Reviewer's report

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

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Reviewer: Xi-Nian Zuo

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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.

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.
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.

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.

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?

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

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”.

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.