Reviewer's report

Title: Clinical significance of biomarkers and neuropsychological performances in patients with temporal lobe epilepsy

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Reviewer: Hosung Kim

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General
In this manuscript, the authors describe a quantitative analysis on the association between the level of serum biomarkers, and damages in brain structures and a decline of cognitive abilities in temporal lobe epilepsy (TLE). This type of biomarkers has been considered to be linked with central nervous system (CNS) damage in neurological conditions. Accordingly, the authors found, in TLE, significant correlations of the level of the biomarkers with ipsilateral hippocampal volume and neuropsychological parameters. This is interesting as such assessment has not been performed in TLE and may promote the value of the serum biomarkers in predicting effects of epilepsy. However, there are several fundamental issues that may misdraw the findings and conclusions.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The implication of the relation between changes in these biomarkers and atrophy in a limited region (i.e., hippocampus ipsilateral to the seizure focus) of the brain is unclear. Even though the biomarker is known to vary with CNS damages and widespread extra-temporal lobe atrophy associated with TLE, why was the correlation found significant only in such a small area? Was this correlation truly limited in the hippocampus or would there be a continuum of correlation varying across structures and may have not been found in the current study due to the sample size and/or technical limitation of voxel-based analysis. If assumed so, the authors are strongly recommended to perform a power analysis to evaluate this.

The 2nd major concern is that the diagnostic value of serological biomarkers in TLE is unclear. Can this type of biomarkers react only upon the disease process of TLE? What about other types of epilepsy or other neurological and neuropsychological conditions? There have been studies that show serum level changes in Alzheimer's disease as well as in healthy elderly. What would be the advantage of using serological biomarkers in specifically diagnosing individual patients with TLE? Can these predict favorable surgical outcome? Can these biomarkers lateralize the side of the seizure focus (i.e., Do these react differently hemispherically according to the seizure focus?)? Such analyses would definitely increase the value of the study.
The 3rd major concern is no information of use of intensity inhomogeneity correction or no use of such a correction prior to spatial normalization. This correction is a crucial step which significantly increases the accuracy of subsequent brain tissue segmentation. Relative to lower tesla, in 3T, incorrect tissue classification due to no use of such a correction will highly impact on a morphological analysis and may ultimately lead wrong biological interpretation (for example, location of atrophy/volume growth). The authors should redo the analysis if the correction was not included.

The final major concern is about patient selection. First, no information of the seizure lateralization was given. In VBM, volume changes in TLE was then analyzed with respect to left/right hemispheres instead of the side of the seizure focus. This approach possibly causes two issues in the results. Given that brain structural damages reflect epileptogenic process and/or seizure spread from the seizure origin, the laterality of findings can be obscured if patients were pooled regardless of the side of the seizure focus. If Left and right focused TLE patients were separately analyzed (not likely in this study as no such information was found), the statistical power will decrease.

To solve, the authors could have normalized values at each voxels using z-score normalization based on the mean and SD of controls and then pooled patients with respect to the side of the focus.

The authors claimed that they measured 'Ipsilateral' hippocampal volume from page 18 without explanation how to switch the 'ipsilateral' from 'left' or 'right' in previous pages. This is also unclear.

The authors mentioned that cognitive abilities in TLE declines over time, meaning cognitive parameters are correlated with epilepsy duration. Indeed, the level of serum biomarkers were correlated with neuropsychological performance as well as duration of epilepsy. I wonder if the correlation with cognitive abilities can remain significant when the duration is included as a covariate.

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

In the title, the 'biomarkers' has to be specified as serological biomarkers as a biomarker can be any type measurements from any modality.

P9, 'non-surgical patients with TLE': should specify number of patients who are medically intractable and have gone to surgery after the data were obtained unless all patients are benign (i.e., pharmacologically tractable). The prevalence is important to indicate as severity of brain damages differs between benign and malignant epilepsy (Labate et al., 2011a; Labate et al., 2011b).

P13: What was the 'study-specific template'? Is this an individual template or a template averaged from the used samples? The authors should clarify how to create this template and why this was used than the MNI template (there is a nonlinear MNI template). Why was the template smoothed?
P14: Age frequently correlates with disease duration. Plus, aging effect in patients may also differ from that in controls. Thus, the independency between age and duration variables has to be examined before using age as a covariate in the regression. If age in the patient group is correlated with the disease duration, it cannot be used. In this case, controls’ (normal) aging or age of seizure onset in patients may be used as an alternative covariate.

P14: 'A p value < 0.01 was considered statistically significant'. How was this p-value determined? Why not Bonferroni correction?

P14: 'the whole brain (false discovery rate) with an extended threshold of 250 voxels': This 250 voxels sounds like to control small-size clusters as another type of false positive. But, based on what was '250' chosen?

P20: 'the high morphometric variabilities from the left hippocampus indicated the relatively lateralized nature of TLE.'

This conclusion is most likely to be modified after reanalysis given that major body of previous studies have reported ipsilateral hippocampal atrophy.

P24: 'Therefore, the interpretation presented here might represent the results related to the study group only.'

This statement is poor and unnecessary as it limits the significance and reproducibility of the study. Please improve it.

There are a few typos.
P23, 1st line: between TLE with the controls -> TLE and controls
P24 the 2nd last line in the discussion: there are two 'changes', omit one of either.

Discretionary Revisions (which the author can choose to ignore)
No.

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

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