Author's response to reviews

Title: Assessment of visual fixation in vegetative and minimally conscious states

Authors:

Haibo Di MD, PhD (dihaibo19@aliyun.com)
Yunzhi Nie Msc (nyz5090@163.com)
Xiaohua Hu MD (hu_yi_sheng@126.com)
Yong Tong MD (fliertongyong@163.com)
Lizette Heine Msc (lheine@ulg.ac.be)
Sarah Wannez Msc (swannez@student.ulg.ac.be)
Wangshan Huang Msc (huangwangshan@sina.cn)
Dan Yu MD (yudanwj@aliyun.com)
Minhui He MD (heminhui2003@yahoo.com.cn)
Caroline Schnakers PhD (c.schnakers@ulg.ac.be)
Steven Laureys MD, PhD (steven.laureys@ulg.ac.be)

Version: 3
Date: 27 May 2014

Author's response to reviews: see over
Reviewer's report

Title: Assessment of visual fixation in post-comatose states: use a mirror

Version: 2 Date: 11 April 2014

Reviewer: Marion Luyat

Reviewer's report:

It is a very interesting experiment conducted on a very large sample of patients with very important applications in clinical care.

Minor essential revisions

- the title must be changed because it is the same as a previous publication:


Check this reference in the "reference list" because it seems that "223" is missing at the end.

We thank the reviewers for noticing this error. The title has been changed to “Assessment of visual fixation in vegetative and minimally conscious states” (see the title in the text).

The page number “223” has been added (see the reference list).

- it is not clear for me where the patients had been recruited (on several hospitals?)

The patients were recruited from Wujing Hospital of Hangzhou City, Hangzhou, China. We have made this clearer in the Method section.

- Abstract, section results: in my opinion, the p-value can be removed in the abstract but it is unclear what kind of comparisons (2 by 2) are in fact significant

We thank the reviewer for this comment, we accordingly removed the p-value in the abstract (see results section in Abstract).

The comparisons were between mirror and ball, mirror and light, ball and light. The first two are
significant. We added this information in the abstract: “significantly more patients (39, 48%) had visual fixation elicited by mirror compared to a ball (23, 28%) and mirror compared to a light (20, 25%).

- Page 1. Uppercase for "W" of Wessex Head Injury Matrix

“w” was changed to “W” (see Background section in the text).

- Method section: The method of presentation of the stimuli was not sufficiently presented. Was the ball projected on the screen of a laptop? Was the mirror held by an experimenter? The same for the recordings of the eye movement and visual fixation. Did the experimenter who recorded the eye movements knew explicitely the hypothesis?

We agree with the reviewer that can be explained more clearly. We hope to have sufficiently done so in the text: “In brief, a visual stimulus (i.e., a mirror (round, diameter=15cm), a ball (yellow, diameter=6cm) and a continuous burning light (power=1.2w)) was presented by the experimenter in front of the patient's face (15-20 cm) and then rapidly moved above and below the horizontal midline, as well as to the right and left of the vertical midline. Thus the stimulus moved once in each direction (4 trials),” and “Patients' visual reaction was visually judged by one experienced assessor who was blinded to diagnosis (e.g., did not do CRS-R assessment), and was unaware of the hypothesis of this study” (see Methods section in the text).

- 3 page 3: results section. I don't understand very well to what kind of comparison the p-values were linked. They were local comparisons between frequencies or relatively to the chance-level? What was the global value of the observed Chi-2 statistic?

The comparisons were done between mirror and ball(p<0.001), mirror and light(p<0.001), ball and light(p>0.05). They were local comparisons between frequencies. The global value of the observed Chi-2 statistic was added in the text: “The global value of the observed Chi-2 statistic between the mirror, ball and light was 27.22, and p<0.001”.

- It will be interessant to have some correlational results or results from multiple regression for instance. Did the sex of the patient had an effect?

We agree that this is interesting, however, multiple regression did not show any significant results. We added this in the results: “Multiple regression analysis did not show an effect of sex or age,
and the p values of the partial regression coefficient were 0.174 for sex and 0.553 for age”.

-Figure 1: unresponsive rather unresppnsive (the "o" is missing")

The “o” was added into the “unrespnsive” in the Figure 1.

-discussion section:

In my opinion, the p-value in the discussion section can be removed

The reason for why eye-recorder was not used must be explained (perhaps it could be a brake to have a large sample of patients because less convenient to manage?) or if it is possible, the authors should explain that the results would be confirmed by this kind of methodology in the future

The p-value was removed in the discussion section (see Discussion section).

We also thank the reviewer for the suggestion about the eye-recorder. Indeed, due to its clinical limitations (difficulty of use in our population), we did not use this method. We nevertheless mentioned it in the discussion. You can now read: “One could argue that using an eye-recorder could standardize the way in which the data are collected. However, the use of such method is difficult in our population. Patients recovering from coma often have brainstem lesions or ocular trauma that may affect eye-movements and complicate the use of an automated recording (often validated in healthy volunteers).”

English is not my maternal language, I would prefer to not judge the quality of english. I note "acceptable" because i have no alternative choice in the review process

Level of interest:An article of outstanding merit and interest 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' below
2. Reviewer's report

Title: Assessment of visual fixation in post-comatose states: use a mirror

Version: 2 Date: 23 April 2014

Reviewer: Pietro Pietrini

Reviewer's report:

This paper assesses the feasibility of using mirror (and thus to use self-referential images) to elicit fixation. Fixation can be a useful way to distinguish vegetative state/unresponsive wakefulness (VS/UWS) syndrome and minimally conscious state (MCS). As a matter of fact, by using a mirror the authors were able to elicit fixations in 39 out of 43 MCS patients and in no patients with VS/UWS. Only in one subject it was possible to elicit fixation with light but not with the mirror. The mirror was able to elicit significantly more fixation as compared to light and ball.

The paper is well-written, concise and straightforward. The topic is highly interesting and has a potential important implications also for clinical purposes. However, I believe that some points need to be clarified or re-written to improve clarity.

1) In the abstract it is stated that the “Visual fixation plays a key role in the differentiation between vegetative state/unresponsive wakefulness (VS/UWS) syndrome and minimally conscious state (MCS)”. Thus, the main results of the paper should be that the mirror elicited fixation is a very sensitive, specific and accurate test to differentiate the two clinical conditions. This is indeed the main take-home message.

We thank the reviewer for this observation and have changed the abstract and the discussion in order to better convey this message.
The conclusion of the abstract now reads: “**Conclusion:** The use of a mirror during the assessment of visual fixation showed higher positive response rate, compared to other stimuli in eliciting a visual fixating response. Therefore, fixation elicited by a mirror can be a very sensitive and accurate test to differentiate the two disorders of consciousness”.

2) In the discussion a possible explanation for the fact that one subject responding to light did not respond to mirror was that mirror was presented as the last stimuli in randomized order across subjects. Would it be possible to re-test the subject with the mirror first? Even if this would break the randomization it would strengthen the interpretation of the results. Would it be possible to have other explanations to support this interpretation (for instance is the subject low in the CRS scale)?

The patient has left the hospital therefore re-assessment is impossible. Nevertheless, we agree with the reviewer that “this absence of response could be due to the fluctuations of vigilance that are commonly observed in those patients”. We mentioned this in the discussion.

3) A typo is present in the figure 1 caption “unresponsive”

The “o”has been added in the Figure 1.

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
3. Reviewer's report

Title: Assessment of visual fixation in post-comatose states: use a mirror

Version: 2 Date: 21 April 2014

Reviewer: Yelena Guller

Reviewer's report:

To Whom It May Concern:

Thank you for giving me the opportunity to review the manuscript titled “Assessment of visual fixation in post-comatose states: use a mirror”. The study conducted here provides an important recommendation regarding the methodology of assessing the presence of visual fixation in patients diagnosed with disorders of consciousness. Below are my comments and suggests to the authors.

Major Compulsory Revisions

1. Abstract: Conclusion- The authors conclude that the mirror showed higher “specificity” for assessment of visual fixation compared with other methods, however, a statistical analysis of specificity (i.e. the true positive rate) was not conducted.

   We thank the reviewer for pointing out this misuse of the word “specific”. We have modified the manuscript consequently. You can now read: a) in the abstract: “Therefore, fixation elicited by a mirror can be a very sensitive and accurate test to differentiate the two disorders of consciousness”, and b) in the discussion: “Therefore, using a mirror for visual fixation is sensitive and accurate in the differentiation between MCS and VS/UWS.” and “Although the use of a mirror is a strong and sensitive stimulus to elicit visual responses due to its self-referential value,...”

2. Background: Six methods of assessing visual fixation are listed (i.e. photo of a baby, ball, flashes of light, person, spontaneous eye contract, mirror), but of these six, only two are tested in the study (ball and mirror). Care should be taken when generalizing the results of the study to the methods of assessing fixation
that were not tested.

We agree with the reviewer that there are many ways to assess visual responses. As the CRS-R is currently considered as the gold standard in the assessment of disorders of consciousness (1), we chose the visual stimuli described in the Administration and Scoring Guidelines, that is: a yellow ball as brightly colored object and a light as illuminated object.

We changed the background consequently: “Hence, in this study we choose the visual stimuli described in the CRS-R Administration and Scoring Guidelines: a yellow ball (as brightly colored object), a light (as illuminated object) and a mirror (as self-referential object) to induce visual fixation in patients with DOC.” We also modified the discussion: see comment 13.


3. Method paragraph 1: Please provide further detail regarding the circumstances under which the arousal facilitation protocol was utilized.

More details has been added about the circumstances under which the arousal facilitation protocol was utilized (see Methods section): “If patients exhibited sustained eyelid closure and/or stopped following commands for a period of at least one minute, a standardized arousal facilitation protocol (i.e., deep pressure stimulations from the facial muscles to the toes) was employed in order to prolong the time the patients maintained aroused, and this protocol can be re-administered if patients showed sustained eye closure again or behavioral responsiveness ceased despite sustained eye opening.”

4. Method paragraph 1: Each of the stimuli requires further description. For example, what was the size/color or the ball? What was the size of the mirror?

What kind of a light was used? Was the light flashing as in the Coma/Near Coma Scale? How far away from the patient’s eyes were the stimuli presented?

We have added more details about the stimuli in the methods section: “In brief, a visual stimulus (i.e., a mirror (round, diameter=15cm), a ball (yellow, diameter=6cm) and a continuous burning light (power=1.2w) ) was presented by the experimenter in front of the patient’s face (15-20cm) and then rapidly moved above and below the horizontal midline, as well as to the right and left of the vertical midline. Thus the stimulus moved once in each direction (4 trials).”
5. Method paragraph 1: The statement “To avoid scoring of spontaneous eye movements, stimuli were not presented in the same frequency of the pre-existing spontaneous eye-movements” requires clarification. Were spontaneous eye movements recorded for some period of time prior to stimulus presentation? If so, how was this information used to alter the frequency of stimulus presentation? Were stimuli presented at different frequencies for different patients? An example may be helpful here.

We thank the reviewer for this comment, you can read in the methods section: “Eye movements were observed before administration of stimuli to avoid scoring of spontaneous movements. For example, for subjects with roving eye movements the stimuli were presented in a manner unrelated to pre-existing spontaneous eye movements. When any doubt existed, the movement was not scored. Patients' visual reaction was visually judged by one experienced assessor who was blinded to diagnosis (e.g., did not do CRS-R assessment), and was unaware of the hypothesis of this study, and the same examiner conducted the trials in all patients.”

6. Method paragraph 1: Some additional information regarding data collection would be helpful here: Was the examiner blinded to the clinical diagnosis of the patient? Was the same examiner conducting the trials in all patients? If multiple examiners were conducting the trials, was inter-rater reliability calculated? Some of these points may be discussed in the conclusion when addressing study limitations and directions for future research.

We agree with the reviewer. You can now read: “one experienced assessor who was blinded to the diagnosis (e.g., did not do CRS-R assessment), and “the same examiner conducted the trials in all patients”.

7. Results last line: While this is an interesting result, the comparison here is 3 MCS patients versus 17 MCS patients and these N values should be stated in the text. A total CRS-R score is not provided for the 8 patients who showed visual fixation to only 2 of the three stimuli. This information would be helpful to support the suggestion in the Discussion that occurrence of visual fixation is
related to the behavioral profile. Please also provide the statistical value
associated with the trend of MCS patients responding to all three (or two of three)
stimuli showing a higher total CRS-R score compared to MCS patients showing
no fixation to any object.

We thank the reviewer for this observation. The results about the mean CRS-R total scores and
the numbers of four groups of patients who respectively showed fixation to 0, 1, 2 and 3 stimuli
have been rewritten accordingly in Result section: “In fact, patients showing a response to the
mirror, the ball and the light had a mean CRS-R total score 9.6 whereas patients showing no
fixation to any of the stimuli had a mean score 4.8, and patients having fixation to two (n=8) or
one (n=15) stimuli showed intermediate mean CRS-R total scores of respectively 9.3 and 8.3.
Correlation analysis showed that the rank correlation coefficient between the number of stimuli
fixated by patients and the CRS-R total score was 0.743, p<0.001”.

8. Results, General: Was there a relationship between the order or stimulus
presentation and the presence of fixation? This will be important in light of the
suggestion made in the discussion that one MCS patient did not respond to the
mirror (presented third of three stimuli) due to decreased arousal.

We thank the reviewer for his comment. As we mentioned in the methods, "the order of
presentation was randomized". We therefore do not think that the lower rate of response to the
ball or to the light can be explained by patients' fatigability. We nevertheless mentioned in the
discussion: "One could argue that the order of presentation could have impacted the level of
response of our patients. However, the stimuli were presented in a randomized order and not in a
fixed order; suggesting that the high rate of response observed using the mirror cannot be
explained by the order of presentation."

We nevertheless understand that the absence of response in that one MCS patient is difficult to
interpret and decided to suppress those two sentences: "The one patient that showed visual
fixation to the ball but not to the mirror or light. In this case, presentation of the mirror was the
last stimulus and hence the fluctuating levels of arousal, generally observed in MCS, might
account for the fixation on a ball in the absence of fixation on the mirror."

9. Discussion paragraph 1: The analogy of the cocktail party phenomenon
requires elaboration for those who may not be familiar with its use in this context.

The elaboration of the cocktail party phenomenon was added (see Discussion section: “which
refers to the fact that one’s own name can easily catch his/her attention in a cacophony of
conversations and background noise [8]”) and a related reference in the reference list “[8].”

10. Discussion paragraph 2: The first statement regarding the relationship between the occurrence of visual fixation and the patient’s overall behavioral profile is not supported by statistical results. (See 7. above)

We thank the reviewer for this comment. The mean CRS-R total scores of patients who showed fixation to 0, 1, 2 and 3 stimuli respectively were 4.8, 8.3, 9.3 and 9.6, and the rank correlation coefficient between the number of stimuli fixated by patients and the CRS-R total score was 0.743, p<0.001. This demonstrated the relationship between the occurrence of visual fixation and the patient’s overall behavioral profile, we have tried to make this more clear in the text: “The occurrence of visual fixation seems to be related to the patient’s overall behavioral profile. VS/UWS patients showed no visual fixation, the more stimuli the patient showed fixation to the higher the CRS-R score was (i.e., fixation to 0, 1, 2 and 3 stimuli, obtained a score of 4.8, 8.3, 9.3 and 9.6, respectively)”.

11. Discussion paragraph 2: It is suggested that the 2 patients diagnosed as MCS who had intact brainstem reflexes and reproducible but inconsistent command following and no fixation may have had a visual impairment, but this is not supported by data. It is unclear why reproducible but inconsistent command following suggests visual impairment as command following can be assessed using commands that do not depend on the visual system.

We do not have behavioral data reflecting visual impairments. In fact, as our patients are non-communicative, it is difficult to make sure they have a fully preserved vision. Visual impairments are hence a reasonable possible explanation for those patients’ behavioral responses (for a similar explanation see reference: 6).

12. Discussion paragraph 3: It is suggested that the one patient who fixated on a ball but not a mirror may have had decreased arousal when the mirror was presented because it was presented last. Was there behavioral evidence for decreased arousal in this patient? Is it possible that arousal was also an issue in other cases where the ball or light was presented last and did not elicit fixation?

(See 8. Above)
We thank the reviewer for this idea, and have tested it. A detailed explanation can be found in response to question 8.

13. Discussion: Please include a discussion of study limitations and directions for future research.

We thank the reviewer for pointing this out. We have discussed study limitations and directions for future research in the Discussion section. It now reads: “Although the use of a mirror is a strong and sensitive stimulus to elicit visual responses due to its self-referential value, we have not tested all possible stimuli as advised in other existing scales. As the CRS-R is currently considered as the gold standard in the assessment of disorders of consciousness[4], we chose the visual stimuli described in the guidelines (i.e., a colored ball or a bright light). We here advise to use a mirror in the assessment of visual fixation; however we cannot make any conclusions about the sensitivity and accuracy of other stimuli, like those mentioned in other existing scales. Future research should therefore focus on including more visual stimuli. Besides, in our study, we did not have the opportunity to collect follow-up data. Nevertheless, this could be done in the future. Indeed, as considering visual fixation as a sign of consciousness has been previously debated [15], future studies should investigate if patients showing visual fixation (detected using a mirror) present more frequently a full recovery of consciousness as compared to patients who do not show such behavior.”

14. Discussion/Conclusion: Care should be taken when generalizing the results of this study to future research as not all stimuli previously used to elicit fixation were tested in this study. For example, it could be that a photo of a baby is also an effective method of eliciting fixation, but this was not addressed here.

We agree with the reviewer on this and have addressed this issue in the discussion (see above, our response to comment 13).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Please review the entire manuscript for grammatical and typographical errors (i.e. run-on and incomplete sentences, misuse of words, spelling and capitalization errors, improper use of commas, etc).

We thank the reviewer for pointing out this flaw. We have reviewed the entire manuscript for grammatical and typographical errors.
2. Reference 5: Missing page numbers

3. Reference 6: Journal title is not capitalized

We thank the reviewers for noticing these errors and have changed the manuscript accordingly.

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

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.

Declaration of competing interests:

I declare that I have no competing interests