White matter lesion intensity and cognitive ability: relationships in youth and old age

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Introduction

In this work we investigate relationships between white matter lesion (WML) intensity and measures of cognitive ability obtained in youth and old age in the Lothian Birth Cohort 1936 (LBC1936). This unique cohort of 1091 healthy people, who undertook cognitive testing at ages 11, 70, and 72 years [1], are currently undergoing brain MRI at average age 72 years (range 71 to 73 years). Using structural MRI data, WML volumes were measured and their degree of severity classified according to their appearance on MRI, specifically intense (iWML) and less intense (liWML). We examine how the distribution, extent and severity of WML load are associated with cognitive ability in youth and old age.

Methods

Subjects: The study population was the first 140 participants of the LBC1936 to undergo brain imaging. None showed signs of dementia or mild cognitive impairment (MMSE > 23). These volunteers underwent structural MRI, specifically T_2-, (T_2W), T_2*- (T_2*W) and FLAIR-weighted sequences, and a T_1-weighted volume scan (3D T_1W) on a GE Signa LX 1.5T clinical scanner.

Cognitive tests: Subjects' cognitive ability was tested at age 11 using a version of the Moray House Test (MHT) of verbal reasoning. Between 2004 and 2007 they took a battery of mental tests, including the same version of the MHT they took approximately 60 years earlier, six subtests of the Wechsler Adult Intelligence Scale III^{UK} (WAIS-III^{UK}), Wechsler Memory Scale-III^{UK} (WMS-III^{UK}) and measures of information processing speed (reaction and inspection time).

MRI acquisition: Apart from the FLAIR sequence which had a slice thickness of 4 mm, all three structural scans shared the same contiguous slice locations, field-of-view (256 × 256 mm), reconstructed acquisition matrix (256 × 256) and slice thickness (2 mm), giving co-registered whole brain volumes with resolution of 1 × 1 × 2 mm. The 3D T_1W scan was aligned with the long line of the hippocampus and had 1.3 mm thick slices.

Image processing: Using FSL (http://www.fmrib.ox.ac.uk) tools, the structural sequences were pre-processed to extract the brain and remove bulk patient motion. After interpolation of the FLAIR volume to 1 × 1 × 2 mm resolution, regions of normal appearing white matter (NAWM) and WMLs were identified using the MCMxxxVI (1936) brain segmentation tool [2]. Briefly, the 3D T_1W and T_2W volumes were registered, modulated in green and red channels respectively, fused and colour-dithered by minimum variance quantisation to extract NAWM. The same process was performed with T_2*W and FLAIR volumes to segment WMLs. The resulting NAWM and WML masks allowed the identification of iWMLs, visible in both T_2W and FLAIR, liWML, visible in FLAIR only, and NAWM (see Fig. 1). The iWML and liWML masks from 89 individuals with significant WML load (excluding those with stroke) were normalized into standard space using FNIRT. Standard space group maps of iWMLs and liWMLs were created by summing the normalized binary masks (see Fig. 2). Total brain volume was determined from the T_2*W volumes.

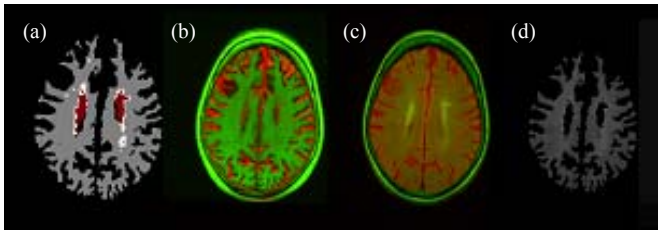

Figure 1. (a) Masks of NAWM, iWMLs (red) and liWMLs (white); (b, c) fused T_1W and T_2W, and T_2*W and FLAIR volumes in RG colour space; (d) NAWM and liWMLs in FLAIR.

Statistical analysis: Correlations between WML volumes and measures of cognitive ability were assessed using Pearson's *r*, controlling for gender and age in days at testing. Since the WML volumes were strongly skewed, a log-transform was used. General factors of cognitive ability (*g*), speed of information processing (g_{speed}), and memory (g_{memory}) were extracted from the WAIS-III^{UK}, WMS-III^{UK}, and reaction and inspection time tests using principal component analysis.

Results

The group maps show that the distribution of iWMLs is predominant in frontal regions while liWMLs are mainly located posteriorly. The maximum frequency of iWMLs is located in the periventricular regions adjacent to the frontal horns of the lateral ventricles, while the maximum frequency of liWMLs spreads between the midbody of the corpus callosum and the superior and posterior corona radiate (Fig. 2). Both are highly correlated (r = 0.70), indicating subjects with high iWML load also have high liWML load. Table 1 shows that WMLs are strongly related to various cognitive abilities, but these relationships are stronger for iWMLs than liWMLs in young and old age. The last two columns indicate that iWMLs relate to cognition independent of liWMLs, but the reverse is not true.

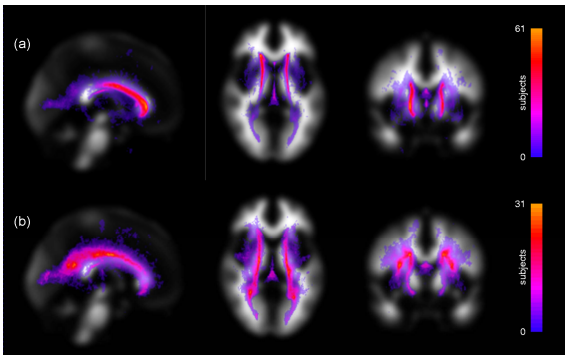

Figure 2. Group maps showing patterns of (a) intense and (b) less intense WMLs.

Discussion

These preliminary results indicate that this methodology is useful for characterizing WMLs in the ageing brain and determining their relationship with cognitive ability. Our findings support the central role of white matter for higher cognitive abilities and the "frontal ageing" hypothesis, which predicts that age-related brain change would selectively impact frontal regions [3]. They also show that there are relationships between early life cognitive ability and disease burden in old age.

	% WML per BT volume	% iWML per BT	% liWML per BT	% iWML per BT, liWML controlled	% liWML per BT, iWML controlled
Age 11 IQ (MHT)	-0.26**	-0.26**	-0.21*	-0.17†	-.04
Age 70 IQ (MHT)	-0.37***	-0.38***	-0.30***	-.25**	-.05
g	-0.32***	-0.31***	-0.28**	-.16†	-.10
g_{speed}	0.20*	0.26**	0.10	.26**	-.11
g_{memory}	-0.23**	-0.22*	-0.21*	-.10	-.08

Table 1. Pearson correlations for intense and less intense WMLs. (†: $p < 0.1$, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$; BT: total brain tissue volume)

References

[1.] Deary IJ, et al. BMC Geriatr 2007;7:28. [2.] Hernández MV, et al. ISMRM 2009;17:1048. [3.] Pfefferbaum A, et al. NeuroImage 2005;26:891-899.