Does white matter lesion load affect the integrity of normal-appearing white matter in the ageing brain?

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Introduction

The role of white matter as a contributor to cognitive ageing is not yet fully understood. White matter damage is commonly seen as hyperintense areas on T2-weighted (T2W) and fluid attenuated (FLAIR) MRI of older people and correlations between white matter lesion (WML) load and cognitive impairment and dementia in older subjects have been reported [1]. However, in the Lothian Birth Cohort 1936 (LBC1936) [2] we have recently found that WML volume is as much associated with IQ measured in youth (age 11) as it is with that measured in older age (early 70s) [3], suggesting that genetic and/or other early life factors, either biological, environmental or lifestyle, might affect white matter and influence both later WML load and differences in cognitive ability. In this work we focus on normal-appearing white matter (NAWM) and investigate whether there is a detectable variation in its integrity related to the presence of WML.

Methods

The current analysis included 449 participants from the LBC1936 (age 72-73 years at brain imaging); no participant had a history of dementia (MMSE > 23). MRI at 1.5 T comprised: T2W, T2*W and FLAIR axial structural scans, diffusion MRI (dMRI) with diffusion-weighted volumes acquired in 64 non-collinear directions (b=1000 s/mm^2) and 7 T2W volumes, T1-mapping using T1W FSPGR sequences with 2º and 12º flip angles, and magnetization transfer MRI (MT-MRI) using standard spin echo sequences with and without a magnetization transfer pulse applied 1kHz from the water resonance. Voxel dimensions were 2×2×2 mm for the dMRI protocol and 1×1×2 mm for the T1-mapping and MT-MRI protocols. All imaging data shared the same field-of-view and slice locations.

The dMRI data were pre-processed and diffusion tensor parameters estimated with the TractoR package [4] using FSL tools [5]. WML and NAWM were extracted from the structural MRI data using a novel multispectral method developed in-house [6]. NAWM masks were transferred to FA, MD, T1 and MTR parametric maps using linear registration [5].

A quantitative assessment of WML load was performed by an expert neuroradiologist who scored FLAIR and T2W volumes using the Fazekas scale which codes separately for periventricular and deep WML [7]. We divided the cohort into subjects with significant WML load (Fazekas scores of 2 or 3 on either lesion subscale) and those without (Fazekas scores of 0 or 1 on both lesion subscales) [8].

We used a one-way ANOVA to compare the mean white matter integrity parameters measured in NAWM of the group with high or low WML incidence coded as above. Effect sizes were estimated using Cohen's *d*.

Results

Figure 1 shows an example of NAWM and WML overlaid on T2W. All masks were checked for mis-registration artefacts before biomarkers were measured. In total 270 MRI scans were rated as having low incidence of WML and 179 rated as high based on the Fazekas scores.

Table 1 and Figure 2 summarize the results from the one-way ANOVA between the two groups:

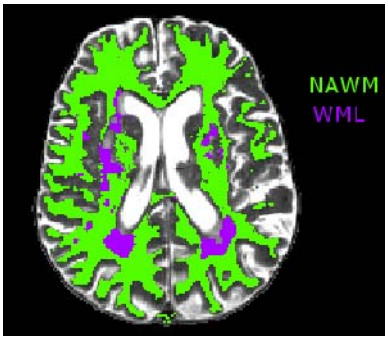

Figure 1. Normal appearing white matter and white matter lesion masks from an LBC1936 participant.

NAWM	Mean ± SD WML = Low	Mean ± SD WML = High	F	*p*	*d*
FA	0.341 ± 0.023	0.330 ± 0.026	21.833	3.943e-06 *	0.45
MD ($10^{-3}mm^2/s$)	0.686 ± 0.036	0.701 ± 0.036	17.275	3.877e-05 *	0.40
MTR	55.18 ± 2.74	54.96 ± 2.91	0.661	0.417	0.08
T1 (s)	1.00 ± 0.10	1.02 ± 0.10	6.017	0.015 †	0.24

Table 1 Summary of one-way ANOVA results and effect sizes when comparing the means of the low and high WML incidence groups. * $p < 0.001$, † $p < 0.05$; Effect size: medium, small.

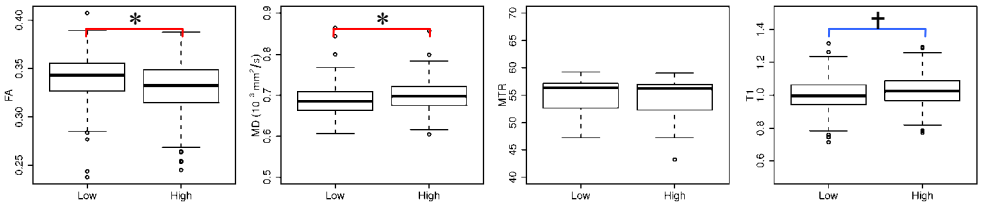

Figure 2. Boxplots of mean FA, MD, MTR and T1 for normal appearing white matter in the groups with low and high white matter lesion incidence

Discussion

We show subtle differences in the integrity of normal-appearing white matter between older people with low and high incidences of WML, as indicated by water diffusion parameters and quantitative T1 relaxation time measurements. FA and MTR have been linked to axonal integrity while MD and T1 are sensitive to microscopic damage and reflect increases in tissue water content, but lack specificity for underlying pathology. This effect, previously observed in smaller cohorts [9;10], either suggests that the pathology responsible for WML also produces subtle changes in white matter that are not visible on conventional T2W and FLAIR, or that reduced white matter integrity may predispose to WML. Studies of cognitive ageing should consider this effect as a possible confounder when examining the role of white matter, to discern whether the associations observed between WML and cognition are truly a consequence of WML, or derived from the preceding changes in NAWM in subjects who later develop WML. Cross-sectional studies of these relationships in older age are not sufficient and longitudinal studies are required.

[1] Debette et al 2010, BMJ 341:c3666; [2] Deary et al 2007, BMC Geriatr 7:28; [3] Valdés Hernández et al 2010 LLCS 1:116; [4] http://code.google.com/p/tractor/ [5] www.fmrib.ox.ac.uk/fsl; [6] Valdés Hernández et al 2010 Eur Radiol 20:1684-91; [7] Fazekas et at Am J Roentgenol 149:351-6; [8] MacLullich et al 2009 Stroke 40:3869-3871; [9] Bastin et al 2010 NeuroImage 51:1-10; [10] Vernooij et al 2008 NeuroImage 43 :470-477