Reviewer's report

Title: Aerobic exercise modulates intracortical inhibition and facilitation in a nonexercised upper limb muscle

Version: 1 Date: 18 December 2013

Reviewer: Shaun Boe

Reviewer's report:

Major Compulsory Revisions

Background
1. It is not clear in the first paragraph of the background what the authors are indicating the role of aerobic exercise is in a clinical setting. Given the following paragraph, it seems the intent here is to link the use of aerobic exercise to creating an environment in the brain that will facilitate plasticity. While this is certainly a burgeoning area of interest in research and clinical practice (as noted in the paper), one must not ignore the fact that aerobic exercise in brain-injured populations (and many other clinical population as well) is prescribed for aerobic benefits associated with the heart and lungs. Perhaps indicating that aerobic exercise is prescribed in a more traditional sense for these benefits (citations may include MacKay-Lyons et al), with the added bonus that it looks to also create an optimal environment to induce plastic changes in the brain.

Methods (TMS)
2. The amount of time post-exercise for which changes in inhibition and facilitation persist are important to know for eventual clinical applications. Given the amount of time required to properly set-up a subject using neuronavigated TMS (i.e., with Brainsight), it would be good for the authors to clarify some details about how this was done. For instance, were the subjects anatomical landmarks co-registered with the template brain during the pre-session only, with these same measures used for the post 1 and 2? Alternatively, was this co-registration performed a second time at the beginning of post 1? As the three paired-pulse paradigms were randomized, this time delay would impact each the same, however overall if this process were performed at the beginning of post 1 it would delay the actual measures. The authors should provide information about when each of the measures was performed relative to the end of the exercise session. In the case where co-registration was performed once only, is there a chance that the reflective markers used by the brainsight system may have moved?

Minor Essential Revisions

Methods
3. Was there a particular method used to establish the ‘hotspot’ (i.e., the spot where you consistently elicited optimal MEPs and a twitch?). This description
seems somewhat subjective, as you could consistently elicit an MEP and twitch at a number of sites in M1 (hand/arm), albeit with an increased stimulator output intensity. Perhaps a grid was used to target different points on the cortex overlying the representation of the ECR muscle, with points systematically being removed if a MEP/twitch wasn’t elicited?

Discussion
4. 4th paragraph (page 13) - GABAA is repeated twice in a row – the second GABA should be GABAB.

5. 5th paragraph (page 14) – at the conclusion of the section discussion GABA, the authors may consider adding to the last sentence something to the effect that the reduction in the SICI following exercise is modulated by changes in GABA. This is assumed given the previous discussion, but explicitly stating it summarizes well the discussion in the preceding paragraphs.

6. This reviewer would suggest adding to the limitations a statement (albeit brief) reiterating that EMG was not collected from the UE muscles during the aerobic exercise task. While not a fatal flaw in the experimental design, having the data indicating an absence of muscle activity allows one to attribute the changes in cortical excitability entirely to the impact of the aerobic exercise as opposed to any activation of the UE musculature.

7. Last paragraph just prior to the conclusion – when comparing the BDNF findings to those of Cheeran and Li Voti – what are the sample sizes of those studies? It is interesting that the results presented here parallel those of one study, but contrast with another. Does sample size have anything to do with this or is it perhaps based in methodological differences?

Conclusion
8. Second sentence – using the word ‘however’ here indicates a relationship to the preceding sentence when in fact it seems (to this reviewer) that they are not entirely related. The first sentence suggests that in a brain injured individual, the balance of facilitation/inhibition is altered, as such, the findings of the current study may not actually have validity for this population. I would suggest re-ordering these sentences in order to make it clear what the present findings are, and then make the point that while an important step (and it is indeed a key finding), it may not translate to those with brain injury given a) the heterogeneity of injury; and b) the lack of understanding of how the facilitation/inhibition balance is altered.

Figure Legends
Figure 1 – the authors should clearly state in this legend that the representative EMG traces are from a separate bout of aerobic exercise using the same task, but not from one of the subjects used in the current study.

Discretionary Revisions

Conclusion
The authors may want to consider removing the claim of primacy for this study.
Individuals who are aware of the literature will know if this has been done before or not. As well, unless an exhaustive literature search has been completed it is difficult to conclude that this is the first study to do this.

**Level of interest:** An article of importance in its field

**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