Probabilistic diffusion tractography of the spinal cord to assess disability in multiple sclerosis

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Introduction Diffusion tensor imaging (DTI) of the spinal cord is challenging because of the small size of the cord and the motion artefacts arising from cardiac activity and CSF pulsations. However, spinal cord DTI has the potential to be used in the management of patients with multiple sclerosis (MS), since patients' disability often depends on the degree of white matter damage in the cord. Here we applied DTI to the cervical cord of patients with MS at the onset of a spinal cord relapse, which is often associated with severe neurological symptoms. This study was carried out to test the hypothesis that voxel-based connectivity of the tractography-derived cortico-spinal tract (CST) in the cervical cord differs between patients with MS and controls, and correlates with disability. We also investigated whether anisotropy and mean diffusivity in the CST change in MS patients and relate to disability. In order to assess the contribution of axonal damage and demyelination to the diffusion changes we examined the tract directional diffusivities derived from DTI.

Methods *Subjects.* Twelve patients with MS [mean age 36.5 y (SD 8.16), 7 women and 5 men, 11 relapsing-remitting MS, 1 secondary progressive MS, median EDSS 4.5 (range 2.5-6.5)] and 10 controls [mean age 41.2 y (SD 11.9), 6 women and 4 men] were studied. Patients were recruited within 4 weeks of onset of symptoms suggestive of a cervical cord relapse, and all of them had at least one lesion between C1 and C3. All patients were treated with I.V. steroids around the time of the scanning, and were on treatment with disease-modifying drugs. *MRI protocol.* All imaging was performed on a 1.5 T GE scanner with a posterior-neck coil. The diffusion protocol consisted of a single-shot EPI technique, named ZOOM-EPI (zonally magnified oblique multislice echo-planar imaging) [1] which covered the cervical spinal cord from C1 to C7. Parameters used were: FOV 70×47 mm^2, acquisition matrix 48×32, acquired in-plane resolution 1.5×1.5 mm^2 (reconstructed to 1×1 mm^2), number of contiguous axial slices 30, slice thickness 5mm, TE 96, TR = 15RR (≈ 15 sec), 4 $b \approx 0$ smm^{-2} images, diffusion gradients applied along 33 optimised diffusion directions, with max gradient amplitude of $33x10^{-3}$ Tm^{-1}, $b$max 1000 smm^{-2}. Cardiac gating was used to reduce motion artefacts due to pulsation of CSF. The diffusion data acquisition time was 20 min (depending on heart rate). All subjects had also a volume-acquired, inversion-prepared, fast spoiled-gradient (FSPG) echo sequence of the spinal cord [TR 13.2ms, TE 4.2ms, TI 450ms, flip angle 20°, FOV 250×250 mm^2, matrix 256×256, 60 slices, 1 mm slice thickness], which was used to calculate the spinal cord atrophy. *Tractography analysis.* The diffusion data were processed to determine the diffusion behaviour on a voxel-by-voxel basis using Camino (http://www.cs.ucl.ac.uk/research/medic/camino/) [3], from which FA, MD, eigenvalues and eigenvectors maps were calculated. The information contained in these maps was used by the probabilistic tractography algorithm, called PICo (Probabilistic index of Connectivity) [4], to produce probability maps of the bilateral CST in the cervical cord. For each subject, the seed voxels for the right and left CST were selected on the axial $b0$ images laterally in the spinal cord and posteriorly to the denticulate ligaments, to approximate the location of the CST. Their corresponding FA value was checked in order to ensure to be within the white matter. Indeed, all voxels chosen had FA value > 0.58. The PICo algorithm drew 5000 samples going from the seed voxel to any other voxel in the cervical spine between C1 and C3. The output of PICo was a probabilistic map that provided, at each voxel, a connectivity value that goes from 0 to 1. Each connectivity map was thresholded to include voxels with connectivity values > 0.1 that were considered to represent the right and left CST (Figure 1). The mean value of connectivity was calculated for each tract in each subject. The thresholded maps were then transformed into binary images, which were used to mask the FA, MD, and eigenvalues maps, and the mean values of these indices were obtained in all subjects. *Spinal cord atrophy.* Five contiguous 3mm axial slices (perpendicular to the spinal cord) were reformatted from the caudal landmark of C2-3 inter-vertebral disc, and a coil radiofrequency uniformity correction was applied. Cord area was measured using a semiatomated method [5]. *Statistical analysis.* To investigate differences in voxel-based connectivity, FA, MD, eigenvalues in the left and right CST between patients and controls the Mann-Whitney U test was used. Differences in connectivity, FA and MD between the right and left tract were assessed using the Wilcoxon Signed Ranks Test. To investigate the association between connectivity and disability, a linear regression analysis was performed using EDSS as a dependent variable and mean connectivity, age, gender and cord area as independent variables. The same analysis was repeated for FA and MD. Since a reduction in the number of voxels in the CST, which may be a result of the disease process, may reduce patients' connectivity, we tested for differences in the number of voxels of the right and left CST between patients and controls using the Mann-Whitney U test. Finally, the relationship between connectivity and EDSS was checked by adjusting not only for age, gender and cord area, but also for the mean total number of voxels in the CST.

Results *Differences between groups*. Patients showed significantly lower connectivity in both right and left CST (Right: patients= mean connectivity 0.356 vs. controls= 0.402, p0.011; Left: patients= 0.366 vs. controls= 0.398, p0.036). They also showed lower FA in both tracts (Right: patients= mean FA 0.396 vs. controls= 0.479, p0.036; Left: patients= 0.410 vs. controls= 0.523, p0.007). There was an increase in patients in the tract axial diffusivity and a decrease in the radial diffusivities that, however, did not reach statistical significance. There was no difference in any other index between patients and controls and between the right and left side. *Association between diffusion indices and disability*. Mean connectivity of the right and left tract was significantly associated with EDSS when adjusting for age, gender and cord area (p 0.002, partial correlation coefficient -0.88), and when adjusting also for mean total number of voxels per subject (p 0.037, partial correlation coefficient -0.78). However, there was no evidence of association between FA or MD and disability.

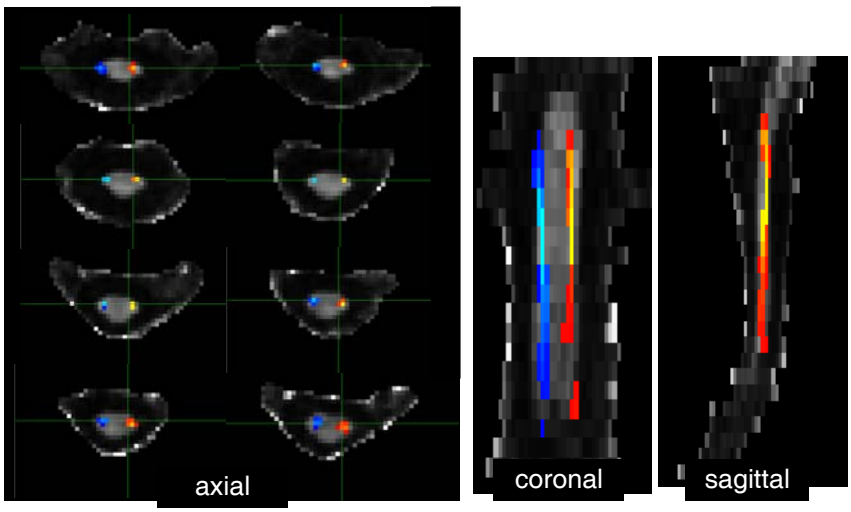

Figure 1. Connectivity maps of the right (blue) and left (red) cortico-spinal tract in the spinal cord overlaid onto FA maps.

Discussion We have demonstrated that axial spinal cord DTI is feasible on a clinical scanner. Diffusion probabilistic tractography allows tracking in-vivo the motor pathways even through demyelinating lesions. DTI-derived indices, in particular FA, are sensitive to tissue damage, and the examination of diffusivities suggests that this damage is caused by both demyelination and axonal loss. The most striking finding of this work is that voxel-based connectivity of the CST between C1 and C3 is lower in patients with MS, reflecting tissue damage, and correlates with disability associated with relapses.

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