Tract-specific measurements within the corticospinal tract in sporadic ALS and patients homozygous for the D90A SOD1 gene mutation

C. R. Blain[1], V. C. Williams[2], M. R. Turner[1], G. J. Barker[3], S. C. Williams[3], P. M. Andersen[4], P. N. Leigh[1], A. Simmons[3], D. K. Jones[3]

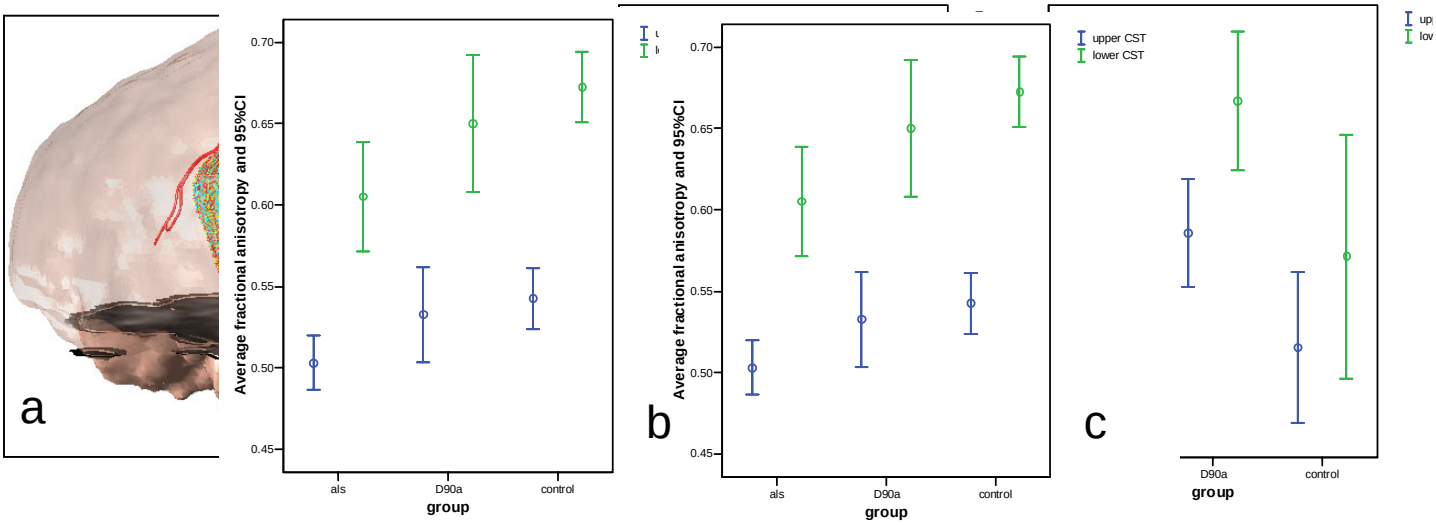
[1]Neurology, Institute of Psychiatry, London, United Kingdom, [2]Neurology, Kings College Hospital, London, United Kingdom, [3]Institute of Psychiatry, P089, Centre for Neuroimaging Sciences, London, United Kingdom, [4]Neurology, University of Umea, Umea, Sweden

Background: We have previously reported the use of DT-MRI to study microstructural pathology *in vivo* in the CST of patients with amyotrophic lateral sclerosis (ALS), based on a region of interest (ROI) approach[1]. However, manual definition of ROIs throughout the length of a specific tract such as the CST can be laborious. Furthermore as individual tracts cannot be directly visualised along their length, accurate delineation is dependent on the anatomical knowledge and expertise of each rater and prone to inclusion of other tracts and tissues. An alternative approach to manual ROI analysis of DT-MRI data has recently been proposed[2], whereby tractography is used to automatically dissect out a tract of interest and obtain multiple samples of diffusion parameters along its length, even if it follows a tortuous route. As the CSTs project directly from the motor cortex inferiorly to the brain stem, obtaining a clean dissection of these tracts is straightforward and does not require accurate anatomical placement of the two bounding ROIs. In this study, we refined our approach to allow measurements to be obtained from distinct segments of the same tract, i.e. the CST segment running from motor cortex to the internal capsule (upper CST) and from internal capsule to pons (lower CST) in healthy volunteers, sporadic and familial ALS. Along with lower motor neuron (LMN) degeneration, the pathological hallmark of ALS is degeneration of the corticospinal tracts (CST), but the distribution of CST damage in sporadic ALS (sALS) patients is heterogeneous, reflected in the variable phenotype. In contrast, familial ALS patients homozygous for the D90A SOD1 mutation (homD90A), show a stereotyped phenotype comprising a slowly ascending spastic paraparesis, with later development of LMN and bulbar signs. We used this tract-specific approach to investigate whether there is a differential involvement of the CST in sALS and homD90a patients.

Methods: Subjects: 10 sALS and seven homD90A patients were compared to 10 healthy age-matched controls. Acquisition: Whole brain DT-MRI data were acquired from all subjects on a GE Signa LX 1.5 T system using an optimized sequence[3]. Tractography: The CST was segmented (by a neurologist blind to subject group) in 2 locations: **a** - white matter adjacent to motor cortex and **b** - pontine region at the level of the superior cerebellar peduncles. To maximise the number of reconstructed pathways passing between regions **a** and **b**, tracking was performed from region **a**. Full details of the tracking algorithm can be found elsewhere[4]. Only the portion of the tracts passing between the two regions was retained for analysis. To distinguish upper and lower CST, we defined a plane at the level of the caudal portion of the internal capsule. In both hemispheres, the mean fractional anisotropy (FA) and mean diffusivity (MD) for the two CST segments above and below this plane were computed from measurements obtained at regular (0.5 mm) intervals. Statistical Analysis: For both FA and MD, repeated measures multivariate ANOVA was used to test for effects of group, region and their interaction and appropriate *post hoc* tests performed.

Results: For FA, there was a significant effect of group alone ($F=8.95$, df (2,23), $p=0.001$). As there was no interaction between group and region, for *post hoc* tests we considered the CST as a whole, rather than the two segments individually. FA was significantly reduced throughout the CST in the sALS group compared to both controls ($p<0.001$) and homD90a group ($p=0.018$). There was a trend towards reduction in FA in the homD90a group compared to controls ($p=0.14$). For MD there was a trend towards a group*region interaction (Hotelling's trace test: $F=3.2$, df(2, 23), $p=0.059$). *Post hoc* tests revealed that in the homD90a group MD was increased in both the upper CST ($p=0.032$) and lower CST segments ($p=0.022$) compared to controls. MD was not significantly increased in the sALS patients compared to controls in either segment, but there was a trend to increase in MD, when the CST was considered as a whole ($p=0.075$).

Figure 1: **a** Right CST - upper (blue) and lower (yellow) segments. Average FA (**b**) and MD (**c**) and 95% confidence intervals from the upper and lower segments of the CST in sporadic ALS patients, ALS patients homozygous for the D90a mutation and controls.



Conclusion: In this study we have successfully dissected out the corticospinal tract between the motor cortex and pons and after initial delineation of regions, automatically obtained measurements from the full length of the CST between these regions and from two distinct segments. This suggests that with further refinement, this technique could be used to obtain tract-specific diffusion measures within different white matter tracts involved in other neurodegenerative disorders, particularly those where it is difficult to place ROIs reliably along their length. As in our previous ROI analysis, we demonstrated that using this method, DTI detects pathology within the CST in both sporadic and familial (homD90a) ALS groups. Moreover, although it did not reach statistical significance, results from the MD analysis suggest that in the homD90a group, there is a differential involvement of the CST, with the lower segment affected more than the upper segment.

References: **1** Ellis CM et al Neurology. Sep 22;53(5):1051-8 (1999). **2** Jones DK et al Proc ISMRM 2003 p244. **3** Jones DK et al HBM. Apr;15(4):216-30 (2002). **4** Catani M et al Neuroimage. 2002 Sep;17(1):77-94.