Structural brain changes throughout adulthood

A. Giorgio[1,2], L. Santelli[3], V. Tomassini[1], R. Bosnell[1], S. M. Smith[1], N. De Stefano[2], and H. Johansen-Berg[1]
[1]FMRIB Centre, University of Oxford, Oxford, United Kingdom, [2]Neurology and Neurometabolic Unit, University of Siena, Siena, Italy, [3]Department of Neuroscience, University of Padua Medical School, Padua, Italy

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; Walhovd 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 correspondence between 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, 33 females; age range 23-81.6 years, all right-handed). None of the subjects had structural 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 the native images to a standard-space template. All modulated 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. To test for linear and nonlinear (quadratic) local correlations between changes in brain volumes and age, separate regression analyses were performed using age and age^2 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 ($(\lambda_2 + \lambda_3)/2$) 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 mapped onto the skeleton by using the projection vectors from each subject's FA-to-skeleton transformation. The FA and MD data were analysed using the same models and statistical inference as for the GM and WM volume analyses described above. In addition, parallel and perpendicular diffusivity data were also processed using the TBSS protocol.

Results

Correlations of grey and white matter volume with age across the whole group

Most cortical regions, with the exception of occipital regions, showed an extensive linear GM volume decrease with increasing age. Deep GM volume decrease was found in the caudate nucleus, pallidum, amygdala and hippocampus bilaterally. The correlation between volume averaged across all the GM clusters and age was $r=-0.84$, $p<0.001$. Significant linear decreases in WM volume with increasing age were found in the right forceps minor, internal capsule (IC) and external capsule (EC) bilaterally, right uncinate fasciculus (UF), right inferior longitudinal fasciculus (ILF) and cerebral peduncle (CP) bilaterally. The correlation between volume averaged across all these WM clusters and age was $r=-0.79$, $p<0.001$. Significant nonlinear (quadratic) relationships between WM volume and age were found in the superior corona radiata (SCR) bilaterally.

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 mean FA and age was $r=-0.61$, $p<0.001$ (Fig. 1B). To test whether the linear decrease in FA was due to changes in parallel and/or perpendicular diffusivity, we computed the mean of these diffusivities across voxels within all significant clusters and tested for correlations with age. This analysis revealed significant increases in perpendicular ($r=0.54$, $p<0.001$; Fig. 1C) but not parallel ($r=0.14$, N.S.; Fig. 1D) diffusivity with increasing age. MD showed a positive linear correlation with age in many WM regions, with the posterior regions being less extensively affected. The correlation between MD values averaged across all these WM clusters and age was $r=0.52$, $p<0.001$.

Comparisons of grey and white matter volumes and DTI metrics between age subgroups (Fig. 2)

There was an early frontal GM decrease followed by a later more widespread decrease. Specifically, decrease in GM volume was found in the MA 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 gyrus, 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 volume 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 FA 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.

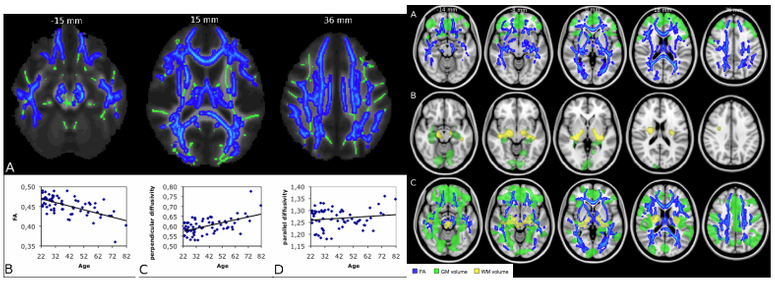

Figure 1 (*left*): (A) Blue voxels show WM regions where FA shows a significant negative linear relationship with age. Voxels are overlaid on the WM skeleton (in green) and the group mean FA image (greyscale). (B, C, D) Plots to illustrate the relationship between age and mean FA (B), perpendicular diffusivity (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. Green, yellow and blue represent GM, WM volumes and FA, respectively.

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 neurons/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 detected earlier 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

Salat, D.H., Tuch, D.S., Greve, D.N., et al., 2005. Neurobiol Aging 26, 1215-1227.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., et al., 2006. Neuroimage 31, 1487-1505.
Sowell, E.R., Peterson, B.S., Thompson, P.M., et al., 2003. Nat Neurosci 6, 309-315.
Walhovd, K.B., Fjell, A.M., Reinvang, I., et al.,, 2005. Neurobiol Aging 26, 1261-1270.