Author's response to reviews

Title: Prognostic Value of Cortically Induced Motor Evoked Activity by TMS in Chronic Stroke: Caveats from a Revealing Single Clinical Case

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Author's response to reviews: see over
To the attention of the Editor
BMC Neurology

Dear Sir/Madam

We thank you for giving us the opportunity to revise our manuscript to BMC Neurology entitled “Prognostic Value of Cortically Induced Motor Evoked Activity by TMS in Chronic Stroke: Caveats from a Revealing Single Clinical Case” (MS Reference: 1432892316749231). We are also very grateful to the reviewers for their thoughtful and enriching comments, which have contributed to improve the quality and breath of the current manuscript. After carefully considering each of the reviewer’s comments, we have modified the text of the manuscript accordingly.

A point-by-point response specifying these changes is provided below. We are confident that the manuscript has been improved thanks to the reviewers’ comments and we hope the manuscript would be now considered ready for acceptance in BMC Neurology.

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REVIEWER #1:

Compulsory revisions:

Comment 1: “There are numerous grammatical mistakes throughout the new additions, which at times are nearly incomprehensible. Please address”

We are grateful to the reviewer for her caveats on the proficiency and quality of the English. A native English expert has carefully revised the manuscript and has made it more comprehensible.

Comment 2: “The clinical description section could benefit from a clinical-language proofreading”.

After an extensive review of the clinical description section, we have considered and corrected all the issues that the reviewer has suggested in the manuscript. We thank the reviewer for her help on the improvement of this section

Comment 3: “Pag 6: clinical tests- please explicitly state that the clinical tests were performed only once.”

According to the reviewer suggestion, we have added the requested information on the method sections, page 7, lines 7-8:

“Clinical motor function tests were performed in an independent session of the computerised tests. Both sessions were performed within the same week”

Comment 4: “It is stated (pg 8): ‘The FCR and MBB were added to the protocol in order to rule out failures in the peripheral nerve degeneration… etc’ However, you rule out these pathologies with peripheral nerve testing/CMAPs, so this rationale no longer makes sense. It would be sufficient to state that these muscle representations were examined to explore differential recovery processes for more proximal muscles (if this was indeed your rationale).

In agreement with the comment of the reviewer, we consider also that the description on the original manuscript of the rationale of the inclusion of FCR and MBB could be confusing. Indeed, as the reviewer suggest in her comment, we pretended to extend the neurophysiological results (the absence of MEP) to other muscles to increase the soundness of our findings. Also, by a peripheral nerve testing (CMAPs), we aimed to discard any nerve dysfunction, task in which we succeeded. We have adapted the methodological part of the electrophysiological recordings adding the following sentence into the manuscript. (page 7, lines 24 and 25; page 8, line 1)

“In addition, both flexor carpi radialis (FCR) and both biceps brachii (BB) were examined to explore differential recovery processes for muscles proximal to the first dorsal interossei”

Comment 5: “The lack of TMS evoked MEPs found from the affected (left) hemisphere for the contralesional (right) FDI and FCR muscles can be made extensive to an arm muscle as the biceps brachii (MBB: I don’t understand what this statement means. Please clarify”

In agreement with the comment of the reviewer, this sentence on the original manuscript is confusing. Our rationale was based on the assumption that the absence of MEP in one proximal and distal muscle can be extended to other muscles, as MBB. That is the way we use to justify the inclusion of other muscles in our extended neurophysiological test. After the reviewer’s suggestion, we consider that this sentence does not contribute to increase the understanding of the neurophysiological results, and we agree to remove it from the manuscript.
Comment 6: “Similarly, the activation of the affected (right) hand during both grasping and pinching evoked EMG activity only in the FDI muscle and eventually for grasping also the FCR muscle of this very same (right) limb, whereas EMG signals recorded in homologue muscles of the opposite affected (left) hand remained again at baseline levels.” I don’t understand what this statement means. Please clarify.

We thank the reviewer for her warning on the construction of this sentence. We have modified this sentence, accordingly. (Page 16, lines 25 and 25; page 17, lines 1-3)

“Grasping and pinching of the right hand evoked EMG activity in the right FDI muscle. In addition, right FCR muscle eventually showed a spared activation during grasp movements. Left FCR and FDI muscles remained inactive during right grasping and pinching of the right hand.”

Comment 7: “Pg 7: you are recording from FDI, FCR and BB, yet only FDI and BB seem to be the only ones mentioned for the neurophysiological testing in the methodology section (‘both muscles’ is often stated). In the results, FCR again makes an appearance. Please clarify.”

In agreement with the reviewer, we have adapted the methodological approach and results description section trying to improve the understanding of the text.

Page 7, lines 19-25; Page 8, line 1:

“MEPs were recorded with surface Ag/AgCl disk electrodes in a belly-tendon montage from both left and right first dorsal interossei (FDI). This muscle was selected due to its essential involvement in skilful finger movements. Such movements were impaired in this patient as a result of his stroke. For this reason the left and right first dorsal interossei were chosen as sites for electrophysiological recordings. In addition, both flexor carpi radialis (FCR) and both biceps brachii (BB) were examined to explore differential recovery processes for muscles proximal to the first dorsal interossei.”

Page 8, lines 18-21:

“For each hemisphere we determined the resting motor threshold (RMT) and the active motor threshold (AMT) for FDI and FCR. MEP latencies were calculated for FDI, FCR and BB. Intracortical inhibition was assessed by using the cortical silent period (CSP) for contralateral FDI and FCR muscles”

Page 8, lines 1-3:

“In order to record any ipsilateral activation, EMG traces from left/right FDI and left/right MBB were recorded from both sides at the same time”

Page 9, line 1:

“For FDI and FCR of either arm …”

Page 16, line 15-16:

“No ipsilateral MEP activity was observed in left/right FDI or left/right MBB muscles”

Comment 8: Pg 11,17: “LC is the latency of the D-wave…” D and I waves are not detectable by standard surface EMG recordings. Please change to ‘latency of the ONSET of the MEP’.”

We agree with the comment on the reviewer, and we have corrected both sentences as the reviewer suggests:

Page 11, line 1-2:
“...LC is the latency of the onset of the MEP...”

Page 17, line 16:

“...where LC was the latency of the onset of the MEP...”

Comment 9: “The authors do not appear to understand my concern that the data they are reporting as similar (frequency of pronation-supination of the affected vs unaffected limb) are quite dissimilar in their actual results. Especially if the patients is very consistent in his movements, as the authors suggest, running very simple statistics is appropriate and expected. Why the resistance here? While the deletion of the ‘meaningless’ qualifier is heading in the right direction, reporting this result as a ‘slight difference’ is still unacceptable. A simple t-test on the pronation-supination frequency data gives me values of: t=5.1, p=0.0068. This finding is consistent with the idea that the patient is still mildly impaired in some movements, and would not negate the other results reported. The authors should keep well in mind that their credibility and objectivity are called into question when they state that a difference is ‘meaningless’ or ‘slight’ when clearly is not. Please change the language and report the simple statistics.”

We agree with the reviewer and we also apologize to erroneously insist on this issue. We overestimated the mild impairment present on the affected hand, as we thought that a patient with such neurophysiological recordings might be poor recovered, which is not the case. However, according to the reviewer, the reported data does not show a clear evidence of statistical slight differences between the affected and preserved hand. We have removed from the text all these issues, reporting the data and modifying the following sentences:

Page 15, lines 13-14:

“Data from various motor tasks revealed that the patient presented a mild affected level of performance for fine and gross movement when tasks were performed with the affected right hand.”

Page 15, lines 19-22:

“We found differences in frequency in the forearm pronation and supination task and NIV during hand tapping task between the affected (right) and unaffected (left) hands.”

Page 20, lines 3-7:

“Fine motor control of the affected hand, measured by the number of inversions of velocity per cycle (NIV) during diadocokinetic movement tasks, was close-to-normal in two of the three tested movements. However, results from the frequency tests reveal the right hand to be mildly affected.”

Comment 10: The discussion of the clinical data in the discussion is nearly absent. It would be worth a small paragraph to give a quick summation of your results. Here is where the authors can add in the justification of using NIV over frequency as the better estimate of impairment (as described in their response to me and Reviewer 2).”

According with the reviewer comment, we have included a paragraph at the beginning of the discussion section that summarizes the most interesting findings of this case:

Page 18, line 20-25; page 19, line 1-3:

“We used different neuroimaging techniques (fMRI, DTI, TMS) and several methods to valuate the motor performance, with the aim to fully describe this case and thus explain the seemingly contradictory clinical/TMS results. The most relevant results were (1) the absence of any MEP activity in contralateral FDI, FCR and BB after stimulation on the left (affected) hemisphere and (2) a mild paresis of the affected (right) fine motor performance measured with computerised and non-computerised movement tests and (3) a FA asymmetry of the cortico-spinal tract below .25 in the internal capsule.”
Also, we added to the discussion section another paragraph, in order to emphasize the mild affectation of the affected hand:

“Fine motor control of the affected hand, measured by the number of inversions of velocity per cycle (NIV) during diadocokinetic movement tasks, was close-to-normal in two of the three tested movements. However, results from the frequency reveal a mild affectation of the affected (right) hand.”