Author's response to reviews

Title: Neck muscle cross-sectional area, brain volume and cognition in healthy older men; a cohort study

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Author's response to reviews: see over
Dear Professor Wai Kwong Tang,

Thank you for reviewing our article entitled, “Neck muscle cross-sectional area, brain volume and cognition in healthy older men”.

We thank both reviewers for their useful comments, which we have addressed below.

We hope you feel these changes make a much improved article and look forward to hearing from you in due course.

Thank you for your ongoing input.

Yours sincerely,

Dr Alixe HM Kilgour

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Reviewer 1 (Katsuo Fujiwara)

“The present study examined neck muscle cross-sectional area and brain volume (whole brain, ventricular, hippocampal and cerebellar volumes) in 51 community-dwelling healthy older men, using neuroimaging method. Furthermore, the study executed multiple cognitive tests.

The whole brain volume was significantly and positively related to the neck muscle cross-sectional area. The other brain volume parameters did not correlate with the neck muscle cross-sectional area. In addition, most results of the cognitive test were not significantly and positively related to the neck muscle cross-sectional area. Rather, the result in National Adult Reading Test was negatively related to the neck muscle cross-sectional area.”

Thank you for this synopsis of our main results.

“The neck muscle cross-sectional area and brain volume was properly measured in the present study. However, there are serious problems in which the hypothesis in the present study and the interpretation of the results are not clear at all. You assumed whether neck muscle size was positively associated with cognition and brain structure in older men. However, in Background, you did not describe theoretical background associated with the hypothesis. You should indicate the theoretical background and the significance of the study. In Discussion, you introduced the previous studies that the lean body muscles mass or fat volume was related to the cognitive function. You should clearly describe the relationship between the results in the present study and the previous findings.”

We thank the reviewer for these useful comments which we have now addressed (see below).

However, in Background, you did not describe theoretical background associated with the hypothesis. You should indicate the theoretical background.

We agree that it is important to cite some theoretical mechanisms underpinning our hypotheses. In the Background section we have now included further details of the possible theoretical background for the hypothesis in the following paragraph.

“Possible mechanisms which might account for the shared variance in muscle and brain size and function with healthy ageing include: the role of hormones and growth factors (eg glucocorticoids) [1, 2]; immunosenescence and inflammation (eg IL6 and CRP) [3, 4]; oxidative stress and mitochondrial ageing [5, 6]; decreased stem cell activity [7, 8]; and environmental and lifestyle factors (eg smoking) [9, 10].”

and the significance of the study.

We agree that it is helpful to explain why this study is needed (i.e. its significance). We have now added the below section on the possible significance of the study.

“The above findings showing association between brain and muscle structure and function add support to the common cause hypothesis [11-14], that core underlying processes determine the rate of ageing in
each organ throughout the body. If we are able to demonstrate an association between muscle size and brain size and function, this could add further weight to the common cause hypothesis. This would have large implications for future treatments designed to modify the rate of ageing, which could possibly target several organs at once (eg muscle and brain) as opposed to individualised treatments being developed.”

We have already noted the paucity of data in this field in the introduction, specifically that there is only one other study which has looked at brain volume and muscle bulk, which includes Alzheimer’s disease patients and that the other studies looking at cognition and muscle bulk have used only tests designed to screen for dementia, not to accurately test for current cognition. None have included a measure of prior or pre-morbid cognition.

**In Discussion, you introduced the previous studies that the lean body muscles mass or fat volume was related to the cognitive function. You should clearly describe the relationship between the results in the present study and the previous findings.”**

We thank the Reviewer for this helpful comment. In the Discussion section we have now made the relationship between the present study and previous studies far clearer. (Changes in **bold italic**)

“We found only one previous study which investigated the relationship between muscle size and brain size, *and this study also found a positive relationship between muscle bulk and whole brain volume*. In the above study Burns et al also investigated the relationship between MMSE and a measure of global cognitive performance (a composite score made up of the results of a battery of tests, including the DSST and verbal fluency) with muscle mass [15]. They found a significant positive association between both the global cognitive performance score (Beta .12, p=.007) and MMSE (Beta .11, p=.009) and muscle mass, controlling for age and sex but not for prior cognition which we have shown to correlate with both brain and muscle size (Table 3). **Our study was able to investigate the relationship between cognitive decline, by adjusting for prior cognition using the NART score, and current cognition, whereas this study only looked at cross-sectional data from current cognition. This may explain why they found an association between current cognition and muscle mass and we did not.**

Several large studies have also investigated the links between muscle size and cognition. In a large cross-sectional study of community dwelling women aged 75 or over (n=7105), Nourhashemi et al found that low cognitive function was associated with low fat free mass [16]. However the cognitive test used was the Short Portable Mental Status Questionnaire (SPMSQ), which consists of only 10 questions and is mainly used as a screening test for cognitive impairment.

Conversely, Wirth et al studied 4095 consecutive geriatric hospital patients and found that fat-free mass was not associated with cognitive dysfunction, measured using MMSE, after adjusting for age, sex and Barthel index [17]. Also, Auyeung et al studied 2737 cognitively normal older people and found that appendicular skeletal muscle mass (ASM) was significantly predictive of MMSE 4 years later in men but not women [18]. However, after adjustment for age, years of education and baseline MMSE score, the relationship in men was not significant either.
Our study has the benefit of including tests of both prior and current cognitive function. This allows us to look at cognitive decline rather than purely at current cognitive ability, and is the only study we could find that specifically tested the relationship between prior cognition and muscle size. Also, the three large studies mentioned above used cognitive tests which are primarily designed to screen for cognitive impairment (i.e., SPMSQ and MMSE) rather than to detect the subtleties of change in cognition with age [17-19], for which our cognitive tests were specifically chosen. Burns et al. used more detailed cognitive tests, however the numbers involved in their study are much smaller compared to the other three studies. Our study is the first to measure muscle cross-sectional area and cognition or brain size; the above mentioned studies used either bioimpedence analysis or DEXA as the measure of muscle bulk.

Reviewer 2 (Christian Benedict)

“This is a well-written study, and the authors are experts in the field.”

We thank the reviewer for these positive comments.

“Major Compulsory Revisions: Education is such an important predictor of brain health in humans (e.g., Hum Brain Mapp. 2011 Sep;32(9):1371-82.). That said, as long as you have not controlled your analysis for education, I cannot draw any definite conclusion on the validity of your study findings.”

Thank you for this comment. Unfortunately we do not have data recorded for educational achievement for this set of subjects. However, educational achievement and pre-morbid cognition (of which NART is an estimate) are known to correlate highly (r=0.81) [20]. Therefore we feel that the addition of a measure of education would add very little to the variation seen with NART in our ageing cohort. In fact, even if we had the number of years of education, it might be difficult to construct robust models because of potential colinearity. We have added the following sentence to the manuscript in the methods subsection, “Tests of cognitive function”, to explain this to the reader.

“Due to the strong correlation between pre-morbid cognitive ability (of which NART provides an estimate) and educational achievement [20], it was decided to include only NART and not educational achievement as a predictor variable.”
