

**Potential effect of skull thickening on the associations between cognition and brain atrophy in ageing**

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**Running Title:** Skull Thickening Could Distort Cognition-Brain Atrophy Association

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## **Abstract**

**Background:** Intracranial volume (ICV) is commonly used as a marker of premorbid brain size in neuroimaging studies as it is thought to remain fixed throughout adulthood. However, inner skull table thickening would encroach on ICV and could mask actual brain atrophy.

**Objective:** We investigated the effect that thickening might have on the associations between brain atrophy and cognition.

**Methods:** The sample comprised 57 non-demented older adults who underwent structural brain MRI at mean age  $72.7 \pm 0.7$  years and were assessed on cognitive ability at mean age 11 and 73 years. Principal Component Analysis (PCA) was used to derive factors of general cognitive ability (g), information processing speed and memory from the recorded cognitive ability data. The total brain tissue volume and ICV with (estimated original ICV) and without (current ICV) adjusting for the effects of inner table skull thickening were measured. General linear modelling was used to test for associations.

**Results:** All cognitive ability variables were significantly ( $P < 0.01$ ) associated with percentage total brain volume in ICV measured without adjusting for skull thickening (g:  $\eta^2 = 0.177$ , speed:  $\eta^2 = 0.264$  and memory:  $\eta^2 = 0.132$ ). After accounting for skull thickening, only speed was significantly associated with percentage total brain volume in ICV ( $\eta^2 = 0.085$ ,  $P = 0.034$ ), not g or memory.

**Conclusions:** Not accounting for skull thickening when computing ICV can distort the association between brain atrophy and cognitive ability in old age. Larger samples are required to determine the true effect.

## **1. Introduction**

Brain atrophy helps in understanding brain volume changes and their association with ageing, neuropsychological conditions and cognition[1,2]. Estimation of brain atrophy in neuroimaging studies normally requires the use of a marker of premorbid brain size. Intracranial volume (ICV) is commonly used for this because it is generally believed not to be affected by disease or age-related changes[3]. However, in other areas of imaging practice, it has long been recognised that thickening of the inner skull table occurs in variable amounts as part of normal ageing, more so in women than men[4,5].

Previous studies have reported that the association between cognitive ability and brain atrophy is stronger for women than men and for adults than children[1,2]. However, the brain shrinks with advancing age, and the atrophy rate is faster in men than women[1,2]. Hence it is possible that inner table skull thickening could distort the association between cognition and brain size/atrophy with advancing age.

In a previous study[6], we found that not accounting for inner table skull thickening in the computation of ICV could underestimate brain atrophy by about 5.3%, potentially obscuring gender differences. In the present exploratory study, we investigated whether the inclusion of inner table skull thickening during measurement of ICV could affect the association between estimated brain atrophy and cognitive ability.

## **2. Methods**

### *2.1. Subjects*

Study participants were members of the Lothian Birth Cohort 1936 (LBC1936;[7] who underwent brain Magnetic Resonance Imaging (MRI,[8]), and detailed cognitive and medical assessments[7] at mean age 73 years. Written informed consent was obtained from all participants under protocols approved by the Lothian (REC-07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committee. For the present study, a representative sub-sample of 60 out of 672 participants were selected by visual inspection of MRI data to include subjects with a range of representative skull thickening, from obvious thickening of the inner skull table to little or no thickening, blind to the cognitive ability scores. Three of the originally selected 60 subjects were excluded because of incomplete data leaving 57 subjects (30 men), aged 71.1 to 74.3 years (mean 72.7, SD 0.7 years).

### *2.2. Brain MRI Acquisition*

Subjects were imaged with a GE Signa Horizon HDxt 1.5 T clinical scanner (General Electric, Milwaukee, WI, USA) using a self-shielding gradient set with maximum gradient strength of 33 mT/m, and an 8-channel phased-array head coil. The imaging data included: T<sub>1</sub>-weighted and T<sub>2</sub>-weighted whole brain [8].

### *2.3 Brain Tissue Volume Measurements*

All image analysis was performed blind to subject details, cognitive and clinical data. After pre-processing (please see Appendix 1 in the supplementary data). The total brain tissue

volume excluding the cerebrospinal fluid, was segmented using a multispectral image processing tool, MCMxxxVI[9].

Two estimates of ICV were recorded (full description provided elsewhere [6] and in Appendix 2, supplementary data). Briefly, the first measured ICV did not adjust for the effect of inner table skull thickening, termed 'current ICV' (Figure 1; top right panel). The second estimated the original ICV prior to development of inner table skull thickening by estimating where the original inner skull was, termed "estimated original ICV" (Figure 1, bottom right panel). Both current and estimated original ICV include veins and meninges in the ICV, as veins and meninges increase in size with increasing brain atrophy[10].

#### *2.4.Cognitive Parameters*

The cognitive ability assessments have been described elsewhere[7]. Briefly, subjects were assessed on a battery of cognitive tests at mean age 11 and 73 years. These were used to derive cognitive ability variables at age 73, that is: the general factors of cognitive ability (g, Appendix 3 supplementary data), processing speed (speed) and memory (memory).

#### *2.5.Statistical Analysis*

All statistical analyses were performed using IBM SPSS version 19 (IBM Inc. New York, USA), with all statistical tests being two-tailed, and P-values < 0.05 being considered statistically significant. For each subject, total brain volume was normalised to the subject's ICV (current and estimated original ICV) and expressed as percentages of ICV. The normalised brain volumes were used as measures of atrophy.

General linear modelling (GLM) was used to investigate associations between cognitive parameters (dependent variables) and atrophy measures (independent variables, Figure 1). Covariates were gender, age in days at age 73 years, and age 11 IQ. Separate GLM were used to investigate the association between age 11 IQ (independent variable) and atrophy measures (dependent variables).

### 3. Results

Appendix 4, supplementary data, presents descriptive statistics for all brain and cognitive variables. We have previously reported the difference between current ICV and estimated original ICV in the same sample[6]. Estimated original ICV was significantly greater than current ICV. The percentage of brain tissue in current ICV was significantly larger than the percentage of brain in estimated original ICV. The total brain tissue volume occupied a larger proportion of current ICV in women than in men. There was no sex difference in the proportion of estimated original ICV occupied by total brain volume.

GLM (Table 1, Appendix 6 supplementary data) showed that, after adjusting for age in days, gender, and age 11 IQ, cognitive ability in old age was significantly associated with the percentage of brain tissue in current ICV (*g*:  $F=11.2$ ,  $P=0.002$ ,  $\eta^2 = 0.177$ ; *speed*:  $F=18.31$ ,  $P<0.001$ ,  $\eta^2 = 0.264$  and *memory*:  $F=7.88$ ,  $P=0.007$ ,  $\eta^2 = 0.132$ ). However, only *speed* ( $F=4.73$ ,  $P=0.034$ ,  $\eta^2 = 0.085$ ) was significantly associated with the percentage of brain tissue in estimated original ICV, although with a substantially attenuated effect size, but not *g* ( $F=2.64$ ,  $P=0.11$ ,  $\eta^2 = 0.048$ ) or *memory* ( $F=2.40$ ,  $P=0.127$ ,  $\eta^2 = 0.044$ ). Please see Appendix 5, supplementary data, for associations between age 11 IQ and atrophy. Appendix 7 presents the statistical comparison of associations between atrophy and cognitive ability.

#### **4. Discussion**

In this exploratory sample, we show that inner table skull thickening can distort associations between lifetime cognitive change and brain atrophy measured as percentage of brain tissue in ICV in older subjects. When ICV was computed without accounting for inner table skull thickening, the percentage of total brain tissue volume occupied a larger proportion of ICV in women than in men in preceding work[1]; accounting for skull thickening removed this gender difference. Furthermore, the use of current ICV showed that the percentage of brain tissue in ICV is associated with all cognitive parameters whereas the use of estimated original ICV revealed that the percentage of brain tissue in ICV is only associated with speed, not g or memory. The difference in the brain size-lifetime cognitive change association when skull thickening is or is not accounted for might explain why the association between brain size and cognitive ability was found to be stronger in older adults than in children, and in women than in men in previous studies[1,2], i.e., it could in part be an artefact of change in ICV over the lifecourse. These results show that ICV computed without accounting for skull thickening may falsely inflate the relationship between lifetime cognitive change and brain atrophy.

We used validated image processing tools, accounted for the entire intracranial contents, carefully estimated the effect of inner table skull thickening, and used a sample of older subjects manifesting a range of skull thickening. We corrected atrophy-cognitive ability associations for childhood IQ, assessed over 60 years earlier. These associations therefore reflect lifetime cognitive change.

A possible limitation of this study is the assumption that ICV reflects maximal brain size in youth. Ideally serial MRI of a large sample should be used to assess whether ICV does in fact remain stable from late childhood to old age, however this is currently impossible. The study sample size is small, chosen as a sub-sample of a large cohort in order to determine if inner table skull thickening was worthy of further evaluation. It is clear that a larger sample is required to confirm the findings and test gender-related differences, also in other populations. The method used for determining original ICV in this study is time consuming which was why we selected a sample for this study, automation becomes necessary if future studies are to account for skull thickening routinely. Clearly, as inner table skull thickening may be an important methodological point in studies of the ageing brain, further research is now warranted to determine the best method to account for inner table skull thickening in ICV and brain measurement.

Future studies of brain atrophy, and its association with cognitive ageing, should evaluate the necessity of adjusting for inner table skull thickening when measuring ICV. These findings call for attention to a typically overlooked aspect of cognitive ageing research. Further research in larger samples is required to investigate the true effect of inner table skull thickening on the associations between brain atrophy and cognition, and to derive the true relationship between ICV and inner table skull thickening in older adults.

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**Conflict of Interest**

None

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## Figure captions

**Figure 1:** Schematic representation of the GLM modelling of the association between cognitive ability (g, speed, memory) and brain atrophy measures (percentage of brain tissue in current ICV and percentage of brain tissue in estimated original ICV). Model controlled for age in days, age 11 IQ and gender. Top panel: ICV without accounting for inner table skull thickening, bottom panel: inner table skull thickening accounted for in the computation of ICV. Values are  $\eta^2$  and p value. Predictors and outcome variables are represented in boxes while circles are used to represent covariates.

**Table 1:** Association between brain atrophy measures and cognitive ability (g, speed, memory) using GLM with and without accounting for skull thickening in the computation of ICV.

<b>ICV without accounting for skull thickening</b>									
	g			Speed			Memory		
	F	P	$\eta^2$	F	p	$\eta^2$	F	p	$\eta^2$
% Brain in current ICV	<b>11.2</b>	<b>0.002</b>	<b>0.177</b>	<b>18.3</b>	<b>&lt;0.001</b>	<b>0.264</b>	<b>7.88</b>	<b>0.007</b>	<b>0.132</b>
Age in days	0.7	0.40	0.014	0.4	0.526	0.008	0.29	0.591	0.006
Gender	<b>9.6</b>	<b>0.003</b>	<b>0.155</b>	<b>16.0</b>	<b>&lt;0.001</b>	<b>0.238</b>	<b>35.85</b>	<b>&lt;0.001</b>	<b>0.408</b>
Age 11 IQ	<b>34.3</b>	<b>&lt;0.001</b>	<b>0.397</b>	<b>9.5</b>	<b>0.003</b>	<b>0.158</b>	2.97	0.091	0.054
<b>ICV accounting for skull thickening</b>									
	g			Speed			Memory		
	F	P	$\eta^2$	F	p	$\eta^2$	F	p	$\eta^2$
% Brain in Estimated ICV	2.6	0.11	0.048	<b>4.7</b>	<b>0.034</b>	<b>0.085</b>	2.4	0.127	0.044
Age in days	0.3	0.58	0.006	0.4	0.508	0.009	0.15	0.697	0.003
Gender	3.7	0.06	0.066	2.6	0.117	0.048	0.6	0.441	0.011
Age 11 IQ	<b>32.7</b>	<b>&lt;0.001</b>	<b>0.386</b>	<b>14.9</b>	<b>&lt;0.001</b>	<b>0.226</b>	<b>35.25</b>	<b>&lt;0.001</b>	<b>0.404</b>

Model controlled for age in days, age 11 IQ and gender. Dependent variables were g, speed and memory. Gender was used as fixed factor while percentage of brain tissue in current ICV, percentage of brain tissue in the estimated original ICV, ages in days and age 11 IQ were used as covariates.  $n = 57$ , the degree of freedom for each of the covariates and the fixed factor was 1.  $\eta^2 =$  partial Eta Squared. % Brain in current ICV = Percentage of brain tissue in current ICV and % Brain in estimated ICV = Percentage of brain tissue in estimated original ICV

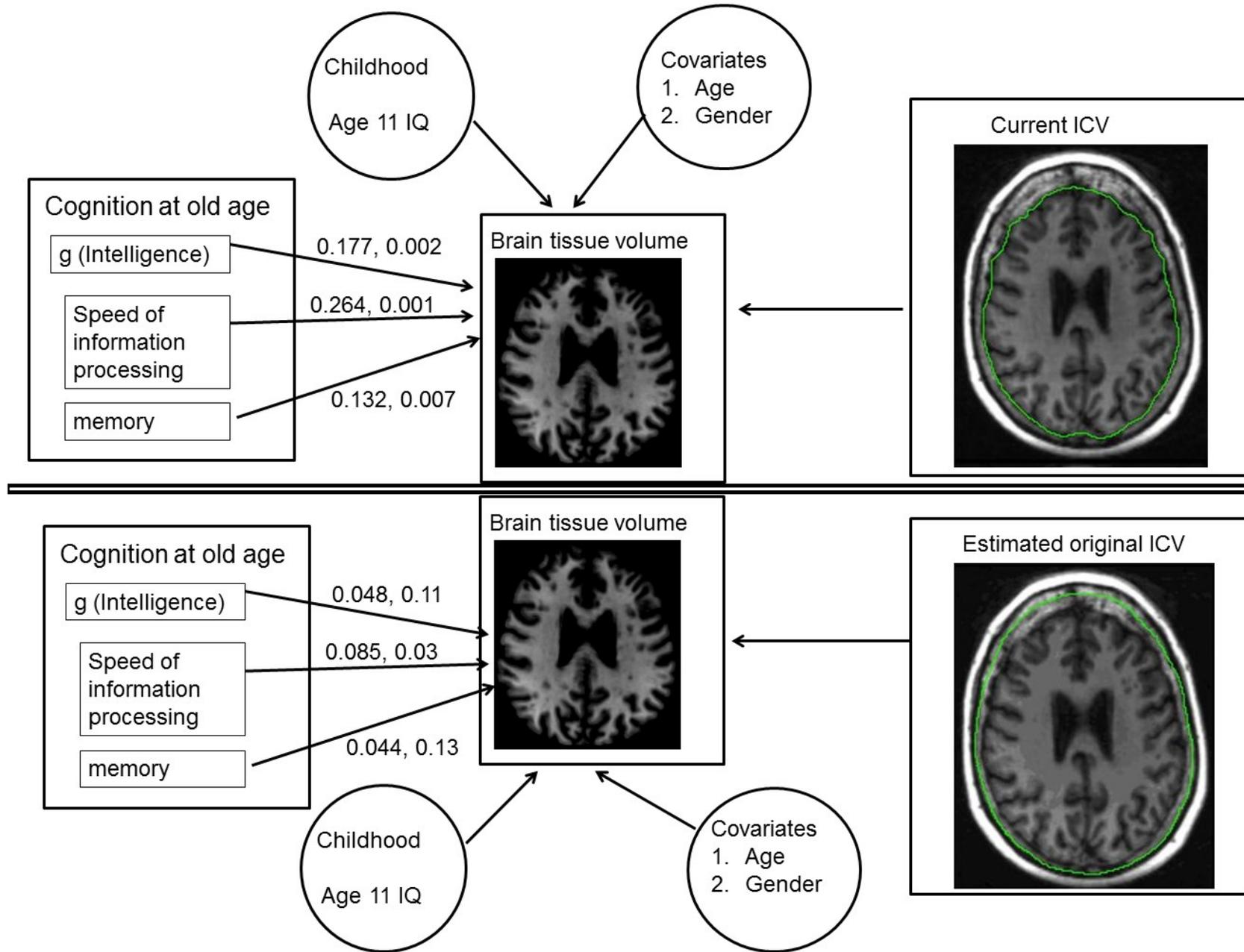


Figure 1