must be noted that both the evaluating physicians and patients groups were aware of receiving a novel treatment for their SAD condition and therefore were not blinded to the treatment.

We are sorry to hear that the reviewer found the description of our study as a randomized, controlled, double-blind to be misleading. We used the word “controlled” to describe our study because there is a controlled amount of light given in the three different conditions. We used the word “randomized” because the group assignment was done by an independent person outside the study team (page 7; line 177). We used the word “double-blind” because neither the study team nor the participants knew which light intensity they would receive. The light devices were externally identical. The difference in light intensity was only clear if the devices were turned on and examined side by side. Because each patient saw only his own light device, he would not know whether the light intensity was set to the high, medium, or low intensity output.

Furthermore, the chosen description of the study design is in line with a comparable light study that used a conventional bright light device (Baxendale et al. 2013). Therefore, no changes were made to the revised manuscript.


2. The lack of placebo control is a major confound in the study. Without a placebo control or even a follow-up measurement when the patients did not receive treatment, it is not possible to delineate whether the reduction in depression scores was a direct effect of treatment or a time-into study effect confounded by a placebo effect.

We agree with the reviewer that the lack of a placebo control group is a limiting factor to our study. Nonetheless, several light dose response studies, e.g. Chang et al. 2012, have been conducted without a placebo, or in this case a dark control group, yet these studies still satisfy the criteria of a dose-response study.

With respect to the question of how much of the symptom reduction was due to the treatment, vs. the time into the study or a placebo effect, the effect size of the placebo effect in earlier bright light studies has varied between 21% and 41% (Levitt et al 1996; Eastman et al. 1998; Desan et al. 2007). Examples
from earlier pharmaceutical studies in patients with depression report a placebo effect of approximately 30% (Walsh et al. 2002). It is assumed that sham devices used in trials for the treatment of depression have higher response rates than placebo pills (e.g. Kaptchuk et al. 2000). However, a meta-analysis by Brunoni and colleagues (Brunoni et al. 2009) has reported that transcranial magnetic stimulation (TMS), which is a non-pharmacological treatment for major depression, has a smaller placebo effect than pharmacological treatments.

The treatment effect measured in our study was higher than the placebo effect that has been reported in corresponding studies, which suggests that the effect is not due to a placebo. However, because a placebo group was not included in this study, we have stated in the discussion chapter that the findings of this study should be interpreted with caution (page 17; line 419). Future studies on transcranial bright light TBL should include a placebo control group.

References:


3. Although the authors propose a saturation effect for the lack of a dose-response it is quite likely that the response is a placebo effect therefore all doses appear to elicit the same response. Since the patients were blinded to the dose but knew that they are receiving treatment for their SAD symptoms they can be expected to show the same level of placebo effect irrespective of the treatment dose.

We thank the reviewer for this observation, and refer the reviewer to our previous response regarding the possibility that the observed effect is due solely to a placebo effect. As for the lack of a dose-response, it is not uncommon to fail to find a clear distinction in effectiveness across dosages in studies on depression (Preskorn 2012). For example, Baxendale and colleagues recently published a study in
which they failed to find a clear dose-response of a conventional bright light device for the treatment of depression and anxiety in subjects suffering from epilepsy (Baxendale et al. 2013). We have now added the latter reference to the revised manuscript (see page 16; line 392).

References:


Baxendale S, O’sullivan J, Heaney D: Bright light therapy for symptoms of anxiety and depression in focal epilepsy: Randomized controlled trial. BJP 2013, 202:352-356.

4. Do we know anything about the regularity of sleep/wake cycles in these patients before and during treatment? Moreover do we know the ambient light intensity at home during treatment? It is possible that patients maintained more regular sleep/wake cycles and therefore light/dark cycles during the treatment phase coinciding with the timing of transcranial light therapy that helped to stabilize circadian rhythms and likely counteracted the typical phase delay observed in SAD patients. Is there any assessment of circadian phase before and after treatment and the correlation is change in phase and treatment outcome? It is not necessary that the benefits of transcranial light exposure treatment in SAD is mediated by the circadian system but then it needs to be shown that the improvements in depression ratings in this study population is independent of changes in circadian phase alignment.

We agree with the reviewer that more detailed information as to the regularity of sleep/wake cycles in the participants would have been beneficial for the interpretation of the results. However, the focus of this study was to investigate whether a dose-response for TBL in the treatment of winter depression symptoms exist. We did not design the study to investigate the potential circadian properties of TBL. We cannot exclude the possibility that TBL does have an impact on the sleep/wake cycle of the participants, and that this in turn may have reduced feelings of depression and anxiety. We do agree that any further study on the long-term effects of TBL in patients with SAD should investigate the possible phase shifting effects of the light treatment. We have now included a discussion of these issues under the section that describes limitations of this study (see page 16; line 398).

The overall ambient light at home was not controlled during the study period. However, we are not aware of changes in ambient light at home during the study period. Subjects were not allowed to use any other light therapy devices during the study period. We have now added this information to the Methods section (see page 7; line 173).

5. The authors state that “bright light used in this study was visible to the patients, even though it was administered using extra-visual routes” (pg. 14 first paragraph). Please elaborate on this statement providing details on the light levels that the patients may have received via the eyes and how frequently this may have occurred.
We apologize for the unclear wording on whether the participants were able to see the light. The intended statement was “Based on an earlier study [42], the duration of the treatment was fixed to 12 minutes in the device settings. Patients were carefully instructed to turn on the treatment device only when the ear plugs were inserted in the ear canal. After 12 minutes, the treatment device turned off automatically. We have incorporated these changes to the text on page 7, line 170.

6. What is the justification for using a blue-enriched light source? If the responsible for mediating these effects are the deep brain photoreceptors instead of the ocular photoreceptors then the light reaching those photoreceptors are likely the longer wavelengths due to tissue interference. The long wavelength portion of the visual spectrum appears to be minimal in the spectral composition of the light source used in the study. The authors need to construct action spectra to show the spectral sensitivity of this response to demonstrate that the response is truly short-wavelength sensitive that would warrant using short-wavelength enriched light.

Based on the earlier studies from Ganong et al. 1964, Vigh et al. 2002 and Persinger et al. 2013, we know that light is able to penetrate the skull of animals and humans. We agree with the reviewer that the spectrum of light has effects on the absorption and that longer wavelengths penetrate the skull bone and other tissues more easily than shorter wavelengths. As we have discussed in our manuscript (page 17, line 411): “Haemoglobin and skin melanin are the main absorbers of visible light (Moan et al. 2001) while bone structures and many types of cells primarily scatter light (Ugryumova et al. 2004). The relative absence of skin melanocytes and the small amount of blood haemoglobin in the ear keeps the light absorption in this design at a minimum before entering the brain tissue (Starck et al. 2012)”. The mechanism of action of transcranial bright light is not yet known; therefore, there is no reason to limit the range of wavelength based on the assumption that shorter wavelengths may not penetrate to the deeper brain layers as easily as the longer wavelengths.

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 opsins found outside of the retina (Blackshaw and Snyder 1999, Kojima et al. 2011, Koyanagi et al. 2013, Tarttelin et al. 2003, Kumbalasiri and Provencio 2005, Lein et al. 2007) have similar features to the ones located in the retina, it is not unreasonable to assume that the extra-retinal light opsins may also be maximally sensitive to shorter wavelengths.

As interesting and informative it would be to construct an action spectrum for the spectral sensitivity of the TBL light source, we do not believe that the reviewer’s request for establishing an action spectrum is within the scope of this manuscript because we are not making any claims that our results are superior to any potential result from a light source with a different spectral composition.

References:


7. The authors need to present and discuss the results of Bromundt et al., 2013 (Chronobiology International 2013 Nov. 13) that show a lack of improvement in alertness or reaction time in response to 12-min transcranial light exposure, which contrast the results presented in this current study.

We are happy to include the article of Bromundt et al. in the revised manuscript, but would like to point out that the present results, i.e. a reduction of depressive and winter depression related symptoms over
the course of 4 weeks, do not contrast the results of Bromundt and colleague. In fact, the study of Bromundt et al. 2013 confirmed our findings that we presented at the International Forum on Mood and Anxiety Disorder IFMAD congress in Barcelona 2012 (manuscript resubmitted), which showed that transcranially administered bright light does not suppress melatonin secretion. The article of Bromundt et al. claims that transcranially administered bright light for 12 minutes does not affect subjective sleepiness or performance, and therefore does not acutely influence the human circadian timing system. Because a limited number of parameters were measured at one time of day (late evening) only, it is a slight exaggeration to generalize the findings to the circadian timing system across the entire day. Furthermore, the results of Bromundt et al. clearly show that the study failed to find a positive effect of the ocular light condition on subjective sleepiness or performance.

Moreover, light-induced melatonin suppression is not always associated with psychophysiological alterations. Evening bright light treatment (e.g., 30 min for 2 weeks between 17:00 and 20:00 h) was shown to alleviate symptoms of winter depression and subjective sleepiness without changes in melatonin secretion (Partonen et al., 1997). Daytime bright light exposure had no effects on nocturnal melatonin surge but reduced sleepiness and increased vigilance (Phipps-Nelson et al., 2003). Nighttime light of 100 lx exposed to the nasal or temporal parts of the retina did suppress melatonin secretion but did not affect sleepiness or fatigue (Rüger et al., 2005). Moreover, nocturnal bright light exposure by wavelengths above 480 nm has been found to increase cortisol secretion and improve alertness, mood, and vigilance without affecting nocturnal melatonin secretion (Rahman et al., 2011). Thus we do not consider the mood uplifting effects of transcranial bright light in SAD patients to be mediated via melatonin.

In this study, we measured the long-term effects of transcranially administered bright light. The lack of acute effect on subjective sleepiness and attention in healthy subjects in the evening does not necessarily prove that transcranially administered bright light cannot have long-term effects on cognitive parameters in participants suffering from SAD. As the reviewer has suggested, we have added the reference of Bromundt et al., 2013 to the revised version of the manuscript (page 5; line 121). The following sentences have been added to the introduction section: “Moreover, a recently published study showed that transcranial bright light administered in the evening does not suppress melatonin secretion (Bromundt et al. 2014). The ability of light to suppress melatonin secretion is well-established to be mediated via the RHT (Berson et al. 2002). Thus, we hypothesize that some effects of external light are mediated via routes without the function of the eyes.”

References:


Reviewer 2:

1. It is encouraging to see that the authors are investigating the effects of a new device in treating Seasonal Affective Disorders. However, this study has some serious flaws: The major problem is that, till now, there is no evidence that TLB can treat SAD. There is an interesting study published in Medical Hypothesis, which should be the first step to an RCT. Unfortunately, this study is not that study. There is no placebo condition. Just with this treatment modality, TLB, a placebo condition can be realized. A placebo condition is not possible in light treatment conditions where patient have to receive the light through the eyes. But using TLB as a treatment device, it is possible to create a real placebo condition. Therefore, the reason mentioned by the authors that: Since the treatment was carried out at home, without supervision through the investigators, it was not possible to create a proper placebo condition in this study, is not satisfying. If that is the case, this study should have carried out in the clinic in controlled surroundings, because, till today I don’t know a study in which the effect of TLB is shown. If a placebo condition is not allowed (some ethical committees don’t approve such studies because of withholding a patient from an effective treatment) a comparison should be made with the effect of the most well known effective and accepted (light) treatment using light through the eyes.

   Please see responses 1 and 2 to reviewer 1 regarding the lack of a placebo control group and the possibility of the results being due solely to the placebo effect.

2. Besides this major problem, there are some other issues: It is not clear why dose response differences should have any differences in treatment response using a light fixture in the ears. What are the theoretical assumptions?

   There are controversial findings regarding the dose-response effect in earlier dose-response studies that used conventional bright light therapy. In earlier studies on dawn simulation and a dawn pulse, a light intensity of 250 lux was found to be as effective as 10000 lux in alleviating symptoms of SAD (Terman & Terman 2006; Avery et al. 2001). In addition, a recent study from Baxendale et al. has shown that the antidepressive effect of a 2000 lux light treatment is comparable to the effect of a 10000 lux light treatment (Baxendale et al. 2013). Reviewer 1 also paid attention to this issue. Please see also our answer to him (reviewer 1, comment 3).

   A dose-response effect has been found for other parameters of interest, such as melatonin suppression. Because the treatment examined in the present study is novel and the “effective dose” has not previously been defined experimentally, there was a need to explore the possibility of a dose effect for TBL. The measurement of side effects at different dosages was also an important component of this study.

References:


Baxendale S, O’sullivan J, Heaney D: Bright light therapy for symptoms of anxiety and depression in focal epilepsy: Randomized controlled trial. BJP 2013, 202:352-356.

3. The population in this study suffers from SAD and, based on the scores on the Hamilton Anxiety Scale, anxiety. This combination of complaints is not mentioned very clear and differs from other studies investigating treatments of SAD. The means scores on the BDI are related to a moderately severe depression. The HAMD scores are also related to the same range of depression. The SIGH-SAD scores are rather high, and is the sum of HAMD and Atypical scores. The BDI shows lots of questions which are related to the Atypical scores of the SIGH-SAD. One should expect that the scores on the BDI should be higher in relation to the scores on the SIGH-SAD. The authors should discuss this phenomenon. It is curious the allow participant to use TLB till noon, and ask them to follow some bedtime instructions before the two measurement days. What is the reason? No reason is mentioned why participants should have no coffee or alcohol related to the assessment days, while no rules for the other days in the 4 weeks of investigation are mentioned. For example: is it allowed to drink lots of alcohol during the other days? There is a difference in response percentage related to the assessment instrument. The percentage of response of SIGH-SAD is lower than the response as assessed with the BDI. The BDI is a self rating instrument and the SIGH-SAD is rated by a blind rater. An explanation for this difference might be the effect of suggestion or placebo.

Participants in this study were diagnosed with SAD. Because anxiety commonly co-occurs and has a neurochemical similarity to depression (Youngstedt et al. 2011), the measurement of anxiety symptoms is justified. We believe that the measurement of anxiety symptoms is a significant strength of this study and we have added this information to the discussion section (page 13, line 307) of our revised manuscript. Our inclusion criteria in this study were analogous with the criteria used for evaluating the response to treatment in patients with SAD in previous studies; expect that the patients suffering from bipolar disorder were excluded from this study. This may have reduced the occurrence of spontaneous remissions. We have added this information to revised manuscript (see page 13; line 321).

As the reviewer mentioned, a difference between baseline and response scores measured by the BDI and SIGH-SAD inventories was found in this study. We have added the following section to the discussion of the revised manuscript to discuss this phenomenon (see page 14; line 342): “One strength of our study is that we used both observe rating SIGH-SAD and self-rating BDI to assess the severity of depressive symptoms. SIGH-SAD as a sum of HAM-D and atypical scores covers symptoms of both atypical and melancholic depression, while atypical symptoms are far less relevant in the BDI version used in this study (Cusin et al. 2010). HAM-D and BDI overlap on only half of the items. These scales therefore rate different aspects of the disease and thus poor concordance between scores might be...
predicted (Möller et al. 2000). Patient or observer biases, severity of illness, age, education, sex, and personality variables affect the level of correlation between observer and self-rating scales (Möller et al. 2000, Schneibel et al. 2012, Enns et al. 2000). These aforementioned issues may cause differentiated scores on the SIGH-SAD and BDI inventories. Thus, comparisons between scales should be conducted with caution (Möller et al. 2000).”

To diminish the acute effect of sleep, exercise, alcohol, caffeine, and other factors on our measurements, these factors were standardized for all participants during the assessment days. The standardization method used in this study is commonly used in physiological studies. In field studies several factors are left uncontrolled. The use of alcohol was one factor that was uncontrolled in this study. However, subjects who reported alcohol abuse were excluded from the study during the pre-screening phase.

References:


4. In the abstract the high response rates as assessed with the BDI are only mentioned. That selection sounds as a commercial for TLB, in which in a selective way only the best results are mentioned.

We thank the reviewer for their opinion, but we disagree that the results in the abstract were selected as part of a commercial strategy. It is not uncommon to present only the strongest result of a study in the abstract. The study of Bromundt et al., for example, chose their only real finding for the title and the abstract, and did not report in their abstract that they failed to show an effect on performance and sleepiness in the ocular light condition.

Reference:

5. Related to this last point: In the list of affiliations on the title page, the CSO and shareholder of Valkee, Juuso Nissila is mentioned to have a relation with the University of Oulu, Institute of Health Sciences. At the end of the paper his relation with Valkee is mentioned. At least, this way of presenting affiliations is remarkable.

The presentation of author affiliations was also not part of a commercial strategy. We are happy to add Juuso Nissilä’s affiliation with Valkee along with his university affiliation in the author information. This affiliation has also been added for Heidi Jurvelin. Nonetheless, we are somewhat taken aback by the reviewer’s suggestion that not reporting the authors’ affiliation with Valkee on the title page is part of a commercial strategy.

6. On page 4, 70 % sitting in front of bright light is uncomfortable and reason for some SAD sufferers to cease BLT for that reason. This seems a rather selective way of referring to the, rather old, literature. Nowadays light fixtures are more convenient and are improved ever since. It is also possible to refer to literature in which SAD sufferers are very happy with the light treatment.

As the reviewer pointed out, there are also studies that show higher levels of adherence to the bright light treatment. In two SAD studies, the total time that light boxes had been switched on was observed to match with the required treatment times (Michalak et al., 2002, 2007). However, the fact that a light is switched on does not necessarily mean that the participant is in the same room as the light. This interesting phenomenon was observed in a recent bright light study on elderly patients with non-seasonal depression who were using light sensors on their wrists during the study. The study showed that the measured light intensity during the treatment (247 lx) was far below that recommended to have a therapeutic effect (Lieverse et al. 2011). In addition, according to a recent study that used a conventional bright light treatment (Hsu et al. 2013), the non-adherence to the conventional bright light treatment was found to vary between 18-39% depending on the settled criteria for adherence. One observation of that study was that 21% of the subjects might have framed the treatment condition by setting the light/activity detector in front of the bright light device. It is unknown where the subjects were during the treatment. Although the studies we refer to are rather old, these more recent studies (Lieverse et al. 2011; Hsu et al. 2013) on adherence to bright light therapy are in line with the finding of Schwartz et al.1996. Although bright light devices have been improved since the 1990s, the fact that bright light treatment usually requires sitting a certain distance from the light device still exists and putatively causes inconvenience.

However, the purpose of this manuscript is not to compare TBL and conventional bright light treatment, thus we omit the following references from the manuscript: Schwartz et al. 1996, Oren et al. 1991. “Although BLT is effective, about 70% of SAD patients complain that sitting in front of the bright light is uncomfortable [20], and almost one in five SAD patients cease BLT for this very reason [21]."
References:


7. There is no reference to the article of Bromundt et al. 2013 about some aspects of a possible working mechanism of TLB, which is not in favor of TLB. This article should be mentioned and discussed. Although a lot of scientific work is presented, before publishing the present study, at first an RCT study should be presented in which TLB has been showed to be effective compared to placebo or ocular light studies. In the present study, most results can be explained by a possible placebo effect. Furthermore: a scientific paper should discuss the results more critical and, as mentioned before, not only mentioned the most favorable results in the abstract. In the present presentation the impression exist that there is some competing interests which is a leading factor in the paper.

As mentioned earlier (reviewer 1, comment 7), we have added the reference of Bromundt et al. to the revised manuscript (see page 5, line 121). As discussed earlier (reviewer 1, comments 1 and 2) the size of the response rate found in this study suggests that the response is not likely to be due solely to a placebo effect. However, the lack of a placebo control group is a limitation of this study. Therefore, we claim in the discussion section that the findings of this study should be interpreted cautiously (see page 17; line 419) and that the effect of placebo should be carefully scrutinized in future studies (see page 15; line 362). The competing interests are mentioned properly in this manuscript. Furthermore, as discussed earlier, it is very common to present only the strongest results of the study in the abstract section.

Reference:
