Decreased Apparent Fibre Density in Dravet Syndrome

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Target Audience: Neurologists and paediatricians studying epilepsies, particularly epileptic encephalopathies, such as Dravet syndrome, and researchers that perform diffusion-weighted imaging and analysis.

Purpose: To investigate white matter abnormalities in Dravet Syndrome.

Introduction: Dravet syndrome is a devastating disease characterised by the onset of infantile seizures, typically involving prolonged hemiclonic or generalised convulsions associated with fever[1]. Other seizure types subsequently develop including myoclonic, focal, and absence seizures. Development is normal in the first year of life before developmental slowing and often regression occur, resulting in intellectual disability in most patients. Conventional MRI in these patients is often normal, although minor abnormalities have been reported[2,3] including hippocampal sclerosis, and non-specific findings such as mild cerebral and cerebellar atrophy.

In contrast to conventional MRI, diffusion-weighted imaging (DWI) provides unique information by exploiting the interaction between diffusing water molecules and tissue microstructure. In this work we use DWI to compute Apparent Fibre Density (AFD)[4], a quantitative measure proportional to the intra-cellular volume of axons (i.e. density). Unlike diffusion tensor-derived measures, each AFD measurement can be associated with a specific population of fibres within a single voxel and is therefore robust in regions with crossing fibres. Herein we coin the word *fixel* to refer to specific fibre population within a single voxel. In this study we performed whole-brain fixel-based analysis of AFD in patients with Dravet syndrome compared with controls.

Method: Patients with Dravet syndrome (9 patients, 6 female, mean age 16.7, range 8-28) were compared to healthy controls (24 controls, 13 female, mean age 17.8, range 9-30). Patients were recruited with Dravet syndrome and an *SCN1A* mutation. DWIs were acquired on a 3T Siemens Tim Trio (60 directions, b=3000 s/mm^2, isotropic voxel size 2.5mm). Pre-processing involved motion and bias field correction, intensity normalisation and up-sampling by a factor of 2[4]. Fibre Orientation Distribution (FOD) images were computed by Robust Spherical Deconvolution[5] using MRtrix and registered towards an unbiased population-specific FOD template[7]. FODs were modulated to account for axon loss manifested as atrophy while preserving the total amount of AFD[4]. For each fixel, we computed the AFD by integrating the associated FOD 'lobe'. Whole-brain fixel-based analysis of AFD was performed using tractographic threshold-free cluster enhancement[8] using age and intracranial volume as covariates of no interest. Corrected p-values were assigned to each fixel using permutation testing (5000 permutations). Significant fixels ($p<0.05$) were displayed using tractography streamlines, and colour coded by direction and by effect size.

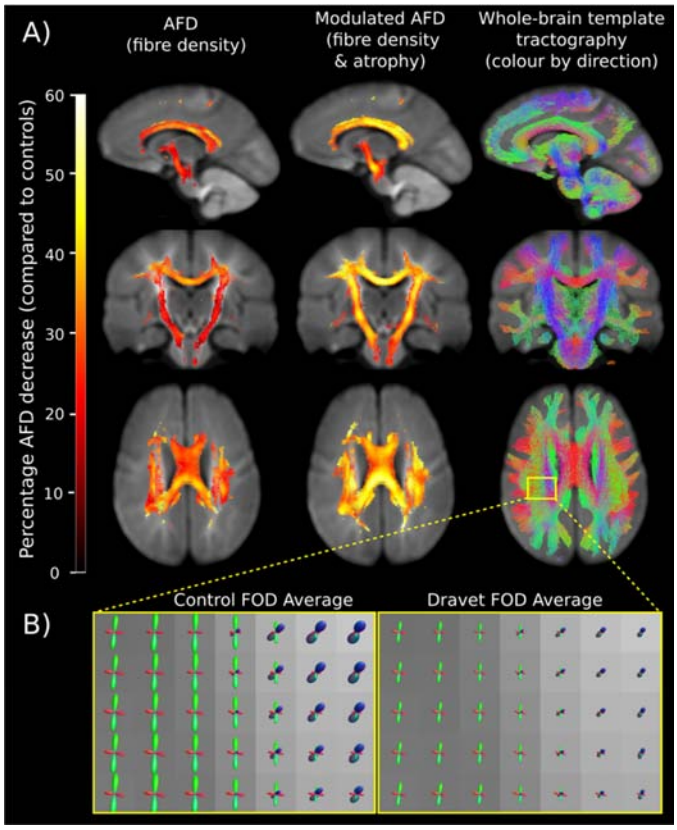

Figure 1. A) Significant AFD decreases in Dravet syndrome vs healthy controls ($p<0.05$, corrected). **Left:** Significant AFD decreases without modulation (i.e. a reduction in axon density), colour-coded by percentage decrease (with respect to controls). **Middle**: Significant AFD decreases with modulation (axonal loss due to density of fibres within the bundle and reduction in the volume of the bundle itself). **Right**: Whole-brain population-average tractogram included as an anatomical reference image, colour-coded by direction (red: L-R, green: A-P, blue: I-S). **B)** A comparison of the control and Dravet group average FOD image (modulated) in an example ROI.

Results: A significant decrease ($p<0.05$) in AFD was detected in patients with Dravet syndrome compared to controls participants and involved the bulk of the white matter (Fig 1a.). Column 1 shows the percentage of AFD decrease that can be attributed to a reduction in axon density (relative to the control group). When atrophy is taken into account via the AFD modulation step, we observed a further decrease in AFD, in addition to more widespread involvement of the white matter (column 2). Column 3 is an anatomical reference image that shows the whole-brain population-average tractogram used in the statistical analysis. The reduction in AFD can be clearly seen by the reduced FOD size in the Dravet group average images compared to controls as shown in the example region of interest in Fig 1.b.

Discussion: Despite a well-recognised molecular etiology for Dravet syndrome, little is understood about the pathophysiology of this complicated disorder. MRI abnormalities to date have been relatively sparse and not reflective of the severity of the clinical picture. Here, in the first study of Dravet Syndrome with diffusion MRI, we show marked imaging changes in Dravet syndrome compared with controls. The substantial decrease in AFD in Dravet syndrome can be interpreted as an overall reduction in the number of axons throughout the white matter. We note that extensive abnormalities are observed in the corticospinal tract and mid body of the corpus callosum, which may reflect the mild pyramidal signs that emerge as the child with Dravet syndrome goes into puberty and develops a crouch gait[9]. How the *SCN1A* mutation pathology results in these extensive white matter changes is not known, but this imaging technique may be an avenue to monitor changes and to study novel therapeutic approaches to improve outcome in this devastating disorder.

References: **[1]** Dravet C (2005) Epileptic Syndromes in Infancy, Childhood and Adolescence. 125-156. **[2]** Dravet C (2011) Epilepsia. 52:3-9. **[3]** Harkin LA et al, (2007) Brain. 130:843-852. **[4]** Raffelt et al (2012) Neuroimage. 59:3976-3994. **[5]** Tournier D et al., Proc. ISMRM 21, 0773 (2013). **[7]** Raffelt D et al. (2011) NeuroImage 56(3):1171-80, **[8]** Raffelt D et al., Proc. ISMRM 21, 841 (2013), **[9]** Rodda JM et al (2012) Archives of neurology. 69(7);873-8.