Author's response to reviews

Title: Pre-dementia in Alzheimer's disease

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Version: 3 Date: 1 October 2010

Author's response to reviews: see over
Response to Reviewers’ comments:

Editor’s comments:

We appreciate the careful revision of the text and the relevant suggestions.

1. Title: the title has been changed as suggested.

2. Abstract: all edits have been incorporated to the abstract, rendering it more fluent and shorter. We rephrased the notion on ‘AD epidemics’ both in the abstract and introduction.

3. Main text: edits, suggestions and clarifications have been incorporated to the text. These modifications appear in red in the various sections of the manuscript.

4. Figures: we agree that the present review will benefit from a few visual aids. Therefore we included three figures illustrating the neuropathological cascades of AD (Fig. 1); a hypothetical timeline illustrating the progression of cognitive deficits and pathological process in the different stages of AD (pre-clinical, pre-dementia and dementia) (Fig. 2); and a tree-diagram illustrating the putative outcomes of the distinct MCI subtypes. All figures have been created by the authors for the present manuscript (Fig. 3).

5. Summary and conclusions: we expanded the ‘Summary and future directions’ session of the manuscript, addressing the next challenges that have been raised in this field of research in the light of the present developments. Textual information in this section is supported by two tables presenting in a schematic way the most relevant biomarkers in current AD research (Table 1) and an integrational view of neuropathological findings, related biomarkers and perspectives of disease-modifying interventions (Table 2). A sharp but conservative ‘Conclusion’ is also provided.

Reviewer 1:

We were delighted to receive such a positive evaluation from Reviewer 1. No major revisions were required, and the minor changes pointed out by the Reviewer were added to the text.

- Minor essential revisions: The statement that current AD treatments might prolong life expectancy was removed from the text.

- Discretionary revisions: We also included in the text (Introduction, second paragraph / Summary and future directions, last paragraph), additional information on the terminology ‘pre-clinical’, ‘prodromal’ and ‘clinical AD’. These notions were reinforced by recent NIA / Alzheimer’s Association documents on diagnostic criteria for ‘AD dementia’, ‘MCI due to AD’, and ‘Pre-clinical AD’. Further clarification on this terminology is provided in Figures 1 and 2.
Reviewer 2:

We appreciate the general comments by Reviewer 2 describing this article as well-written and organized, and agree that the major points raised are indeed very relevant. Therefore we included more neuropathological information in several segments of the text, and tried to integrate these notions with the clinical and biomarker-based concepts. Undoubtedly these amendments rendered the review much more precise, and we are thankful for this important contribution to our work.

1. We rephrased or deleted dubious statements according to the comments provided by Reviewer 2. Several statements regarding the progression of neuropathological changes were included in the text. The new paragraphs appear in red in the section ‘Alzheimer’s disease: translating neurobiological knowledge into clinical practice’, (1st, 2nd, and 3rd paragraphs).


3. This imprecise statement was removed from the text.

4. We included more information on autopsy-based studies in several segments of the text, but we felt that basic notions about structural neuroimaging were already covered in the original version of the manuscript. For the sake of conciseness, we maintained two paragraphs on this matter in the ‘Structural and functional neuroimaging’ sub-section, along with approximately ten core references.

5. Action taken (‘Summary and future directions’), in line with previous suggestions by former reviewers.