Can Structural Connectivity Analyses Measure Brain Plasticity in Amyotrophic Lateral Sclerosis?

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Introduction: There is a growing interest in improving our understanding of how neurological disease processes affect the integrity of neural networks in the living brain. This can be achieved using measures of structural connectivity derived using diffusion tractography in conjunction with cortical parcellation of high resolution MRI, to define the anatomical conformation of multiple intra- and interhemispheric white matter (WM) pathways (1, 2). As the number of streamlines connecting target regions is difficult to compare across participants, connectivity matrices are often encoded with diffusion anisotropy summary measures which can be used to provide information about the integrity of WM networks across subject groups (3,4). A potential limitation of this approach is that the magnitude of anisotropy indices derived for a specific WM connection can be influenced by the presence of crossing fibre networks. To overcome this problem, we generated connectomes based on measures of fractional anisotropy (FA) and amplitude of the Fibre Orientation Density (FOD) function (5) and compared these connectivity measures in patients with Amyotrophic Lateral Sclerosis (ALS) and matching control subjects. The amplitude of the FOD relates primarily to the organisation of WM bundles along a given orientation which provides a quantitative, surrogate measure of WM pathology. Here we assume that the amplitude of the FOD will be less sensitive to contamination from crossing fibres than the FA. To assist in the interpretation of results, we also measured the reproducibility of these connectomes over time in control participants.

Methods: Structural MRI (1 mm isotropic resolution) and HARDI data (64 diffusion encoding directions, b = 3000 mm/s^2, 2.2 mm isotropic resolution) were acquired from 13 ALS patients with mixed upper and lower motor neuron signs and 13 controls 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 with the FOD calculated using constrained spherical harmonic deconvolution (CSD) (5) and probabilistic diffusion tractography performed using 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 linearly registered (dof=6) to the sMRI and the inverse transformation applied to the parcellated cortical masks. Connectivity matrices were then generated by hit-testing every streamline's terminal end with every cortical parcellation, see Figure 1 (7). A termination mask was applied to prevent streamlines from crossing cortical folds. Each element within the connectivity matrix (i.e. cortical connection) was encoded with the mean FA and median FOD amplitude (50% percentile) value along that trajectory. Statistically significant differences in corticomotor connectivity between the ALS and control group were detected by applying a nonparametric Mann-Whitney test (applying a FDR of 10%) to both FA and FOD connectomes. Eight control subjects were scanned twice over a period of 6 months to assess reproducibility.

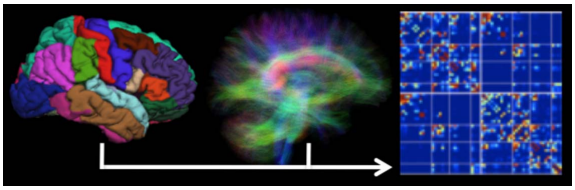

Figure 1. Freesurfer parcellation of the cortex (left), whole brain tractogram (middle) and connectivity matrix (right).

Results: Based on the serial data acquired from control participants, the reproducibility of the main corticomotor connections for the measures of FA and FOD amplitude were within 5%. Comparing FA connectomes across ALS and control participants revealed significant loss in connectivity within a number of primary and somatosensory cortical regions, including corticospinal tracts (CST). Analysis of the FOD connectomes revealed a similar pattern of loss in corticomotor connectivity, albeit with an increase in connectivity in WM projections associated with the inferior parietal lobe (IPL) in the ALS patients compared to controls, see Figure 2. There was a trend towards an increase in FA within these analogous projections that did not reach a level of statistical significance after correction for multiple comparisons. This paradoxical finding suggests a mechanism of neuronal reorganisation within the motor system in ALS patients with upper and lower motor neuron involvement.

Discussion: The concept of using structural connectomes to measure neurological disease processes has a number of useful advantages. The technique enables the interrogation of multiple cortical networks, in an automated fashion, without the need for registration of sMRI and HARDI images across subject groups. The reduced connectivity associated with the precentral (preCG) and postcentral (postCG) gyri corroborate previous findings based on TBSS analyses of FA measures (8). With respect to increased connectivity within the IPL, previous fMRI and functional PET studies have shown an increase in activation within ALS patients compared to controls within a number of somatosensory regions including the IPL during performance of a motor task (9,10). Our findings also support a concept of increased neuronal plasticity within the motor system in ALS. Such results highlight the utility of structural connectivity analyses in studying neurodegenerative disorders.

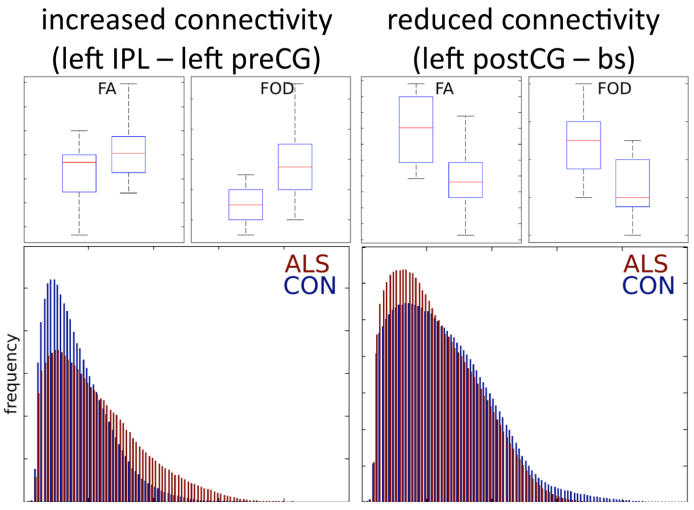

Figure 2. Representative summary measures for connections involving the IPC and preCG (left), and postCG and brainstem (bs) (right). The top plots show representative box-whisker plots for the IPL connections (increase in FOD amplitude and FA) and postcG (showing the predicted reduction in FOD amplitude and FA). Histograms demonstrating the FOD amplitudes along the IPC and postCG trajectories are given below.

References: (1) Hagmann P et al., J Neurosci Methods 2010 [Epub ahead of print]; (2) Johansen-Berg H et al., Ann Rev Neurosci 2009;32:75-94; (3) Wee CY et al., Neuroimage 2010 [Epub ahead of print]; (4) Robinson EC et al., Neuroimage 2010;50:910-919; (5) Tournier J-D et al., Neuroimage 2007, 35:1459; (6) Sage CA et al., Human Brain Map 2009;30:3657-75; (7) Pannek K et al., Neuroimage 2010;53(3):1044-53; (8) Ciccarelli O et al., Human Brain Mapping 2009;30:615-24; (9) Konrad C et al., Exp Brain Res 2006;172:361-69; (10) Kew JJM et al., Brain 1993;116:655-80.