# A multiparametric study of white matter integrity and cognition in old age

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## Introduction

The aim of this work is to understand how brain white matter integrity contributes to age-related cognitive decline in humans. The Lothian Birth Cohort 1936 (LBC1936) is a unique group of 1091 healthy people who undertook IQ testing at age 11 years and are returning for testing again in old age [1]. Using contemporaneous brain MRI data and cognitive scores from about age 72 years we examined how white matter integrity relates to cognitive changes in these subjects. We segmented white matter tracts and used fractional anisotropy (FA), mean diffusivity (MD), magnetization transfer ratios (MTR) and longitudinal (T1) relaxation times as markers of white matter integrity.

## Methods

The first 318 participants from the LBC1936 (mean age 72 years; 55% men) were included in the current analysis; no patient had a history of dementia (MMSE > 23). Imaging comprised the following protocols: diffusion MRI (dMRI) with diffusion-weighted volumes in 64 non-collinear directions (b=1000 s/mm$^2$) and 7 T2-weighted volumes, T1-mapping using T1-weighted FSPGR sequences with 2° and 12° flip angles, and magnetization transfer MRI (MT-MRI) using standard spin echo (SE) 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 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 using FSL tools [2]. Tracts-of-interest (TOI) were segmented using probabilistic neighbourhood tractography, an automated tract segmentation method [3] based on BEDPOSTx/ProbTrackx [4] with a two-fibre model. The following TOI thought to be affected by age were segmented: callosal fibres (genu and splenium of the corpus callosum), and fronto-temporal association fibres bilaterally: cingulum bundles, uncinate and arcuate fasciculi. T1 and MTR parametric maps were calculated as described previously [5, 6] and segmented tracts were transferred to these maps using linear registration [2]. Tract-averaged mean FA, MD, T1 and MTR were measured and correlated (Pearson's r) with five cognitive variables: IQ at ages 11 and 70 years (Moray House Test [1]), and factors representing general cognitive ability (g, determined from 6 subtests of the WAIS-III$^{UK}$), processing speed ($g_{speed}$, determined from simple and 4 –choice reaction time and inspection time tests) and memory ($g_{memory,}$ determined from 5 subtests of the WMS-III$^{UK}$) at age 72.

## Results

Figure 1 shows examples of tracts overlaid on T1 and MTR maps after registration. All tracts were visually checked and only those following the expected path were used in the analysis. Outliers greater than ±3 SD from the population mean were also excluded from all variables. Pearson's r values for tracts with significant correlations are shown in Tables 1 and 2. Significances are corrected for multiple comparisons.

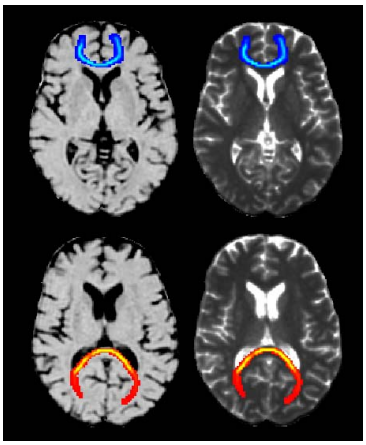

**Figure 1**: Genu (blue) and splenium (red) of the corpus callosum segmented from diffusion MRI data and registered to MTR (left) and T1 (right) maps.

| | Cingulum *Right* | | Uncinate *Left* | | Uncinate *Right* | |
|---|---|---|---|---|---|---|
| | **FA** | **MD** | **FA** | **MD** | **FA** | **MD** |
| ***Age 11 IQ*** | 0.09 | -0.03 | 0.17 | -0.02 | 0.12 | -0.05 |
| ***Age 70 IQ*** | 0.02 | 0.04 | 0.18 | -0.01 | 0.13 | -0.05 |
| ***g*** | 0.12 | -0.04 | 0.28 | -0.14 | 0.19 | -0.12 |
| $g_{speed}$ | -0.11 | -0.02 | -0.15 | 0.08 | -0.10 | 0.10 |
| $g_{memory}$ | 0.07 | -0.03 | 0.22 | -0.04 | 0.13 | -0.07 |

**Table 1** Correlations of FA (first number in cell) and MD (second number in cell) with cognitive parameters; p<0.01; p<0.05

| | Corpus callosum *Genu* | | Corpus callosum *Splenium* | | Arcuate *Left* | | Arcuate *Right* | | Cingulum *Left* | | Cingulum *Right* | | Uncinate *Left* | | Uncinate *Right* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **MTR** | **T1** | **MTR** | **T1** | **MTR** | **T1** | **MTR** | **T1** | **MTR** | **T1** | **MTR** | **T1** | **MTR** | **T1** | **MTR** | **T1** |
| ***Age 11 IQ*** | 0.19 | 0.01 | 0.09 | -0.04 | 0.13 | 0.02 | 0.12 | 0.03 | 0.05 | 0.11 | 0.11 | -0.04 | 0.18 | -0.03 | 0.22 | -0.01 |
| ***Age 70 IQ*** | 0.09 | 0.00 | 0.08 | -0.06 | 0.13 | -0.04 | 0.14 | 0.01 | -0.03 | 0.07 | 0.08 | -0.04 | 0.10 | -0.07 | 0.14 | -0.03 |
| ***g*** | 0.10 | -0.08 | 0.06 | -0.10 | 0.10 | -0.17 | 0.19 | -0.15 | 0.05 | -0.07 | 0.13 | -0.12 | 0.07 | -0.15 | 0.11 | -0.08 |
| $g_{speed}$ | -0.10 | 0.14 | -0.06 | 0.13 | -0.05 | 0.17 | -0.07 | 0.15 | 0.02 | 0.19 | -0.06 | 0.12 | -0.06 | 0.13 | -0.04 | 0.10 |
| $g_{memory}$ | -0.01 | -0.07 | 0.02 | -0.11 | 0.06 | -0.13 | 0.15 | -0.08 | -0.04 | 0.00 | -0.04 | -0.06 | -0.06 | -0.06 | 0.02 | -0.09 |

**Table 2** Correlations of MTR (first number in cell) and T1 (second number in cell) with cognitive parameters; p<0.01; p<0.05

## Discussion

Previous work showed that water diffusion parameters measured in uncinate and arcuate fasciculi correlated with IQ and processing speed respectively [7]. In a larger sample of the same cohort we have replicated the uncinate fasciculus results bilaterally, now with additional correlations between FA and g, $g_{speed}$ and $g_{memory}$ and correlation of the right cingulum FA with g. The relation between arcuate water diffusion parameters and cognition was not replicated. However, MTR and T1 measured in this tract show correlations with g, $g_{speed}$ and $g_{memory,}$ suggesting that processes affecting the integrity of this tract are related to cognition in old age as predicted by the parietal-frontal theory of intelligence [8]. MTR also correlated with childhood IQ in genu and both uncinate fasciculi, and with age 70 IQ in the right uncinate. T1 relaxation time is predominantly related to $g_{speed}$, showing significant correlations in genu, both arcuate fasciculi and left cingulum. In this study both MTR and T1 parameters proved to be more sensitive to changes in cognition than water diffusion parameters. Both FA and MTR are thought to be markers of white matter integrity and are linked to the degree of myelination. Both parameters have previously shown a strong relationship in areas of white matter lesions but not in normal appearing white matter [6]. Like MD, T1 is sensitive to microscopic damage by reflecting increase in tissue water content, but lacking in specificity for underlying pathology. T1 and MD have also been correlated in brain pathology but not in normal brain tissue [6]. The separate study of areas with and without visible white matter pathology, such as white matter lesions, in these tracts could help understanding the relationship between the two sets of parameters. In conclusion, by registering white matter tract segmentations to MTR and T1 maps we have revealed new relationships between the integrity of these white matter tracts and cognition in old age not shown by water diffusion parameters. This work suggests that a multi-parameter approach could unravel the effects of ageing on the brain and cognition better than the use of dMRI on its own.

[1] Deary IJ, et al 2007, BMC Geriatr 7:28; [2] FMRIB, Oxford, UK, www.fmrib.ox.ac.uk; [3] Clayden JD et al 2009, NeuroImage 45:377-385; [4] Behrens TE et al 2007, NeuroImage 34:144–155; [5] Armitage PA et at 2007, Mag Res Imaging 25:303-310; [6] Bastin ME et al 2009, Neurobiol Aging 30:125-136; [7] Muñoz Maniega et al ISMRM 2009, p 3236; [8] Jung RE et al. 2007, Behav Brain Sci 30:135-154