ONLINE SUPPLEMENTARY DATA

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

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Appendix 1: Brain Magnetic Resonance Imaging Pre-processing

The DICOM files were converted into Analyze 7.5 format [1], and the T2*- and FLAIR-weighted volumes were co-registered to the T_2-weighted volumes using FLIRT [2], an automatic linear registration tool from the FMRIB software library (FSL; http://www.fmrib.ox.ac.uk/fsl).

The total brain volume, namely the brain tissue volume excluding the cerebrospinal fluid, was segmented using a multispectral image processing tool, MCMxxxVI [3] (available for download at http://sourceforge.net/projects/bric1936). This semi-automatic segmentation tool fuses pairs of MRI sequences (e.g. T_2*-weighted and FLAIR) in the red-green colour space to enhance signal differences between tissues, hence improving computational differentiation of signal differences and increasing accuracy of extraction of specific features-of-interest.

Brain tissue volume segmentation was performed by first extracting the Intracranial Volume (ICV) i.e. the ‘current ICV’, followed by the segmentation of the Cerebrospinal fluid (CSF). Then CSF mask was subtracted from ICV to get the brain tissue volume. ICV was segmented in Analyze 10.0 [1, 4] as summarised in the main text and described in full elsewhere [5]. T1-weighted and T2-weighted were fused and used to segment CSF using MCMxxxVI.

Appendix 2: Segmentation of Intracranial Volume

The Current ICV was segmented on the T_2*-weighted volumes using the Object Extraction Tool available in Analyze 10.0 [1, 4], followed by manual editing to correct any segmentation errors. The estimated original ICV was measured by manually editing the current ICV to include the inner skull table thickening within the ICV. Most of the inner table skull thickening occurs in the vault particularly in the frontal regions. Repeatability measures show that [5] the intra-class correlation coefficient for current ICV was 0.98 and the inter-class correlation coefficient was 0.96; and for estimated original ICV the intra-class correlation coefficient was 0.98 and the inter-class correlation coefficient was 0.98.

Appendix 3: Measurement of Cognitive Variables

The cognitive ability assessments have been described elsewhere [6, 7]. Briefly, subjects took the Moray House Test No. 12 [6], a paper-and-pencil IQ-type test with a preponderance of verbal reasoning items, at an average age of 11 years. This allowed IQ-type scores from childhood and old age to be derived. Concurrently with MRI scanning at mean age 73 years, subjects completed six subtests of the Wechsler Adult Intelligence Scale III^{UK} (Symbol search, Digit Symbol, Matrix Reasoning, Letter-Number Sequencing, Digit Span Backward and Block Design) [6]. Principal Components Analysis was used to extract a latent general cognitive ability factor (g) [8] that accounted for 51.0% of the total test variance [9, 10]. Furthermore, subjects completed three cognitive processing speed tests (simple reaction time, 4-choice reaction time, and inspection time) [6, 7], from which a general processing speed factor (speed) [8] was extracted that explained 58.6% of the total speed variance (higher scores indicate worse performance) [9, 10]. Six subtests of the Wechsler Memory Scale III^{UK} (Logical Memory immediate and delayed recall, Spatial Span forward and backward, Verbal

Paired Associates I (1st recall) and II) [6] formed a memory factor [11, 12] that accounted for 41.0% of the total memory test score variance [9, 10].

Appendix 4: Descriptive statistics for cognitive ability and brain atrophy measures.

Measures		Mean±SD	P-value, t-test
Total brain volume (mm^3)		1128984±153488	
ICV(mm^3)	current ICV	1443472±210721	<0.0001
	Estimated original ICV	1544435±215448	
Percentage of brain tissue in	current ICV	78.42±04.02	<0.0001
	Estimated original ICV	73.24±03.97	
Childhood cognition	Age 11 IQ	102.00±16.00	
Late Life Cognition	Logical Memory Total 1st Recall WMS-III	44.85 ± 10.6	
	Logical Memory 2nd Recall WMS-III	29.2 ± 8.27	
	Verbal Paired Associates 1st Recall WMS-III	19.68 ± 8.21	
	Verbal Paired Associates 2nd Recall WMS-III	6.05 ± 2.27	
	Spatial Span Forward WAIS-IIIUK	7.52 ± 1.64	
	Spatial Span Backward WAIS-IIIUK	6.77 ± 1.78	
	Simple Reaction Time Mean Score	0.28 ± 0.06	
	Choice reaction Time Mean Score	0.65 ± 0.1	
	Inspection Time Total Correct Responses	111.41 ± 11.42	
	Digit Symbol WAIS-III^{UK}	56.07 ± 11.59	
	Digit Span Backward WAIS-III^{UK}	7.23 ± 2.61	
	Block Design WAIS-III^{UK}	33.6 ± 10.55	
	Letter-Number Sequence WAIS-III^{UK}	10.85 ± 2.96	
	Matrix Reasoning WAIS-III^{UK}	14.15 ± 4.97	
	Symbol Search WAIS-III^{UK}	24.57 ± 6.82	

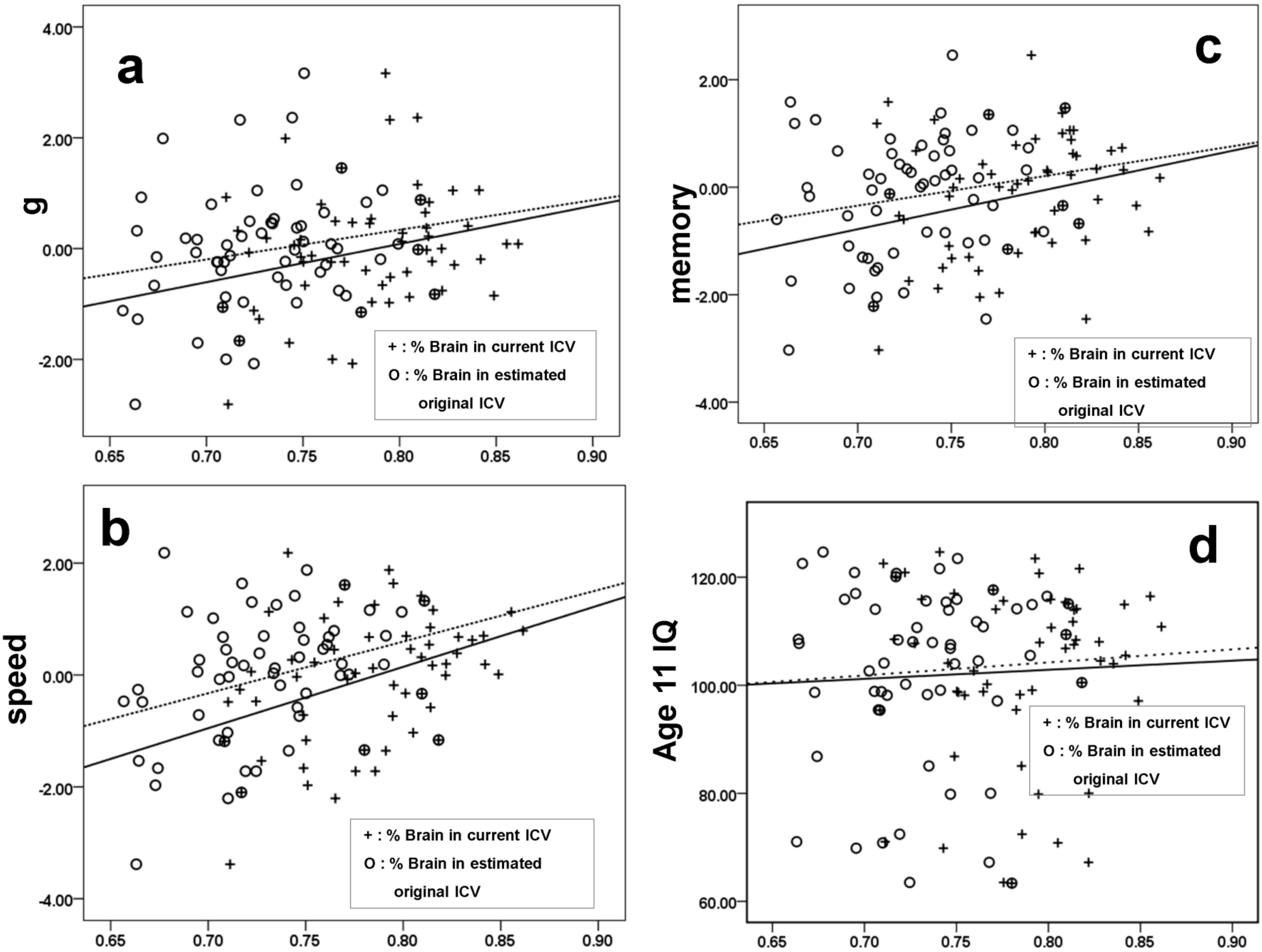
P-values give the result of t-test comparisons of measures with and without accounting for thickening in ICV computation.

Appendix 5: Association between age 11 IQ and brain atrophy measures using GLM with and without accounting for skull thickening in the computation of ICV.

	Percentage of Brain Tissue in current ICV			Percentage of Brain Tissue in Estimated original ICV		
	F	p	η^2	F	p	η^2
age 11 IQ	0.7	0.40	0.014	0.26	0.614	0.005
Age in days	6.1	0.02	0.103	14.2	<0.001	0.211
Gender	15.7	<0.001	0.228	3.3	0.077	0.058

Model controlled for age in days and gender. Dependent variables were percentage of brain tissue in current ICV and percentage of brain tissue in the estimated original ICV while age 11 IQ was the independent variable. Gender was used as a fixed factor while age in days was a covariate. n = 57, the degree of freedom for each of the covariates and the fixed factor was 1. η^2 = partial Eta Squared.

After correcting for age in days and gender (Appendix 5, Appendix 6), there was no significant association between age 11 IQ and any of the brain atrophy measures, before (percentage of brain tissue in current ICV: F=0.73, P=0.40, η^2 = 0.014), or after (percentage of brain tissue in estimated original ICV: F=0.26, P=0.61, η^2 = 0.005) accounting for skull thickening in the computation of ICV.



Appendix 6: Scatter plots with regression lines of (a) g against % of brain tissue in: current ICV (bold line, $\eta^2 = 0.048$, p= 0.11) and estimated original ICV (dotted line, $\eta^2 = 0.177$, p= 0.002) (b) speed against % brain tissue in: current ICV (bold line, $\eta^2 = 0.264$, p= 0.001) and estimated original ICV (dotted line, $\eta^2 = 0.085$, p= 0.03). (c) memory against % brain tissue in: current ICV (bold line, $\eta^2 = 0.132$, p= 0.007) and estimated original ICV (dotted line, $\eta^2 = 0.044$, p= 0.13). (d) Age 11 IQ against % brain tissue in: current ICV (bold line, $\eta^2 = 0.014$, p= 0.40) and estimated original ICV (dotted line, $\eta^2 = 0.005$, p= 0.614). The association between *g* and the % brain tissue in current ICV was significantly larger than with % brain tissue in estimated original ICV. The association between speed and the % brain tissue in current ICV was also significantly larger than with the % brain in estimated original ICV. The association between memory and the % brain tissue in current ICV was on the borderline of being significantly larger than the association between memory and the % brain in

estimated original ICV. There was no significant association between age 11 IQ and % brain tissue in: current ICV or original estimated ICV.

Appendix 7: Statistical Comparison of Associations between atrophy and cognitive ability

The association between *g* and the percentage of brain tissue in current ICV ($\eta^2 = 0.177$) was significantly larger than the association between g and the percentage of brain tissue in estimated original ICV ($\eta^2 = 0.048$; Steiger's paired t=2.67, n=57, P=0.01; [13]. The association between speed and the percentage of brain tissue in current ICV ($\eta^2 = 0.264$) was also significantly larger than the association between speed and the percentage of brain in estimated original ICV ($\eta^2 = 0.085$; Steiger's paired t=3.16, n=57, P=0.003). The association between memory and the percentage of brain tissue in current ICV ($\eta^2 = 0.132$) was on the borderline of being significantly larger than the association between memory and the percentage of brain in estimated original ICV ($\eta^2 = 0.044$; Steiger's paired t=1.97, n=57, P=0.054).

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