Symptomatic White Matter and Gray Matter Changes in Mild Traumatic Brain Injury

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Introduction: Simultaneous detection of the gray matter and white matter microstructural lesions is important in understanding the pathophysiologic mechanisms following brain injury. However, any single neuroimaging modality is not capable of monitoring both structural and functional changes. The goals of this study is to use multimodal imaging techniques to add strength of providing a quantitative measure of the contribution of each metric for identifying disrupted brain networks in traumatic brain injury (TBI) patients.

Methods: Participants included 70 wounded mild TBI (mTBI) warriors (non-penetrating injury, age = 32.8 ± 7.3 years, 1 female, 35 subjects with PTSD comorbidity, 16 of them injured within a year) with persistent symptoms and 20 healthy controls (HC, age= 33.6 ± 10.6 years, 10 females) who underwent a series of structural and functional scans on a 3T scanner (Philips Achieva), including diffusion-weighted imaging (32 directions with b=1000), and pseudocontinous arterial spin labeling (pCASL) imaging. Diffusion tensor imaging (DTI)-metrics, including fractional anisotropy (FA), mode of anisotropy (MO), *trace* (tr), axial diffusivity (AD), and radial diffusivity (RD) of whole brain and skeletonized white matter, as well as regional major fiber tracts (**Fig. 1**) segmented using probabilistic tractography combined with a global fiber tracking method (TRACULA)[1] were used to assess white matter integrity. Specifically, high-dimensional tensor-based image registration[2], including symmetric normalization and diffeomorphic deformation (DTITK toolbox) of diffusion tensor images for spatial normalization followed by tract-based spatial statistics (TBSS)[3] analysis was used to assess whole brain white matter integrity. pCASL data were processed using a standard kinetic model, embodying a special case of the general kinetic model[4] for parameter estimation by applying a probabilistic inference approach for nonlinear model[5] to estimate cerebral blood flow (ml/100g /min). In addition, the voxel-wise image of left-right hemispheric asymmetric index (L-R / (L+R)/2) was also created voxel-wisely for assessing the group difference of asymmetry between TBI and controls. To find the weighted combination of the multivariate metrics to best separate the TBI and HC two groups, and TBI group with and without comorbid PTSD, multivariate tests using linear discriminant analysis (LDA) with the related Fisher's linear discriminant[6] were used to maximize the ratio of the between-group variance to the within-group variance, with the linear discriminant function (**L**) written as $L = a_0 + a_1x_1 + a_2 x_2 + ... + a_nx_n$. , where the weighting parameters (a_n) were the discriminants of different modalities (x_n) that maximize the between-group discrimination. Voxel-wise between-group comparisons were conducted using general linear model by regressing out the effects of gender and age (corrected $Pc < 0.05$). TBI groups were further broken down to TBI with and without PTSD (2 TBI groups plus controls), and TBI with and without PTSD who were injured less or longer than a year. Mixed modeling by taking within-subject variability of regional white matter tract was utilized to analyze the regional difference between TBI patients and controls.

Results: Fig. 1 illustrates an example of segmented fiber tracts from one TBI participant. Fig 2. Clusters with significance of group difference.

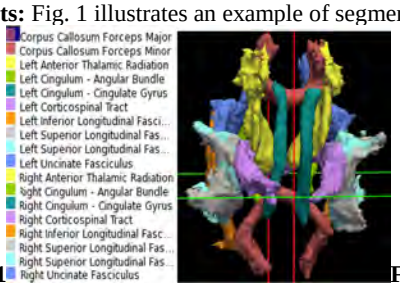

Fig. 1

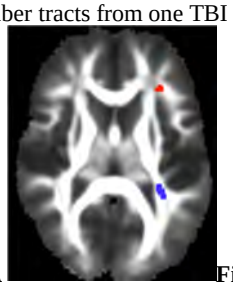

Fig.2A

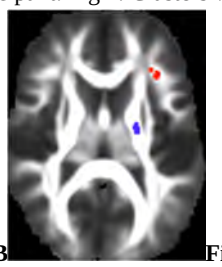

Fig. 2B

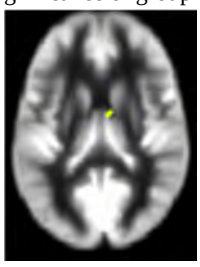

Fig.2C

Using univariate analysis of DTI measures based on whole brain TBSS (thresholded at FA >=0.2), no statistically significant cluster of group difference (control vs TBI) was found. After breaking TBI group into 2 groups with or without PTSD, the PTSD-TBI as a group had lower FA as well as higher RD than NonPTSD-TBI in the region of left sagittal stratum (blue in **Fig.2A**), and higher MO in the region of left superior longitudinal fasciculus over the frontal region (red in **Fig. 2A**). These findings suggest that de(dsy)-myelination, instead of axonal injury itself, contributes to white matter disruption in PTSD patients. No significant group difference of DTI measures between chronic TBI (injured more than a year ago) and subacute TBI (injured within a year) was revealed. Larger and greater numbers of clusters were identified by multivariate LDA method using FA, MO, AD and *trace* modes (**Fig. 2B**). TBI as a group was different from the controls in the region of the posterior segment of left internal capsule on the path of left cortico-spinal tract (blue in **Fig. 2B**). The significant clusters of PTSD-TBI and NonPTSD-TBI also became larger at the similar location found using univariate analysis, demonstrating that the multivariate analysis is more sensitive in diagnosing TBI than using the univariate. For the region of interest analysis (ROI) of DTI metrics on the segmented major fiber tracts, TBI as a group had lower FA in the left CST (p=0.02), consistent with the results using LDA multivariate analysis, and lower AD in the forces minor (p=0.04) than the control group, indicating the TBI patients of this cohort were more likely to have motor dysfunction due to TAI. There is no statistical significance of the voxel-wise CBF values between TBI and controls after correcting for multiple comparisons. However, there is significant difference of L-R asymmetry over the anterior part of the thalamus (**Fig. 2C**), adjacent to the genu of internal capsule where LDA found group difference.

Discussion and conclusions: In summary, aberrant gray matter and white matter caused by TBI likely has different pathophysiologic mechanisms from that of PTSD by itself. Different injury mechanisms in each individual greatly impedes the sensitivity of voxel-wise group analysis. Combining multivariate analysis along with tractography techniques would allow us to have a better understanding of neurophysiologic consequences of the disrupted brain networks, and has potential in differentiating "pure" TBI from TBI comorbidity, such as comorbid PTSD and TBI

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