Structural Connectivity of Military-related Traumatic Brain Injury and its Relations with Neurocognition

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Introduction: Traumatic brain injury (TBI) accounts for the majority of explosive blast injury and combat causalities in recent conflicts. The variable nature of TBI presents numerous problems for medical and psychological assessment, treatment, and outcome prediction. Diffuse axonal injury (DAI), a white matter abnormality arising from applied tearing or shearing forces caused by sudden rotational acceleration/deceleration force of head injury [1], is thought to be responsible for the majority of TBI-related neurocognitive deficits [2]. 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 identify structural connectivity change after TBI and to evaluate the utility of diffusion tensor tractography for predicting cognitive changes and neuropsychologic symptoms of military-related TBI patients.

Methods: Participants included 37 TBI (29 mild, 7 moderate, 1 severe; 19 blast injury, M/F=29/8) with and without loss of consciousness (age 28.2±6.1 years, 334.5±503.8 days out from injury) and 14 healthy controls (HC, M/F= 10/4, age 26.3± 5.2 years, all R handedness). Diffusion-weighted imaging (3T GE750 Systems equipped with a 32-channel phased array head coil, dual spin echo, peripheral gated, TR/TE~10000/90ms, 2.0x2.0x2 mm^3, 256mm, 128x128, 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. We used a global tractography method, i.e. defining both end regions of the pathway and searching the space of all possible connections between these regions for the connection. Incorporation of prior anatomical information for the pathways from a set of training subjects based on an atlas facilitated the automated reconstruction of major white matter pathways, including corticospinal tract (CST), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), anterior thalamic radiation (aTR), cingulum bundles (including cingulate (CCG) and angular bundles (CAB)), superior longitudinal fasciculus (including parietal (SLFp) and temporal (SLFt) bundles), corpus callosum (including forceps major (Fmaj) and forceps minor (Fmin)), (**Fig. 1**) [3]. Fiber tract volume (corrected by total intra-cranial volume (ICV)), number, mean length, fiber density (number/volume), and diffusion tensor-derived diffusive measures (i.e. fractional anisotropy (FA), mean diffusivity (MD), parallel ($\lambda 1$) and radial ($\lambda 2+\lambda 3/2$) diffusivities, and their lateralization indices (L.I.) (e.g. (L FA – R FA) / (L FA + R FA)/2 for FA L.I. [4]), were used to evaluate group difference between TBI and HC after taking gender and age effects into account. Cognitive function, including measures of processing speed (digit symbol), memory (California Verbal Learning Test (CVLT)), verbal fluency, executive function, vocabulary (The Wechsler Test of Adult Reading (WTAR)), working memory, and clinical symptoms, i.e. post-traumatic stress (PCLC) and neurobehavioral symptom inventory (NBSI) were used for investigating possible inter-relationships between white matter changes and cognitive function/neuropsychologic symptoms in TBI patients. We also applied canonical correspondence analysis [5], a multivariate statistical technique, to evaluate the predictors among the tractography measures in classifying TBI and HC.

Results: For group comparisons of DTI tractography measures, TBI had a lower R aTR volume than HC (0.88± 0.18% vs 1.03± 0.2% of ICV, p=0.01), and a tendency of lower mean FA of L aTR (0.42±0.02 vs 0.44 ± 0.02, p=0.056); but a greater fiber density of L CST (0.45±0.07 vs 0.41±0.06, p=0.01), and longer mean fiber length of Fmaj (129 ± 11 mm vs 122± 9 mm, p=0.03). **Fig. 1** and **Fig. 2** are the examples of reconstructed pathways, a whole major white matter tracts (**Fig. 1**), CAB (L/R) of TBI (**Fig. 2A**), SLF (**Fig. 2B**) and CCG (**Fig. 2C**) (HC vs TBI). For comparing lateralization index, TBI as a group had greater R lateralization of CAB FA than HC (-0.050±0.057 vs 0.008±0.078, p=0.02) (**Fig. 3**), but a less L.I. in UF FA (0.006±0.147 vs -0.030± 0.072, p=0.04). In addition, TBI had a smaller L.I. of UF fiber length (-0.043±0.147 vs -0.150±0.170, p=0.036), and less R lateralization of CST MD than HC (0.002±0.171 vs -0.009±0.014). Partial least-squares regression showed significant ($p < .05$) correlation between verbal fluency and the volumes of L SLFt (r=0.8) (**Fig. 4A**) and L CST FA (r=0.75); CVLT delayed recall scores and L CCG fiber length (r=-0.8); CVLT immediate recall scores and R CCG volume (r=0.83); processing speed (digit symbol) and R CCG fiber number; WTAR and R CCG fiber number (r=0.67); mean reaction time of working memory and L aTR FA (r=-0.79); total PCLC score and R CCG fiber number (r=-0.7) (**Fig. 4B**) and L UF fiber density (r=0.69); NBSI and the volumes of R SLFp, aTR, and Fmin (r=-0.65 ~ -0.7). The days since injury correlated negatively with reaction time (throughputs) and spatial memory (r=-0.75), but positively with the fiber length of L CAB and L ILF (r~0.66). The discriminators explaining the majority of variance between TBI and HC measures included FA L.I. of CAB, MD L.I. of CST, fiber length L.I. of UF, FA L.I. of UF, and $\lambda 1$ L.I. of CST in the order of a less significance ($p < 0.05$).

Fig. 1 

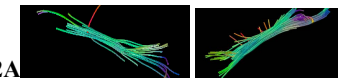
Fig. 2A 

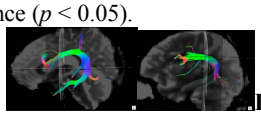
Fig. 2B 

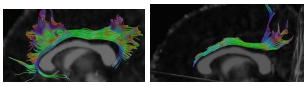
Fig. 2C 

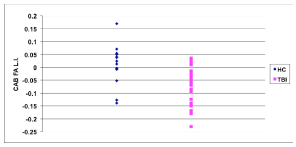
Fig. 3 

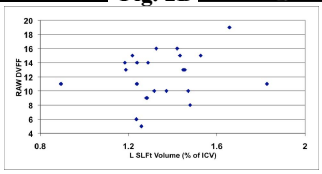
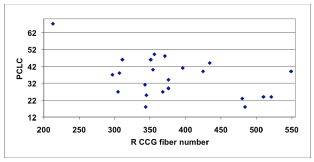
Fig. 4A 

Fig. 4B 

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 diffusion tractography ROI methods incorporated with L vs R asymmetry analysis may improve the sensitivity of detecting microstructural injury in TBI. This study also provides evidence of compromised integrity of the fronto-temporo-parietal circuits, which play an important role of executive control and memory function in TBI.

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