Probabilistic diffusion tractography: a potential tool to assess the rate of disease progression in ALS

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Introduction The pathological hallmark of Amyotrophic Lateral Sclerosis (ALS) is the degeneration of both the upper and lower motor neurons. A novel method for investigating upper motor neuron differences between ALS patients and controls is probabilistic diffusion tractography, which generates probabilistic maps of fibre connectivity between brain regions (Parker 2003, Behrens 2003). Here we present the development of voxel-based connectivity measures along the tractography-derived cortico-spinal tract (CST). We investigated (i) whether these connectivity measures are different in patients with (ALS), reflecting the upper motor neuron damage, and correlate with the rate of disease progression, and (ii) whether fractional anisotropy (FA) is reduced in the CST of ALS patients and relates to disease progression rate.

Methods *Subjects* We recruited 13 patients with probable or definite ALS and 19 healthy controls. All patients were scored on the ALS functional rating scale (ALSFRS). The disease progression rate was calculated as follows (Ellis 1999): Disease progression rate= (40 – ALSFRS score) / disease duration.

MRI protocol All imaging was performed on a 1.5T GE scanner with a maximum gradient strength of 22 mT m^{-1}. The diffusion protocol consisted of a single shot DW-EPI sequence [FOV 220×220, matrix 96×96 reconstructed as 128×128, giving a final in-plane resolution of 1.7×1.7 mm^2, 60 contiguous axial slices, 2.3 mm slice thickness]. The diffusion gradients were applied along 54 directions (δ=32 ms and Δ=40 ms, max. b-factor b=1,150 s mm^{-2}). Six diffusion-weighted volumes (b=300 s mm^{-2}) and six volumes with no diffusion weighting were acquired. The data were then processed to determine the diffusion behaviour on a voxel-by-voxel basis, from which FA maps were calculated. All subjects also underwent a 3D IR-SPGR sequence of the brain that was used to calculate the white matter fraction (WMF).

MRI analysis We used the tractography algorithm (Behrens 2003) to delineate the CST in each subject. First, we performed a connectivity-based segmentation of the internal capsule, and then tracked connections between the internal capsule and the primary motor cortex. We then plotted the voxel values of FA and connectivity within the CST in each subject, and aggregated them over subjects, in order to select the summary statistic that best describes changes in the FA and connectivity distributions. Due to the symmetric nature of the distribution of FA values within the CST (Fig. 1), the mean FA was considered to be a good summary statistic for the FA in each patient. On the other hand, the distribution of connectivity voxel values was rapidly skewed to the right (Fig. 1). We therefore chose the two following summary measures, which focused on the right tail, with higher connectivity values: 1) from the voxels aggregated over all subjects, those below the 75th centile connectivity value were discarded, leaving the top quarter of voxels; then, for each subject, the mean connectivity value was derived and called the "top quarter mean connectivity". 2) the 95th centile connectivity value in voxels aggregated from all subjects was chosen as a threshold; then, for each subject, the proportion of their voxels exceeding this threshold was derived. We also computed the within-subject mean connectivity of the CST.

Statistical analysis Patients were classified as having moderate or rapid disease progression rate, depending on whether or not their disease progression rate was less than the median value (0.472). We investigated differences in FA and connectivity between patients and controls, using linear regressions with the within-subject measure as a response variable on patient indicator, age and WMF as covariates. To investigate the association between FA or connectivity and the disease progression rate, the latter was regressed as a continuous response variable, with age and WMF as covariates.

Results Differences in FA between patients and controls

Patients with rapid disease progression rate had a significantly lower mean FA than controls in both the left (patient-control difference -0.0464, P 0.002, 95%CI -0.0741, -0.0186) and right CST (-0.0407, P 0.007, 95%CI -0.0694, -0.0120). Patients with moderate disease progression rate showed a lower mean FA in both tracts, although these differences did not reach statistical significance.

Differences in the summary connectivity measures between patients and controls

Patients with rapid disease progression rate had a significantly lower top quarter mean connectivity (-1172.5, P 0.014, 95%CI -2083.2, -261.8) and a significantly lower proportion of voxels with connectivity higher than the 95th centile (-0.0447, P 0.025, 95%CI -0.0981, -0.0063) in the left CST, but not in the right CST. Patients with moderate disease progression rate and controls had a similar summary connectivity measures in both tracts.

Differences in mean connectivity between patients and controls

Patients with rapid disease progression rate had a borderline significantly lower mean connectivity than controls in the left CST (-541.4, P 0.08, 95%CI -1169.6, 86.8), but not in the right CST. Patients with moderate disease progression rate and controls had a similar mean connectivity in both tracts.

Association between FA and connectivity and disease progression rate in patients

Disease progression rate was significantly associated with (1) the top quarter mean connectivity value (Fig. 2) (P<0.001, (partial correlation coefficient (pcc) -0.90), and (2) the proportion of voxels with connectivity value above the 95th centile (P 0.001, pcc -0.83) in the left CST. There was also a significant negative association between the mean connectivity of the left CST and disease progression rate (P 0.002, pcc -0.82). There was no evidence of association between disease progression rate and any of the connectivity measures of the right CST and FA in the bilateral CST.

Discussion The novelty of our study is that, by plotting the distribution of connectivity values over subjects, we were able to take into account their asymmetric distribution. We selected two measures of connectivity that were expected to be sensitive to changes occurring in the "tail" of the distributions and reflecting the underlying pathological changes. We found that patients with rapid disease progression rate had significantly lower connectivity measures than controls in the left CST. On the other hand, only a borderline difference was found in the mean connectivity between patients with rapid disease progression rate and controls, confirming that the newly developed summary measures were more sensitive than the mean connectivity to pathological changes. This study also demonstrates that there is a strong association between these summary connectivity measures and the rate of disease progression, suggesting that the pathological damage in the left CST detected by connectivity measures is a significant factor contributing to the rapidity of disease progression in patients with ALS.

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Fig. 1.

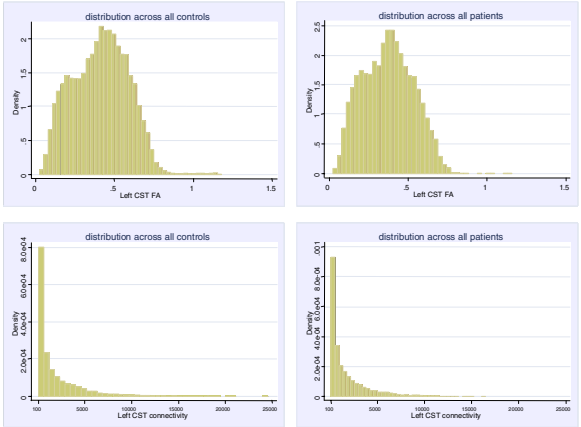

Fig. 2.