Author's response to reviews

Title: Pre-dementia in Alzheimer's disease

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Version: 4 Date: 22 November 2010

Author's response to reviews: see over
RE: MS 4669039894287986 – Forlenza et al., Pre-dementia in Alzheimer’s disease

Second Revision – residual points raised by Reviewer 2 itemized according to Editor’s notes.

1) As you will see, there are some further comments about the figure.

   Figure 1 is confusing. There are lots of arrows, some of which have very little experimental support. The reason for the solid and dotted lines is never explained in the text or in the legend. If the intention is that the solid arrows represent some main pathway to dementia and the dotted arrows possible side paths, Figure 1 is incorrect. Recent studies have demonstrated that while accumulation of soluble A beta is likely the initial event, induction of NFT is essential to the subsequent atrophy and dementia. Putting NFT in a side path with a dotted arrow does not make sense. If the authors wish to use this figure, they must explain the pathways they show. Also, atrophy subsequent to NFT formation is an important part of the pathway to dementia, but is omitted in the Figure. Because Figure 1 opens Pandora’s box, the authors may simply want to eliminate it altogether. The text is very general, but no misstatement is made.

Response: The first query regards the accuracy of Figure 1, which was taken as ‘confusing’ by the reviewer. As one may recall, this figure was inserted in the first revised version of the manuscript following the Editor’s suggestion to include a visual aid to support the text (‘the review would be enhanced by some visual display items, a schematic overview of the pathogenesis of pre-clinical AD would be a nice addition’).

Figure 1 is a schematic representation of the amyloid cascade and attempts to integrate neuropathological elements along the clinical staging of the disease (i.e., the hypothetical pathological events that evolve in pre-symptomatic, pre-dementia, and clinically-defined dementia phases of AD). Given the complexity of the subject, we do not have doubts that it is a difficult task to put all the elements together. We agree that any such figure and may look confusing at first sight, particularly to those who are not familiar with the basic notions of the amyloid cascade, or when the comprehension of the proposed schema is somewhat biased by the individual appraisal of the subject. (There are many different ways to put the parts together – to make it short, one can mention the ‘Baptist vs. Tauist’ reading of the AD neuropathology).

Although it might have been easier simply to delete the figure, we feel that keeping the illustration may indeed help the reader understand the complex notions that we present in the text. Therefore, we have made changes to the figure addressing the allegedly unclear aspects pointed out by the reviewer (e.g., dotted vs. solid arrows). We also included a detailed footnote to walk the reader through the figure. We honestly believe that no single figure will capture the complex mechanisms and competing hypotheses of the pathological process in AD (please find the new figure, legend and footnote below).
Figure 1. Hypothetical model of the pathological processes in Alzheimer’s disease (AD), focusing on the amyloid (Aβ) cascade. (Other relevant mechanisms have been omitted or presented in a secondary perspective for didactic purposes).

Aβ, amyloid-beta peptide; APP, amyloid precursor protein; PS, pre-senilins 1 and 2; TAU, microtubule-associated protein Tau. Dotted arrows indicate possible or secondary mechanisms affecting core pathological processes within the amyloid cascade. Background shades of gray separated by dotted lines are a schematic representation to integrate the progression of pathological events along with the development of the cognitive syndrome of AD (these thresholds are arbitrary and not experimentally validated, and represent the authors’ point of view of the disease process). Three clinical phases of the disease are defined: pre-symptomatic (or pre-clinical) AD may last for several years or decades until the overproduction and accumulation of Aβ in the brain reaches a critical level that triggers the amyloid cascade; in the pre-dementia phase, compatible with the definition of mild cognitive impairment secondary to AD, early-stage pathology is present in varying degrees, from mild neuronal dystrophy to early-stage Braak pathology, according to individual resilience and brain reserve. Finally, in the clinically defined dementia phase, there is a progressive accumulation of the classical pathological hallmarks of AD, i.e., neuritic plaques and neurofibrillary tangles, bearing relationship with the progression of cognitive deficits and the magnitude of functional impairment.
2) The referee has indicated that the review would benefit from further elaboration about the timing for the earliest pre-dementia changes. In particular, they highlighted the limitations on using fibrillar A-beta or its CSF correlate as opposed to earlier effect of AB oligomers. As we feel that this would strengthen this section of the manuscript, we would ask you to consider elaborating on this discussion point.

Response: Additional information on Aβ oligomers was added to the text. This is an important issue and represents a important methodological development in the search for new amyloid-related CSF biomarkers.

Page 16, Sub-section ‘Cerebrospinal fluid biomarkers’:

New technologies targeting Aβ oligomers in the CSF will add important insights in this field in the forthcoming years. The neuropathology of AD has been linked to the accumulation of non-fibrillar forms of neurotoxic Aβ oligomers. There is evidence that soluble Aβ oligomers, more than amyloid fibrils per se, play a critical role triggering early pathological events of the amyloid cascade. High levels of Aβ oligomers are observed in the brain and in the CSF of patients with AD, underlining their potential for the early diagnosis of the disease [61]. In a recent study using a specific method for the detection of high molecular weight (40-200 kDa) Aβ species in the CSF, Fukumoto et al. [62] showed that the measurement of Aβ oligomers may be more accurate differentiating patients with MCI and AD from normal controls, as compared to the usual methods based on fibrillar forms of the peptide. Oligomerization partially explains the lowering of Aβ42 in the CSF of patients with AD, since the presence of Aβ oligomers can interfere with the analyses of the peptide by conventional methods, causing underestimation of Aβ levels due to epitope masking [63]. Therefore, the determination of Aβ oligomers in the CSF, in addition to being useful as a diagnostic marker for AD, can be also viewed as a potential surrogate marker for disease severity [62].


With respect to ‘the timing for the earliest pre-dementia changes’ we believe that the reviewer perhaps did not note that the action had already been taken in the previous review of the manuscript. We added one additional comment on this subject to the concluding remarks of the article.

Page 5, Section ‘Alzheimer’s disease: translating neurobiological knowledge into clinical practice’:

Recent models based on neuropathological, biochemical and neuroimaging methods have proposed that intracerebral amyloidosis precedes the onset of cognitive symptoms by several years, if not decades. Autopsy studies have shown that intracerebral amyloidosis may be observed in some subjects as early as in the third or fourth decades of life, with increasing magnitude in late middle age, and highest estimates in old age [10-
The exact proportion of amyloid-positive normal adults who will ultimately develop AD is still uncertain, and critically dependent on the age and genetics of the cohort; yet, cortical amyloid load in cognitively normal older adults seems to be associated with a higher rate of progression to symptomatic AD in the long term [13].

Page 21. 'Conclusions':
Individuals with mild cognitive deficits do display signs of AD pathology, since approximately 50% are already in Braak neurofibrillary stage III or higher, and 20% are likely to be in more advanced stages of neuropathology [108]. It is likely that those with considerable brain or cognitive reserve will be able to compensate cognitive deficits until very close to the onset of the dementia, rendering the diagnostic work-up of pre-dementia AD based solely on cognitive measures insensitive. Therefore, the development of biomarkers for AD is needed to target the severity of underlying brain pathology independently of brain reserve.