Using Advanced MR Techniques to Investigate Traumatic Brain Injury

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Background /Objectives: Traumatic Brain Injury (TBI) causes Diffuse Axonal Injury (DAI); damage that affects the brain's white matter tracts and underpins cognitive deficit by disrupting neural networks[1]. MR techniques can be used to investigate this; Diffusion Tensor Imaging (DTI) can be used to quantify axonal microstructural changes[2] and Magnetic Resonance Spectroscopy (MRS) can evaluate changes in concentrations of neural metabolites[3]. While changes in chronic TBI patients are well documented for each method, acute and mild patients have shown more variable alterations compared to more severe injury. Previously we reported elevated FA following acute mild TBI[4] and a negative correlation between increased FA and worsening cognitive performance. Here we combine MRSI observations with a more detailed DTI analysis in this group to provide greater insight into the pathophysiology of acute mild TBI.

Methods: Fifty-three patients (44 mild, 9 moderate as measured by the Glasgow Coma Scale) were scanned 6 days (*SD* = 3.2, *range* = 1-14 days) post injury. Thirty-three age, gender and educationally matched controls were recruited for comparison. A 3T Philips MRI scanner was used: DTI; single shot EPI diffusion sequence (TR/TE=2524/71ms, 24 slices, b=0,1000smm^{-2}, 16 directions, 2x2x6mm^3 resolution), MRS; slice selective MRSI sequence (TR/TE=3450/35ms, 1x1x1.8cm voxels in a 24x20 matrix, 5 slices, 1 average, 1024 samples, spectral bandwidth of 2500Hz). All participants completed a neuropsychological test battery. DTI data were subject to voxelwise analysis using Tract-Based Spatial Statistics[5]. Patient Mean Diffusivity (MD), Fractional Anisotropy (FA) and Axial and Radial Diffusivity (AD/RD) were compared against control values and regressed against Verbal Letter Fluency (VLF) performance, controlling for IQ as measured by the National Adult Reading Test. MRS data were analysed using the QUEST fitting algorithm in jMRUI. Voxels were bilaterally placed in the ascending fibres of the corpus callosum. Patient peak amplitudes of N-acetylaspartate (NAA), Choline and Creatine were compared to control values and correlated with multiple psychometric test scores.

Results: *DTI*: Patient MD and FA were increased in multiple locations (driven by increased AD, while RD was unchanged, Fig. 1). In multiple locations patient FA regressed negatively with VLF while RD regressed positively (AD/MD did not show a relationship with VLF, Fig. 2). *MRS*: Unexpectedly, patient NAA was increased (p=0.024) and correlated negatively with Digitspan (r=-0.343, p=0.038) in the right hemisphere. Creatine was increased in the left hemisphere (p=0.039) and correlated negatively with Design Learning in the right hemisphere (r=-0.392, p=0.018). Patient Choline was unchanged but positively correlated with duration of loss of consciousness in the left hemisphere (r=0.405, p=0.01).

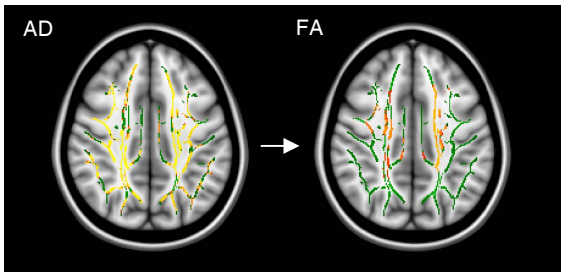

Fig 1. Outputs to show AD-driven increased patient FA.

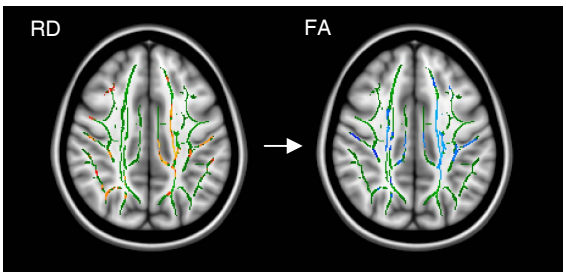

Fig 2. Outputs to show RD-driven negative regressions between FA and VLF.

Conclusions: *DTI*: Raised acute FA has previously been linked to cytotoxic oedema, although this occurs in conjunction with decreased MD[2] meaning this is an unsuitable hypothesis for our results. Raised FA has also recently been linked to astrogliosis[6] which seems more fitting for our findings due to the increased AD. We also report a negative regression between FA and VLF, driven by a decrease in RD. This is suggestive that patient RD is also subtly decreased to an extent that is undetectable in the groupwise comparison, but that it is this physiological change which is influencing cognitive deficit in VLF. Unhealthy neurofilament has been related to decreased axonal diameter and conduction velocity[7]. *MRS*: Increased NAA due to TBI is a novel finding. This could reflect increased neuronal density again due to axonal compaction (the magnitude of these NAA changes are too large to be explained by altered relaxation times at our TR and TE). Creatine is often assumed to be stable, but our finding of an increase and its negative correlation with Design Learning supports recent work[3] which suggests that it is subject to change following TBI. Choline's correlation with loss of consciousness (an indirect measure of injury severity) supports its use as a marker of cellular damage. These findings provide new insights into the neurobiological basis of cognitive function following TBI, presenting fresh avenues for future research.

References: 1. Adams, J. H. et al. (1982). *Annals of Neurology, 12*(6), 557-563. **2.** Chu, Z. et al. (2010). *Am J Neuroradiol, 31*(2), 340-346. **3.** Yeo, R. A. et al. (2011). *J of Neurotrauma, 28*(1), 1-11. **4.** Croall, I. D. et al. (2012). *BC-ISMRM*. **5.** Smith, S. M., et al. (2006). *Neuroimage, 31*(4), 1487-1505. **6.** Budde, M. D. et al. (2011). *Brain, 134,* 2248-2260. **7.** Kriz, J. et al. (2000). *Brain Research*, *885*(1), 32-44.