Author's response to reviews

Title: Retinal nerve fiber layer thickness and cognitive ability in older people: the Lothian Birth Cohort 1936 study

Authors:

Augustinus Laude (draugustinuslaude@googlemail.com)
Gerassimos Lascaratos (glascaratos@gmail.com)
Ross D Henderson (rhender4@staffmail.ed.ac.uk)
John M Starr (jstarr@staffmail.ed.ac.uk)
Ian J Deary (iand@staffmail.ed.ac.uk)
Baljean Dhillon (Bal.Dhillon@luht.scot.nhs.uk)

Version: 5 Date: 26 January 2013

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

We would like to thank the reviewers for their helpful comments and suggestions. We have taken great care to address the points raised in this point-by-point response to the reviewers and have revised the manuscript accordingly. Many thanks once more for helping improve the quality of the final submission.

Reviewer 1:

This study investigated the relationship between the retinal nerve fiber layer (RNFL) thickness as measured by optical coherence tomography (OCT) and lifetime cognitive change in healthy older people. And their conclusions was increased RNFL thickness appeared to be associated with lower general processing speed and lower general cognitive ability when age 11 IQ scores were included as a covariate in a community dwelling cohort of healthy older people. This is an interesting study, but it is an opposite direction when comparing with previous report by van Koolwijk. When we meet contradictory results, we should be cautious to the later results inevitably.

Major problems
1. Because old people usually have more major eye problems (such as cataract, retinal disorder, glaucoma) than young people, ophthalmologic examinations which could exclude eye diseases are essential in this study. The authors should describe how to prove healthy in the subjects. If not, the limitation of this point should be described carefully.

We thank the reviewer for their comments and we agree that it is essential to ensure that our sample is indeed healthy. We have revised the manuscript to explain that “Prior to the OCT measurement, a dilated fundus examination was also performed and wide field fundus photographs (Optos) were taken to exclude major eye diseases, such as retinal disorders or glaucoma, that could act as confounders.”

2. It is well known that visual impairment may be associated with low cognitive function. The authors also need to describe visual status of the subjects.

We have reviewed our database and presented our findings in the Results section: “The mean visual acuity was 0.11 (Range: 0.00 to 0.50; SD=0.14).” We found that our cohort had overall good visual acuity with a lower end measure of 0.50.
3. The authors need to describe and discuss in more detail why the results of their study are contradictory to previous study by van Koolwijk.

We have revised our discussion accordingly to discuss the results of the van Koolwijk study and compare to our findings: “This finding differed from a recent population-based study by van Koolwijk et al. who found that, although there was an association between thicker RNFL and higher cognitive functioning in the younger population, this diminished to non-significance in those aged 40 and over [37]. They concluded that this lack of association in older individuals suggested that loss of neurons in the cerebrum and retina were not concomitant and might have different origins. In our study, RNFL thickness was also found to be a potential biomarker of relative cognitive status in the older age group, albeit in an unexpected direction, with a thicker RNFL being associated with a lower cognitive functioning. The reasons for this are not entirely clear, although different techniques were used to measure RNFL thickness in both studies (scanning laser polarimetry [37] as opposed to optical coherence tomography in our study). Moreover, in the study by van Koolwijk et al. the vast majority of participants (78%) had consanguineous parents and were derived from an isolated population, which may not necessarily represent the general population.”

**Minor problem**
1. Part of some misspellings;
   - The second line on page 5; IT -> It

   This has been addressed.

   - It seemed to need to use consistent abbreviation either “S.D.” or “SD”.

   This has been changed as requested and “SD” has been used throughout the text.

   - It would be better to add micrometer unit (µm) when describing the RNFL thickness.

   This has been changed, as requested, both in the text and in the tables.

2. In the results from the analysis of RNFL thickness measured by OCT, three more or less standard deviation is classified as outlier. The authors need to describe why exclusion criteria were caught.

   In this study, we chose to exclude these outliers in the analysis because extreme values can have a disproportionate influence on results. We have therefore ammended the following line in the Results section: “Any points which fell more than 3 standard deviations above or below the mean were treated as outliers and excluded because extreme values can have a disproportionate influence on results.”
Reviewer 2:
This is an interesting report that tries to correlate cognitive ability with RFNL thickness in healthy elderly individuals. The concept to evaluate RFNL thickness in neurodegenerative diseases is now quite well advanced and this work propose to extrapolate this concept to cognition. There are several important questions that should be addressed.

1. It is now admitted that the reduction of RFNL thickness might be linked to primary or secondary neuronal loss in Alzheimer’s Disease, Multiple sclerosis or other diseases. The question addressed in this paper is not clear at least for this reviewer. Do the authors think that neuronal loss occurs in normal aging?

We agree with the reviewer that reduction of RFNL thickness might be linked to primary or secondary neuronal loss in Alzheimer’s disease or other diseases, and we felt that these findings raise the possibility of RNFL thickness to be used as a biomarker of non-pathological cognitive ageing. Our motivation for this study was therefore to look at the association of RNFL and cognitive function in a normal elderly population. That is, in a sample of similar chronological age, we sought to find out if RNFL thickness contributed to variation in cognitive ability in old age over and above cognitive ability from a youthful baseline?

Do the authors think that cognitive modifications detected in elderly individuals and marked by reduced speed processings could have a link to RFNL thickness?

We found that, when age 11 IQ was included as a covariate, increasing RNFL thickness was associated with lower general cognitive ability and general processing speed. These results challenge our traditional views on the subject and suggest that cognition in the ageing brain may be a complicated phenomenon and one that may not be explained by the loss of neurons in the retina. Of course, the direction and magnitude of our findings requires replicating in other studies. We have been appropriately cautious in our revised discussion and conclusions.

The switch from neurological diseases to cognitive modifications observed in elderly should be explained by a proper review of the literature of the RFNL in aging to bring about a clear rational.

We thank the reviewer for their suggestion and have revised the introduction to present evidence from the literature that thinning of the RNFL is noted with aging.

The following references have also been added:


2- Are there any statistical changes between the clinical findings of the Lothian Birth Cohort and the sub-sample. Why the authors have chosen these 105 subjects?

We reported on the findings from the first 105 consecutive subjects who took part in our study. These represented an unselected group and so we did not expect them to be different from the rest of the cohort. We have included further information relating to this in the Methods section: “This consecutive series of unselected sub-sample (n=105) underwent OCT testing performed by two ophthalmologists...”.

3- RFNL thickness seems to be reduced in patients with Mild Cognitive Impairment. Since all MMSE scores were in the normal range, how the authors have excluded monodomain or multidomain MCI?

No cognitive exclusions were made other than by low MMSE score (<24) and self-reported dementia.

4- Did the subjects have brain MRI to exclude sub-clinical neurological diseases?

In this study, we did not include the MRI findings to exclude sub-clinical neurological diseases but relied on the MMSE scores and self-reported dementia for screening.

5- A major question is the link between 11 IQ test and cognition in elderly. Cognitive ability might depend upon IQ but also on cognitive reserve acquired at least by education which can be evaluated by cognitive reserve. All those results should be adjusted to the level of cognitive reserve (years of education?) that can delay the onset of cognitive troubles while CSF biomarkers and brain lesions are progressing.

We thank the reviewer for raising this point about the cognitive reserve. The estimation of cognitive reserve is not established, with different proxies described in
the literature, including variables descriptive of lifetime experiences (eg. educational attainment, income or social attainment) [38]. Premorbid IQ (in our series, the age 11 IQ) has been shown to be a powerful measure of cognitive reserve [39-42]. However, despite our having this rarely-available datum, we did also include years of education as a further indicator of reserve [43]. When we reanalysed our data to include number of years of education as a variable, we found that there were no longer significant associations between the RNFL thickness and cognitive scores.

We included the following lines and references to the Discussion section to address these findings: “The role of cognitive reserve in influencing the cognitive ability later in life was considered. The estimation of cognitive reserve is not very well established, with different proxies described in the literature, including variables descriptive of lifetime experiences (eg. educational attainment, income or social attainment) [38]. Premorbid intelligence (in our series, the age 11 IQ) is a powerful measure of cognitive reserve [39-42]. However, education and other life experiences may impart reserve over and above that obtained from childhood intelligence [43]. When we re-analysed our data to include the number of years of education as a variable, we found no significant associations between the RNFL thickness and cognitive scores.”


Reviewer 3:

The authors analyze the relationship between the RNFL thickness as measured by OCT and lifetime cognitive change in healthy older people. They conclude that
increased RNFL thickness appeared to be associated with lower general processing speed and lower general cognitive ability. The paper needs a major revision. 

Introduction. Page 5, last sentence. The authors should mention several recent papers dealing with the role of OCT in other neurodegenerative disorders with frequent cognitive changes like schizophrenia (1), obstructive sleep apnoea syndrome (2), or acute mountain sickness.(3)


These additional recent papers have been added, as requested, and the references have been renumbered accordingly.

Methods. The study was not randomized and, as the authors say when discussing the limitations of the study, they should have taken into account the lens status and the refractive error of the examined subjects, because both of them are important confounding variables which may produce distorted results.

We agree with the reviewer’s comment and have made clear in our discussion that “we have not controlled for all potential confounders such as refractive error that might possibly affect the OCT measurements. Although it is known that myopia is associated with correlates of cognitive functioning such as intelligence and educational attainments, the prevalence of myopia is considered low in the elderly population”.

Results.
How can the authors explain that in present study an increased peripapillary RNFL thickness was associated with lower general cognitive ability and general processing speed,. whereas previous studies have shown a decreased peripapillary RNFL thickness in mild cognitive impairment and Alzheimer disease patients –as they mention in the introduction-?

We would like to thank the reviewer for this comment have therefore added the following lines to the Discussion section to address the issues raised and to include the limitations of the different studies and the need for replicating our findings in different populations: “…although previous studies have shown a decreased peripapillary RNFL thickness in mild cognitive impairment and Alzheimer disease patients [9, 13], these studies included only a small number of patients and no detailed cognitive function measures were employed [35], as in this study. Despite the proposed link between decreased RNFL thickness and cognitive impairment in a disease context, the Lothian Birth Cohort 1936 study suggests for the first time that this may not be the case in healthy individuals and that the link between parallel processes in RNFL and cognitive function may be more complex than previously
thought, especially when considering not only cognitive function at the age of 72, but also lifetime cognitive change between 11 and 72. We can only speculate that changes in cognition in the ageing brain are a complicated phenomenon and one that may not be explained by the loss of neurons in the retina. The direction and magnitude of our findings would also need replicating in a different population.”

Have the authors studied the OCT macular thickness and volume parameters?

In this study, we performed the OCT scans using the Fast RNFL scan protocol and did not measure the macular thickness and volume parameters.

Discussion. Another limitation would be that all the cognitive data were collected at a prior assessment (mean time elapsed between assessments= 381 days).

This separation in time would be associated with very little change in individual differences (rank order, which is what matters) in cognitive abilities or other variables. Indeed, we have shown that even three years in the early 70s does not change individual differences much at all (Johnson, W., Gow, A. J., Corley, J., Redmond, P., Henderson, R., Murray, C., Starr, J. M., & Deary, I. J. (in press). Can we spot deleterious ageing in two waves of data? The Lothian Birth Cohort 1926 from ages 70 to 73. Longitudinal and Life Course Studies.)

In page 12, paragraph of discussion, the authors should clarify which study used scanning laser polarimetry and which one optical coherence tomography.

This has been clarified, as requested.

Page 8, 1st paragraph, 2nd line. “IT is a computerized task (…)” must be changed by “It is a computerized task (…)”

We are sorry for the misunderstanding and have replaced IT by ‘Inspection time’ to avoid confusion.

Page 11, last sentence. The sentence “found that these were all the in a negative direction” must be replaced by “found that these were all them in a negative direction”

This has been corrected.