Author's response to reviews

Title: Visual fixation in the vegetative state: an observational case series PET study

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Author's response to reviews: see over
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Melissa Norton, MD  
Editor-in-Chief BMC Neurology  
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United Kingdom

REF: Revised MS 1067988700304908 entitled “Visual fixation in the vegetative state: an observational case series PET study”

Dear Ms Norton,

Please find herewith our revised MS entitled “Visual fixation in the vegetative state: an observational case series PET study” which we resubmit to BMC Neurology.

We thank the reviewers for their constructive comments and have changed the MS according to their concerns. Please find below our responses to both reviewers.

Marie-Aurélie Bruno  
Neuropsychologist, PhD student

Steven Laureys, M.D.  
Neurologist  
Belgian National Fund for Scientific Research
Comment 1

“One potential worry is that 5 patients in each group is not a very large sample and power to detect a difference (were it there) would be quite low. The presentation of single-subject data in the lower half of Fig 1 makes it patently clear that this is not a significant worry (there is almost complete overlap between the two patient groups), but the authors might want to point this out in the Discussion, to make sure that their finding as the impact that it deserves.”

We agree with the Reviewer and have included a paragraph on the limited sample size as requested.

In the revised discussion section it now reads:

“We also point to the difficulty with non-significant findings in small cohort studies where the lack of difference may be the result of weak statistical power. However, the graphical illustration of the single-subject data of the functional segregation analysis show an almost complete overlap between both patient groups and the functional integration analysis shows comparable cortico-cortical connectivity with visual areas between patients without and with visual fixation.”

Comment 2

“Their measure of 'good outcome' was defined as recovery of functional communication. Given that very few of these patients will recover functional communication within the first year, I would be interested to know whether there were any differences in outcome at all. That is to say, were there any notable differences at all a year after scanning between the two groups? This
only requires a sentence or two to be added to the manuscript, but I think it is important to establish whether fixation in this group is associated with any improved outcome at all (I assume it doesn't, but it should be stated)."

We agree with the Reviewer and have included a paragraph on outcome as requested.

In the revised results section it now reads:

“The follow-up study showed no differences in outcome between both groups at 12 months follow-up (see Table 1).”

And in the results:

“Finally, patients’ one year follow up showed similar bad outcome in patients with and without visual fixation (none recovered command-following), in line with previous outcome data for anoxic VS.”

Comment 3

“In my opinion the very last sentence of the manuscript should be modified slightly such that 'higher order frontoparietal cortical brain function' (as measured by FDG-PET) is not equated with conscious awareness, but rather is assumed to reflect it. That is to say, one can not unequivocally assume no conscious awareness on the basis of reduced frontoparietal cortical brain function. All that is required is a slight modifier to along the lines of "....frontoparietal cortical brain function which is assumed to be associated with conscious awareness". They may be similar assumptions made elsewhere in the manuscript in which case they should be similarly fixed, but this will only require the addition of a word or two.”
We agree with the Reviewer and have made the changes as requested.

In the revised conclusion it now reads:

“…not accompanied by higher order frontoparietal integrative cortical brain function which is assumed to be associated with conscious awareness”.

Referee 2

Comment 1

“This is a straightforward study that was clearly presented and easy to follow. However, one of the difficulties with a nonsignificant finding is determining if the lack of difference is true or the result of weak statistical power. There were only 5 patients included in each group and, therefore, it is difficult to rule out the latter in this study. In order to provide a convincing argument that their conclusions are sound, the authors should address this point. Perhaps the authors could compare the metabolism in cortical regions associated with visual fixation?”

We agree and have compared brain metabolism in visual areas as requested and performed additional cortico-cortical functional connectivity studies with the visual areas and failed to find any significant differences between both patient groups.

These data were added in the revised version. It now reads:

“We observed no difference in metabolism in visual areas (V1 and V2) and no difference in cortico-cortical connectivity with these visual areas between patients with and without visual fixation.”

As for the limitation due to the small sample size (also see comment by Reviewer 1) this caveat was explicitly discussed as requested.
It now reads in the discussion section:

“We also point to the difficulty with non-significant findings in small cohort studies where the lack of difference may be the result of weak statistical power. However, the graphical illustration of the single-subject data of the functional segregation analysis show an almost complete overlap between both patient groups and the functional integration analysis shows comparable cortico-cortical connectivity with visual areas between patients with and without visual fixation.”

Comment 2
“A minor point is the lack of units in Figure 1.”
We thank the reviewer for this correction and have added this in the revised legend. It now reads (also see Voss et al J Clin Invest 2006 and Laureys et al Neuroimage 1999): “expressed in arbitrary units as normalized [18F]-fluorodeoxyglucose neuronal uptake”

- Comments from the Associate Editor

Comment 1
“The paper is of considerable interest to clinical neurologists, who have taken fixation and following as being an important step in recovery of consciousness after TBI or various brain insults. The authors might add a note the significance of the their study and about what further steps should be taken and whether other behavioural phenomena might be similarly explored.”
We thank the Editor and have added this in the discussion. It now reads:
“In our view, the present results are of interest to clinical neurologists, who have taken visual fixation and tracking as being an important step in recovery of consciousness from the vegetative state. The here presented novel approach of
correlating specific behavioral signs in disorders of consciousness with functional neuroimaging results could help identifying their underlying functional neuroanatomy and possible reflection of conscious awareness. Future studies should employ this methodology to increase our understanding of remaining ambiguous signs of consciousness such as for example the presence of orientation response to auditory stimuli or grimaces, abduction, flexion or orientation responses to noxious stimulation”.

- Editorial requests
  Request 1
  “Copyediting - We recommend that you copyedit the paper to improve the style of written English.”
  The MS was corrected for English as requested.

  Request 2
  “Competing interests - Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write : The authors declare that they have no competing interests”
  We added competing interests in the MS as requested

  Request 3
  “Authors’ contributions - Please include an Authors’ contributions section before the Acknowledgements and Reference list.”
  We added an authors’ contribution section as requested

Sincerely yours,
Marie-Aurélie Bruno, PhD Student
Steven Laureys, M.D.