Can structural connectivity studies be performed in children with servere ataxias?

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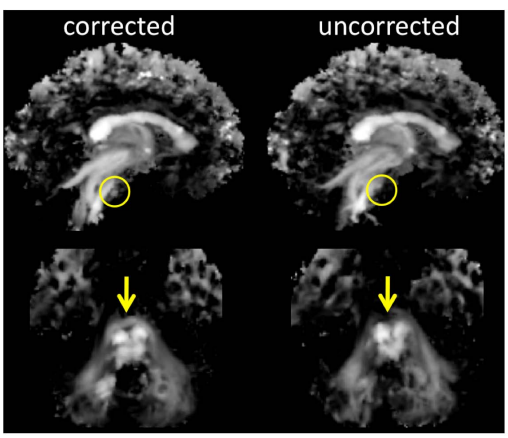
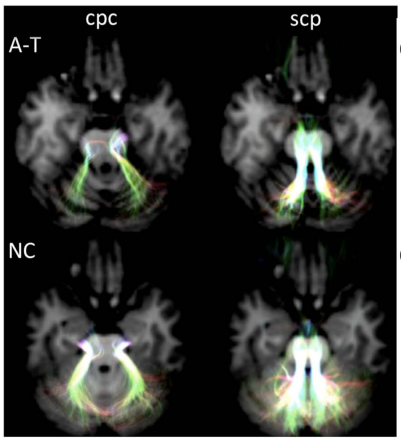
Introduction: Progressive loss of movement, co-ordination and control of gait in children is often associated with the degeneration of key corticomotor-cerebellar networks. Structural connectivity studies employing diffusion-weighted MRI (dMRI) and probabilistic tractography can provide new insight into the loss in integrity of these important white matter (WM) motor pathways. However, such imaging studies in children with severe ataxias present a significant challenge, due to the likelihood of artifacts induced by involuntary head movement. To overcome this constraint, we have developed an image processing strategy to reduce such effects and present novel information about the degeneration of specific cerebellar-corticomotor pathways in children with ataxia-telangiectasia (A-T). A-T is a rare autosomal recessive genetic disorder characterised by progressive neurodegeneration, a high risk of cancer and immunodeficiency. The progressive cerebellar ataxia represents the most debilitating aspect of this disorder. Little in known about the relationship between the degeneration of corticomotor-cerebellar networks and the genetic and clinical phenotypes found in A-T.

Methods: Four children with A-T (age 7-12 years) and an equal number of age matched control participants were scanned using a 3T Siemens Trio, employing a 32channel head coil without sedation. dMRI data was acquired using HARDI (b = 3000 s/mm^2, 64 directions, 2.2 mm isotropic resolution, acceleration factor of 4, 9 minute scan time). A field map was also acquired for susceptibility distortion correction. Data pre-processing included eddy-current, susceptibility distortion, and intensity inhomogeneity correction. For each voxel, the fibre orientation distribution function (FOD) was calculated using constrained spherical deconvolution (constrained SD) [1] and probabilistic tractography was performed using MRtrix. To help reduce head motion incuded artifacts and physiological noise, outlier voxels were identified based on the fit of the SD and replaced using the DROP-R method [2]. Two corticomotor-cerebellar networks, namely the afferent cortico-ponto-cerebellar tracts (cpc) that transfer information from the motor cortex to the cerebellum, and the corresponding efferent superior cerebellar peduncle tracts (scp), which relay information from the cerebellum back to the various corticomotor areas, were investigated. The trajectories for these cerebellar networks were reconstructed using previously described anatomical targets for fibre tracking [3]. A quantitative, average pathlength map (APM) [4] was generated for each participant to measure degeneration of the cerebellar pathways. Streamline normalisation to standard space was used to enable the comparison of pathlength measures between control and A-T groups (*i.e.* adjusted for different brain sizes).

Results: As shown in Figure 1, a signficant improvement in the delineation of cerebellar tracts was achived using the above-mentioned strategy to reduce motion-induced artficats. For the A-T subjects, a reduction in median tract pathlength was found for both the cpc and scp fibre tracts compared to the control particpants, indicating signficant degeneration of these WM pathways. Comparative data highlighting these findings are given in Figure 2.





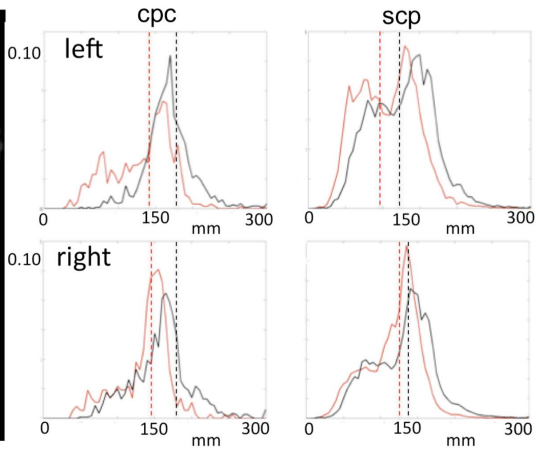


Figure 1 (left). Representative APMs for a A-T participant showing improved delineation of the tranverse fibres (TF) asssociated with scp. The TF's were only discernable (yellow circle and arrow) when the outlier identification and replacement strategy was employed. **Figure 2 (right).** Representative tractography maps in MNI152 space showing the cpc and scp tracts for a A-T (top) and age matched control participant (bottom). The histograms (far right) show the distributions of fibre tract pathlength for the A-T (red) and control subject (black) for the left and right hemispheres respectively. Median values for the distributions are given as colour-coded hashed lines.

Discussion: Diffusion tractography offers a non-invasive strategy for investigating the degeneration of corticomotor-cerebellar networks in children with ataxias. However, due to involuntary head movement and inherent physiological noise (i.e. cardiac pulsatile motion), which can impact on the accuracy of diffusivity metrics derived from cerebellar regions [5], it is important to include within image processing pipelines a method for identifying outlier voxels. In this study we introduce a novel approach based on the fit of the SD and incorporate with this strategy the replacement of outlier voxels [3]. In addition, we show that quantitative measures of pathlength can be used to measure WM tract degeneration. This processing strategy enabled novel observations regarding the integrity of corticomotor-cerebellar networks, improving our understanding of the clinical phenotype in A-T.

References: [1] Tournier et al., Neuroimage 2007;35(4):1459-1472. [2] Morris et al., Magn Reson Med 2011;66(1):92-101. [3] Catani et al., Neuroimage 2008;41:1184-1191. [4] Pannek et al., Neuroimage 2011;55:133-141. [5] Walker et al., Neuroimage 2011;54(2):1168-1177.