Deformable Registration and Tract-based Spatial Analysis of Diffusion Tensor MR Images in Mild Traumatic Brain Injury of Military-related Blast Injury

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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. Diffusion tensor imaging (DTI) provides insights of both microstructural (physiological) [2] and macrostructural (geometric) [3] features of tissue. The goal of this study was to apply tract-based spatial analysis on DTI data from a clinical scanner to evaluate the micro- and macro-structural changes of mild TBI (mTBI) in military-related blast injury, and evaluate their relationships with neuropsychologic symptoms. Our hypothesis was that, using the optimized spatial normalization method would improve the sensitivity for detecting WM injury in mTBI. **Methods:** Participants included 37 documented male mTBI with and without loss of consciousness (age 28.7±7.8 years, 77.6±56.2 days out from injury) and 11 healthy male controls (HC, age 22.7± 2.6 years). Diffusion-weighted imaging data (1.5T GE Signa, HDx-rev 14.0, TR/TE=7000/90ms, effective voxel size 1.0x1.0x6.5 mm^3, FOV= 256mm, acquisition matrix=128x128 with padding to 256x256, 24 slices, 1 NEX) were acquired by using diffusion sensitizing gradients along 24 non-colinear uniformly distributed directions (b-value=800s/mm^2), together with additional acquisition of one non-diffusion weighted (b=0). A simple least squares fit of the tensor model [4] and diffusion tensor-derived diffusive (fractional anisotropy (FA), Trace, major ($\lambda1$) and minor ($\lambda2+\lambda3/2$) diffusivities) [2] and shape (linear (($\lambda1-\lambda2/\lambda1$), planar (($\lambda2-\lambda3/\lambda1$), and spherical (($\lambda3/\lambda1$) measures were evaluated. Two methods were implemented for whole brain tract-based spatial analysis, high-dimensional tensor-based registration (Tensor Based Morphometry (TBM)) using symmetric normalization and diffeomorphic deformation method [5] reconstructs study population atlas and DTI scalar measures in template space; while skeleton-based WM representation using non-linear co-registration of FA images and warping to standard space (Tract-Based Spatial Statistics (TBSS)) [6]. Analysis of covariance (ANCOVA) and general linear model (GLM) analysis evaluated the local group difference (HC vs mTBI) across the whole WM after smoothing (FWHM=7mm) (TBM) and WM skeleton without smoothing (TBSS) (both thresholded to FA=0.12) after regressing out age effect. Psychopathy Checklist-Revised (PCL-R) [7] assessment was used to evaluate the neuropsychologic symptoms of mTBI subjects. The linear associations of DTI measures and PCL-R scores in mTBI group were evaluated by accounting for the age covariate. The mTBI subjects were further divided into 3 groups (n=12 each, based on the z-score (low (L), moderate (M-), high (H-mTBI), higher scores, greater symptoms) of PCL-R by assuming the HC has no psychopathic symptoms, and the subgroup differences of DTI measures were re-evaluated using the approaches as described above. Monte Carlo (MC) simulation created a distribution of cluster size (P_u =0.01) with clustering and a permutation-based non-parametric approach with threshold-free cluster enhancement (TFCE) [9] were both utilized for correction of multiple comparisons with controlled family-wise error rate (corrected $P_c < 0.05$).

Results: There is no significant group difference (HC vs mTBI) or association between DTI measures and severity of psychopathic symptoms using TBM or TBSS after correcting using MC (46 voxels, t=2.7 for group comparison, 14 voxels, t=3.6 for regression) or permutation test for multiple comparisons. However, mTBI group has lower $\lambda1$ and trace near left superior longitudinal fasciculus (*SLF*) (Fig. 1a), but higher FA at left anterior corona radiata (*ACR*) and bilateral optic radiations (Fig. 1a) and lower spherical measure at left occipital region (Fig. 1c) at smaller cluster size thresholding (t=2.5, $P_c < 0.05$). Psychopathic severity is inversely associated with FA and positively with spherical measure at right optic radiation and planar measure at left splenium (Fig. 2b) at smaller cluster size (t=3.0, $P_c < 0.05$). H-mTBI has the bilateral microstructual changes in the projection and long association fibers involving the connections of dorso-lateral prefrontal cortex to other (sub)cortices, i.e. high FA at the junction of right superior corona radiata, dorsal cingulum and body of corpus callosum (*CC*) (Fig. 3a, yellow), low FA at right thalamus, right corticospinal tract (*CST*), and left *SLF* (Fig. 3a, blue), through the cortico-striato-thalamic-cortical, fronto-cerebellar, fronto-limbic circuits and the inter-hemispheric connections. M-mTBI has the most of the changes in the unilateral long association fibers (high FA in Fig. 3b); while L-mTBI has WH disruption mostly involved in the short association fibers in the frontal and temporal subcortical regions (Fig. 3c). L-mTBI has high FA and $\lambda1$, but low spherical measure at the posterior body of *CC* compared to HC.

Discussion and conclusions: 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 the mTBI might relatively increase the directionality due to more coherently oriented fibers. This may explain higher FA, but geometric changes in mTBI at the posterior part of CC fibers where *CST* intersects with splenial fibers, and the junction of external capsule and posterior limb of internal capsule. Bilateral hemispheric micro-, and macro-structural changes of opposite directions in H-mTBI compared with HC might be caused by the compensatory neuroplasticity from the repair process. This study provides evidence of compromised integrity of the inter-hemispheric connections, fronto-limbic and cortico-striatal circuits and motor control in mTBI. These abnormalities could be partially responsible for neuropsychopathic symptoms in mTBI.

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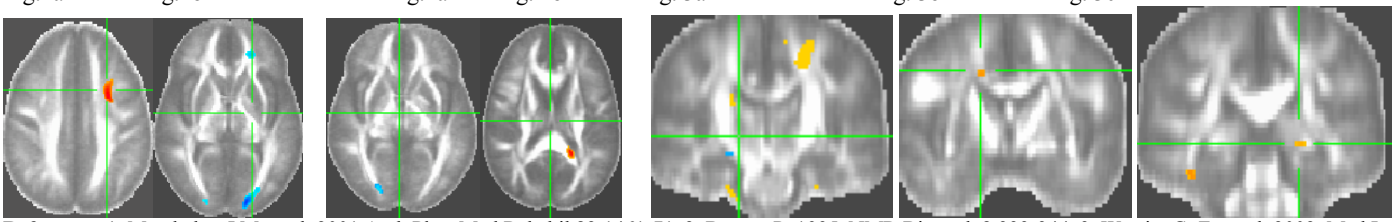
Figures: TBM results overlaid on the mean FA image

Fig.1a Fig.1b Fig.2a Fig. 2b Fig. 3a Fig. 3b Fig. 3c



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