Reviewer's report

Title: Atypical language organization in temporal lobe epilepsy revealed by a passive semantic paradigm

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Reviewer: Helene Van Ettinger-Veenstra

Reviewer's report:

Summary:
The authors have investigated language lateralization in the temporal lobe in patients with mesial temporal lobe epilepsy (MTLE) with the use of a passive semantic language task, presenting spoken sentences and pseudosentences. The authors found that there was a pronounced difference in dominance, which was more right-lateralized for patients with MTLE in the left hemisphere. Moreover, this right-lateralization was more pronounced in patients with early-onset MTLE.

General comments and recommendation:

The manuscript was well-written and in general an interesting read.

Major Compulsory Revision

However the introduction was very restricted. Indeed, it is of importance to investigate of passive-listening fMRI paradigms to investigate language lateralization in people with MTLE. Therefore the introduction needs more background about the studies that did use passive listening for lateralization purposes, rather than stating that there are a few. Some suggestions: a study that seems to be relevant but is not referred to, maybe because it was published very recently, is the study of Ives-Deliperi (2013, S Afr Med J 103(8)), but there are also studies to be found on children with epilepsy (e.g. Vannest et al., 2009, J Magn Reson Imaging 29(4)).

The review on fMRI laterality measurements by Seghier (2008, Magn Res Imaging 26(5)) discusses different issues with the use of laterality measurements such as the difference that can be found in language laterality between the frontal and the temporal lobe, a very interesting finding in the light of the questions asked in the current manuscript. I strongly suggest that the authors go deeper into the problems that epilepsy patients have with non-passive language tests and, importantly, how passive language tests are used previously to assess laterality.

1. Is the question posed by the authors well defined?
The authors ask whether a passive, non-collaboration dependent, semantic fMRI language task can reliably evaluate language lateralization patterns in patients with MTLE. This is both a concise and an important question that is well-defined.
2. Are the methods appropriate and well-described?

The authors clearly describe the methods that they used and how they executed the study. The authors used the bootstrapping method from Wilke and Lidzba to calculate the laterality index for their study, which is an appropriate method as it is not dependent on chosen threshold.

Minor Essential Revisions:

A point of interest arises in their demographic description. First, in the introduction was stated (last paragraph, page 5), that the healthy group was “well-matched” to the epilepsy group. In the methods (Neuropsychological testing, page 6) they show that years of education did not significantly correlated to group (epilepsy or control), with a p-value higher than 0.06. I assume that this means the p-value was between 0.06 and 0.07. Without statement of the authors what their accepted significance threshold was, this is very close to the 0.05 threshold and therefore could be regarded as a trend. Especially so since the authors state in the Results (first paragraph, page 11) that there was a trend found for another analysis although the p-value was only around 0.19, although admittedly the r-value was an interesting 0.40. The authors should decide on the same margin to appoint trends and change the description of one or the other.

In short, the preprocessing of the fMRI images is described, however some important details are not explicitly stated. Such important details as what the purpose of their segmentation was, and to which template was normalized (even though it can be taken from Table 2 that it is an MNI template).

The authors do not describe adequately how they chose their regions of interest; e.g. which atlas from the WFU PickAtlas toolbox was used, and whether the anterior temporal lobe was included.

Discretionary Revision:

It would have been very interesting to have a distinction in temporal regions as regions of interest, for example anterior and posterior.

3. Are the data sound?

Minor Essential Revisions:

in Table 1 and Figure 2, the authors state that LIs are considered strongly lateralized if the exceed |0.4|. This term is not used in the method section and it can be discussed whether a score higher than |0.4| is strongly lateralized. I suggest that the authors follow their Methods description and omit the word ‘strongly’.

Also Table 1: the SD of years of education is missing. Also, several measurements are not explained in the table text, such as Handedness, and all measurements of fluency and memory.

It is unclear to me why the authors state in the text that task versus rest contrasts are thresholded at an uncorrected p-value, while in the tables and figures a corrected p-value is reported. Why did the authors mention the uncorrected
individual data, were the LIs not calculated independent from a threshold? Why did the authors look at individual data in the fMRI results (page 10) to determine the relevance of SEN versus PSEN rather than doing an ANOVA to test for significance? I feel that this unnecessary complicates the manuscript.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

The fMRI analysis and results are reported according to fMRI standards. A discretionary suggestion would be to test the data if it would be significant at (the even more stringent) FWE-correction, since there are large clusters and large t-values reported. However, an FDR correction is also within fMRI standards, and no revision is necessary.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The authors summarize what has been presented in the Results, and present a recommendation to use more passive listening paradigms and test in the temporal lobe for laterality in epilepsy patients.

Major Compulsory Revision

The authors do not discuss in-depth the reasons for the results for left MTLE patients that were found, but only state that it agrees with previous results. Without describing a strong framework of neural plasticity in left MTLE patients, it is difficult for the reader to come to the conclusion that the passive listening task is reliable in determining language laterality. To include point 6. Are limitations of the work clearly stated? in this reasoning for a major essential revision; the authors do not present any limitations, however a strong limitation is the lack of comparison to other laterality measurements; such as to more conventional non-passive language tasks and to laterality indices in the frontal lobe. If the authors cannot include this data, the manuscript needs a stronger Discussion (that should be supported by presenting more similar studies in the Introduction) as to argument why this passive paradigm would indeed be reliable (the term the authors used in their aims, see also point 1).

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

The authors do acknowledge work upon they are building, but they could be more descriptive in how previous studies have touched upon the same interests (described in the beginning of this review).

8. Do the title and abstract accurately convey what has been found?

The title and abstract are accurate and descriptive of the contents.

9. Is the writing acceptable?

The writing is good, the manuscript is well-readable.

Minor Essential Revision:
there are only a few small typo’s that I have found:
‘corregistration’ (page 8 fMRI analysis and Laterality Index calculation)
some abbreviations such as FDR and FWHM are not written out.
‘found on table 4’ (page 10 – Lateralization index)
odd sentence that may have an untimely period: ‘For example in previous study [10].’ (Page 13)

Overall it was an interesting read, and it would be very important to know indeed if this way of testing language laterality is reliable and a good alternative.

**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