Author's response to reviews

Title: Lewy Bodies and neuronal loss in subcortical areas and disability in non-demented older people: A population based neuropathological cohort study

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Author's response to reviews: see over
Reviewer: Yunhwan Lee

Reviewer's report:

Minor Essential Revisions
1. It appears that the ADL and IADL instrument the authors used is an abridged version (only 3 ADL and 3 IADL items). Traditional items, such as toileting and eating, are not included. Please give more details on the ADL/IADL instrument, supporting it as a validated tool.

The entire instrument is actually given within the interview data (as described within the text), but the use of the hierarchical measurement has been investigated previously in further work on the disability concept within CFAS (now referenced). It is this hierarchical measure that has been used in this paper.

2. In the text, the authors state that using the toilet is included in the instrument, but does not appear in the table (Table 1).

That is due to the hierarchical nature of the ADL instrument being used. It is a more severe ADL than the bath item and therefore does not include any new individuals that were not already marked as being severely disabled.

3. The assumption that “functional disability is unlikely to improve” is not well-grounded. Refer to Hardy and Gill’s paper (JAMA 2004;291:1596-1602). Is it possible that misclassification bias has been introduced?

With this level of severity and the age of the population very few individuals recover (<1%) within the longitudinal period of the study. Therefore whilst there may be some bias, we do not think it will be extreme. We have included a comment in the discussion “Though there is some possibility that in a minority of individuals function may improve.”

Discretionary Revisions
4. It is possible that ADL/IADL is not a sensitive tool for detecting early changes in the brain structure. Assessment of functional limitations, a pre-disability state, that include muscle strength, upper and lower body mobility, and balance, may better serve to reflect early brain changes.

We agree and this should be an investigation for future research within other cohorts where objective measurements of physical ability have been undertaken. Unfortunately we do not have these measurements, a comment has been added to the discussion “The measures of disability may not be sensitive enough to brain changes which may require the use of objective measurement.”

5. Coming back to the point on the progression/reversibility of disability, it would be interesting to investigate, longitudinally, whether changes in disability states over time are correlated with pathologic changes.
This indeed would be of general interest, but is beyond the scope of this paper.

Reviewer's report
Reviewer: Catherine Brodeur
Reviewer's report:
Discretionary revisions:
1. in the 1st sentence of the abstract, you say that functional decline is associated with ageing... but can't this be perceived as ageism? In fact, usually this is not the case, with the elderly population being more healthy and active than years ago. Maybe you could say that usually we can find diseases that explain the functional decline, but sometimes not.

It is indeed the case that individuals may well be more active than previous cohorts of the same age, but it is equally true that more individuals lose the ability to carry out daily tasks unaided as they age. We are not suggesting that this loss is an essential part of the ageing process. We have modified the abstract slightly "Functional disability, the loss of ability to carry out daily tasks unaided, is a major adverse outcome more common with increasing age”

2. I understand that you use only the MMSE as a screening test for all people (GMS restricted to just some people)... are you afraid you could have missed subcortical-frontal cognitive disorders, as we can find in subcortical pathologies? I suggest that for a future study you use tools such as the Frontal Assessent Battery (FAB) by B. Dubois et al.

All individuals within the neuropathological substudy have a dementia diagnosis based on the AGECAT organicity algorithm. We have excluded those individuals where the dementia status was unknown. We are aware that some pathologies are associated with prominent cognitive changes that are not primarily amnestic. In particular the attentional and executive function deficits associated with subcortical small vessel ischaemia, and to some extent with synucleinopathy, are not well captured by the MMSE. As yet the development of screening instruments for these psychological modalities has not yet progressed to the stage of such widely accepted tools as MMSE and these were not available when CFAS was designed and specified. Clearly there are opportunities for new work in this area but we are unable to contribute within this phase of CFAS.

3. Related to comment 3: if we make an assumption that the people evaluated in your study had undetected subcortical-frontal cognitive disorders, could this contribute to the impairment in IADL? (more cognitive-related).

This is of interest but beyond the scope of the current paper. CFAS does not have the data to address these interesting issues around frontal-subcortical neuropsychological deficits and their relation to IADL and pathology. This
paper is intended to raise awareness of the probability that loss of ADLs is frequently associated with organic brain disease that does not meet diagnostic criteria for specific clinicopathological diseases. We hope that we and others may be stimulated to design studies that can address this in the future.