Author’s response to reviews

Title: Personalized objects can optimize the diagnosis of EMCS in the assessment of functional object use in the CRS-R: a double blind, randomized clinical trial

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Author’s response to reviews:

Dear Editor, Dear reviewers

Thank you for your attention and for the reviewers’ comments concerning our manuscript entitled “Personalized Objects can Optimize the Diagnosis of EMCS in the Assessment of Functional Object Use in CRS-R: A double blind, randomised clinical trial” (ID: NURL-D-17-00458R1)”. We thank the reviewers for the time and effort that they have put into reviewing the previous version of the manuscript. Their suggestions have enabled us to improve our work. Based on the instructions provided in your letter, we have studied comments carefully and have made correction which we hope meet with approval. We uploaded the file of the revised manuscript. Accordingly, we have uploaded a copy of the original manuscript with all the changes highlighted by using the track changes mode in MS Word.
Appended to this letter is our point-by-point response to the comments raised by the reviewers. The comments are reproduced and our responses are given directly afterward in a different color (red).

We would like also to thank you for allowing us to resubmit a revised copy of the manuscript.

We hope that the revised manuscript is accepted for publication in the BMC Neurology.

Thank you and best regards.

Yours Sincerely,

Haibo Di

Responds to the reviewer’s comments:

Reviewer #1:
Peter Charles Watson (Reviewer 1):

Statistical review of Personalised objects can optimise the diagnosis of EMCS in the assessment of functional object use in CRS-R: a double blind randomised clinical trial NURL-D-17-00458R1

I notice from Table 1 that each patient appears to be assessed on more than one functional object and that (page 8, lines 3-9) interest is in comparing the stimulants representing each functional object use implying within patient comparisons.

If so, does the chi-square test take this dependency into account? Something like a McNemar test or Cochran's Q or mixed model would compare 0/1 frequencies recorded on the same person.
Reply: Considering the Reviewer’s suggestion, we do agree that McNemar test is more suitable in comparing 0/1 frequencies recorded on the same person in our research. The revised has been made accordingly (Lines 19 to 21, page 8).

Is there an effect size for the chi-squares such as that presented on page 8, line 40 comparing performance on objects within patient within the CRS-R group. These could be inserted into the text where the p-value is quoted.

Reply: The effect size for the chi-squares has been added in the text (Line 53, page 8)

Page 8, line 53. What do the authors means by "significantly increase"? Is this a change above a clinical threshold?

Reply: All the patients has been re-diagnosed as EMCS, so it is a change above a clinical threshold (Lines 43 to 46, page 8).

Reviewer #2:

Luigi Trojano, M.D. (Reviewer 2): The authors assessed 21 patients in minimally conscious state (MCS) with the standard version of the Coma Recovery Scale-Revised (CRS-R) and with a modified version in which the Motor Subscale is administered using 'personalized' objects instead of common-use objects (comb, cup). The authors reported that 5/21 patients showed functional use of 'personalized' objects (thus warranting a diagnosis of emergence from MCS) but of common-use objects.

According to the authors such findings confirmed that personal salience of items might exploit responsiveness in some patients with disorders of consciousness.

Reply: Thanks for the encouragement.

The paper addresses a very relevant issue for clinicians dealing with patients with disorders of consciousness, i.e. diagnostic challenges, but I believe that it presents several weaknesses that have to be tackled with in a revised manuscript.

1) The authors stated that all patients included in this sample "had the motor ability to move their hands and arms" (P.6). It is not clear how this clinical feature was assessed, which movement
could be observed and in which context. This should be made explicit. Moreover, it is common experience that not all MCS patients show movements of the upper limbs, so the authors should clarify whether this was one of the selection criteria.

Reply: Thanks so much for the reviewer’s carefully revision. In fact, all patients had motor ability to move their hands and arms, the evidence is that we used noxious stimuli to upper limbs, and score is one or more in motor sub-scale score of CRS-R. Detailed information has been provided in the text (Lines 31 to 33, page 6). We have also added a reference to support it (Line 33, page 6).

2) The authors stated (P.7) that CRS-R was administered twice with standard procedures (by examiner A) and twice with personalized objects (by examiner B). However, for diagnostic purposes CRS-R has to be performed more than twice and in different days to reduce diagnostic fallacy in these patients, who often show remarkable fluctuations of their clinical state. Therefore the authors should state explicitly the procedures they used for setting diagnosis.

Reply: The diagnosis was based on standard diagnosis procedure using 4 times CRS-R within 2 weeks (Lines 24 to 27, page 6). According to the reviewer’s suggestion we have stated explicitly the procedures we used for the setting diagnosis (Lines 16 to 25, page 7).

3) Related to this, it appears that in all patients CRS-R with personalized objects was always administered after standard CRS-R. the authors should state clearly whether this was the case. Order of administration of the two versions should be counterbalanced across subjects.

Another important issue is timing of the examinations reported in the result section. How long time intervened between assessment sessions? Were motor responses consistent across repeated examinations?

Reply: We are very sorry for our vague expression. The order of the stimuli and assessors were randomized, and the interval between the two assessors was as short as possible. The revised has been made accordingly in the text (Lines 16 to 29, page 7).
4) The authors stated that 'personalized objects' have been chosen by 'family members or nurses' among objects patients used in 'previous daily live'. Apart from typo, it is not clear how the nurses could guess which objects the patients were accustomed to most in premorbid life. It is also important to understand whether objects were selected among actual patients' personal belongings. This is an important point as, after all, a comb and a cup are objects of daily use. In this respect it is also important to acknowledge that, as far as I know, no prescription is present in standard CRS-R instructions, but comb and cup are only suggested as instances.

Reply: Yes, some patients were lack of family members accompany. It was primarily nurses who were responsible for the care of these patients, so they knew more information from their friends.

5) Without having clear all the info specified above, it is not simple to read and understand the value of the results presented in Table 1. Among the five patients showing an improvement of their motor responses with 'personalized' objects, in one MCS+ patient (Case 3) functional use of personalized object might not be very surprising, as s/he showed a quite high CRS-R profile. Instead, some MCS- patients presented very low level motor responses at standard evaluation (abnormal posturing or flexion withdrawal) and yet showed functional object use with personalized objects. It is quite difficult to understand the value of these observations without the info specified above (e.g., in relation to point 1 above: do these patients showed motor abilities in different contexts, and across repeated evaluations? in relation to point 2 above: in which order were the two assessment procedures performed? in relation to point 3 above: how long time did elapse between standard and 'personalized' assessments?). Moreover, some patients showed a parallel improvement on the motor and on the arousal scale during the 'personalized' examination. Could the improvement on motor scale be related to enhanced arousal?

Reply: As mentioned in reply 1 to 3, the assess of the motor abilities was under strict control, the order of the two assessor patients was randomized and elapse between standard and 'personalized' assessments was set as short as possible. The result is unexpectable for us at the beginning, but it is acceptable now. It also means that the importance of the usage of the personalized objects is important for the diagnosis.

For the last question, 2 patients showed a parallel improvement on the motor and on the arousal scale during the 'personalized' examination. But others with positive results have no enhanced arousal. The accurately conclusion about the improvement on motor scale be related to enhanced arousal cannot be reached.
6) The discussion section might be shortened. In its present form it substantially recaps arguments and results presented in the introduction and in the result section.

Reply: Thanks for suggestions to the discussion section. The discussion section has been shortened. “Four out of twenty-one patients who were diagnosed as MCS (1MCS+, 4MCS-) appeared to significantly increase the use of personalized objects, but had no response to general objects like a cup or a comb. Only one patient diagnosed as MCS- showed object use to both the personalized objects and non-personalized objects (the comb and mobile phone). There are two patients had response to the paper and the pen, and the remaining three patients had response to the phone and the tooth brush, the comb and the phone, the phone and the fan, respectively” has been removed.

7) Several typos and English usage mistakes can be found throughout the manuscript. A very careful editing is necessary. Below some instances from the introduction.

P3, Lines 50-53: which presented in a random order. The rest assessments

P5, Line 1: cognitive mediated behavior.

P5, Lines: When the patient shows Functional Object Use (score 6 in the motor function scale) or functional and accurate communication (score 2 in the communication scale) they are diagnosed as the emergence of MCS (EMCS), which is no longer a DOC.

P5, Lines 31-33: response than that of non-self-referential stimuli [5, 6].

P5, Lines 37-39: sound stimuli when patients are applied with PET [7]

Reply: We are so sorry for our incorrect writing. And we have modified the English usage mistakes and typos throughout text.