Reviewer’s report

Title: Altered structural and causal connectivity in Frontal Lobe Epilepsy

Version: 1 Date: 28 Mar 2018

Reviewer: Charles Ákos Szabó

Reviewer's report:

This study evaluated differences in voxel-based morphometry and effective connectivity in people with frontal lobe epilepsy and healthy controls. They encountered differences in gray matter volumes were most apparent in the basal ganglia, including the putamen bilaterally and in the right caudate. Resting-state functional MRI results were analyzed using the Granger causality analysis (GCA), demonstrating altered causal connectivity of the caudate, with decreased causal influence exerted by the cerebellar vermis on the caudate. The authors suggest that the altered causality may result in defective in motor control and that the structural and functional abnormalities may reflect markers of medically refractory frontal lobe epilepsy.

The study is indeed relatively novel in its focus on FLE, and appears to demonstrate rigor in image processing and analysis. However, there are some major problems that need to be assessed:

1. The image processing needs to be described in more detail and the approaches need to be adequately justified.

   a. There is not much detail regarding the VBM methods used in this study.

   b. Regression of "head parameter" is unclear. Is this motion parameter regression? If so, how many parameters. Six motion parameters are the bare minimum; 24+ is recommended.

   c. Why was the global signal regressed out of the fMRI? Several studies have shown that global signal regression a) introduces anti-correlations and b) reduces the actual signal you are trying to model/analyze. It is strongly recommended that the CSF and white matter signals are regressed and that the global signal is not. The global signal correction may have reduced the regional cortical differences of connectivity, thereby decreasing the number of potential interactions. The authors should run their GCA analysis using this preprocessing scheme to make sure that their GCA results were not biased by global signal regression.
2. The patient information is rather limited. The table should include handedness, structural MRI findings, such as underlying lesions, even ictal EEG information. Were these patient only evaluated with scalp EEG? Especially in the setting the right caudate being the only structure demonstrating significant changes, it would be important to compare dominant and nondominant hemispheres, right and left lateralized seizure onsets (and definitely removing bilateral cases). There is a high likelihood of misclassifying parietal, neocortical temporal or even idiopathic generalized epilepsies as frontal lobe epilepsies based upon interictal data only. The ideal study group would be restricted to patients, who are seizure free after frontal lobectomies, topectomies or lesionectomies.

3. There are numerous typos and grammatical errors in the manuscript and the references. I recommend having a proficient English speaker review the manuscript before submission.

Particular recommendations:

Pg. 7-8: The equations are not complete or have misleading coefficients. Should Equation 2 not be Xt? The A, B, C, A', B', and C' coefficients are not consistently listed.

Pg. 8: The authors should describe the concept of GCA in more detail. Specifically, explain that their VBM seed regions are used to determine causality both to and from the all other regions (i.e. whole) in the brain.

Pg. 9:

1. It is odd that they removed two patients because they are "outliers." Did they remove them from the other analyses? If not, then why not?

2. The authors should define what they mean be "outflow" and "inflow" in relation to their GCA results. Do positive GCA values mean "inflow" and negative mean "outflow"?

Pg. 10: Table 3, only the Caudate is listed. What about the putamen? Also, the "Peak T" values are both negative, yet the two regions are listed as "inflow" and "outflow". Please explain. It would also be helpful to explain why the putamens were dropped from the analyses.

Pg. 12: The authors should avoid referring to "basal ganglia", when they are merely referring to the right caudate.

Pg. 18: The Figure Legend had numbers that are out of order/missing.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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