Author's response to reviews

Title: Poor balance and lower gray matter volume predict falls in older adults with mild cognitive impairment

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Author's response to reviews: see over
Referee 1:
The authors describe this as a longitudinal of subjects with MCI who were recruited from a larger RCT study of an exercise program. They had MRI and physical abilities measured at baseline and were followed for 1 year to see if they fell. One fall over the next year was sufficient to refer to the subjects as "fallers".

MRI measures (specifically VBM) were used to see if gray matter was different between those who fell and those who did not. Those who fell had smaller frontal cortical volumes and had worse performance on some physical performance measures. The performance measures were adjusted for age and sex but it is not clear to me that the MRI measures were similarly adjusted.

I agree with the limitations that the author discussed in the manuscript, such as the fact that falls were self-reported in only 2 interviews. Subjects or their informants may have forgotten falls in the interim between interviews or may be biased in their reporting. I also agree that the definition of "faller" may not be adequate.

There is no description of how the 50 subjects in the referenced RCT were recruited into this substudy of 42 subjects. The authors assume that all MCI patients are otherwise similar, but cognitive performance and stage of disease can differ within the syndrome group of MCI. There is no accounting for cognitive performance and stage of disease, which is especially important given that some of the subjects may have progressed longitudinally to dementia over the course of one year. It may be that those who fell had also progressed cognitively in their disease process.
Response
We appreciate all of your comments and indications. We have added some sentences including the recruitment information in the form for the MCI studies to the Methods section, in accordance with your comments. Regarding your comments, we agree with your statements that cognitive performance and stage of disease are important and that some of the subjects may have progressed longitudinally to dementia over the course of 1 year. In this study, none of the subjects progressed during the 12-month follow-up period. We confirmed that there were no differences in the baseline scores of cognitive performance including the executive function and visuospatial tasks between our groups of subjects (please see the table below). To avoid confusion of interpretation, we did not provide these data. However, for further clarification of these points, our sample is not sufficiently large and the study design is limited. We consider that future studies, including larger numbers of subjects, are needed. Our main responses and revised points in accordance with your comments are below.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Non-fallers</th>
<th>Fallers</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey_copy (points)</td>
<td>33.9 ± 1.6</td>
<td>34.1 ± 2.0</td>
<td>0.737</td>
</tr>
<tr>
<td>Rey_recall (points)</td>
<td>15.0 ± 7.0</td>
<td>14.3 ± 7.6</td>
<td>0.783</td>
</tr>
<tr>
<td>TMT-A (sec)</td>
<td>137.1 ± 58.3</td>
<td>142.9 ± 47.1</td>
<td>0.768</td>
</tr>
<tr>
<td>TMT-B (sec)</td>
<td>223.5 ± 159.4</td>
<td>239.8 ± 138.4</td>
<td>0.765</td>
</tr>
<tr>
<td>DSC (points)</td>
<td>44.2 ± 15.3</td>
<td>37.0 ± 8.5</td>
<td>0.147</td>
</tr>
</tbody>
</table>

Rey: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; DSC: Digit Symbol Coding tasks.

Location in the text
Page 6/ Lines 18:
A total of 100 participants took part in the RCT and completed neuropsychological assessments including language, memory, attention, and executive function tests. All subjects in this study had objective impairments at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. The participants were classified to an amnestic MCI (aMCI) group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were then randomly...
assigned to either a multicomponent exercise group or an education control group using a ratio of 1:1. The sample for this longitudinal study involved participants in a control group. Of the 50 participants in the control group, 42 completed fall follow-up assessments during the 12-month follow-up period.

Page 9/ Lines 25-:
Age and sex were included as covariates.

Page 14/ Lines 16-:
We performed the VBM analysis to identify the locations of group differences in gray matter volume. Therefore, we consider that our results cannot provide evidence for whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and the fall risk.

Page 14/ Lines 23-:
To clarify these points, we consider that future studies including larger numbers of subjects and countable data for structural changes in the brain (e.g., described volumes in cubic millimeters) are needed.

Referee 2
The manuscript describes a longitudinal study assessing the association between baseline physical performance and gray matter volume, and risk of falling in 42 community-dwelling older adults with mild cognitive impairment followed up for a 12-month period – 11 individuals experienced a fall during the study period. The investigators were than able to compare clinical and performance characteristics as well as MRI volumes between those who fell (n=11) vs. those who did not fall (n=31).

Overall, the paper is well written. The findings suggest that poor physical function as measured by walking speed and balance and lower gray matter volume predict incident falls over the follow-up period. Identification of risk factors for falling in the MCI population – an at-risk group is an important issue. Inclusion of brain imaging data adds merit to the project and furthers our understanding of the link between brain structural changes, cognitive impairment,
and risk of falling. However, there are some issues that this reader would like to comment on with the goal of improving the quality of the paper.

Response
We appreciate all of your comments and indications. Our responses to your specific comments are below.

Major Compulsory Revisions:
1. Although the primary results of the trial have been published, there are details missing from this manuscript that would be helpful to the reader. Nowhere in the methods section is the form of MCI studied (amnestic, non-amnestic, single, multidomain) or how the MCI evaluation was performed is described. MMSE scores are not sufficient to characterize the sample described here.

Response
Thank you for your helpful suggestions. We have added some sentences including the information in the form for the MCI studies to the Methods section.

Location in the text
Page 6/ Lines 18-:
A total of 100 participants took part in the RCT and completed neuropsychological assessments including language, memory, attention, and executive function tests. All subjects in this study had objective impairments at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. The participants were classified to an amnestic MCI (aMCI) group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were then randomly assigned to either a multicomponent exercise group or an education control group using a ratio of 1:1. The sample for this longitudinal study involved participants in a control group. Of the 50 participants in the control group, 42 completed fall follow-up assessments during the 12-month follow-up period.

2. This reviewer therefore assumes that a larger neuropsychological evaluation was performed. Even though MMSE scores were not different between Fallers
and Non-fallers, what about other cognitive tasks. For example, were there differences in executive or visuospatial tasks between the groups?

Response
We confirmed that there were no differences in the baseline scores of the executive function and visuospatial tasks between our groups of subjects (please see the table below). To avoid confusion of interpretation, we did not provide these data. Thank you for your helpful comments.

<table>
<thead>
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Rey: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; DSC: Digit Symbol Coding tasks.

3. History of falling has been identified as a significant predictor of future falling. However, this factor has not been addressed in the manuscript. This reader suggests that this information, if available, should be taken into account in data analysis (added to the multivariate models to control for its impact on fall risk).

Response
Thank you for your helpful comments. Actually, we think that history of falling could be a significant predictor of future falling. We compared the history of falling at baseline between the groups, and have added the data analysis. Consequently, we needed to revise parts of the Results and Discussion sections according to the revision of the analysis. In addition, the title has been revised.

Location in the text
Title:
Poor balance and lower gray matter volume predict falls in older adults with mild cognitive impairment
Chi-square tests for differences in proportions were used to compare differences in sex and history of falling in the past year at baseline between the faller and non-faller groups. To describe variations in different physical performance factors related to falls, multivariate logistic regression analyses were performed to reveal the physical performance factors independently related to falls during the 12-month follow-up after adjusting for age, sex, body mass index (kg/m$^2$), and history of falling in the past year at baseline. We calculated the odds ratios (OR) with 95% confidence intervals (CI).

In addition, the faller group had a significantly higher rate of fall history at baseline compared with the non-faller group ($p < .01$).

In the multivariate logistic regression, OLS time (sec) (OR [95% CI]: 0.89 [0.81, 0.98], $p = .02$) was associated with a significantly lower rate of falls during the 12-month follow-up after adjusting for age, sex, body mass index, and history of falling in the past year at baseline. There was no statistical evidence of associations between falls and knee-extension strength (Nm) (1.02 [0.96, 1.08], $p = .59$) and walking speed (m/min) (0.91 [0.81, 1.03], $p = .13$).

4. Given the correlations between structural changes in the brain, physical functionality, and fall risk, it may be important to assess whether the effects of physical performance are independent of gray matter volume or whether the latter confounds the association between the former and fall risk.

**Response**

Thank you for your helpful comments. We agree with your statements that it may be important to assess whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and fall risk. However, we performed the VBM analysis to assess whether there were group differences in the gray matter volume and to identify the locations of group differences in the gray matter volume. Therefore, we consider that our results cannot provide evidence for
whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and the fall risk. To clarify these points, we consider that future studies including larger numbers of subjects and countable data for structural changes in the brain (e.g., described volumes in cubic millimeters) are needed. We have added sentences to the study limitations, in accordance with your suggestions.

**Location in the text**

Page 14/ Lines 16--:

*We performed the VBM analysis to identify the locations of group differences in gray matter volume. Therefore, we consider that our results cannot provide evidence for whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and the fall risk.*

Page 14/ Lines 23--:

*To clarify these points, we consider that future studies including larger numbers of subjects and countable data for structural changes in the brain (e.g., described volumes in cubic millimeters) are needed.*

**Other points for major revision**

In the previous version of our manuscript, we made a small mistake in deciding the locations of the group differences in the gray matter volume, because of confusion regarding the MNI and Talairach coordinates (please refer also to our response to Minor Essential Revision #8). Therefore, we needed to revise parts of the Results and Discussion sections. We apologize for the confusion concerning the Results and Discussion sections in the original version of our manuscript.

**Location in the text**

The whole Results (second paragraph, Table 3, and Figure 1) and Discussion sections.

**Minor Essential Revisions**
5. The issue of why increased fall risk is important in the context of mild cognitive impairment should be more emphasized in the background section. This would imply making the connection to the Alzheimer’s Disease/dementia process as well.

Response
Thank you for your helpful comments. We have added some sentences in the Background section, in accordance with your comments.

Location in the text
Page 4/ Lines 19-:
In addition, people with cognitive impairment recover less well after a fall than those without cognitive impairment [11]. Therefore, the falling may have negative impact on health in older people with cognitive impairment compare with those without cognitive impairment. In older individuals with mild cognitive impairment (MCI) in particular, consideration of a broad range of causes of falls could play a role in reducing the fall risk and providing strategies to prevent falls among the high-risk population.

6. Given the finding that gray matter volume in certain areas of the brain appears to be an important predictor of fall risk in older individuals with MCI, having something in the background section that addresses the link between different brain areas and fall risk may help provide some direction as to what the expectations were at the onset of the study.

Response
In the Background section of the revised manuscript, we have added a sentence concerning the different brain areas and the fall risk.

Location in the text
Page 5/ Lines 22-:
In particular, a smaller volume of the prefrontal area might be associated with poor physical performance [22, 23], such as slower gait and poor balance, but no evidence has been reported that smaller brain volume of specific regions is related to the occurrence of subsequent falls in older adults with MCI.
7. Which leg was used to measure isometric knee extension strength and why (page 4)?

**Response**
In the present study, isometric knee extension strength was tested twice from the dominant leg. Since we were examining older adults with MCI, the physical performance tests in this study were conducted to maximize safety and ease of completion.

**Location in the text**
Page 7/ Lines 9-:
Isometric knee extension strength was tested twice using a dynamometer (Model MDKKS, Molten Co Ltd, Hiroshima, Japan) from the dominant leg (self-reported side they would use to kick a ball as far as possible).

8. The ‘magnetic resonance imaging procedure’ section on page 5 could be improved by describing how gray matter atrophy was measured and used in data analysis.

**Response**
Thank you for your helpful suggestions. We have added some sentences in the corresponding section, in accordance with your suggestions.

**Location in the text**
Page 8/ Lines 23-:
Tissue segmentation, regulation, registration, and normalization were conducted in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2010a (Mathworks). Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) [29] was conducted for the image analysis. The normalized images were transformed into Montreal Neurological Institute space. The gray matter images were then smoothened using a Gaussian kernel of 12-mm full-width at half-maximum.
9. Why was the statistical threshold for the VBM analysis set for p<0.001 (page 6)? This looks like a multiple comparison correction, although the authors state this was uncorrected.

Response
In the present study, we selected an unpaired t-test group analysis as a statistical model in the SPM and covariates (age and sex) were also selected, as reported previously for similar methods (Lim TS, et al. 2010; Schmidt-Wilcke T, et al. 2009). Actually, there were various statistical thresholds for the VBM in each study. We set the height of the threshold (p<0.001), and used the standardized value in the VBM analysis. Parts of the Statistical Analysis and Results sections have been revised to avoid misleading our readers.


Location in the text
Page 9/ Lines 25-:
Age and sex were included as covariates.

10. The results section mentions that fallers and non-fallers were compared in terms of body mass index (page 6). This appears ‘out of the blue’ without a connection had having been made between BMI and fall risk.

Response
We did not find a significant group difference in BMI, and considered that BMI was not an important variable to describe the fall risk in this study. The results for
BMI have been deleted from the revised manuscript.

**Location in the text**

**Results section:**

There were no significant differences between fallers and non-fallers in age, sex, and body mass index.

11. This reviewer would advise the authors to replace the term ‘reduced’ when describing baseline levels of gray matter volume. Since ‘reduced’ suggests decline in volume over time, a more appropriate term would be ‘lower’. Do this throughout the manuscript.

**Response**

We have replaced the term ‘reduced’ with ‘lower’ when describing the baseline levels of gray matter volume throughout the manuscript. Thank you for your helpful suggestions.

**Location in the text**

The whole manuscript.

12. Although the brain imaging findings were understandably emphasized in the discussion section, the findings on physical functionality should not be ‘brushed-off’. The authors could expand the second paragraph on page 7 to discuss the importance of physical functionality on fall risk in the context of MCI. How current findings relate to previous reports should be discussed here.

**Response**

Thank you for your helpful comments. The importance of physical functionality for the fall risk in MCI subjects and interpretations of the revised results have been included in the Discussion section.

**Location in the text**

Page 11/ Lines 25-:
Although fallers exhibited slower walking speed compared with non-fallers, walking speed was not associated with the occurrence of subsequent falls after adjusting for age, sex, body mass index, and history of falling at baseline. There was no difference in the extension strength between fallers and non-fallers. The results of this study indicate that poor balance is the important factor related to an increased risk of falling among people with MCI. Muscle weakness and problems with mobility had been considered to be the important contributors to the risk of falling in older people [5], and there are presumably some relationships. In study cohorts including older people with MCI and similar lower muscle strength, like the present study, poor balance may have a greater impact on increased risk of falling than walking performance. Certainly, poor balance could be one of the predictors of walking decline among older people [39].

Balance ability may be an important dimension of physical functioning to predict the occurrence of subsequent falls among older people with MCI, as well as those with intact cognition. The present study has advantages including the examination of occurrence of subsequent falls during a 12-month follow-up period and neuroimaging assessments in older adults with MCI. However, our sample was not large, and selection bias may affect the results of the relationships between physical performance and occurrence of subsequent falls. Therefore, future studies with larger numbers of MCI subjects and a longitudinal design are needed to add evidence to the present results.

13. Could the authors elaborate on why muscle strength was not important in predicting fall risk in this population?

Response
We have included these points in the responses to comment #12.

14. The authors could elaborate a little more on the last point they make in the conclusions section. Is there evidence that age-related declines in physical function and brain structure can be prevented?

Response
We have elaborated a little more on the last point in the Conclusions section.
The current findings indicate that poor balance predicts falls over a 12-month period, and that lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with falls in older adults with MCI. Maintaining physical function, especially balance, and brain structural changes through many sorts of prevention strategies in the early stage of cognitive decline may contribute to decreasing the risk of falls in older adults with MCI.