Author's response to reviews

Title: MRI-negative PET-positive Temporal Lobe Epilepsy (TLE) and Mesial TLE differ with Quantitative MRI and PET: a case control study

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Author's response to reviews: see over
Re: MS: 1163920501258368
MRI-negative PET-positive Temporal Lobe Epilepsy (TLE) and Mesial TLE differ with Quantitative MRI and PET: a case control study
Ross P Carne, Terence J O'Brien, Christine J Kilpatrick, Lachlan R MacGregor, Lucas Litewka, Rodney J Hicks and Mark J Cook

Thank you for the Reviewer’s constructive criticisms and suggestions regarding the above paper.

Reviewer PD has made several further carefully considered and constructive comments and in response major and minor revisions to the paper have been undertaken. I will comment on the Reviewer’s comments – presented in italics - in turn:

_The authors have clarified a number of points which has improved the manuscript but two major comments remain: only very large structures (except for the hippocampus) are studied and the heterogeneity - if existing – within these structures is not studied (with VBM or related methods). The second comment relates to partial volume effects. One has to be careful in using the argument that “it is unlikely that partial volume effects have played a significant role in the reported results given the marked metabolic (FDG PET) asymmetries seen in structures shown to be volumetrically much less asymmetrical” because in the large structures studied, heterogeneity may be present which may have many causes (besides partial volume effects). The results obtained in this manuscript may therefore still suffer from a lack of partial volume correction. I respect the decision of the authors not to add additional analysis but I feel that they should at least discuss these points as limitations of their study in the discussion section._

Both points are very valid. To address the Reviewer’s second point and acknowledge the potential limitation of the study through not including partial volume effects we have added the following statement in the Discussion (p23):

‘Nevertheless, this contribution cannot be excluded, particularly from PET measurements in smaller structures such as the hippocampus, and is a potential limitation of the study. Further analysis with partial volume correction, or
alternatively with voxel based morphometric methods to more closely delineate sites of structural or metabolic heterogeneity may help to clarify this further.'

To address the Reviewer’s first point and acknowledge the limitation of predominantly measuring large structures (except the hippocampus) (p24):

“Another potential limitation of the study is that we did not assess for changes in smaller subregions of the brain. The large structures assessed (i.e. hemispheres) are heterogeneous and therefore focal changes at lobar and sublobar levels could easily have been missed. However, the limited number of subjects that were available for inclusion in this study did not allow the statistical power to assess multiple regions of interest. Future studies, involving larger numbers of patients, should extend from our results by investigating for regional changes particularly in the cortex.”

Add the standard deviation in tables 4, 5, 6 and 7 so that the reader has an idea about the variability.

These data have been added as requested. Figure 3 – previously added at Reviewer PD’s suggestion - similarly gives some idea of the variability within individuals and across the population.

It is important to note that the mean and standard deviation quoted represent statistics across the whole population, while the p values quoted relate to side to side comparisons within individuals, and then between cases and controls across the group. The ‘Key Tables 4-7’ has been added:

‘The p-value quoted relates to side-to-side comparisons within individuals across the group. The between group comparison relates to comparison of the case to the age and sex matched control, performed across the group, rather than being a population comparison of ipsilateral to contralateral mean volumes.’

Remove the sentence “OSEM provides significant resolution recovery and minimizes partial volume effects” on p9 since OSEM may provide resolution recovery but it cannot be considered a partial volume correction method (as might be concluded by some readers).

The sentence has been removed as suggested by the Reviewer.

Add the iteration scheme used during OSEM (number of iterations and subsets) since this directly influences the results of the PET data (relating to convergence of the solution).

The iteration scheme has now been described in more detail, and the FDG-PET methods section altered to read (p9):

‘…Measured, segmented attenuation correction was derived from a rotating ‘single photon’ Cs-137 source. The data were processed using a Wiener prefilter (scaling value = 0.5) and ordered-subsets expectation maximization (OSEM) iterative reconstruction performed with 4 iterations and 8 subsets. OSEM significantly reduces
the degree of statistical noise in the reconstructed images compared to previous filtered back projection techniques on this system. The Wiener pre-filter improved resolution by enhancing the frequencies that define the resolving power of the system modulation transfer function (MTF)…”

I thank both Reviewers again for their thoughtful and considered responses.

I look forward to your reply.

Yours Sincerely,

Dr Ross Carne for the Authors.