Microstructural Correlations of White Matter Tracts in the Human Brain

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Introduction

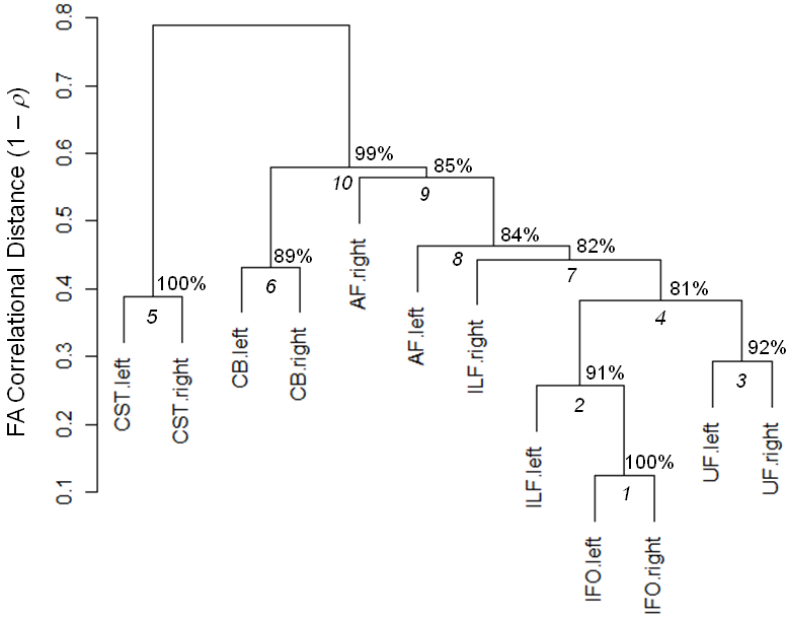
While there has been rapid growth in the understanding of how the microstructural organization of white matter pathways correlates with behavior, to our knowledge there has not been a systematic examination of whether quantitative DTI parameters of different tracts co-vary with each other across individuals. The assumption implicit in many DTI studies is that a particular metric such as fractional anisotropy (FA) is independent across white matter tracts; hence, each pathway is analyzed separately with respect to its contribution to cognitive ability. Conversely, different tracts may be treated as if they were equivalent, such as when measurements in homologous tracts of the left and right hemispheres are averaged. But the precise degree to which microstructural covariances exist between tracts is largely unknown. The purpose of this study is to investigate whether specific patterns of correlation exist in tract-based measurements of DTI parameters across white matter pathways in the normal adult human brain, and whether the strength of these putative correlations might reflect phylogenetic and functional similarities between tracts.

Methods

3T DTI was performed on 44 healthy young adults (24 men, mean age 30.8 ± 7.8) using a multislice single-shot echoplanar sequence with 1.8-mm isotropic voxels and 55 diffusion directions at b = 1000 s/mm^2. The diffusion-weighted images were corrected for motion and eddy currents using FLIRT (www.fmrib.ox.ac.uk/fsl/flirt) and tractography was performed in DTIStudio v2.4 (www.mristudio.org) with start FA>0.3, stop FA<0.2, and stop angle>50^0. Individual tracts were then selected using the protocols of Wakana et al.[1] for tract-based measurements of mean FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in 12 fiber pathways: the cingulum bundles (CB), arcuate fasciculi (AF), inferior fronto-occipital fasciculi (IFO), inferior longitudinal fasciculi (ILF), uncinate fasciculi (UF), and corticospinal tracts (CST) bilaterally. A correlation matrix was generated for each of the 4 DTI parameters by pairwise correlation of the 44 subject-specific DTI parameter values in each of the 12 tracts with those in each of the 11 other tracts. Since many of the DTI parameter distributions departed from normality, the Spearman's rank correlation coefficient ρ was employed. Each correlation matrix has 66 unique elements, excluding the trivial values of unity along the main diagonal. Each correlation matrix was tested for equivalence to the identity matrix, i.e. no significant correlations, and for homogenous structure, i.e. all off-diagonal correlations are equivalent, using the methods of Rencher[2]. Specific patterns of inter-tract correlation were investigated using data-driven agglomerative hierarchical clustering with multiscale bootstrapping to assess the statistical significance of the tract groupings, as implemented in the pvclust function of R v2.9.2 (Suzuki & Shimodaira[3]).

Results

The inter-tract correlation matrices for FA, MD, AD, and RD were all found to have significant correlations ($p<0.0001$) and significant variations in correlation strengths ($p<0.01$). The FA correlation matrix showed a wide range of ρ between homologous tracts, from low values of 0.50 for the AF and 0.57 for the CB to a high of 0.88 for the IFO. Surprisingly, ρ between certain pairs of strongly linked non-homologous tracts exceeded that between some homologous tracts: left ILF - left IFO (0.75); left ILF - right IFO (0.73); left UF - left IFO (0.70); right UF - left IFO (0.70); and right UF - right IFO (0.71). Hierarchical clustering of FA correlational distances displayed as a dendrogram (Figure) shows that the 2 projection pathways (left and right CST) were the most distant outgroup compared to the 10 association pathways at a 99% confidence level. Also, the 2 limbic pathways (left and right CB) clustered separately from the 8 neocortical pathways (bilateral AF, IFO, ILF, & UF) at an 85% confidence level. The MD dendrogram showed some points of correspondence with the FA dendrogram, with homologous tracts tending to form pairs, but important differences as well; hence, MD correlational distances may convey at least partially distinct microstructural information compared to FA. As expected, the RD dendrogram resembled that of FA, but with lower levels of statistical confidence. The AD dendrogram lacked statistically significant clusters at the 95% confidence level, suggesting less correlational structure than the other three DTI parameters.



Discussion

We have established that there are significant variations of inter-tract correlations in tract-based measures of FA, MD, AD, and RD from the normal adult brain. Results of data-driven hierarchical clustering indicate that specific patterns of microstructural correlation may reflect phylogenetic and functional similarities between fiber pathways. Tracts with the greatest known hemispheric asymmetry, such as AF and CB, had the weakest left-right correlation. Certain pairs of non-homologous tracts were more strongly coupled than some pairs of homologous tracts. Projection tracts correlated weakly with association tracts and, among association tracts, limbic tracts correlated weakly with neocortical tracts. Studies of brain development in infants and children will hopefully elucidate the extent to which these correlations are the result of genetic programming and how much may instead reflect usage-dependent neuroplasticity, perhaps even extending into adulthood and modulated over time by changes in cognition and other aspects of behavior. Further investigation of inter-tract DTI correlations encompassing many more pathways in a larger cohort will likely provide a wealth of novel and interesting information about the architecture of human brain networks, especially in combination with functional connectivity data from fMRI (Fox et al.[4]) as well as macrostructural covariance data from structural MRI measures of regional cortical thickness (He et al.[5]). Greater knowledge of the microstructural relationships between white matter pathways might aid studies of the genetics and of the behavioral effects of white matter architecture, as well as provide a revealing new perspective with which to investigate neurologic disorders such as brain malformations, brain injury, and neurodegeneration.

References and Acknowledgements: [1] Wakana S et al. Neuroimage 2007; 36:630-44. [2] Rencher AC, 2002. Methods of Multivariate Analysis, 2nd ed. Wiley Interscience, Hoboken, NJ. [3] Suzuki R, Shimodaira H. Bioinformatics 2006; 22:1540-2. [4] Fox et al., PNAS 2005; 102:9673-8. [5] He et al., Cereb Cortex 2007; 17:2407-19. This study was funded by grants from the James S. McDonnell Foundation, the Charles A. Dana Foundation, the American Society of Neuroradiology, and the U.S. National Institutes of Health.