Author's response to reviews

Title: Cognitive Training Can Reduce the Rate of Cognitive Aging - Evidence from Cohort Neuroimaging Data

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Version: 3
Date: 23 July 2015

Author's response to reviews: see over
Dear Dr. Pieter Jelle Visser,

Thank you for your letter dated 23rd Jun. 2015. We were pleased to know that our manuscript was rated as potentially acceptable for publication in BMC Geriatrics. We have revised our manuscript in line with the comments from the reviewers. Appended to this letter is our point-by-point response to the issues raised by the reviewers. We would like to take this opportunity to express our sincere thanks to the reviewers whose suggestions, we believe, have greatly improved the paper. We would also like to thank you for your editorial efforts.

We hope that the revised manuscript meets your approval for publication in the nearest issue of BMC Geriatrics.

Sincerely Yours,

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Response to reviewers

Reviewer 1:

The authors would like to thank the reviewer for his wonderful comments that help to improve the manuscript. For details, please refer to the responses as follows.

Reviewer's report
Title: Cognitive Training Can Reduce the Rate of Cognitive Aging - Evidence from Cohort Neuroimaging Data
Version: 2 Date: 2 March 2015
Reviewer: Christos Frantzidis

Reviewer's report:
The authors employed single and multi-domain training of healthy senior citizens. Time and functional domain entropy features on BOLD signals were employed as outcome measures. The authors investigated whether training induced neuroplasticity effects to the mature human brain. The topic is of crucial importance and the study could greatly contribute to the better understanding of this methodology. However, the study seems to suffer from certain methodological limitations and the manuscript needs major compulsory revision prior to its publication:

• Please rephrase the sentence within the Abstract-Background section. Maybe it would be better to divide that sentence in two separate sentences.

Thanks for your advice. We have modified this as you suggested.

• The Results section within the Abstract is extremely vague. More specifically, it reports statistically significant results regarding the mean rate of increase of the functional entropy, the mean-rate of decrease of the time-domain entropy and then the mean rate of increase for the functional entropy. Based on these results
the authors conclude then that training induced neuroplasticity. However, this conclusion was not justified, while it is not clear the physiological meaning of the aforementioned features. A better linkage should be done.

Thanks for your advice. We have modified this as you suggested.

• The Introduction Section does not address properly the previous literature on non-pharmaceutical training approaches, the neuroplasticity issue and the evaluation through neurophysiological outcome measures. A more update description would be very informative for the reader and would help the authors to state the novelty of their approach.

Thanks for your advice. We have modified this as you suggested.

• As the authors state, time-domain entropy is computed for a single time-series. Therefore it quantifies the complexity of the specific region and is reduced with aging. Due to its univariate nature it may not be a proper measure of neuroplasticity since it cannot quantify the co-operative degree of distant brain regions. Moreover, it is not clear why improvement due to cognitive training is related with increasing complexity during a resting-state period.

We understand that only time-domain entropy may not quantify the co-operative degree of distant brain regions, thus we applied the functional entropy constructed by functional connectivity of all brain regions which quantity the co-operative degree of distant brain regions.

Thanks for your advice, we show that complexity is affected by age in the supplementary materials and benefits are revealed in two intervention groups. Thus, we believe that cognitive training is related with complexity.

• The authors should give additional details about the two types of interventions. They clearly state the cognitive function that are trained but do not report the
training procedure. Moreover, it is not clear whether the control group is an active or a passive (no-contact) one.

Thanks for your advice. We have added more details about the training as you suggested. In our previous article focusing on the cognition effects of the training, the interventions were described in more detail (Cheng Y, Wu W, Feng W, Wang J, Chen Y, Shen Y, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. BMC Med. 2012; 1030.). The control group was an active one and attended a lecture about healthy living every two months together with the other two groups.

- The authors state that cognitive assessment was performed during baseline (prior to the training onset) and then was repeated one year after the intervention. If I understand it correctly, no assessment was performed after the intervention end. However, almost all the trials perform the second assessment some days after the intervention end and a follow-up one year after. Why the authors selected to alter this methodological practice? Please elaborate.

In our study, the cognitive assessment was performed at baseline and immediate, 6-month and 12-month follow-up after training completion. But the fMRI scanning was conducted at baseline and 12-month follow-up after training completion. In order to imploring the changes of fMRI, the performance induced by cognitive training, and the relationship between them, we analyzed the cognition data collected at baseline and 12-month follow-up after training completion, and the fMRI data collected at the same two time points.

- The parameters of the Approximate Entropy are different than those that are commonly employed. Please elaborate.

We show in Supplementary Materials Section 2 and Figure S2 that the time-domain entropy will represent an extreme value with \( r = 0.12 \) SD, thus we believe
this parameter should be fine here.

- *The Pearson correlation coefficient was used to transform the AppEn from the time to the functional domain. However, this is a very naïve way of quantifying functional interactions and may not capture dynamic or non-linear interactions. Please elaborate your choice.*

Thanks for your advice. Yes, this is a quite naïve way to do statistics. Since we do not have lots of subjects, we just want to capture the basic relationship between MRI data and behavioral information. We just worry about that more complicated statistics inference method may lead to larger noises and deviations.

- *The participants of the single-domain cognitive intervention seem to have less (3) years of education than the other two groups. However the overall statistical analysis did not yield significance. I am not sure about the validity of the analysis conducted. Maybe, authors or a more experienced reviewer in the statistics field would provide further insight in this methodological limitation.*

Thanks for your advice. We analyzed the difference of the education years among the three groups again. The results are the same with those in our paper. Details about the statistical analysis are as follows.

1. Baseline

<table>
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<tr>
<th>Descriptives</th>
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<tbody>
<tr>
<td>Education</td>
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<th>Std.Error</th>
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<th>Upper Bound</th>
<th>Minimum</th>
<th>Maximum</th>
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Test of Homogeneity of Variances

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<td>df2</td>
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<td>.143</td>
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ANOVA

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<td>828.378</td>
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2. One year after training

Descriptives

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<td>Std.Error</td>
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<td>Upper Bound</td>
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<td>4.21676</td>
<td>.99390</td>
<td>7.2919</td>
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Test of Homogeneity of Variances

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ANOVA

Education
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<td>47</td>
<td>13.216</td>
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<tr>
<td>Total</td>
<td>668.180</td>
<td>49</td>
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- The authors should check the manuscript and follow the same paragraph layout to the whole document.

Thanks for your advice. I have checked paragraph layout to the whole document.

- The effect of decrease of the mean increase rate of functional entropy seems to be much more prominent in the single-domain training rather than the multi-domain. This seems to be a very odd finding. One would expect that multi-domain intervention would be more robust than single-domain. Please elaborate.

- The authors state that multi-domain is more advantageous than single-domain training. However, the results of the functional entropy mean increase rate are not in line with that claim. Please elaborate.

Yes, we agree with you that the functional entropy in the single-domain training group held a higher functional entropy than multi-domain training groups. We just state that multi-domain is more advantageous than single-domain training because of the results combined by time-domain entropy (Figure 2) and links held significant functional connectivity improvement (Figure 3). Taken together, multi-domain training groups held a better performance after interventions.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer 2:

The authors would like to thank the reviewer for his wonderful comments that help to improve the manuscript. For details, please refer to the responses as follows.

Reviewer's report
Title: Cognitive Training Can Reduce the Rate of Cognitive Aging - Evidence from Cohort Neuroimaging Data
Version: 2
Date: 5 June 2015
Reviewer: Xi-Nian Zuo

Reviewer's report:
In this manuscript by Li et al., the authors reported a comprehensive study on brain network changes induced by multi-domain or single-domain cognitive training on aged population. Aged participants were assigned into multi-domain training, single-domain training, and a control group. Time-domain entropy and functional entropy were compared between baseline scans and 1-year follow-up scans. The authors found that the increase of functional entropy with age was significantly reduced in both cognitive training groups, and that the decrease of time-domain entropy (with age) was also significantly reduced. Additionally, the authors reported that the descending trend in the asymmetric of functional entropy was reduced by cognitive training. Cognitive performance changes were also associated with entropy changes.

This work is a comprehensive investigation on the effects of cognitive training. It would have a great impact to the research field of cognitive aging. It Provides both solid evidence for the benefits of multi-domain cognitive training and a sensitive index (entropy) to measure brain network changes induced by cognitive training. The study design is rigorous, and the analysis is sound. Nonetheless,
there are several problems in the presentation, as follows.

Major Compulsory Revisions

1. The results section of this manuscript reported results from multiple aspects, such as changes in functional entropy and time-domain entropy (both regional and whole-brain), asymmetric changes of entropy, and cognitive performance associations. Given these results, the introduction seems over-simplified. The current introduction reviewed cognitive aging studies and only hypothesized entropy changes with cognitive training. To improve the clarity and logic of the manuscript, the aims/hypotheses of the study could be listed as three-fold: 1) entropy change with cognitive training; 2) asymmetric change with cognitive training; 3) brain changes with cognitive performance. Otherwise, if the authors choose to focus on a single point, the results should be cleaned up accordingly.

Thanks for your advice. We have revised the introduction as you suggested.

2. In the methods section, the statistical inference should be improved by including more details regarding the significance test on the entropy, instead of the test for the Pearson’s correlation. The definition of “the mean rate of decrease of the time-domain entropy” should be explicitly defined here. It is not very clear what the “mean rate” indicates.

Thanks for your advice. Yes, we agree that this is a quite naïve way to do statistics. Since we do not have lots of subjects, we just want to capture the basic relationship between MRI data and behavioral information. We just worry about that more complicated statistics inference method may lead to larger noises and deviations.

About the mean rate of decrease, we just extracted the decrease of time-domain entropy in different subjects and then calculated the mean rate of all subjects.

3. In results, it is not very clear why the “links between amygdala and the middle orbitofrontal cortex” was presented. This piece of result has no contribution to the
aim of the study.

We just represent that some single/specific functional connectivity had been improved in the multi-domain group, which strengthened that cognitive functions of multi-domain group became better with different levels of evidence.

4. In the third point of the results, it is not clear if the results were from the current study or Yao et al., 2013. Consider to revise the starting sentence.

The results were from the previous studies including Yao et al., 2013, which had been described in the introduction section. We have deleted this repeating part to avoid future misunderstanding.

5. In the discussion section, the second paragraph reads “To our knowledge, this study is the first exploration of the effects of CogTr on measurements of both brain structure and functional connectivity, as measured by entropy.” Where is the brain structural results?

Thanks for your advice, the brain structural results are shown in Fig4 (c) and (d). Moreover, we have modified our representation.

6. The supplementary material needs a careful revision. It contains large pieces of information that is not relevant to the current manuscript.

Thanks for your advice, we have revised our supplementary materials.

Minor Essential Revisions

1. Two typos: Line 2 of the first paragraph of results, “themulti” should be “the multi”; Line 5 of the first paragraph of results, “including 2 participants, who suffered intestinal cancer” should be “including 2 participants who suffered intestinal cancer”.

Thanks for your advice, we have revised these as you suggested.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Reviewer 3:**

**Reviewer's report**

**Title:** Cognitive Training Can Reduce the Rate of Cognitive Aging - Evidence from Cohort Neuroimaging Data

**Version:** 2  
**Date:** 5 June 2015

**Reviewer:** Jose Ma Tormos Muñoz

**Reviewer's report:**

*The paper is well written, the topic is of great interest for neurology and gerontology as well as for cognitive science and neuropsychology communities.*

*The methodology seems correct to me.*

*Data seems reliable.*

*I have no major revisions.*

*I would suggest some minor essential revisions:*

119 *Our results imply that cognitive training can induce the plasticity of intrinsic *

*I WOULD SUGGEST “PLASTIC CHANGES AT THE LEVEL” INSTEAD OF “THE PLASTICITY” BECAUSE THE TERM PLASTICITY CAN BE LINKED TO CHANGES AT DIFFERENT LEVELS, WHICH ARE NOT SUSTAINED BY THE DATA SHOWN IN THE PAPER.*

475 *functional connectivity from resting-state fMRI data. The trend of the Functional*

476 *entropy to increase, as observed in healthy individuals, was significantly*
I WOULD SUGGEST NOT TO USE THE TERM HEALTHY, AS THIS COULD BE SUGGESTING LACK OF PROBLEMS, WHEN THE AUTHOR SEEMS TO MAKE REFERENCE TO THE SITUATION LINKED TO COGNITIVE DECLINE IN AGING POPULATION I WOULD RATHER SUGGEST AGING INDIVIDUALS 477 reduced in both cognitively trained groups. Moreover, lateralization, assessed 478 by different entropy indices, was significantly altered in the multi-domain

I WOULD SUGGEST “CHANGED” INSTEAD OF “ALTERED” BECAUSE IT COULD INDUCE TO READERS THAT THOSE ARE CHANGES LINKED TO WORST PERFORMANCE WHILE IS NOT THE CASE OF THE OBSERVED RESULTS

479 cognitive training group, together with a gray matter change in both training 480 groups. Finally, behavioral improvements including memory and attention 481 were significantly correlated with brain activity changes after training. In 482 conclusion, our results provide explicit evidence that cognitive training can 483 induce the plasticity of the intrinsic activity-pattern of elderly individuals. This is I WOULD SUGGEST “PLASTIC CHANGES AT THE LEVEL” INSTEAD OF “THE PLASTICITY” BECAUSE THE TERM PLASTICITY CAN BE LINKED TO CHANGES AT DIFFERENT LEVELS, WHICH ARE NOT SUSTAINED BY THE DATA SHOWN IN THE PAPER.

484 mainly through modifications of the functional connectivity and brain structure, 485 which are thus likely to be some of the neural mechanisms underlying the 486 effects of cognitive training.

590 To summarize, CogTr could induce the plasticity of intrinsic activity patterns in

I WOULD SUGGEST “PLASTIC CHANGES AT THE LEVEL” INSTEAD OF “THE PLASTICITY” BECAUSE THE TERM PLASTICITY CAN BE LINKED TO CHANGES AT DIFFERENT LEVELS, WHICH ARE NOT SUSTAINED BY THE DATA SHOWN IN THE PAPER.
Thank you for the reviewer’s wonderful advices, we have revised the manuscript as he suggested.

**Level of interest:** An exceptional article  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
I declare that I have no competing interests