

The FA Connectome: a Quantitative Strategy for Studying Neurological Disease Processes

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Introduction: There is a growing interest in improving our understanding of how neurological disease processes affect the complex intra and interhemispheric transfer of sensory, motor and higher order cognitive information in the brain. Structural connectivity indices derived using diffusion based HARDI or *q*-ball imaging in conjunction with functional parcellation of the cortex from high resolution MRI, has provided insight into the anatomical conformation of many of the important neural networks in the living brain (1, 2). Although such approaches provide knowledge of functional anatomy, how to apply this new technology in clinical populations to improve our understanding of the aetiology of disease processes presents a significant challenge. One of the key questions relates to the problem of quantification. How can we quantify changes within such neural networks to enable statistical comparison of indices across time and between patient and control groups? A solution to this problem is to combine a measure of fractional anisotropy (FA), a quantitative diffusivity metric that reflects the integrity of WM pathways, with the connectivity matrix. We are developing the concept of an *FA Connectome* to study the integrity of corticomotor networks in patients with Amyotrophic Lateral Sclerosis (ALS).

Methods: Structural MRI (1 mm isotropic resolution) and HARDI data (60 diffusion encoding directions, $b = 3000 \text{ mm}^2/\text{s}^2$, 2.2 mm isotropic resolution) are being acquired from ALS patients and control participants using a 3T Siemens Trio scanner. For each subject, the cortex of each hemisphere was parcellated into 33 regions based on gyral and sulcal structure using Freesurfer (<http://surfer.nmr.mgh.harvard.edu/fswiki>) with the fibre orientation distribution calculated using constrained spherical harmonic deconvolution (3) and probabilistic diffusion tractography performed using MRtrix (<http://www.nitrc.org/projects/mrtrix>). Fifty streamlines were seeded for every voxel of the entire brain volume. To ensure generation of connectivity indices in diffusion space, whole-brain track density maps were nonlinearly registered to the sMRI and the inverse transformation applied to the parcellated cortical masks. Connectivity matrices (1,2) were then generated by hit-testing every streamline's terminal end with every cortical parcellation. A termination mask was applied to prevent streamlines from crossing cortical folds. For each element within the connectivity matrix (i.e. cortical connection) the mean FA value within that WM pathway was calculated and visually represented as a multi dimensional FA connectome, suitable for statistical analysis.

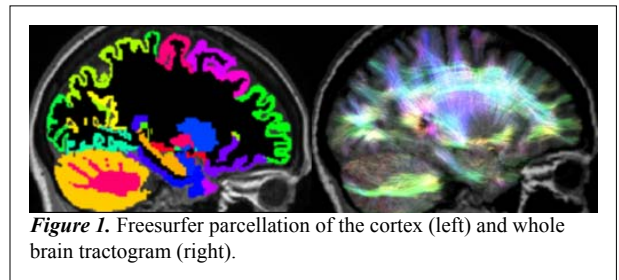


Figure 1. Freesurfer parcellation of the cortex (left) and whole brain tractogram (right).

Results: Representative Freesurfer parcellation and wholebrain tractography maps for an ALS patient (47 years old, ALSFRS-R 45) are given in Figure 1. Figure 2 shows the corresponding FA connectomes (patient and matched control participant (44 years old)). The strength of connectivity for the individual cortical parcellations (diagonal elements) and cortico-cortical connections (off axis elements) is given by the column height, with the mean FA for the particular pathway colour coded in the third dimension. A reduction in mean FA value for a number of key corticomotor pathways is clearly evident in the patient's FA connectome (labelled *).

Discussion: The concept of using FA connectomes to measure neurological disease processes has a number of useful advantages. Generation of the FA connectomes can be achieved in a fully automatic fashion, not requiring manual seeding of tractography algorithms. The process has the potential to interrogate multiple cortical networks, without the need for registration of sMRI / HARDI images across patient and control cohorts. The same methodology can be applied to other diffusivity indices such as mean diffusivity (MD). Statistical analysis of diffusivity indices can be achieved offline, or by creating two-dimensional connectivity maps (encoded with mean FA measures) and applying permutation-modelling employing randomise (4). Current work is being focussed towards developing robust methods of normalising connectivity measures, which in combination with the FA connectome, would provide a powerful strategy for studying neurological disease processes.

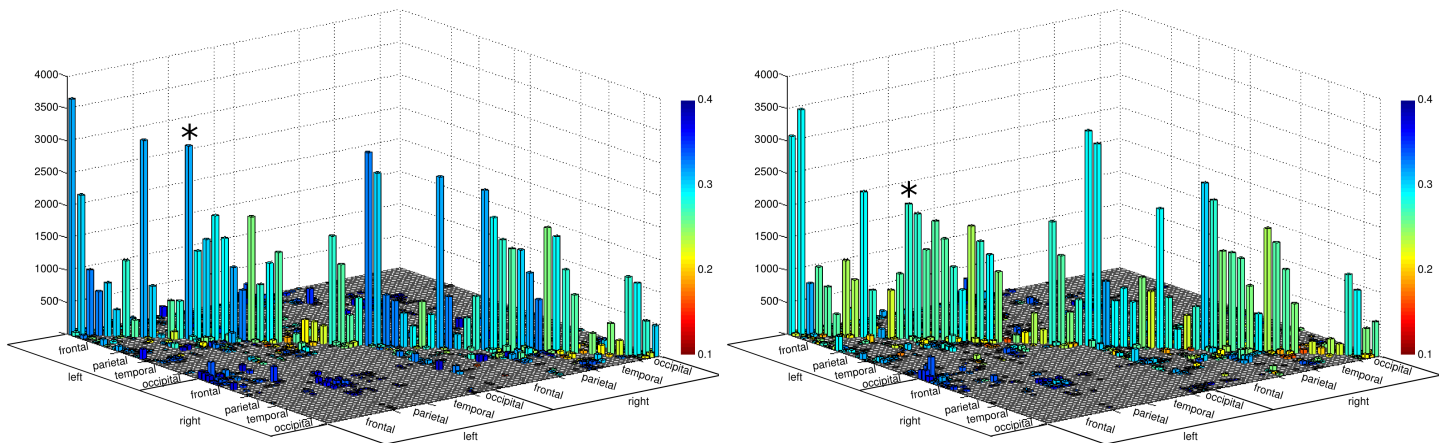


Figure 2: Representative FA connectomes for an age matched control (left) and ALS patient (right). There is a significant decrease in FA within many cortical networks, especially those involving key corticomotor pathways (*).

References: (1) Perrin M et al., *Int J Biomed Imaging* 2008. 368406; (2) Johansen-Berg H et al., *Ann Rev Neurosci* 2009;32:75-94; (3) Tournier J-D et al., *NeuroImage* 2007, 35:1459; (4) <http://www.fmrib.ox.ac.uk/fsl/randomise/index.html>.