Author’s response to reviews

Title: Functional MRI study in a case of Charles Bonnet syndrome related to LHON

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Author’s response to reviews:

Dear Editor,

We thank the reviewers for their overall appreciation of our manuscript and their very useful comments and suggestions. Please find below a point-by-point reply to Reviewer’s comments.

Reviewer reports:
N. R. Miller (Reviewer 1):

The authors of this manuscript describe a man with molecular genetically documented (11778 G to A mutation) Leber Hereditary Optic Neuropathy (LHON) who developed Charles Bonnet syndrome characterized by unformed hallucinations that, interestingly, were triggered by unexpected auditory stimuli. The patient also had mild sensorineural hearing loss. The authors performed fMRI studies in this patient and found that some sound-triggered hallucinations were linked to bilateral activation of both primary and secondary visual cortex as well as cuneus,
precuneus and insula. The hypothesize that these auditory-triggered hallucinations were due to
cross-modal plasticity of the visual and auditory networks, possibly influenced by the patient's
mild hearing loss.

This is a very interesting case report and one that is quite unique with respect to the triggering of
the hallucinations and the fact that they are unformed rather than the more common formed
hallucinations that occur in Charles Bonnet syndrome.
Author’s reply: we thank Prof. Miller for the general appreciation of our report.

I only have a few comments:

1. There are a number of errors of syntax and grammar that need to be corrected if the paper is to
be accepted for publication.
Author’s reply: we extensively reviewed the syntax and grammar errors

2. It would be helpful to know the level of visual acuity in the patient's eyes at the time he
developed the hallucinations.
Author’s reply: the visual acuity of the patient at the onset of visual hallucination was HM in OD
and CF in OS. We added this information in the text.

3. It would also be interesting to know the patient's color vision status, particularly as the
hallucinations are somewhat (blue and white flashes) colored.
Author’s reply: color vision was 0/12 at Ishihara plates. We added this information in the text.

4. Finally, what type of field defects did the patient have? Pure central or cecocentral scotomas?
How dense? Any peripheral field constriction?
Author’s reply: Visual fields showed a generalized defect in OD and pseudo-altitudinal defect in
OS (see VF images in the attached file titled response to reviewers). The latter is most probably
due to eccentric fixation of the scotoma. We now present the VF defect as Supplementary
Figure.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

RELEVANCE - Does this case report make a contribution to medical knowledge, have
educational value, or highlight the need for a change in clinical practice or diagnostic/prognostic
approaches?
Yes, this report contributes to medical knowledge
CASE DESCRIPTION - Are the details of the case sufficiently well described to understand the patient's symptoms and course of treatment?
No - there are major issues

DIAGNOSIS/INTERPRETATION - Based on the facts presented, are the diagnosis, interpretation, and course of treatment medically sound?
Yes, the work described is medically sound

DISCUSSION OF THE CASE - Does the discussion appropriately analyse the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Has an adequate literature review pertinent to the case been included?
Yes, the case is discussed fully in the context of the literature

OVERALL MANUSCRIPT POTENTIAL - Could an appropriately REVISED version of this work represent a technically sound contribution?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: Authors present an interesting case of CBS with a unique finding of visual hallucinations after a non random auditory stimuli. Though the case is unique and of interest to the readership, some more details of the case are essential.
Author’s reply: we thank also this reviewer for the general appreciation of our report.

REQUESTED REVISIONS:
My comments:
In the abstract, please present what was the visual acuity in both eyes at the time of CBS presentation? Some other details of the ophthalmic condition such as field of vision, etc. will also be helpful. Please include this in the main text if there is an issue with the word count in the abstract.
Author’s reply: the details on visual function at the onset of visual hallucination are now added to the manuscript and in Supplementary Figure 1.

Including a patient with coexistent sensorineural deafness is adding a degree of confounding to this whole case. It might have been better to study someone with other faculties intact. But given the rarity of the diagnosis, this seems passable.
Author’s reply: While we may understand the reviewer’s comment, however, we think that the presence of the auditory-triggered hallucinations due to cross-modal plasticity of the visual and auditory networks, possibly influenced by the patient's mild hearing loss, makes the case possibly more interesting and informative, even if, we agree with the reviewer, this case is an exception in the LHON scenario and not the canonical situation.

- Can the authors quantify the dB of the random clap given? How many claps were given over the 10 minutes period? Were the dB of the claps the same or were varied? Were the same MRI changes noted uniformly at the time of all the claps? How was the non-random bip different from the clap? What instrument was used to provide the bip and at what intensity (dB)?
Author’s reply: Six identical claps were administrated; the dB were not assessed, however the intensity of each claps was the same. All the claps were part of the same explanatory variable in the GLM design, therefore the overall MRI changes were evaluated. The beep was generated through the software “Audacity”, whereas the clap sound was recorded.

- Given that the MRI is a very noisy machine for the patient, what influence did this have on the stimuli?
Author’s reply: The auditory stimuli (i.e. clap and beep) were administrated through MR compatible earphone that isolate from the background MRI noise. Moreover, the MRI noise was constant during the fMRI acquisition, therefore did not influence the GLM design. In addition, in order to familiarize with the MRI noise, patient underwent first structural sequences, then fMRI paradigms.

The explanation of acquired auditory-visual synesthesia to explain the fMRI findings and responses with a non random clap is quite plausible and acceptable.
Author’s reply: We thank the reviewer for this comment.

ADDITIONAL REQUESTS/SUGGESTIONS:

None