Delayed, progressive white matter loss following traumatic brain injury, demonstrated using probabilistic tractography

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Introduction: Traumatic brain injury is a major cause of morbidity and mortality worldwide. Greater understanding of the mechanisms leading to the neurocognitive and physical deficits that accompany TBI would be of great benefit. We have previously shown an association between clinical outcome and the burden of white matter injury, quantified by diffusivity parameters (fractional anisotropy, apparent diffusion coefficient) late after TBI in a region of interest analysis. However, we need better quantification of these findings for two reasons: First, this would allow us to relate the burden of white matter loss to behavioral and cognitive disability. Second, we could characterise the temporal pattern of these changes, in order to identify therapeutic windows for intervention to prevent such white matter loss and its cognitive consequences.

Methods: Twelve patients underwent MR imaging using a 3 Tesla Siemens TIM Trio system at three time points post injury; once in the acute phase while in intensive care (median 2 (range 1 to 8) days) and twice during the chronic phase at a median of 7 (6 to 18) months and 20 (12 to 34) months. Assent from next of kin for the first scan and informed consent for subsequent scans was obtained in all cases. Ethical approval was obtained from the Local Research Ethics Committee. Forty controls underwent an identical imaging protocol which included a 3D T1-weighted structural sequence (MP-RAGE), as well as diffusion tensor imaging (DTI; 12 non-collinear directions, 5 b values ranging from 338 to 1588 s/mm^2) These subjects had the sequence chosen as multiple b-values allows accurate characterization of edema in the acute phase, as it has been shown that the use of multiple b-values for a smaller number of unique gradient directions provides ADC results that are more robust than ones obtain with a higher number of sampling directions but only one b-value.[1] The data was not eddy current corrected as the distortion due to eddies was very small as a twice refocused spin echo sequence was used. Local diffusion parameters were estimated using FSL's BEDPOSTX,[2] which runs Markov Chain Monte Carlo sampling to build up distributions on diffusion parameters at each voxel. The number of samples used was 20000. Tractography was seeded from the corpus callosum and thalamus to target cortical regions which included; the prefrontal, premotor and supplementary motor, primary motor, primary somatosensory, posterior parietal, occipital, and temporal cortices. These ROIs were transformed into native diffusion space using the vtkCISG normalised mutual information algorithm.[3] ROI definition was restricted to voxels in the cortex with a grey matter content of above 30% (based on FAST[2]). Probabalistic tractography was performed using PROBTRACKX[2] with the specified seeds and masks. Fractional anisotropy was not used to constrain tracking to keep the analysis independent of FA, which has previously been found to be lower globally in a similar patient group. We calculated an overall track count that reached the specified cortical targets, and compared changes in these measures over time using non-parametric statistics.

Results: There were no significant differences in global track counts between controls and patients at the acute phase of injury. However, the patient group showed significant reductions in track counts at both later points when compared to controls. Critically, pairwise comparisons in patients showed a significant and progressive reduction in track numbers between the acute (median time point: ~ 2 days post TBI) and early follow up (median time point: ~ 7 months post TBI) time points, and between the two follow up images (median time points: ~7 and ~20 months post-TBI, respectively).

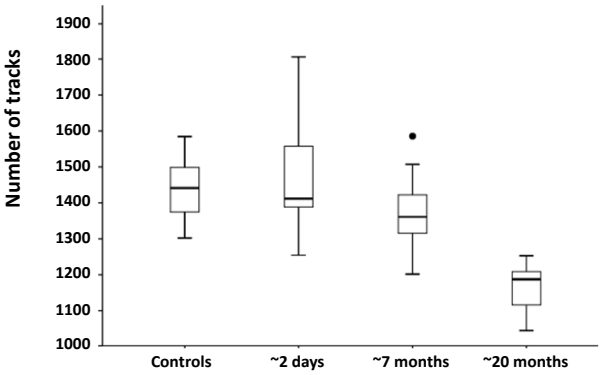

Figure 1: Change over time for number of tracks detected using the corpus callosum as the seed region, one of the most common sites of damage post TBI. Acutely there is no decrease in tracts. However, at track count is decreased at the first chronic time points and continues to decrease at the second chronic scan (Mann-Whitney U, p =0.015). The central lines in the boxes denote the median values, the upper and lower edges the 75th and 25th percentiles, the error bars the 90th and 10th percentiles.

Discussion: The relatively preserved track count at early imaging suggests that traumatic axonal injury, or at least the maturation of its imaging features, is not a process that is completed within hours of injury. The subsequent reduction in track counts at follow up imaging suggest that white matter injury progresses beyond the acute phase, and the significant change between the two follow up imaging time points suggests that this progress continues for months to years post-TBI, consistent with evolving conceptions of TBI as a chronic progressive disease. 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. 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 progression following TBI.

References:

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