Peer Review File

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Review Comments (Round 1)

Reviewer A

The submitted manuscript has some merit but it is at a very elementary stage to be published for one main reason that the number of subjects in the study is only 7! Thus, none of the statistical results, indeed, mean anything.

Thank you for your valuable comments. We agree with you; due to the small number of subjects and absence of a control group, the efficacy of this study cannot be established. However, we wish to submit this as a feasibility study that is focused on the side effects, participant satisfaction, and adherence to the training. In short, results are provided only for descriptive purposes. We decided to highlight the meaningful gains experienced by the participants, instead on focusing on inferential statistics. Kindly refer to the following: pages 7, lines 221-222, page 8, lines 249-256, page 9, lines 280-290, and table 5.

With regards to the training efficacy, a randomized control trial is currently being conducted.

The lack of subjects along with the fact that this is a well studied field, makes the paper unsuitable for journal or even a conference publication with such low number.

There have been theses and papers on application of VR in dementia and MCI population that the authors have not referred to any of them. I am sure they can gain more insight to the issue by doing a thorough literature review.

Thank you for your comments. As you mentioned, this is a well-studied field. However, we noticed that our study highlights two unique findings, which are outlined below:

1. Most VR studies in people with mild dementia have utilized only two levels of immersion: low or semi-immersive type. However, there are only a few documented cases of the fully immersive type of VR.

Reference:

https://doi.org/10.3389/fnagi.2021.586999

2. Most of the VR studies in people with mild dementia are focused on cognitive improvement, but this study is focused on the instrumental activities of daily living (I-ADL).

Reference: https://content.iospress.com/articles/journal-of-alzheimers-disease/jad210672

This is the first study to directly provide I-ADL contents for participants who were having difficulties carrying out their daily life activities.

Although the maintenance of I-ADL is important for people with mild dementia, I-ADL training is not easy to implement in a resource-limited environment, such as a hospital.

Therefore, we believe that this study on the intervention using VR can be of great help in the future.

Another issue that makes the results of the study in such small number of subjects, unreliable is the simulator sickness effect of full immersive VR tasks. The authors have reported only one out of 7 with a minor simulator sickness. However, other studies with larger number of subjects have already reported more simulator sickness. This issue needs a thorough discussion (again no reference to any paper that have addressed that amongst older adults). The tasks given to subjects (judging based on the figures) do not require much motion and therefore they may not cause much simulator sickness but again this is an issue that needs a proper discussion. The simulator sickness amongst older adults is a very serious issue.

Thanks for your valuable comments. It appears that we underestimated motion sickness. We conducted a literature search thoroughly on motion sickness and added the relevant information to the manuscript. Please refer to page 9, lines 269-277.

Change in the text:

It is well known that VR is safe and acceptable in people with mild cognitive impairment and dementia. However, In a review by Papaioannou et al., most studies utilized a non-immersive type (30). There is not much data on the fully-immersive type. In addition, it is known that susceptibility to motion sickness may increase with aging (35). This can be fatal in people with dementia. Thus, in this study, to minimize these risks, participants sat down in a chair and the therapist helped them reduce unnecessary movements while performing the VR intervention. Because it is known that side effects may be reduced by minimizing factors that cause motion sickness, such as standing and head movements

Reviewer B

First of all, congratulations on the article. It is an interesting and well-written paper. I found the VR IADL program very unique and helpful. The measures used for addressing feasibility, tolerability, and immersion were adequate, as well as the analysis performed.

We thank you very much for your kind praises. Your words are very encouraging to us, and we are moved by your positive comments.

I have only two points to address:

The first and most important one is the concept of Mild Cognitive Impairment. As the authors correctly state in the introduction "the onset of MCI, which has not yet progressed to ADL impairment, is a good time to begin training". By definition, when a patient is diagnosed with MCI he/she does NOT have ADL impairment, therefore, he/she does NOT have dementia. I found authors using the terms MCI and Mild Dementia interchangeably, but they are not the

same thing. Besides deciding which term to use during the manuscript, the authors should revise if participants had indeed MCI or mild dementia. it would be important to train ADL in MCI to prevent decline, but the VR program would probably not improve it much, since it should be just mildly impaired or not impaired at all. On the other hand, the VR program seems valuable for Mild dementia cases, which would have initial ADL impairment that could be trained and rehabilitated.

In addition, the authors present the diagnosis of vascular, Alzheimer and Frontotemporal dementia for participants in Table 2, once more stating that they had dementia and not MCI. So, please review the correct diagnosis of the study participants, and use the correct term throughout the manuscript.

Thank you so much for your pertinent comments and suggestions. As you have noted, we used MCI and mild dementia interchangeably. The correct diagnosis for these participants is mild dementia because they already presented with challenges or problems in ADL. Therefore, we have consistently modified the term to reflect only "mild dementia" throughout the manuscript.

The second point refers to the S-IADL measure. As I understood it is the validated Korean translation of the Lawton Instrumental Activities of Daily Living Scale, correct? If not, please provide further explanation in the manuscript. The question is that IADL scale ranges from 0 (severe impairment) to 8 (no impairment) and Table 4 provides scores ranging from 14 to 36. So, is it the same scale? Once more I got the sense that some participants had important ADL impairments, hence not allowing for the diagnosis of MCI.

Thank you for your valuable comments. Upon reviewing, we think that not enough explanation was given, so we have added more information about this in our manuscript (see page 6, lines 189-191)

Revisions:

S-IADL consists of 15 I-ADL items, and each item is rated from 0 (no impairment) to 3 (severe impairment), with a highest possible total score of 45 points. Both participants and caregivers answered the questionnaire.

Finally, in the Discussion, I would like to point out that results from this manuscript do not allow for the statement that "a fully immersive method may result in greater efficacy" (line 218). This is not a comparative study and efficacy was not a reliable finding with this sample. Authors may change to something like "a fully immersive method is feasible" or that it has the potential of being more naturalistic for IADL training.

Thank you for your comments, we modified our text as advised. (see page 8, line 239-241)

Revisions:

This study showed that fully immersive VR, which utilizes an environment that is closer to reality, also shows similarly high levels of satisfaction.

Reviewer C

This is a mostly well written and interesting manuscript adding to the evidence base for immersive virtual reality for people with dementia. I have a few comments to be considered by the authors:

We thank you very much for your kind words. We are very much encouraged by your positive comments.

I suggest writing in paragraph form, rather than including so many one sentence paragraphs.

Thank you for your suggestion, I have revised the manuscript accordingly.

The title of the paper and several sections refer to MCI, however, Table 2 lists the participants as having dementia. Please clarify.

Thanks so much for your important comments.

As you have noted, we used MCI and mild dementia interchangeably in the manuscript. The correct diagnosis for these participants is mild dementia because they already presented with challenges or problems in ADL. Therefore, we have consistently modified the term to reflect only "mild dementia" throughout the manuscript.

Please make it clearer in the results and tables that only five participants completed the TMT-B.

Thank you for your valuable comment. To aid in the clarity of our presentation of the results, we have marked with a symbol the two people who did not complete the TMT-B. We have also highlighted this as a comment in the legend of Table 5

Additionally, we specified that only five people completed the whole TMT-B (see page 7, line 224-226).

Change in the text:

Two participants, however, failed to complete the TMT-B test due to impairments in their cognitive functioning. Thus, only five people successfully completed the TMT-B test.

Introduction: There are several reviews on this topic that should be very briefly mentioned and cited:

https://doi.org/10.3389/fnagi.2021.586999

https://content.iospress.com/articles/journal-of-alzheimers-disease/jad210672

https://doi.org/10.1159/000500040

Thank you for your suggestion, we added it to the manuscript. Please refer to page 4, lines 104-105, page 8, lines 238, and page 10, line 299.

Line 35: Please use "people" instead of "patients". Relevant for entire manuscript. In some instances, participants or people with dementia may also be more appropriate.

Thank you for this suggestion. We have revised the use of "patients" to "people" or "participants" in the whole manuscript.

Line 65: Please use "older people" rather than "elderly". Relevant for enter manuscript.

Thank you for this suggestion. We revised the word "elderly" to "older people" on page 3 line 79.

Line 108: What is the rationale for the sample size?

Thank you for this relevant question. Based on previously published studies, at least seven to ten participants are needed to confirm feasibility. We were unable to mention this in the manuscript initially, therefore we added this to the revised manuscript (see page 4, lines 114-115).

Reference:

1. Hodge J, Balaam M, Hastings S, et al., editors. Exploring the design of tailored virtual reality experiences for people with dementia.

2. Kim J-H, Park S, Lim H. Developing a virtual reality for people with dementia in nursing homes based on their psychological needs: A feasibility study. BMC Geriatr 2021;21:1-10.

Line 217: As this study did not compare semi- and fully-immersive VR, it is not possible to make this statement. Please re-write the sentence.

Thank you for your valuable comments, we modified our text as advised (see page 8, line 239-241).

Change in the text:

While most previous studies used semi-immersive VR techniques, this study showed that fully immersive VR, which utilizes an environment that is closer to reality, also shows similarly high levels of satisfaction.

Reviewer D

This is an interesting paper that merits publication, perhaps as a brief report or letter. However, the diminutive sample size and lack of scientific rigor preclude publication of efficacy analyses.

First, with such a small sample and no control group, it is not reasonable to suggest that there has been a treatment effect. All of this could very reasonably be driven by practice and/or placebo.

We thank you very much for your kind consideration. We are encouraged by your positive comments.

I agree with your advice.

Due to the small number of subjects and absence of a control group, the efficacy of this study cannot be established. However, we wish to submit this as a feasibility study that is focused on the side effects, participant satisfaction, and adherence to the training. In short, results are provided only for descriptive purposes. We decided to highlight the meaningful gains experienced by the participants, instead on focusing on inferential statistics. Kindly refer to the following: pages 7, lines 221-224, page 8, lines 248-256, page 9 lines 280-289, and table 5.

With regards to the training efficacy, a randomized control trial is currently being conducted.

In fact, looking at the Table 4 it appears that only 2 participants, #2 and #3 would show a clinically significant improvement. The biggest improver overall, #2, had a normal MMSE to start with, was only 57 years old, and appeared to drive the group level improvement on the IADL scale. Given vascular basis for dementia, I would wonder this might represent post-stroke recovery? Or, with a baseline BDI of 31, perhaps pseudodementia?

Thank you for your important question. As you mentioned, the statistical significance can be over-interpreted due to case #2. Therefore, as you advised, we added the interpretation of case #2 (see page 8, line 249-256).

On a related note, because this exercise was meant to build capacity skills, the marked reduction in depression scores (BDI) suggests that the intervention may have more to do with behavioral activation and social interactions with the OT and study staff – this would also be expected to produce the slight gains seen on the cognitive tests.

Thank you for your comments. We agree with you, mood changes may have influenced other outcomes as well. Therefore, this was added to limitation section (see page 10, line 311-313).

Change in the text:

A positive change in mood was seen in all participants. These changes may have affected cognition and function as a secondary gain. In the future, it will be necessary to analyze the correlation of each factor.

Also, unless parallel forms of the CERAD-K with different word lists were used, the miniscule gains are to be expected in the group, and none of the gains I see would indicate statistically and clinically significant improvement.

Last, it does not state whether the patient, family member / caregiver, or OT completed the IADL measure. This is very important, as patients with MCI and early dementia are notoriously poor at reporting functional capacity.

Thank you for your valuable comments. I added I-ADL measurement methods and result in page 6, line 191 and page 7, line 218.

With these concerns in mind, my recommendation is to focus the paper on the feasibility and acceptability outcomes. For the IADL measure, I would keep Table 4 and highlight whichever participants evinced a meaningful gain rather than the improper and uninterpretable inferential statistics. I would also briefly explain why the apparent improvement in #2 could not be accounted for by other factors unrelated to the VR intervention. I would leave the cognitive measures out altogether. If they are to be left in, I would underscore that this was exploratory to identify possible cognitive correlates of treatment response, and results are provided only for descriptive purposes. If there are any notable participants who showed change, perhaps highlight that but not group level analyses.

Thank you for your valuable comments. The participant with meaningful gain was highlighted in Table 4 and a description of case #2 was added in the manuscript (see table 4 and see page 8, line 249-256).

As for the improvement of cognitive function based on treatment, the results were provided for descriptive purposes only and statistically significant conclusions were excluded (see page 9, line 280-290 and table 5).

Reviewer E

This is a well organised and very interesting feasibility study and I would like to see it published to develop interest in this area. It is important to address several issues below prior please.

We thank you very much for your kind words. We are very much encouraged by your positive comments.

Abstract

Line 33: To retain neutrality ‘The purpose of this study was to confirm that’ would better read ‘The purpose of this study was to confirm whether’

Thank you for your suggestion, we have made the necessary revision (see page 2, line 40).

Line 52-55: This was a small feasibility study involving seven participants and without a control group. Very limited measures were completed and causality cannot be inferred. These conclusions are not justified and should be significantly moderated to reflect these issues as you do in lines 268-271.

Thank you for your valuable comments. We agree with you, our conclusion seems to be misleading. We have revised our manuscript accordingly (see page 2, line 63-65).

Change in the text:

However, further research is needed for fully immersive virtual reality instrumental activities of daily living training before it can be considered as a treatment option in people with mild dementia.

Methods

It is important to know how the iVR tasks were chosen and validated. Is this a separate publication?

Thank you for your comment. The VR task was developed by determining the most necessary task for people with mild dementia with reference to the S-IADL item, which is the outcome of the study. The validation of each task was not carried out separately, and we tried to check its feasibility through this preliminary study. There are no other publications related to this. However, the lack of a validation process or procedure for each task was presented as a limitation of the paper (see page 9, lines 308-311).

Results

You mention multiple Wilcoxon signed-ranks tests but no Bonferroni correction to reduce the risk of false positives following multiple comparisons. This will need addressing please.

Thank you for your valuable comments. This study aims to confirm feasibility. Additionally, a randomized controlled trial is currently in progress to assess the effects of this treatment. In order to clarify the purpose and feasibility of this study, the result of the CERAD-K was provided for descriptive purposes, rather than as statistically significant values. Also, as you pointed out, we recognize that the number of participants is small and there is a multiple comparison problem in the use of CERAD-K. Therefore, some statistical findings were deleted from CERAD-K, while notable items which showed significant change were highlighted. (see table 5)

It would be interesting to know details of how much of each task patients completed and whether there was a difference for those with more severe impairment.

The execution time per mission was measured by adherence (see page 5, line 164-166 and Table 3). Unfortunately, the execution time of each subtask was not measured. In the next

follow-up study, we will also measure the time of each subtask. Changes based on severity will also be assessed and discussed in another follow-up study.

Discussion

Line 209-210 The first two lines of the discussion suggest that the authors are linked to bHaptics but the nature of this relationship/ level of involvement in the material design is not explained elsewhere. Please clarify.

Asan Medical Center and bHaptics have been developing VR for I-ADL training. Our research team presented the contents and methods of the VR. Technical implementation and development were carried out in bHaptics. We have added these pertinent information to our Methods session (see page 4, line 129-132). Additionally, the funding for this clinical research was supported by bHaptics, which is mentioned in our Acknowledgments section.

Line 217 refers to previous studies but does not give a reference.

We added the reference as your comment (see page 8, line 238).

Line 221 you suggest patients with MCI lack IADL capacity but this is not measured or discussed elsewhere.

Thank you for your valuable comments. That statement was written vaguely. Our intention for that was that the VR program provided the I-ADL contents, which outlined what the patient was having difficulties with in real life. We re-wrote the details in pages 8, lines 244-246. This was also mentioned in our Methods section (see page 4, line 140)

Change in the text:

This study is the first to directly provide the I-ADL contents that the participants were having difficulties with in daily life.

Line 222 refers to cortical reorganisation but this there is no detail in the study to suggest how this is inferred.

The ambiguity in this sentence seems to have caused some misunderstanding. It emphasized that this VR training is a task-specific intervention; doing so by presenting, as a task, the I-ADL that the patient is having difficulty with. There have been previous studies reporting that cortical reorganization is stimulated when the intervention is task-oriented. We modified our manuscript accordingly (see page 8, line 259-261)

Line 222 and 224-226 Please clarify who completed the S-IADL measure. Were objective improvements seen or did higher scores reflect greater confidence/ general familiarity.

Thank you for your valuable comments. I added I-ADL measurement methods and their corresponding results in page 6, line 191 and page 7, line 218.

Lines 255-265 Very good appraisal of the studies limitations which gives ideas for next steps. As you note there was a very diverse range of cognitive presentations included in the study. It would be interesting to look in more detail at differences based on diagnosis/ severity of dementia.

Thank you for your kind comments. Additional research is currently being conducted by way of a randomized control trial. In this study, we will look at the differences based on diagnosis / severity of dementia.

Review Comments (Round 2)

Reviewer A

Many thanks for resubmitting your article with extensive improvements. This article now offers a much more grounded perspective and I think is ready for publication.

We thank you very much for your kind praises. Your words are very encouraging to us, and we are moved by your positive comments.

My only comments are that you mention 'mild cognitive impairment' in your abstract (line 43) but throughout the rest of the article refer to patients with mild dementia. Please correct/ clarify this.

Thank you for your comments, we revised the word "mild cognitive impairment" to "mild dementia" on page 2 line 37.

Also in the abstract I don't think you can really comment on treatment efficacy in a feasibility study so would drop point 2 (lines 43-44).

Thank you for your valuable comments, we modified our text as advised (see page 2, line 37-38).

Reviewer B

The authors successfully addressed the points I have highlighted, and, therefore, I endorse publication. There are two minor mistakes in the text I would like to point out, but I am not sure they require going back to the authors. These are:

We thank you very much for your kind words. We are very much encouraged by your positive comments.

ABSTRACT: The authors have changed the terms mild cognitive impairment (MCI) to mild dementia, according to my orientation. However, they seem to have missed the term in the "Background" where they state their purpose.

Thank you for your comments, we revised the word “mild cognitive impairment” to “mild dementia” on page 2 line 37.

DISCUSSION: In line 352, the authors state that motion sickness could be "fatal" to people with dementia. I am not sure what the authors meant by that, but I don't believe fatal is a wise word choice.

Thank you for your comments. We modified our text as advised (see page 8, line 252).