Author’s response to reviews

Title: Effects of Attentional Bias Modification on Residual Symptoms in depression. A Randomized Controlled Trial.

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Dear Editor

The following rebuttal letter address the points raised by the Editor and Reviewer 2. in the same order as they appear in the response letter, and describe exactly what amendments have been made to the manuscript text and where these can be viewed (line number).

Editor Comments:

1) In the abstract, please remove the section Aims and integrate the text into the Background section.

Response: Done, line nr 65
2) In the Trial Registration information please include the date of registration. In addition, I note that you state the trial is partially retrospectively registered. A clinical trial is retrospectively registered if registration took place after the first participant was enrolled. Please clarify.

Response: Done, line nr 87 and 162-163.

3) Please describe the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Response: Done, line nr 457-458

Reviewer 2.

GENERAL COMMENTS: I appreciate the authors' effort in this revision, the statistics are much clearer to me now.

1) For the post hoc tests, the authors state that "There are no post-hoc t-tests in results, as time is the pre-post factor that interacts with the dichotomous ABM vs. placebo variable. There is therefore also no variable that distinguish e.g. symptom improvement from symptom worsening or combined factors that warrants post-hoc comparisons."

This may be true for Figure 1 (Line 258-265), although one can still do post-hoc comparison between groups at same time (e.g., placebo vs. ABM at baseline, or at 2 week follow up) or within group but across time (e.g., placebo baseline vs. placebo 2 week) to figure out what exactly is the driving force behind the interaction. To say that there's a significant interaction, and then stop the analysis, is somewhat surprising to me, because we need to know what's driving the interaction.

This is no longer an issue in the analysis from Line 267 to 276, because the scores between ABM and placebo are matched at baseline, so post-hoc tests should be doable and without any difficulty to explain the observed significant effect (if any).

I think it's okay to not have any significant post hoc tests, it only means that we have to be more conservative when explain the origin (or direction) of the significant interaction. Right now the manuscript emphasizes the therapeutic potential of ABM, but that's not entirely clear yet (see my next comment).

Response: We thank the reviewer for suggesting this post-hoc test. The post-hoc test shows that clinician rated symptom changes (HRSD) was only statistically significant within the ABM group, indicating that the observed mean negative changes within the placebo group did not drive the ABM effect. The post-hoc test is now present in the results (line 265-267 and 285-288) and is followed up with a comment in the discussion section (line 356-361).
2) Since the effect of ABM seems to be driven by the worsening of the placebo group (whereas the ABM group remains stationary), there are 2 possibilities for the ABM effect: 1) patients’ HRSD worsens over time, but ABM is improving something else, so the two cancels each other out, or 2) ABM is targeting the exact thing that's worsening in placebo group, and prevents it from worsening, so ABM is protective against worsening of depression. Although the 2 sound similar, #1 is indicating an improvement in one domain, but worsening in another separate domain (the improvement account); whereas #2 is claiming no improvement, but no worsening either (the protective account). Might be worth mention in the discussion, and based on Figure 3, probably #1 the improvement account is more likely.

Response: We think the reviewers’ points here are very good and relevant and this is now elaborated on in the discussion section (line 361-376).

3) But this brings me to my previous review, and I still stand by my last comment from my last review: "Since Figure 3 clearly shows that ABM works differently for everyone, and may even backfire for some patients, the key finding from this study for me is that "AB change may be a useful clinical measure since it is sensitive to individual differences in HRSD", as opposed to ABM as a treatment."

Even if we think that ABM is inducing improvement (instead of protective), it clearly does not work for everyone even in the ABM group. There are quite a few individuals who had worse HRSD after ABM, which is okay, because no treatment is perfect. But the most intriguing finding is that these people's worsening in HRSD is actually (mildly) predicted by their ABM performance. This, to me, is actually the most valuable finding from this study because this can actually predict treatment outcome and the variances within the patients (not a lot of measures can do that). This is why I'm perplexed by the direction of this manuscript, it's trying to describe ABM as a potentially useful treatment, which is only half true because it's clearly not for everyone (and can even make some people worse; though I think the authors can argue that worsening is on par with the placebo group so that ABM is simply not working for these people, but the worsening is not coming from ABM). But the ability of AB change to predict HRSD change is interesting (because we can explain variability of treatment outcome using an attentional and mechanistic account), yet the manuscript downplays this point. But anyway, I leave it to the authors to decide whether this point is worth mentioning in the manuscript or not.

Response: We agree with the reviewer in that the AB change to predict HRSD is valuable and interesting and have made this point explicit in the first paragraph of the discussion section (line 331 – 333).

Again, we thank the reviewer and Editor for the comments and suggestions that we think strengthened the analysis and interpretations.

Kind regards
Dr. Rune Jonassen & Professor Nils Inge Landrø