Author's response to reviews

Title: Positron Emission Tomography in the Differential Diagnosis of Dementia in Young Adults: A Prospective, Community-Based Study

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Author's response to reviews: see over
Reviewer 1

Specific points

1. Previous studies are being criticised for not reflecting primary care settings. This study too was certainly not conducted in a primary care setting but in a secondary or tertiary specialist clinic. No information is given about the selection pathway and patient recruitment criteria at the referral level.

Data now provided in the ‘Methods’ section, under ‘Participants’ and study design pathway has been incorporated into a new figure (Figure 1).

2. Calculation of likelihood ratios does not really provide new information, as it is derived directly from sensitivity and specificity. It would, however, allow estimating post-test probability from pre-test probability. Thus the latter is crucial to overcome previous study limitations, but has not been provided in this study either.

Post-test and pre-test probabilities are now discussed at the end of the ‘Methods’ section (see page 11).

3. The diagnostic pathway at the center is not being described sufficiently, and criteria and tests used for clinical diagnosis have not been detailed. The process of PET reading is not described, clinical information given to PET readers, reading performed independently or by consensus, which intensity scaling, which normal reference population used, criteria for diagnosing depression on an FDG PET scan are all missing. Important information on scanning parameters (dose in injected [XMBq is not a number], time of data recording, correction for attenuation and scatter) is missing too.

The diagnostic pathway is now described in the ‘Methods’ section, under ‘Participants’ (see page 8) and detailed in a new figure (Figure 2). Scanning parameters are given in the ‘Methods’ section, under ‘Pet Imaging and Data Analysis’ (see page 9). Details regarding time of data recording, correction for attenuation and scatter now also appear on page 9. The process of PET reading is described on page 11.

Minor points

4. The reference to this patient group as “dementia in young adults” is misleading – 60 year olds are not exactly young, whereas Down syndrome patients with dementia in their 30s or 40s might fit the term. Most frequently the term “early onset dementia” is used internationally for the patient group studied here.

The term “early-onset dementia” has now been used throughout the manuscript.
5. Figure 1: Sagittal scans are difficult to evaluate without knowing the level of the cut (esp. for 1b, where a parasagittal cut close to the midline could suffer heavily from partial volume effects in the frontal lobe)

Figure 1 has been revised.

Reviewer 2:

The title and abstract are misleading and need changing:

1. Most subjects studied are not young adults; most of us would call them middle-aged. Perhaps it would be more accurate to term this differential diagnosis of young-onset dementia.

Title amended and the term "early-onset dementia" is now used throughout.

2. This is not a community-based study. Individuals were recruited from a subspecialty clinic, not the community. If there is evidence that this group represents a large proportion of the total number of individuals with suspected young-onset in a specific community or population, it should be presented.

Now detailed in the ‘Methods’ section, under ‘Participants’ (see page 8).

3. Positron emission tomography is an imaging technique that can use many ligands. The title and abstract don't specify that FDG is the specific ligand used and that relative rates of glucose metabolism is the outcome. Over the next several years it is likely that similar studies with amyloid PET and other modalities will appear.

FDG-PET now specified.

Further details are needed to clarify this study:

4. There should be an explicit statement about whether or not the results of FDG-PET were included in the “final clinical diagnosis”.

The results of FDG-PET were not included in the final clinical diagnosis. This is now stated in the manuscript (see page 8).

5. Apparently Neurostat SSP-Z statistical maps were used for the visual assessment of FDG-PET results. If so, why are these images not used in the figure? Were other images also considered?

Figure 1 has now been updated to reflect this.
6. **SSP uses comparison with a database of images from normal subjects. What are the characteristics of the subjects in the database used in your study?**

   Characteristics of subjects is now provided in the ‘Methods’ section, under ‘Pet Imaging and Data Analysis’ (see page 10).

7. **SSP displays values relative to a reference region. What reference region was used in this study?**

   Added to ‘Methods’ section, under ‘Pet Imaging and Data Analysis’ (see page 10, last para).

8. **Criteria for making a specific diagnosis from the FDG-PET are briefly referred to in the figure 1 legend. These should be expanded upon in the text and include criteria for a scan suggesting depression. For example, what how was a case classified if frontal hypometabolism was very prominent, but there also was parietal hypometabolism.**

   Now detailed in the ‘Methods’ section, under ‘Pet Imaging and Data Analysis’ (see page 11).

9. **Two nuclear medicine physicians were involved in image interpretation. Did they both review each scan? If so, what if they disagreed on the diagnosis?**

   Two nuclear medicine physicians reviewed each scan independently and, if there was disagreement, conclusion was reached by consensus. This is now stated in the ‘Methods’ section (see page 10).

10. **This appears to report the experience of a consecutive clinical series. Is this the case, or does this represent a subset of cases. Were there any excluded cases? If not, this means about 25 cases were evaluated in this clinic annually. Is that correct? Was there IRB approval for this study?**

    Now discussed in the 2nd paragraph of the ‘Conclusion’ (see page 13). Ethics Committee approval was sort and this is stated in the ‘Methods’ section under ‘Participants’ (see page 8).

**Minor Essential Revisions**

1. **It is quite appropriate to use likelihood ratios. Please indicate the range of ratios considered to be relevant in the methods and in the results indicate PLR and NLR not just as LR.**

   Details have been included at the end of the ‘Methods’ section (see page 11).
2. The clinical diagnosis was based partly on longitudinal clinical assessment. How long was the length of follow-up (mean and range), and how often was this information available.

This data is now provided at the end of the ‘Methods’ section (see page 9, first paragraph).

Discretionary Revisions

1. The discussion could be improved by expanding on whether FDG-PET is more or less relevant in young-onset than in late-onset dementia and whether there are any situations that it was found to be particularly helpful.

Now incorporated into ‘Results’ section (see pages 13 & 14).

2. What % of all FDG-PET studies was interpreted as normal? In what % of each group was the FDG-PET study considered to be normal? Is this what accounts for the insensitivity, or were there frequent misclassifications based upon FDG-PET (for example, FDG-PET indicated FTD while clinical diagnosis was another dementing disease)? It would be very relevant to determine the significance of a “normal” scan in this situation.

This is now discussed in the 2nd paragraph of the ‘Conclusion’ (see page 13).