

October 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14117-review_Revised.doc).

Title: Auditory hallucinations: A review of the ERC "VOICE" project

Author: Kenneth Hugdahl

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 14117

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

PRE-REVIEW

a) You mention the finding that normally functioning men and women report AVR. What is the difference - according to the proposed model - to patients with schizophrenia

Response: The main difference when it comes to cognitive functioning and brain activation between clinical and non-clinical AVH individuals is intact attentional top-down cognitive control of the "voices" in non-clinical individuals, coupled with intact frontal lobe functioning and increased activation in these regions. This has been added to the revised ms. p. 24, substantiated by two references.:

"The Voice" model does also cover non-clinical voice hearers, i.e. individuals in the general population who share the experience of hearing voices but who are not clinically handicapped by their experiences (Johns & van Os, 2001). A major difference between clinical and non-clinical AVH individuals is intact attentional top-down cognitive control of the voices in non-clinical individuals, coupled with intact frontal lobe functioning and increased activation in these regions (Johns et al., 2014; Kompus et al, 2013)."

b) What about the metacognitive level? Since metacognitive interventions are helpful, there may be a difference in metacognitive skills that determines whether AVH results in impaired function

Response: The possible importance of meta-cognitive understanding is added to the same page after the addition mentioned under a).

"Another difference between clinical and non-clinical voice hearers is that the former lack a meta-cognitive understanding of the subjectivity of their experience and to a higher degree ascribes the experience to external factors."

REVIEWER 1

a) First, I suggest to add a specific Methods section that is currently lacking throughout the main text. Here, the author could specify which type of keywords have been used and in which databases the search has been conducted. Also, the criteria used for initial screening and subsequent inclusion of the main full-text articles in this manuscript needs to be clearly specified.

Response: There must be a misunderstanding here, the paper is not a formal review, like a meta-analysis or comprehensive literature review, but is a selective review of findings and results related to a specific project, with extensions to the general literature when relevant. Thus, there is no formal method or screening of articles and other publications. This was stated explicitly in the Abstract in the original submission and is now also substantiated on p. 4 in the revision:

"The research presented in this article was funded by an ERC Advanced Grant VOICE to Kenneth Hugdahl, and is thus a selective review of the results obtained. In this sense, this is not a formal review of the literature, nor a formal comparison of findings in the literature at large."

b) In addition, the "Neuronal correlates of AVH" section (in particular, structural imaging section) seems to widely focus on grey matter abnormalities in AVHs whereas the author does not cite the relevance of white matter brain alterations in AVHs.

Response: The reason for a focus on grey matter changes is that this is what was studied in the Voice project, and grey matter abnormalities are also much more frequently reported in the schizophrenia literature. I have however added relevant literature on white matter changes on p. 16 in the revised ms, in particular DTI studies:

"With regard to white matter changes and abnormalities in the brains of AVH patients, there is less known compared to grey matter abnormalities. Allen and Modinos (2012) reviewed the white matter literature, based on diffusion tensor imaging (DTI), and fractional anisotropy (FA) which is an index of the difference in flow of water molecules along versus across axonal fibers. In general, these studies have shown both increased and decreased FA values in patients with schizophrenia, in particular for connections between anterior and posterior brain regions. Interestingly, schizophrenia patients experiencing AVHs show increased connectivity between frontal and temporal/parietal areas (Shergill et al., 2007) which could be a white matter structural correlate to the linguistic nature of AVHs."(p. 16)

c) When the author stated that glutamate is supposed to have an effect on positive symptoms associated with schizophrenia through balancing sub-cortical dopamine release, they correctly mentioned the prominence of dysfunctional NMDA receptors (NMDAR). NMDAR inhibition is currently used as a model for inducing a psychotic state. However, NMDAR inhibition is also associated with an antidepressant-like activity. The author should provide more insights and an expert opinion into this area of research. The manuscript is currently lacking in this regard. Similarly, when the author stated that healthy individuals who have been given ketamine and phencyclidine, these individuals showed signs and symptoms of a psychosis. According to the recent literature, there are consistent evidence suggesting that ketamine may be successfully used in refractory-depression as well as to treat suicidal ideation.

Response: While we agree with the Reviewer that NMDA receptors and glutamate concentrations are also of relevance for depression, I fail to see why a review of depression-like states should be the topic of a review of auditory hallucinations in schizophrenia. Extending the review to also cover depression would be a completely different paper, and is beyond the scope of the current review. In fact, one would then also have to cover clinical and cognitive aspects of depression which would actually de-focus the ms, and would thus be in conflict with the recommendation of Reviewer 4 "to narrow the focus of the review". I hope the Reviewer has understanding for the decision not to include the literature on glutamate and NMDA receptors in depression.

d) Figure 1 is difficult to follow and needs to be replaced by a more clear figure.

Response: Figure 1 is replaced with a figure with higher resolution.

e) Finally, the manuscript needs to be revised by a native English speaker for the quality of language.

Response: A native English speaker, professor Robert Murison, University of Bergen, Norway has read and corrected the English language (see attached certificate)

REVIEWER 2

a) Minor comments: Page 5, line 4th: SAPS is: Scale for the Assessment of Positive Symptoms. Page 20, line 16: the structure of the sentence is not clear.(control is doubled, or a ',' is missing...) Page 21, 1st sentence is not entirely clear.

Response: The language has been corrected as suggested by the Reviewer.

REVIEWER 3

This is a well written, very good paper and the author's effort is appreciated. I have no comments.

REVIEWER 4

a) I think that the author should consider narrowing the focus of the review and leave out sections, which may not be directly relevant to the neurobiology of AVH.

Response: I agree about narrowing the focus, and have taken out large parts of the sections on cultural

aspects, dimensions and the citation by Bleuler and subsequent on p. 9 and subsequent discussion of dimensions. I feel however that the rest of the section on dimensions is important for the outline of the ms, since these dimensions (perceptual, cognitive, emotional) are central in the "Voice" project and provide a conceptual framework for the neurobiology part in the review .

b) I think that the author could include another advantage, that a single symptom could also serve as an endophenotype, which can add to the genetic understanding of the broader phenotype of schizophrenia.

Response: I thank the Reviewer for this suggestion, and a fourth advantage is now added on p. 5.

c) I have given some examples of the more obvious grammatical errors below. There are many more, which need to be corrected.

Response: The examples of grammatical errors provided by the Reviewer have all been corrected, the ms. has in addition been corrected for language errors by a English native speaking person who also know the research field (prof. Robert Murison, University of Bergen, Norway, certificate attached with the revision).

Bergen 12-08-2014
Kenneth Hugdahl

