Author's response to reviews

**Title:** The synergistic effect of acupuncture and computer-based cognitive training on post-stroke cognitive dysfunction: a study protocol for a randomized controlled trial of 2x2 factorial design

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**Version:** 2  
**Date:** 8 July 2014  

**Author's response to reviews:** see over
Dear Dr. Rowles,

Thank you very much for your kind letter and encouragement, along with the constructive comments of the reviewer concerning our manuscript entitled “The synergistic effect of acupuncture and computer-based cognitive training on post-stroke cognitive dysfunction: a study protocol for a randomized controlled trial of 2×2 factorial design” (MS: 4036911831299991). We have thoroughly considered all the comments of the reviewer’s and substantially revised our manuscript. We wish to resubmit the revised manuscript for consideration for publication as a “study protocol” in BMC Complementary and Alternative Medicine.

The point-to-point responses to all comments are listed below this letter. All changes made to the text are in red so that they can be easily identified.

We have tried our best to address all the concerns raised by the reviewer. However, deviation of understanding the reviewer’s comments might exist. If does, please do not hesitate to let me know.

We hope, with these modifications and improvements based on the reviewer’s comments, the quality of our manuscript would meet the publication standard of the journal.

Once again, thank you very much for your attention to our manuscript. If you have any question about this manuscript, please contact us without hesitate.

With best wishes,

Yours sincerely,

Haicheng Ye
Reviewer's comments:
Firstly, in this protocol, there are four groups, which want to test the hypothesis that synergistic effect of scalp acupuncture and RehaCom cognitive training is greater than employing either method. For my opinion, it likes a”1+1>1”argumentation which seems a matter of course.

Response:

We thank you for raising this important issue, which has been further clarified in the revised version of the manuscript. Sorry for not making it clear in our previous manuscript about our aims due to unclear description.

We totally agree with your opinion that ”1+1>1”argumentation seems a matter of course. However, what we actually wanted to find out is the argumentation of “1+1>2”. Our primary aim of this study is to evaluate the synergistic effect of acupuncture and RehaCom cognitive training on cognitive dysfunction after stroke.

On one hand, acupuncture with the acupoints of Baihui (DU 20) and Shenting (DU24) appears to be effective in improving intelligence, stimulating consciousness and enhancing memory from the holistic conception of Traditional Chinese medicine, due to activation and/or stimulation the regions responsible for cognition. On the other hand, RehaCom cognitive training can compensate for an impaired nervous system by systematic treatment that can cause functional changes in which to enhance the impaired cognitive functions. Therefore, acupuncture focuses on the global cognitive function, while the RehaCom cognitive training concerns the specific impaired cognitive functions which need to be trained. So, we believe that the interaction of multiple therapeutic strategies (the combination of acupuncture and RehaCom cognitive training) to produce an effect greater than simply the sum of the individual effects of each intervention if they were used separately. In other words, the combined effect (synergistic effect) is not simply the sum of the geometric problem, but “1+1>2”.

Besides, the effects of acupuncture and RehaCom cognitive training have not been systematically compared, nor has the possibility of a synergistic effect of combination of the two therapeutic modalities been evaluated. Nonetheless, after
reviewing a great amount of literature, we found that few studies had addressed these questions. So it is still unclear whether the combination of acupuncture and RehaCom cognitive training can be considered as a treatment of choice. The convincing evidence is still lacking.

So we hypothesized that: 1. The synergistic effect of acupuncture and RehaCom cognitive training is greater than the sum effect of employing either method; and 2. The acupuncture or RehaCom cognitive training significantly improves cognitive outcomes, or to a similar extent, assessed after the intervention, compared to the control group.

To test these hypotheses, after intense discussion among the study members and invited experts, we decided to propose a randomized controlled trial with 2×2 factorial design in which the two interventions (acupuncture and RehaCom training) are to be delivered to four groups defined by the presence or absence of each intervention, with one arm without both interventions as a control group. The reason is a factorial design allows the effects of several factors and even interactions between them to be determined at the same time with a high degree of accuracy.

In this trial, our first aim is to evaluate the synergistic effect of acupuncture and RehaCom cognitive training on cognitive dysfunction after stroke. Our second aim is to determine whether acupuncture and RehaCom cognitive training, alone or in combination, are more effective than conventional treatment on the rehabilitation of post-stroke cognitive dysfunction.

Secondly, the definition of scalp acupuncture is not selecting acupoint on the head. It is a modern acupuncture therapy which divide scalp according to anatomical location of the brain, such as sensory area, motor area, etc. Selecting baihui and shenting is not scalp acupuncture.

Response:
Thank you for your critical and valuable comment, which we totally agree with. Accordingly, we have changed ‘scalp acupuncture’ to ‘acupuncture’ throughout the manuscript in the revised version.
Thirdly, in the background, the author mentioned "Several life style interventions (such as smoking cessation, moderation of alcohol intake, healthy diet (e.g. Mediterranean diet), weight control and physical activity) have been used in clinical practice, which potentially can help to prevent progression or occurrence of vascular cognitive impairment ", while the conventional treatment also include healthcare education. The protocol should explain and control this influence factor.

Response:

Thank you very much for the constructive comments which are of great help to improve the quality of our manuscript.

It is recognized that the life style interventions (such as smoking cessation, moderation of alcohol intake, healthy diet, weight control and physical activity) can help to prevent progression or occurrence of vascular cognitive impairment. But the intervention in any of the four groups is based on the same conventional treatment as shown in Table 2, though the healthcare education is also part of the conventional treatment in the present study.

As the present study was designed to be a randomized controlled trial which can minimize allocation bias and balance both known and unknown prognostic factors. In the assignment of treatments, we randomly divide the patients into four groups in 1:1:1:1 ratio, so the effect caused by the lifestyle interventions or healthy education will be balanced in all the four groups. Thus, it will be possible to test the real effect of the major interventions without considering the confounding effects due to the lifestyle interventions or healthcare education.

In response to your concern about the lifestyle interventions which include smoking cessation, moderation of alcohol intake, healthy diet, weight control and physical activity mentioned in the background, we will precisely documented the frequency (quantity) of related factors applied to the patients in the CRFs for further analyze, in order to determine whether confounding effects have taken place by the relevant influence factors. Accordingly, we have incorporated this critical point in the revised manuscript (Page 10, Line 18-19).
Table 2 Groups and intervention allocation

<table>
<thead>
<tr>
<th>Groups</th>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>control group (CG)</td>
<td>Conventional treatment</td>
</tr>
<tr>
<td>RehaCom training (EG1)</td>
<td>Conventional treatment + RehaCom cognitive training</td>
</tr>
<tr>
<td>Acupuncture group (EG2)</td>
<td>Conventional treatment + Acupuncture treatment</td>
</tr>
<tr>
<td>Combination group (EG3)</td>
<td>Conventional treatment + Acupuncture treatment + RehaCom training</td>
</tr>
</tbody>
</table>