Reviewer’s report

Title: Clinical correlation of subcortical gray matter alterations of MRI-negative neocortical epilepsy

Version: 2
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Reviewer: Gavin Winston

Reviewer’s report:

Peng and colleagues describe an interesting study looking at grey matter changes in MRI-negative neocortical epilepsy, a topic that has previously only been well addressed in generalised seizures (JME, CAE, IGE) and those with focal TLE.

Major Compulsory Revisions

1. The title of the article is perhaps misleading as the bulk of the results and discussion relates to the absolute changes in the grey matter structures relative to healthy controls. Only minimal attention is given to the correlation with the two clinical variables assessed (age of onset, duration) which is presented in a supplementary table. The title and background should be revised accordingly.

2. The background and methods are generally clear. However I have some concerns regarding the statistical analysis:

a) The two clinical variables explored (age of onset and disease duration) are not independent, so was any correction performed for this in the individual analyses?

b) The Student’s t-test for volumes performed was one-sided which assumes a reduction in the volume of these structures whereas the possibility that there could be an increase should not be discounted when such a population has not been studied before especially such a heterogeneous population. I note that a two-sided test was used for the diffusion parameters.

c) The clinical correlations assessed are 7 structures x 2 sides x 3 imaging parameters x 2 clinical parameters = 84 comparisons in total. There does not appear to be correction for the multiple comparisons performed so it is hard to interpret these results. Without appropriate correction it may be better to remove this and concentrate on the absolute differences.

3. The discussion is sound although in the second paragraph states that the reduction in subcortical grey matter is universal among patients with frontal, lateral temporal, parietal or occipital lobe seizures. The data do not prove this and instead show that as a whole, a group involving patients from these groups shows a reduction in volume of these structures. It may be that some subgroups do not show changes which could only be answered by considering the subgroups separately with much larger numbers.
4. I am not clear what the "antecedent and progressive factors" referred to in the Abstract, Conclusions are and need clarification of similar references in the conclusion stating "Chronic neocortical epilepsy is antecedent to TLE and IGEs..."

Minor Essential Revisions

5. Abstract, Background - this states the aim and does not frame the background for performing this study

6. Abstract, Methods - refers to ADC here and throughout the paper but given this measure derived from DTI would it not be better termed MD (mean diffusivity)? This is what FDT in FSL generates

7. Abstract, Results - amgydale is a typo for amygdala here and elsewhere in paper

8. Methods, Subjects - state years as units for age of patients and give gender breakdown for patients (only given for controls)

9. Methods, MRI acquisition - the FOV is 22x22cm, not 22cm^2. Please clarify the voxel size and slice thickness for DTI as the voxels appear very anisotropic

10. Results, second sentence - what does "seizures in the forehead" mean - frontal lobe seizures?

11. Results, changes in subcortical structures - give statistics, p-values for non-significant difference in brain volume; "interested regions" should be "regions of interest"

12. Discussion, 4th paragraph - what is an "altered linearity" in the subcortical structures - is this referring to altered diffusion parameters?

13. Discussion - "Tendency of the left hemisphere to predominant observed in our study" does not make sense

14. Table 1 - multiple patients are listed with an "undetermined" seizure focus - therefore on what basis is the diagnosis of a focal rather than generalised seizure made?

15. Table 2 - the results for FA and ADC (MD) need to be given to 3dp since changes are small e.g. from 0.21 to 0.20

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

I declare that I have no competing interests