

# Serial diffusion tensor imaging suggests progressive pathophysiology for weeks following traumatic brain injury, and possible white matter repair months after injury

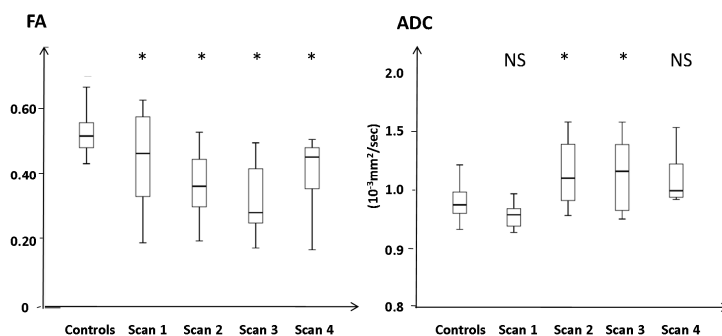
V. Newcombe<sup>1</sup>, G. Williams<sup>2</sup>, J. Outtrim<sup>1</sup>, D. Chatfield<sup>1</sup>, M. G. Abate<sup>1</sup>, T. Geeraerts<sup>1</sup>, A. Manktelow<sup>1</sup>, P. Hutchinson<sup>3</sup>, J. Coles<sup>1</sup>, and D. Menon<sup>1</sup>

<sup>1</sup>Division of Anaesthesia, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, <sup>2</sup>Wolfson Brain Imaging Centre, University of Cambridge, <sup>3</sup>Academic Department of Neurosurgery, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom

**Introduction:** It is becoming clear that many of the sequelae of Traumatic Brain Injury (TBI) are not just a direct consequence of the acute event, but represent a dynamic process, with changes occurring many years after the event. Such ongoing pathophysiology raises the hope for effective late treatments. However, a rational definition of the therapeutic window critically depends on being able to define the temporal pattern of such progression. Diffusion tensor imaging (DTI) is more sensitive than conventional CT or MR at showing the extent and distribution of injury following TBI, and so is a promising imaging marker for TBI. However, data on the temporal pattern of changes in diffusivity parameters remain incomplete.

**Methods:** Ten patients (six male) underwent MR imaging on a minimum of three occasions; within the first 48 hours of injury (scan1), at approximately six weeks post injury (range 29 to 87 days) (scan 2), and at least six months (range 6 to 9 months) (scan 3) after injury. Of these, seven also had a scan at least one year post injury (range 1 year to 2.6 years) (scan 4). Neuropsychometric testing including motor latency was undertaken with Scans 3 and 4, and correlated with imaging findings. The mean age at injury was 33.4 (SD± 7.2) years, the median Glasgow Coma Score was 5 (range 3 to 7), median Glasgow Outcome Score was 4 (3 to 5). 40 age matched healthy volunteers (mean age 35.6 (±9.1) years, 28 male, 12 female) were used as a control group. Ethical approval was obtained from the Local Research Ethics Committee and informed consent was obtained in all cases. MR imaging was performed using a 3 Tesla Siemens TIM Trio, and included a 3D T1-weighted structural sequence (MP-RAGE), as well as spin echo planar diffusion weighted imaging (DWI; acquired using 12 non-collinear directions, 5 b values equally spaced from 300 to 1500 s/mm<sup>2</sup> with 4 b = 0 images). The diffusion weighting parameters were: 20 x 20 cm field of view, 100 x 100 matrix size, 63 axial slices, 2 mm slice thickness, TR = 6000ms, TE = 100ms, diffusion sensitizing duration = 23.5ms (δ); with separation (leading edge to leading edge) = 60ms (Δ). After eddy current correction, FDT (FMRIB's Diffusion Toolbox)<sup>1</sup> was used to fit a tensor at each voxel and create FA and ADC. Regions of interest were manually drawn using Analyze 7.0<sup>2</sup> in MNI125 space using Colin27<sup>3</sup> as a high resolution, high signal-to-noise template. ROIs selected included the anterior corpus callosum, the posterior corpus callosum, frontal white matter and posterior white matter. The DTI data were normalised using the vtkCISG normalised mutual information algorithm.<sup>4</sup> The b=0 image was subsequently coregistered to the subject's own MP-RAGE. The transformation matrix normalising the MP-RAGE was then applied to the b=0 image. All coregistered images were visually inspected to ensure that ROIs corresponded to the regions specified and manually adjusted if they did not. Mean FA and ADC for the different ROIs were calculated. Non-parametric statistics were used.

**Results:** In all ROIs at all time points the patients' FA was significantly lower than controls. FA continued to decrease from the first scan to a nadir at scan 3. FA in patient ROIs remained significantly lower than the control group at Scan 4, but was significantly higher than Scan 3 levels. ADC was significantly increased in the acute phase post injury in all ROIs except for the posterior corpus callosum, and was significantly increased in all ROIs over the subsequent time points except for the posterior corpus callosum ADC in scan 4. The patterns of change in FA and ADC seen across the patient group were consistently reflected in individual data. All patients improved motor latency between Scans 3 and 4, and this change significantly correlated with the change in FA in the anterior and posterior corpus callosum (r = 0.736, p = 0.036 and r = 0.607, p = 0.024 respectively).



**Figure 1:** Example of changes over time in FA and ADC in the posterior corpus callosum, one of the most common sites of damage post TBI. The pattern seen in the FA is consistent with the other ROIs. In the other ROIs (anterior and posterior white matter, the anterior corpus callosum) there was a significant increase in ADC at Scan 1 which was sustained. Comparisons are with control values. \* P < 0.05 NS non-significant.

**Discussion:** FA is low immediately following TBI, and appears to worsen for several weeks, with a nadir at approximately six months. When patients are followed up past the six month time point there appears to be an increase in ADC, which correlates with improving motor function, and may indicate recovery. Such knowledge of longitudinal change is important to aid interpretation of imaging findings. These data can also provide further insight into late pathophysiology, help select appropriate patients for clinical trials, and provide a framework that allows DTI to be used as an imaging biomarker of therapy response.

**Conclusions:** DTI measures of microstructural injury following TBI are consistent with ongoing subacute disease progression, and hint at the possibility of late repair. While further work is needed to correlate these structural data with neuropsychological parameters and functional outcome, and to examine longer time points, these results suggest that DTI may be a valuable tool to examine late neural injury and repair following TBI.

## References:

1. FSL. [www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)
2. Analyze. <http://www.mayo.edu/bir/>
3. Holmes et al. J Comput Assist Tomogr 22:324, 1998
4. vtkCISG. [www.image-registration.com](http://www.image-registration.com)