Reviewer’s report

Title: Principles of brain plasticity in improving sensorimotor function of the knee and leg: A double-blind randomized exploratory trial

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Reviewer: Eleni Kapreli

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General Comments
This paper is very different and interesting as it deals with new aspects of rehabilitation taking advantage of brain reorganization. However, there are a few methodological considerations that authors did not take under account and probably that could have been crucial for their results. The manuscript adheres to the relevant standards for reporting and data deposition but some additional information is needed. Discussion and conclusions are both well balanced and adequately supported by the data, although limitations are not clearly stated and this section needs review. Finally, title and abstract accurately convey what has been found.

Specific comments
Minor Essential Revisions
Abstract
Background
• “Training is included in the treatment of knee injury to improve patient-reported function and sensorimotor function.” Please replace with “….to improve both patient-reported and objective sensorimotor function”.
• “The aim was to investigate…..”. Please add “The aim of the current study was to investigate…..”
• “In a first double-blind exploratory..” Please replace “In this first double-blind exploratory..”

Results
• Please replace “There were no differences between the groups in effects of treatment” with “There were no differences between the groups due to treatment effect.”

Methods
• Authors use the verb “lay” more than once in the section of outcome measures. Please replace “lay” with “laid” (simple past form of the verb) and if possible replace with synonymous to avoid repetition.
• I think that this extensive referral onto the sample size calculation in statistical analysis section of methods is rather confusing… Furthermore, taking under
consideration the fact that no primary outcome measure was determined, this extended section could be avoided. Anyway, the effect sizes in Results section are more reliable and give the same information.

Results
• Table 2. Authors should add t-test values, p values and effect size values in the table for each comparison (t(degrees of freedom) =…, p=…., r=…) replacing mean difference values as it is more appropriate.

Discussion
• Please rephrase as it is not clear what you mean: “Since good sensorimotor function is of importance for the overall outcome after injury [6] and in preventing OA [2] [8], it can be argued that training programs need to be more effective in order to improve or restore sensorimotor function after knee injury and knee OA.”

Major Compulsory Revisions

Background
• The whole second paragraph that describes brain plasticity is poor. For example, plastic changes of the brain do not only include differences in somatotopic representations (expansion). Differences (neuroplasticity) could be found concerning signal amplitude or activation of additional cortical areas. Furthermore, the different types of neuroplasticity should be discussed (long term and short term mechanisms). According to the study design it is more possible that you refer to short term mechanisms of neuroplasticity. I could suggest for example Boroojerdi et al, (2001), titled “Mechanisms underlying human motor system plasticity”.
• Authors should include a brief description of the neurophysiological mechanisms explaining the effect of temporary cutaneous anesthesia on the sensorimotor function of a referred joint rather than simply refer that 3 previous studies have found a positive effect. It is not clear your hypothesis. Please explain why someone could expect both sensory and motor function (especially this) improvement.
• In the last paragraph authors write: “The aim was to investigate if the principle of brain plasticity that has been successfully used on the hand to improve sensory and motor functions, and on the foot to improve sensory function, can be applied on the knee.” I assume that “brain plasticity that has been successfully used on the hand to improve sensory and motor functions” is referred to the study of Bjo¨rkman et al, (2004) as it is the only one that measured motor function. However, it is not true that there were any improvements in motor function according to that study. Please rephrase and add references in order reader to clarify the sources of your statements.

Methods
• Why did you use right leg??? Did you check for footedness?? How did you ensure that all your subjects were right or left foot dominant?? Handedness and footedness influence brain activation during movement of upper or lower limb
respectively. Additionally, this factor also influences function outcomes. Please explain and include in methods. In case you did not take this factor under consideration please discuss it as a study limitation at the end of your discussion section.

• Why did you select to anesthetize these areas above and below knee joint?? If your aim was to elicit brain reorganization in a similar way with those three previous studies then it would be more logically to anesthetize foot and ankle areas. I could suggest Kapreli et al, (2007), titled “Lower limb sensorimotor network: issues of somatotopy and overlap.” According to that area lower limb activation pattern differs a lot with upper limb. They found a large overlap in primary sensorimotor cortex (SM1) and cerebellum representations of the three lower limb joints (knee, ankle and foot). I am wondering if a strong limitation of your study is the application of the anesthetic cream. Please discuss it as a study limitation at the end of your discussion section.

Discussion

• Authors write: “The only difference that we found was a lower value for TDPM, indicating better knee kinesthesia, after compared with before treatment in the placebo group. However, since the 95% CI is close to zero (Table 2), and there may be a learning effect in TDPM [32], the clinical relevance of this improvement of 0.40 degrees can be questioned.” Authors should explain more efficiently this kind of result.

• Authors write: “There may be several reasons for the lack of effect from temporary cutaneous anesthesia of the skin area above and below the knee on sensorimotor function of the ipsilateral knee and leg in the uninjured subjects in our study.” However, authors refer only one reason for the lack of effect (the uninjured subjects). Authors should rephrase or give more reasons.

• Authors give as reason of lack of effect the uninjured subjects that they include in their study. However, the two previous studies that they mentioned had found positive results included similarly uninjured subjects in their study…..Could authors explain why?? Please add a comment in discussion section.

Level of interest: An article of importance in its field

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

Statistical review: No, the manuscript does not need to be seen by a statistician.