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: George Peat

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Summary
This article describes an exploratory RCT of the effects on knee sensorimotor function of applying topical analgesia to adjacent skin in 28 subjects without history of major orthopaedic lesions. The authors report no effect and conclude that although negative, the selection of ostensibly healthy controls and differences in the somatotropic organisation of the knee compare with hand and foot suggest that further investigations in injured subjects are warranted.

I enjoyed reviewing this piece of innovative experimental clinical research. The need to explore and test underlying hypothesised mechanisms of injury/disease and recovery is fundamental to developing new therapies. This particular experiment is original but clearly the latest in a series by these investigators, having previously conducted similar studies with positive findings in the hand and foot. It was clearly written throughout.

Discretionary revisions
My understanding is that the receptor fields of nociceptors and wide dynamic range neurons in the dorsal horn expand under conditions of local inflammation or other peripheral nociceptive stimuli. This is one of the mechanisms producing hyperalgesia and allodynia at sites adjacent to actual tissue damage. By removing sensory input from adjacent areas, aren’t you creating a condition that is more conducive to expansion of nociceptive receptor field in clinical subjects by essentially ‘clearing the way’ for their expansion? In other words, this experiment may produce findings that are completely different in pain-free healthy controls compared with painful clinical subjects? A rebuttal of this argument in your Response or brief inclusion in the manuscript itself would be welcome.

Major compulsory revisions
1. Have the authors correctly identified the reasons for the negative findings in the knee in contrast to the positive studies in the hand and foot?

The authors should provide information or Discuss alternatives. Namely,
- random error in the assessment of outcomes. Unlike self-report outcomes, reliability demonstrated in previous studies may not be sufficient for observer-dependent measures which some of the sensorimotor outcomes were.
Please state who conducted the assessments, what experience they had of each measure, and whether or not any training, pre-piloting or formal pilot studies were conducted with those assessors.

- lack of specificity in the outcome measures, single-leg hop clearly tests the integrity of sensorimotor function beyond just the knee joint.

- the dermatomal area of local cutaneous analgesia (proximal thigh) is innervated by the same spinal levels as the knee joint itself (L2-L4) and overlies the primary agonists of the knee (quadriceps). Is this the same situation as for the hand and the foot?

2. In what way has this study altered the design of planned future studies in clinical, injured subjects? Did this piece of work have any important consequences?

There is an air of inevitability about the conclusion. Was the selection of healthy controls uninformative in the sense that they could not alter the decision about whether to proceed to a trial in clinical subjects? Or did this exploratory study serve other purposes, e.g. to pilot the study procedures, to provide assessors with practical experience in the assessment techniques. Please address in the Discussion.

3. Was local anaesthesia successfully achieved?

Did the authors check whether local anaesthesia of the areas above and below the knee was achieved and how successful this was? If so, please state in manuscript. If not, please Discuss.

Minor essential revisions

i. The manuscript would benefit from being written to conform with CONSORT guidelines. Specifically:

- source of subjects, total number invited to obtain 24 eligible consenting participants
- provide setting and location for data collection
- confirm that the sequence of allocation was concealed until treatment was assigned
- clarify who did the allocation sequence, who enrolled participants, who assigned them to treatment/placebo, who assessed outcomes, who administered treatment, who analysed the data and the extent to which allocation was concealed from each and whether or not the success of blinding was evaluated

ii. p3. Rephrase “...any treatment leading to improved sensorimotor function would be of value for patients...”. Treatments that carry substantial adverse effects may well not be of (net) value to patients.

iii. p3. Typo “..larger areas are assigned to sensitive parts...” (Isn't this argument circular?)
iv. A biostatistician would be able to specifically advise on whether the correct power calculation was used but a sample requirement of 2 subjects based on the single-leg hop seems incredibly low to me. Can you provide your actual calculations in your Response (not necessarily in the main text of the paper)?

v. Clarify whether all sensorimotor outcomes were measured only on the ipsilateral knee. If not, then justify why not and what effect this might have on the results.

vi. Not sure if Figure 2 is necessary. Remove and report figures in Table 2. If significantly skewed then either transform or report medians and IQRs.

vii. It would be helpful to identify in the Title that the study was conducted in ostensibly ‘healthy’ individuals

Level of interest: An article whose findings are important to those with closely related research interests

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