Introduction

The advent of quantitative techniques based on the analyses of MRI structural data, such as Voxel-Based Morphometry (VBM) and volumetric analyses, has allowed a sensitive detection of regional patterns of grey matter (GM) and white matter (WM) volume loss with ageing (Sowell et al., 2003; Wallhovd et al., 2005). More recently, diffusion tensor imaging (DTI) has been used to quantify alterations in WM microstructure in the ageing brain (Salat et al., 2005). However, there is mixed evidence over the cross-section of data changes detected using conventional volume or VBM measurements and DTI. The aim of this study was to determine the timing and spatial distribution of age-related changes using a range of volumetric and DTI-based measures.

Materials and Methods

DTI and T1-weighted images were acquired in 66 healthy subjects (28 males, 38 females; age range 23–81.6 years, all right-handed). None of the subjects had structural or brain abnormalities or WM lesions. We also performed subgroup analyses, dividing subjects into young adults (YA) (n=37, 16 males, 21 females, median age=29.1, range=23.0-40.2 years), middle-aged adults (MA) (n=19, 9 males, 10 females, median age=48, range=41-59.6 years) and older adults (OA) (n=10, 6 males, 4 females, median age=67.9, range=60-81.6 years).

We employed an ‘optimised’ VBM-style protocol using FSL (FMRIB Software Library v4.1, www.fmrib.ox.ac.uk/fsl) tools for brain extraction and tissue segmentation. FMRIB’s Nonlinear Registration Tool (FNIRT) was used to spatially register FA inYA was due to changes in parallel and/or perpendicular normalised GM and WM images were smoothed with isotropic Gaussian kernels with a sigma of 3.5 mm (~8 mm FWHM) and 4 mm (~10 mm FWHM), respectively. Test for linear and nonlinear (quadratic) local correlations between changes in brain volumes and age, separate regression analyses were performed using age and age² as regressors. To compare GM and WM volumes between the different age subgroups, unpaired t-tests were used. Statistical inference was performed using the randomise programme within FSL, which performs permutation testing (5000 permutations). Thresholding was carried out using TFCE (Threshold-Free Cluster Enhancement), a method for finding significant clusters in MRI data without having to define them in a binary way. Clusters were assessed for significance at p<0.05, fully corrected for multiple comparisons across space.

Voxelwise fractional anisotropy (FA), diffusivity parallel ($λ_1$) and perpendicular ($λ_2$) to the principal diffusion direction, and mean diffusivity (MD) were calculated using the FMRIB Diffusion Toolbox (FDT), also part of FSL. We used Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) to test for local correlations between age and FA and MD and to test between subgroups FA and MD differences across the whole brain. WM FA images were nonlinearly (using FNIRT) registered to a high resolution standard-space average of 58 well aligned good quality FA images from healthy subjects and then averaged. The average of the data was thinned to create a WM ‘skeleton’, representing the tracts common to all subjects. MD values were assessed for significance at p=0.05, fully corrected for multiple comparisons across space.

Correlations of DTI metrics with age across the whole group

Linear decreases in FA with increasing age were found in most WM regions (Fig. 1A). Region-of-interest analysis of these clusters showed that correlation between age and FA was $r=-0.61$, p<0.001 (Fig. 1B). To test whether the linear correlations between age and FA and MD were significantly higher in OA compared to YA bilaterally in the frontal lobe, including the caudate nucleus and, to a lesser extent, in the temporal lobe. A decrease in GM volume in the OA compared to MA was present bilaterally in the hippocampus, lingual gyrus, occipital fusiform, Wcs, pallidum and occipital pole. OA showed a widespread decrease in GM volume compared to YA in several cortical regions. Change in WM volume became apparent only in late adulthood. Specifically, we found no significant differences in WM volume between YA and MA whereas OA showed a decrease in WM volume compared to MA bilaterally in the SCR, posterior limb of the internal capsule (PLIC) and CP. The same WM regions showed a significant decrease in OA compared to YA. Widespread FA decreases occurred from middle age. Specifically, MA and OA had lower FA than YA in most of the WM regions. No significant FA differences were found between MA and OA. Interestingly, subgroup analysis suggested that MD increase becomes apparent later than decreases (data not shown). Specifically, MD was significantly higher in OA compared to YA and MA in most of the WM regions whereas no significant differences were found between YA and MA.

Figure 1 (left): (A) Blue voxels show WM regions where FA shows a significant negative linear relationship with age. Voxel sizes are overlaid on the WM skeleton (in green) and the group mean FA image (grey scale). (B, C, D) Plots to illustrate the relationship between age and mean FA (B), parallel diffusivity (C) and parallel diffusivity (D) across all voxels showing a significant linear relationship between age and FA. See text for details. Images are shown in radiological convention.

Figure 2 (right): Comparisons between YA and MA (A), MA and OA (B) and YA and OA (C) subgroups. See text for details. Images are shown in radiological convention.

Conclusions

Our results suggest that widespread reductions in GM volume occur from middle age onwards whereas earlier reductions in GM volume are present in the frontal cortex. Putative mechanisms are ongoing myelination and/or elimination of neurites/synapses (in early adulthood) and shrinkage of large neurons and/or rarefaction of the GM vasculature (in middle and late adulthood). Widespread age-related deterioration in WM microstructure is detected from young adulthood onwards. This WM decline is evident and more sensitively using DTI-based measures of microstructure than using markers of WM volume derived from conventional T1-weighted imaging. Both heavily (e.g., corticospinal tract) and thinly (e.g., frontal association fibres) myelinated fibres seem to be affected by the age-related WM volume decrease. Damage in WM microstructure may be due to degeneration in the myelin sheaths or reduced fibre organisation or packing density (i.e., decrease in the number of axons). The observed spatial patterns and dynamics of normal age-related changes may have important implications for future studies on chronic neurological conditions that show an impact of age on disease onset, course and progression.

References