PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Post-training results from a randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study**
AUTHORS	Wolinsky, Fredric; Vander Weg, Mark; Howren, M. Bryant; Jones, Michael; Martin, Rene; Luger, Tana; Duff, Kevin; Goerdt, Chris; Wolfe, Steven; Dotson, Megan

VERSION 1 - REVIEW

REVIEWERS	**This paper was co-reviewed by the following reviewers:** ***Michael Marsiske, Associate Professor,*** Department of Clinical and Health Psychology, University of Florida, United States, ***Anna Yam, Predoctoral Trainee,*** Department of Clinical and Health Psychology, University of Florida, United States,
REVIEW RETURNED	11-Jul-2011

RESULTS & CONCLUSIONS	The analyses are very careful and meticulous (as is the study design), but there are three issues (all fixable) that we think the authors should address: - Drop the factor analysis, which has no real relation to the results being presented here, and seems to be included merely to fill space, and to develop a (specious) argument suggesting that training effects in this interim analysis will generalize to other outcomes at some future time point. - Supplement the logistic regression, which is atypical in this literature, with a classic ANOVA/mixed effects model. Embedded in that, it is essential to show pre- and posttest means and standard deviations, and to report/compare standardized mean differences in this study to those from previous research. - There are small additional concerns, noted in the review, regarding mental status testing and self-reported vision.
GENERAL COMMENTS	Reports findings from 10 hours of training using Road Tour, a computerized visual speed of processing intervention. Results demonstrate significant post-training improvements in visual processing speed in middle aged and older adult participants under laboratory and self-administered conditions. This study is an innovative entry in the growing literature on older adults, especially that focused on Useful Field of View (UFOV) improvements in this population. The study is carefully done, and the

	investigators show a precision of language and clarity of design that is heartening. These study findings are encouraging and leave us eagerly anticipating future (follow-up/durability) results. The following outlines some comments and suggestions. 1. The crux of this paper is that it provides a pretest-posttest evaluation on a single measure (UFOV composite) of the effectiveness of training. The authors make it clear that this is an interim step, and that future work will present longer-term transfer outcomes. Thus, authors should eliminate all references to the non-UFOV cognitive speed outcomes. Much space is used on an exploratory factor analysis (EFA) of the cognitive speed outcomes. Since none of these are used in the pre-post evaluation, the purpose of this analysis in the context of the manuscript as a whole is not clear. The authors appear to utilize the EFA to speculate on possible findings (i.e., transfer of intervention effects) in future papers. While this is optimistic, there are several problems. First, in future analyses there will be an evaluation of transfer directly, so there is no need for this tangential speculative analysis at this time. Second, if the EFA is being used to support putative possibility of transfer of training, it commits the ecological/atomistic fallacies. That is, correlated individual differences (which is what the EFA shows) do not necessarily indicate that there will be correlated intraindividual differences. The EFA raises two additional points. First, the EFA, since it is non-inferential, does not require normality in any of the variables factored. At the same time, inclusion in the EFA presumes that the measures are continuous and suitable for correlational analysis. Placement of the UFOV in the factor analysis seems to suggest that the UFOV would be suitable for GLM analyses more broadly. However, the UFOV's non-normal distribution is used as justification for the logistic approach used, which appears to be contradictory. In sum, we strongly recommend that the EFA and reference to all non-UFOV measures be struck. Second, the authors note baseline differences among randomized groups in a number of cognitive speed measures. If these cognitive speed measures are associated with the outcome (UFOV) as the authors report, and should the authors wish to retain a version of the EFA analyses, they may wish to output a "cognitive speed factor score" and use that as a covariate in the pre-post analyses. 2. The rationale for the logistic analysis is based on (a) non-normal UFOV scores, and (b) a "clinical significance" criterion of 100 milliseconds. Ignoring (a) for a moment (see next point), the rationale/justification/citation for the clinical significance cutoff is warranted. 3. The logistic analysis is clear and illustrates the results well, however we believe there should also be a traditional analysis of means for the UFOV. Such analyses would illustrate effect size differences between groups. This is essential to facilitate comparison of the results to those from ACTIVE and other UFOV training studies (all of which expressed changes in standardized mean differences). We would request a supplementary "traditional" analysis of the UFOV—there should be space for this if the factor analysis is dropped. 4. Pursuant to the above, the initial descriptive table of all measures (Table 1) should also include standard deviations for all

	measures in all groups. In addition, the pre-post means and SDs by group are needed for the UFOV composite and its subscales. This is important so that the reader is able to judge this sample and outcomes against those in previous research using the same outcomes. We emphasize the UFOV subscales; it would be very nice to see a GLM style (i.e., analysis of means) analysis for the UFOV composite and follow-up univariate analyses on the UFOV subscales. If distribution is a problem, the authors could follow the practice used in ACTIVE (Blom rank transformation to improve normality). 5. The descriptive results show training group differences in odds ratios by age stratum. The critical question, of whether there was an age-by-training interaction (or, in a GLM approach, an Age x Time x Group interaction) seems interesting and essential to present. We recommend these analyses be included. 6. The discussion makes much of the expected transfer to other cognitive speed measures (which we dispute, as discussed above). On the other hand, we feel the discussion sells short many of the virtues of this study: (a) a simple program, which can/was administered at home, can be highly effective; (b) the utility with middle aged adults (which may be comparable or superior to that of older adults—we need the answer from interaction analyses suggested above), is very promising as it opens the door to training of this nature as a "preventative" measure. 9. The authors should clarify that Road Tour is only one-fifth of the full PositScience Insight training program. Rationale for selection of just this component (e.g., it is specifically focused on UFOV?) could be better developed. 10. The Pfeiffer instrument (1975) is not a widely used mental status measure. Given the telephone basis of the screening, and the fact that only a crude tool for the elimination of those with cognitive impairment was desired, the rationale for this measure (as opposed to, for example, the TICSm), could be better developed. 11. The reliance on self-reported vision, while necessary (given phone screening) introduces a source of uncontrolled variation (some visually impaired individuals could easily have enrolled in the study, and vision worse than 20/40 strongly predicts poor UFOV performance) that could be better acknowledged in the limitations. 12. In addition to describing the two age groups, the age range, mean, and standard deviation should be provided for each group. This is essential for understanding how the current sample relates to previous work, and to understanding the real magnitude of differences between groups. 13. The randomization allocation ratio 3:3:4:4 is simple enough to understand, but it is never justified. A brief rationale should be provided. 14. Training seems quite condensed (five two hour sessions). These are very long sessions, and exceed most previous studies. Moreover, the training is much narrower and more focused (Road Tour only) than most other recent training studies. Some discussion (anecdotal) of participant tolerance of this very repetitive, routine task for such an extended period would be desirable.

	15. Although compliance/dosage seems to be somewhat lower in the at-home group, participation rates seem uniformly good. Some discussion about whether the monitoring built into the training program increased participant sense of accountability might be interesting. 16. Figure 1 is unreadable in grayscale. Unless the journal will print in color, it is not helpful. It would almost be better for the authors to simulate key features (with line drawings), or to provide an animated demonstration at a linked URL. In summary, we suggest a more in-depth focus on the main intervention findings, both in analyses and in discussion, and removing the EFA analyses. The expansion of analyses and results as described above would greatly facilitate comparisons with other, similar intervention studies, thus helping to further build the corpus of literature on this very interesting and important topic.

REVIEWER	***Virginia G. Wadley, Associate Professor of Medicine*** Division of Gerontology, Geriatrics, and Palliative Care University of Alabama at Birmingham USA
REVIEW RETURNED	19-Jul-2011

THE STUDY	More detail is needed with respect to the supervised training sessions. What did the supervision consist of, and who did the supervision? Was supervision done on a one-on-one basis or in groups? Did the same person supervise all three lab-based training programs? If not, differences between groups' outcomes may in part be due to different supervisors (e.g., Group 2 appears to have higher odds of improvement on outcomes than Group 1, despite the Road Tour training being identical because no booster training has yet occurred in Group 2). Supplemental documents do not raise questions or conflict with the manuscript.
RESULTS & CONCLUSIONS	Interpretation and conclusions are warranted but are incomplete. It would be provide more balance if the authors would discuss the finding that 66% of the patients assigned to the active Road Tour training arms did not improve at the threshold chosen by the authors to signify clinically meaningful improvement. It also would be important to mention that 23% of the patients in the control training arm also improved as defined by this clinically meaningful threshold, despite having no Road Tour training. What do the authors believe are the reasons for and implications of these two findings?
GENERAL COMMENTS	The authors present a controlled study of cognitive improvements associated with the Road Tour cognitive training software (supervised in the lab or self-administered at home) vs. an attention control training paradigm. This is a well-designed study, and the findings are clearly presented. Demonstration of meaningful improvements in the primary outcome variable (Useful Field of View) as a function of training with a commercially available software product has potential widespread applications.

	Strengths of the study are considerable: its inclusion of a large sample and two age cohorts, random assignment to training arms and a control training paradigm, achievement of demographically similar training arms, pre- and post-training measurement of cognitive performance, use of well-validated neurocognitive instruments, and use of appropriate statistical procedures within an intent-to-treat approach (irrespective of time actually spent in training) among all participants who were not lost to follow-up. Limitations of the study relate to the nature of the study sample, which affects generalizability. I suggest some minor revisions for the authors' consideration: 1. Throughout the abstract and manuscript, please refer to the groups as training groups rather than treatment groups. 2. Abstract Design: Please explicitly state that Group 2 has not yet received booster training and therefore was equivalent in the present analyses to Group 1. 3. Abstract Results: Please include the proportion of pooled Road Tour training participants who improved to criterion and the proportion of control participants who also improved to criterion. 4. Article Focus: In bullet 2, please again specify that booster training has not yet occurred for Group 2. 5. Strengths and Limitations: In bullet 1, the authors allude to overcoming important limitations of a previous multi-site trial. Please specify which limitations were overcome (e.g., broader age range?). In bullet 2, please consider mentioning that generalizability also is limited by restricting enrollment to adults with home computers and internet access. 6. In the Methods section, please provide more detail regarding the logistics of training (number of sessions per week [some of this methodology first appears in the results but would be expected in Methods], whether lab sessions were supervised individually or in groups, nature of the supervision, whether one or multiple supervisors were used, and if the latter whether each enrollees within each group were consistently assigned to the same supervisor. 7. Telephone screening: Five exclusionary criteria are outlined, resulting in 1356 exclusions. It would be helpful to specify how many individuals were excluded based on each criterion, either in text or added to Figure 1, as this would provide additional information on the study sample's generalizability to the population of interest. 8. Cognitive Processing Speed Outcomes: In the first full paragraph on p. 11, first sentence—if the SDMT, TMT, COWAT, DVT, and Stroop were not administered at the first post-training visit, please state this explicitly (e.g., on line 20, add "but were not administered at the initial post-training visit"). If they were administered but were not presented in this report, please so state.

	9. Analysis: P. 13, line 6—"adjusting for the value at randomization." Please specify that this refers to the baseline UFOV score. P. 13, line 11—indicators is misspelled. 10. Figure 2: It may be just the print quality of the graphic, but I cannot locate letters a through f on the six panels. 11. Table 3: In the age-stratified tables, it would be good to include the n in each group. In the key, again please clarify that Group 2 has not yet received booster training. 12. Conclusion: Paragraph 2 (pp. 16-17) reiterates the study design and is unnecessary. In addition to the main finding and study strengths, the conclusion should mention limitations. Please consider commenting on the UFOV improvements found in the control group and how this affects interpretation of improvements resulting from Road Tour training. 13. Competing Interests: I commend the authors for this thorough disclosure statement.

VERSION 1 – AUTHOR RESPONSE

The first request was to edit the article summary to provide a quick snapshot of the article. This has been done, and you will find the article summary to be much shorter and to the point. Second, you raised a question about whether RM meets the ICME authorship criteria. Her individual contributions have now been clarified on page 25. The provenance and peer review statement was based on a misinterpretation of what the journal's guidelines were requesting, and after you clarified this in your decision letter, the statement has been dropped. Finally, the CONSORT statement has been amended since the protocol paper has been accepted and will presently be readily available.

Professor Marsiske and Ms. Yam's Requests:

We now present the results of three analyses (see pages 12-13 in the methods section, and pages 15-18 in the results section), of which this first is our primary approach (as specified in the above mentioned protocol paper) using multiple linear regression with Blom rank transformed UFOV composite scores at post-test and randomization, as well as secondary analyses using general linear mixed effect models with the Blom rank transformed UFOV composite scores, and the multiple logistic regression models reported in the original version of the manuscript. Each approach provides full and complete support for the tested hypotheses in all respects. The issues surrounding the mental status and visual acuity measures are addressed on page 21 as the fourth reason why direct comparison to previous studies is somewhat problematic. With all due respect to these reviewers, the use of less robust mental status and self-reported visual acuity screening tools for exclusion purposes actually enhances the generalizability of IHAMS while biasing its effect size estimates toward the null. Thus, we see this not as a limitations issue, but as an issue to be clarified in making comparisons to the extant literature.

We now turn to their 16 specific points.

1. As indicated above, all reference to the exploratory factor analysis has been dropped, and the issue of effect-transfer to the five other neuropsychological tests will be reserved for our subsequent article that will report on the one-year post-randomization results, once the one-year follow-up interviews are completed in late November, 2011.

2. These reviewers asked us to explain the rationale for the logistic regression threshold of 100 ms. We are pleased to do so, although we believe that this is somewhat moot given the fact that in the new analytic approach requested by these same reviewers, the logistic regression now serves principally as a safeguard for determining that the two analyses of the Blom rank transformations of the UFOV composite scores did not result in statistical artifacts. That said, on page 18, we now note that:

> "An effect threshold of improvements ≥ 100 ms was chosen because it represents an effect size of 0.55 based on the non-transformed baseline UFOV composite, which is equivalent to that observed in Table 3 for the pooled analysis of assignment to any *Road Tour* training in the overall IHAMS sample."

3. As indicated above, analyses using multiple linear regression and general linear mixed effects models have been added.

4. As requested, standard deviations have been added for all measures in Table 1. Moreover, we now present a new Table 2 that focuses solely on the three UFOV subtests, composite, and Blom rank transformed composite scores at randomization and post-training overall, as well as separately within each age stratum.

5. As requested, the appropriate interaction terms involving a binary age strata indicator with the training group markers have been added to all analyses, and none of them are statistically significant. This is reported within the presentations of each analytic approach.

6. The conclusions section has been completely rewritten (see pages 18-23). It no longer merely summarizes the study design, but focuses on elaborating the five major take-home points from the paper, including comparing the IHAMS post-training findings to the extant literature. The conclusion section also now identifies the four main limitations of the study.

7-8. The reviewers skipped numbers 7 and 8 in labeling their specific points.

9. We have clarified throughout that we did not use the four other programs in *Insight* (see pages 6, 8, 13, and 23).

10-11. The measurement differences between our mental status and visual acuity exclusionary criteria and previous studies are addressed on page 21.

12. The age range, mean, and standard deviations have been added to the description of the two age strata on page 7.

13. The rationale for the allocation ratio is now clarified on page 9.

14-15. The logistics of the training, its toleration, and the adherence benefit of the scheduling contacts have now been addressed on pages 7 and 20.

16. The journal will publish Figures 1 and 2 in full color. This will eliminate the readability issue when the manuscript PDF (which is actually in full color) available via the journal's editorial management system is printed on a black and white printer. In addition, we note that very high resolution color versions of both Figures were generated for the accepted protocol paper, and will be used this in paper when it is published as well.

Professor Wadley's Requests:

This is also a very careful and thoughtful review. Professor Wadley makes two general comments, and then 13 specific points. First, she asks for more detail on the training. To address this, we have added a number of clarifications throughout the manuscript. To directly answer the issue of supervision, very little was needed because of the very user friendly nature of *Road Tour*. Here we summarize what is noted more extensively in the referenced protocol paper (citation 25). The three on-site training groups received 10-15 minutes of individual instruction in getting started with *Road Tour*, after which a single "monitor" (usually an undergraduate student trained and certified on both *Road Tour* and the crossword puzzles program) was available in one or the other training lab (which were next door to each other) to provide help with any questions or issues that arose. Thus, although several monitors were needed to accommodate training schedules and specific monitors were not available for the entire enrollment period, at any given training time/session, the monitor was the same. Each of the two intervention-specific training labs (identically configured and furnished with one for *Road Tour* and one for crossword puzzles) had five work-stations. Both *Road Tour* training arms (with and without subsequently scheduled booster training) were trained in the same training

lab. The second general comment notes that while the interpretation and conclusions are warranted, they were incomplete. As noted above, the conclusions section has been completely rewritten to address this. We now turn to Professor Wadley's 13 specific comments.

1. We now refer to "training" rather than "treatment" groups throughout the manuscript.

2. The abstract now clarifies that booster training does not occur until 11 months post-randomization, which is clearly after the 5-8 week post-training assessments.

3. This point requests us to provide the proportion of participants by group who improved at least as much as the multiple logistic regression threshold criteria of $\geq$ 100 ms. This is done on page 18, although given that the analysis has dramatically changed in response to the requests of Professor Marsiske and Ms. Yam, and the logistic regression analysis is now used only as a safeguard against statistical artifacts from reliance on the Blom rank transformed composite scores in the multiple linear regression and general linear mixed effects models, the point is somewhat moot.

4. Given the extensive revision of the article focus requested by the Managing Editor, this clarification is no longer appropriate for the bullet point. However, throughout the article we have clarified that booster training does not occur until 11 months post-randomization, which is clearly after the 5-8 week post-training assessments.

5-6. The four specific limitations that were overcome, and the generalizability limitations are now included in the appropriate strengths and limitations bullets in the article focus section.

7. The numbers of potentially eligible patients excluded for these reasons are now listed in the text (page 9), and similar modifications were made to the flow diagram in Figure 1.

8. It is now clearly stated that the five secondary neuropsychological tests were not included at the post-training assessment (pages 10-11).

9. The specification of the timing (baseline value) of the UFOV adjustment measure has been made (page 12), and we have corrected the misspelling of "indicators".

10. As noted above, very high resolution color versions of both Figures were generated for the accepted protocol paper, and will be used in this paper when it is published as well. That version of Figure 2 clearly designates the "a" through "f" panels of the current figure, which simply assumed for review purposes that the labeling went left to right in the first, second, and third rows in that order.

11. The changes requested for what has become new Tables 3 and 4 have been made.

12. The paragraph in the conclusions section that reiterates the study design has been dropped, and as noted above, the conclusions section has been completely rewritten to focus on the five main take-home points and the four study limitations.

13. We appreciate your commendation on the thoroughness of the disclosure statement. This is an issue that we take very, very seriously.

VERSION 2 - REVIEW

REVIEWER	***Michael Marsiske, Associate Professor,*** Department of Clinical and Health Psychology, University of Florida, United States,
REVIEW RETURNED	04-Aug-2011

GENERAL COMMENTS	The revised manuscript is completely responsive to all questions and suggestions that we submitted previously (and that were

	provided by the editor and the other reviewer). A particular strength of this version is the substantial attention given to effect sizes in this draft. The discussion offers a beautiful exposition of how comparable effect sizes in this study might be to those in previous meta-analyses and studies. It also offers several different ways (pretest-as-covariate; linear mixed effects model) for judging effect sizes. A real strength of this work is its translational piece: This is a "real world" instantiation of a highly "portable" training approach, and thus the results speak strongly to the potential utility of this approach in non-research contexts. An additional strength of this revision is the greater emphasis on the midlife-to-late life comparisons of effect. The absence of age group differences in training effects mirrors some earlier training studies, and builds a stronger rationale for the use of this training as a prevention approach. This paper is poised to make a strong and innovative contribution to the research literature.

REVIEWER	***Virginia G. Wadley, Associate Professor of Medicine*** University of Alabama at Birmingham
REVIEW RETURNED	17-Aug-2011

GENERAL COMMENTS	The authors have satisfactorily addressed most of my questions and recommendations, and the new analyses requested by other reviewers add value to the paper. I suggest that the authors further consider a few issues and minor edits prior to publication. I believe there is still a need to clearly convey that Groups 1 and 2 (on-site Road Tour training groups) are identical at the 5-8 week post-training visit because at the time of this analysis Group 1 had not yet received the assigned booster training. As stated currently, it requires close scrutiny of the paper to make this determination. I believe the abstract should be able to stand alone by including this information. Therefore, I recommend that the abstract be modified along the following lines: Objectives: “This article presents the 5-8 week post-training results for the primary outcome.” Design: [Group} (2) “…standard dose of Road Tour training among participants with 4 hours of subsequent booster training scheduled to occur at 11-months post-randomization (i.e., no booster training had occurred at the time of this analysis).” Similarly, I believe the tables should contain enough information to be understood without referring to the text. Therefore, I still recommend that Table 4 (derived from previous Table 3) should contain the information that the on-site training with boosters vs. with no boosters refers to a distinction in group assignment only, not to a difference in training that could affect the current analysis. This

	could be accomplished in a key below the table, or it could be done by adding the word “future” to the booster group label within the table (Road Tour Onsite with Future Boosters) and dropping “no boosters” from the description of the other on-site training group. The authors’ response letter nicely outlines the training methodology that occurred for the on-site and home-training groups and references an in-press design paper that contains such details. Again, I would like for the current paper to contain at least the bare bones methods (number and length of sessions, nature of instructions and supervision, and instructions to in-home training participants) so that a reader could understand the method without reading the design paper. Finally, I previously asked the authors to consider commenting on the UFOV improvements found in the control group and how this affects interpretation of improvements resulting from Road Tour training. The authors do not explicitly discuss this issue. However, they now note on p. 21 that “IHAMS used an attention control group that was trained using a computerized crossword puzzle program that may have led to some improvement in processing speed beyond the placebo effect.” This is an interesting point that could be further elaborated by direct comparison of the training gains of the IHAMS attention control group in light of the training gains made by the no-contact control group in the ACTIVE study. The ACTIVE control group’s UFOV gains ostensibly were relatively pure practice effects from baseline exposure to the UFOV test, while the IHAMS control group’s UFOV gains likely represent baseline practice plus any benefit of attention and computer exposure, though I would not expect this paradigm to improve processing speed per se.

VERSION 2 – AUTHOR RESPONSE

Managing Editor’s Requests:

Your first request was that we review the ICMJE criteria for authorship, and determine whether MMD, CG, and SW meet them. Upon review, we noticed that an important part of MMD’s contributions had been left out of the authorship text. I apologize for this omission. This information has been added on page 28. At the same time, upon further consideration we concluded that your assessment concerning CG and SW was correct, and we have accordingly dropped them from the authorship list. Their contributions to accessing patients are now acknowledged on page 26.

Your other request was that we clarify how the data will be shared. As noted in a new “data sharing” section on page 27, we plan to deposit a de-identified data set with the Inter-University Consortium for Political and Social Research (ICPSR) on or before December 1, 2014, which will be about three

years after the last interview has been completed. ICPSR is a standard repository for data sets made available for public use.

Editor-in-Chief's Requests

The first request (which carries through the first four paragraphs of the Editor-in-Chief's comments) was to clarify in the title, in the abstract, and throughout the manuscript whether this was a planned interim analysis or not. To be sure, this was a planned interim analysis, and as it is now noted on page 7, this interim analysis was originally specified as hypothesis H1 in the protocol paper coming out in BMJ Open, and in the trials registry entry. We have clarified the language regarding this throughout the manuscript, and have changed the title of the manuscript as requested.

The second request was that we change "to improve cognitive function" in the title to read "to improve visual speed of processing." This has been done. We have not, however, added the suggested "brain training" term because we believe that that this term also represents "over-generalizing."

The third request was to drop the statistical significance testing from Tables 1 and 2, which has been done, although as the Editor-in-Chief noted that it would be appropriate, they are mentioned in the text.

The final request was whether it would be possible to have video clips of Road Tour being played. I have requested them from the vendor, Posit Science, and have been told that they will be forthcoming. In this regard, may we ask what parameters if any you might wish to put on those video clips, such as duration length, maximum file size, etc.?

Professor Marsiske's Requests:

We appreciate enormously Professor Marsiske's enthusiasm for our revised manuscript and its contribution to the field. Because he was fully satisfied with the prior version and had no further requests, we move on to Professor Wadley's requests.

Professor Wadley's Requests:

The first request from Professor Wadley was to clarify in the abstract and in the discussion of the groups in the design section that no booster training had occurred at the time of these interim analyses of post-training effects. This has been done on pages 2 and 7 and elsewhere throughout the manuscript.

The second request was related, and asked for similar clarity in the tables. This has been done on pages 36-38, and 40 using the wording that she suggested.

The third request was to incorporate detail on the training methodology that had previously been conveyed in the response letter. This has been done on pages 10-11 in a new section titled “Group Training Logistics.”

The final request was that we comment on the UFOV improvements found in the attention control group, especially with respect to ACTIVE’s use of a no-contact control group. This issue is considerably more complicated than it might appear, because there are a number of important differences between the two studies besides ACTIVE using a no-contact control group vs. the attention control group used in IHAMS, thus making direct comparisons problematic. For example, ACTIVE used the touchscreen UFOV with four subtests while IHAMS used the mouse UFOV with three subtests. Moreover, in IHAMS the on-site training groups, including the attention control group received their training in two-hour blocks rather than the one-hour blocks used in ACTIVE. That said, we did seriously pursue the matter, and would be willing to add the paragraph below on page 23, if that is your preference. We believe, however, that under the circumstances including this paragraph would be more distracting than enlightening and, consequently, does not merit inclusion in the manuscript.

To gauge the potential difference in post-training effect sizes between IHAMS and ACTIVE that might be attributable to the former using an attention control vs. the latter’s no-contact control group, we calculated the UFOV touch screen composites in ms based on subtests 2-4 as reported by the ACTIVE investigators [16], and the UFOV mouse composites in ms for IHAMS. In ACTIVE, the no-contact control group training gain was -78.89 ms, which was attributed ostensibly to practice effects accruing from having taken the UFOV test at randomization [16]. In IHAMS the attention control group training gain was -35.04 ms. Thus, the absolute improvement over time was lower in the IHAMS active control (crossword) group compared to the no-contact control group used in ACTIVE. Although the reasons for this counterintuitive finding are unclear, it is likely that the different UFOV measures used in the two studies was a major contributing factor.