DTI and Tractography of Military-related Traumatic Brain Injury and Correlation with Neuropsychological Functions

P-H. Yeh[1], B. Wang[1], T. R. Oakes[1], H. Tang[2], J. Graner[1], H. Pan[1], W. Lui[3], L. M. French[4], F. Munter[3], and G. Riedy[3,5]

[1]Henry Jackson Foundation for the Advancement of Military Medicine, Rockville, MD, United States, [2]Uniformed Services University of The Health, [3]National Capital Neuroimaging Consortium, Walter Reed Army Medical Center, Washington DC, [4]Defense and Veterans Brain Injury Center, Walter Reed Army Medical Center, Washington DC, [5]National Intrepid Center of Excellence, Bethesda, MD, United States

Introduction: Traumatic brain injury (TBI) accounts for the majority of explosive blast injury and combat causalities in Operation Enduring Freedom in Afghanistan and Operation Iraqi Freedom. Furthermore, the variable nature of TBI presents numerous problems for medical and psychological assessment, treatment, and outcome prediction. Diffuse axonal injury (DAI) is a white matter (WM) abnormality arising from applied tearing or shearing forces caused by sudden rotational acceleration/deceleration force of head injury [1]. DAI is thought to be responsible for the majority of TBI-related neurocognitive deficits. However, currently there is no standardized way of assessing the severity of DAI nor predicting the prognosis in TBI patients. The goal of this study was to apply tract-based spatial analysis on Diffusion Tensor Imaging (DTI) data from a clinical scanner to evaluate the micro -structural changes of TBI in military-related injury, and evaluate their relationships with neuropsychologic symptoms. We hypothesized that the sensitivity of detecting WM microstructual changes can be improved by combining optimized spatial normalization and tractrography methods,

Methods: Participants included 14 documented male TBI (12 mild, 2 moderate; 10 blast injury, 4 non-blast trauma) with and without loss of consciousness (age 24.9±4.1 years, 145±239.3 days out from injury) and 13 healthy controls (HC, 4 females, 8 males, age 26.1± 5.4 years). Diffusion-weighted imaging data (3T GE750 Systems equipped with a 32-channel phased array head coil, doubly-refocused spin echo, peripheral gated, TR/TE~10000/90ms, voxel size 2.0x2.0x2 mm^3, FOV= 256mm, acquisition matrix=128x128, ~64 slices, 1 NEX) were acquired by using diffusion sensitizing gradients along 48 non-colinear uniformly distributed directions (b-value=1000s/mm^2), together with 7 non-diffusion weighted (b=0) volumes. A simple least squares fit of the tensor model [2] and diffusion tensor-derived diffusive (fractional anisotropy (FA), Trace, parallel ($\lambda1$) and radial ($\lambda2+\lambda3/2$) diffusivities) [3] and shape (linear (($\lambda1-\lambda2/\lambda1$), planar (($\lambda2-\lambda3/\lambda1$), and spherical (($\lambda3/\lambda1$) [4] measures were evaluated. Two methods were implemented for spatially normalizing DTI images onto the template space: high-dimensional tensor-based registration (HDTBR) using symmetric normalization and diffeomorphic deformation method [5] to construct a study population atlas; and skeleton-based WM representation using non-linear co-registration of FA images and warping to standard space (Tract-Based Spatial Statistics (TBSS) [6]. *A priori* hypothesis of the injured fiber tracts, including the corpus callosum (CC), arcuate fasciculus (AF, part of superior longitudinal fasciculus), inferior fronto-occipital fasciculus (IFO), uncinate fasciculus (UNC), and inferior longitudinal fasciculus (ILF) (Fig. 1A-1E), were reconstructed using streamline tractography (FACT algorithm) after warping the white matter atlas [7] to native space using inversed HDTBR method. The PCL-C (post-traumatic stress) and NBSI (post-concussive) questionnaires, California Verbal Learning Test, working memory and digit span performance were used for investigating possible inter-relationships between white matter changes and neuropsychologic symptoms in TBI patients. General linear model (GLM) analysis evaluated the local group difference (HC vs TBI) of scalar DTI measures across the whole WM and regions of interest (ROI) fiber tracts after regressing out age and gender effects. A permutation-based non-parametric approach with threshold-free cluster enhancement (TFCE) [8] was utilized for correction of multiple comparisons with controlled family-wise error rate (corrected $P_c < 0.05$) for the voxel-wise analysis.

Results: There was no significant group difference (HC vs TBI) of any DTI measures using HDTBR or TBSS. However, the *post-hoc* ROI tractography analysis showed TBI as a group had lower mean FA than healthy controls in left SLF (0.34±0.05 vs 0.38±0.02) and bilateral IFO (0.38±0.06 vs 0.42±0.03 at left; 0.39±0.06 vs 0.44±0.03 at right) (Fig.2A-2C).

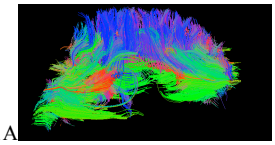
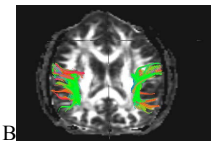
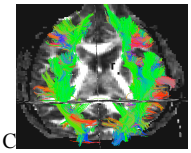
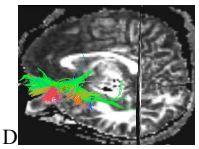
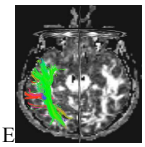
Fig.1A  Fig.1B  Fig. 1C  Fig.1D  Fig.1E 

Fig. 2 shows the box plots of mean FA of HC (left) and TBI (right) participants at left SLF (Fig 2A), left IFO (Fig. 2B), and right IFO (Fig. 2C) (FA scales range between 0.2 and 0.5).

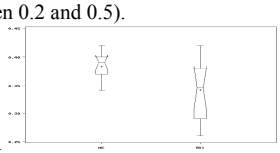
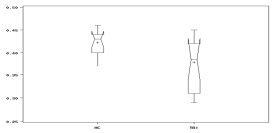
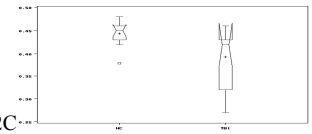
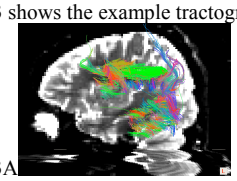
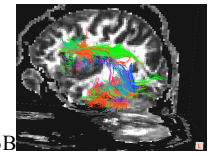
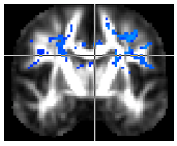
Fig.2A  Fig. 2B  Fig.2C 

Fig. 3 shows the example tractograms of arcuate fasciculus of one TBI participant (Fig. 3A, left) and one healthy control (Fig. 3B. right).

Fig. 3A  Fig. 3B  Fig. 4 

For whole brain regression analysis on DTI measures and neurcognitive functions, the "long delay recall performance" and "working memory percent correct" were found to be negatively correlated with FA, and positively correlated with radial diffusivity in the prefrontal region where anterior, superior corona radiata, cingulum bundle and SLF intersect ($P_c < 0.05$) (Fig. 4), and in trend positively correlated with spherical measure but inversely with planar measure (P_c=0.06). In addition, the mean FA of reconstructed left ILF using fiber tracking was found to be negatively correlated with working memory percent correct in TBI patients (r=-0.59, p=0.03).

Discussion and conclusions: Military TBI subjects likely have heterogeneity of brain changes due to various mechanisms of injury; thus, voxel-wise analysis using spatial normalization may not be effective in detecting microstructural changes in TBI. Our results suggest that using combined spatial normalization and tractography ROI methods may improve the sensitivity of detecting WM injury in TBI. The tensors in the regions where the fibers cross would have spherical shape due to partial volume effects [3]. White matter disruption at the regions of crossing fibers in TBI might relatively increase the directionality due to more coherently oriented fibers. This may explain the findings of inversed relationship between FA and cognitive functions at the intersecting prefrontal fiber tracts of TBI patients. This study provides evidence of compromised integrity of the fronto-temporo-parietal circuits, which play an important role of executive control and memory function in TBI.

Acknowledgments: This research was partly supported by CDMRP Grant PT074437.

Reference: 1. Meythaler, JM et al. 2001 Arch Phys Med Rehabil 82:1461-71. 2. Basser PJ, et al. 1994. J Magn Reson. 103:247-254. 3. Basser, P. 1995. NMR Biomed. 8:333-344. 4. Westin, C-F et al. 2002. Med Ima Anal 6: 93-108. 5. Zhang H et al. 2006 Med Ima Anal 10:764-785. 6. Smith, SM et al. 2006 Neuroimage. 31: 1487-1505. 7. Zhang H et al. 2010 Lec N Comp Sci 6204:83-90. 8. Smith, S.M. et al. 2009. Neuroimage. 44:83-98.