Author's response to reviews

Title: The effect of cognitive-motor dual-task training on cognitive function and plasma amyloid beta peptide 42/40 ratio in healthy elderly persons: a randomized controlled trial

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Author's response to reviews: see over
Dear Prof. Giulia Mangiameli

Thank you very much for your e-mail dated on Feb 5, 2015 concerning our above-titled manuscript. We have sincerely revised our manuscript according to the comments by the reviewers. Each specific response to each reviewer is given in the following pages. We believe that our responses and revisions have well addressed the comments by the reviewers. We hope that our manuscript is now acceptable for publication in *BMC Geriatrics*. Your consideration of this revised manuscript will be greatly appreciated. The authors declare again that they have no competing interests.

I look forward to hearing good news from you at your earliest convenience.

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Response to Dr. Flicker

Major revisions

1. According to comment 1 by Dr. Flicker, we added the details of our randomization procedure to the “Study Design” paragraph in the Methods section of the manuscript. The revision is as follows:

p7 line 19
A disinterested third person performed the randomization by computer processing with the random number generation program to achieve balance on gender, age, years of education, and the total scores of 3MS exam.

2. In regard to the baseline cognitive scores (comment 2), we have already shown the baseline 3MS scores in each group in Table 2 of the original manuscript. We randomized the participants according to achieve balance on the total scores of 3MS exam. Therefore, there was no difference in the total scores of 3MS exam between the groups as shown in original Table 2. We also found no differences in the scores in each cognitive domain of 3MS and in TMT results at baseline.

As Dr. Flicker pointed out, the baseline BMI was different between the two groups, although it did not reach statistical significance, because we did not treat the baseline BMI as a balancing factor at the randomization. It is possible that this difference results in study bias. We added the description about this issue as the limitation to the Discussion section of the revised manuscript. The revision is as follows:

p23 line 8
Third, because we did not treat the baseline BMI as a balancing factor at the randomization, the difference in the baseline BMI between the groups, although it was not statistically significant, might also bring about study bias.

3. In regard to comment 3 by Dr. Flicker, the study protocol was designed as single-blinded study, and the participants were unaware of which of the exercise programs, single-task or dual-task training, they were engaged in. The participants in each group were led to the separate rooms for exercise respectively with caution trying not to come across each other. Therefore, they could not discuss the program they attended, and were unaware of the group identity. In this study, the raters and the instructor were aware of the characters of each exercise program. We decided to mention the issue in the paragraph concerning limitations in the Discussion section of the revised manuscript as follows:
Second, it cannot be completely denied that the greater improvement in cognitive function in the DT group was affected by the single-blinded design in the present study, in which the exercise instructor was aware of the character of each exercise program.

4. In regard to precision and reproducibility of the measurement of amyloid β proteins (comment 4), the cumulative intra-assay coefficients of variation in our laboratory were 6.9% and 5.2% for Aβ40 and Aβ42, respectively. Likewise, the inter-assay coefficients of variation were 2.3% and 8.5% for Aβ40 and Aβ42, respectively. According to the suggestion by Dr. Flicker, we added the description regarding the precision and the reproducibility of Aβ measurement to the Methods section of the revised manuscript. The revision is as follows:

The inter- and intraassay coefficients of variation were less than 10%.

Minor revisions

1. According to comment 1 by Dr. Flicker, we revised a sentence in the Background section as follows:

Conversely, several observational studies with cognitively intact older subjects have to date revealed that high physical activity reduced the incidence of dementia [3, 4].

2. As Dr. Flicker pointed out, it needs to be resolved whether plasma levels of Aβ 40 and Aβ 42 vary following the change in the levels of these proteins in CSF. In addition, the implication of plasma levels of Aβ 40 and Aβ 42 according to the clinical stages in Alzheimer’s disease has not been fully elucidated. We revised the paragraph regarding the utility of plasma levels of Aβ proteins in the Background section as follows:

Recently, the possibility of low plasma Aβ 42/40 ratio as a predictor of increased risk for developing AD has also been reported [9], although the implication of plasma levels of Aβ 40 and Aβ 42 in conjunction with the variation in the levels of these proteins in CSF has not been fully elucidated.
Response to Dr. Kurrle

We are grateful to Dr. Kurrle’s favorable general comments. As she pointed out, 27 eligible persons among 30 applicants participated in the exercise intervention. Among 27 participants, 25 completed the study. The mention related to the study subjects in the Abstract section of the original manuscript could be misunderstood. To make this issue easy to understand, we revised the Abstract section as follows:

p2 line 10
Twenty-seven sedentary elderly people participated in a 12-week randomized, controlled trial.

p2 line 18
Among 27 participants, 25 completed the study.