Diffusion MRI Connectometry Findings and Symptom Reporting Following Traumatic Brain Injury

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Introduction: Traumatic brain injury (TBI) accounts for the majority of explosive blast injury and combat causalities in recent conflicts. TBI patients present numerous problems for medical and psychological assessment, treatment, and outcome prediction. Traumatic axonal injury and its related sequelae such as post-traumatic inflammation are considered as the main underlying pathological causes of the clinical manifestations in TBI patients. However, it is difficult to identify those microstructural white matter changes, particularly in mild TBI (mTBI) patients, let alone to relate the changes to clinical symptoms. The goal of this study was to identify white matter connectivity change after TBI and to relate neuropsychologic symptoms with abnormal white matter connectivity using diffusion MRI connectometry [1].

Methods: Participants included 417 TBI patients (381 mild, 28 moderate, 8 severe; 343 blast injury, M / F = 397/20, age = 34.2 ± 7.9 years) and 29 healthy controls (M/F = 19 / 9, age = 31.0 ± 8.0 years). Self-scored inventories, including neurobehavioral symptom inventory (NBSI, including physical, sensory, cognitive and affective subdomains), post-traumatic stress (PCLC), CES (combat exposure scale), SF-36 (short form health survey), SWLS (satisfaction with life scale), were used to assess severity of neuropsychologic symptoms in TBI patients. Diffusion-weighted MRI (48 direction, b-value=1000s/mm^2, 2.0x2.0x2 mm^3) was acquired using a 3T scanner (GE750 system). Preprocessing steps included correction of geometric distortion, between-volume rigid body co-registration, and eddy current artifact correction. The diffusion-weighted imaging was then transformed to standard space using q-space diffeomorphic reconstruction (QSDR) [2], a method transforming the distribution of diffusion spins to a template space based on a given deformation field. The transformed distribution was used to calculate the spin distribution function (SDF) which scales with spin density, thus making it comparable across voxels and less susceptible to corrupted signals due to partial volume effect [2]. Multiple regression models were conducted on SDFs with the regressors of the scores of neuropsychologic symptoms, age and gender. The statistical significance was determined by applying permutation testing to the group to obtain the null distribution of the track length with a threshold of |t-score| greater than 2. Only the regions found significant difference in the SDFs were used to reconstruct the fiber pathways by a applying deterministic fiber tracking algorithm [3]. Tracks with length greater than 40 mm were collected, and false discovery rate (FDR) of significance was reported (**Fig. 1**).

Results: For comparing TBI to HC, there is no main effect of significant connectivity difference between TBI and control groups. For relating self-reporting symptoms to white matter connectivity in TBI patients, decreased connectivity over the paths of bilateral sagittal stratum (SS) (including inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and posterior thalamic radiations), forceps major, and the bilateral posterior segments of internal capsule was associated with post-concussive symptoms (total NBSI score) (**Fig. 2**) and the symptoms of PTSD (total PCLC score) (both had FDR = 0.01). The physical domain of NBSI was mainly associated with decreased connectivity over the paths of the splenium of corpus callosum (CC), SS, posterior segment of the internal capsule and corona radiata (FDR= 0.03). The sensory domain of NBSI and CES score mainly correlated with decreased connectivity over the genu and bodies of CC, anterior segment of internal capsule, external capsule, and the dorsal cingulum bundles (FDR=0.007, 0.004 respectively). The sum of SWLS correlated with increased connectivity over the pathways interconnecting the parietal region and the temporal region, as well as cingulate (FDR=0.07). No significant correlation was found between SF-36 and white matter connectivity.

Discussion and conclusions: Although diffusion MRI and tractography have become important tools in assessing TBI, there is limited evidence to support a causal link between brain changes and symptom reporting, especially in mild and chronic TBI. Results from correlational studies using DTI metrics were inclusive and varied between (sub)acute stage and chronic stage of brain injury due to the difference of underlying cellular pathological mechanisms, e.g. cytotoxic edema in days vs. gliosis in weeks to months following trauma [4]. In this study, we found that the strength of connectivity in white matter tracts, e.g. the thalamic-cortical projection fibers and fronto-limbic association fibers, is related to clinical symptoms in TBI patients. By quantitating SDFs, the diffusion connectometry method is less susceptible to the loss of diffusion signals and provides an alternative way to evaluate white matter microstructural changes in various stages following TBI.

Figures: Fig. 1. Flow chart of reconstructing connectometry. **Fig. 2.** Pathways associated with decreased connectivity and NBSI.

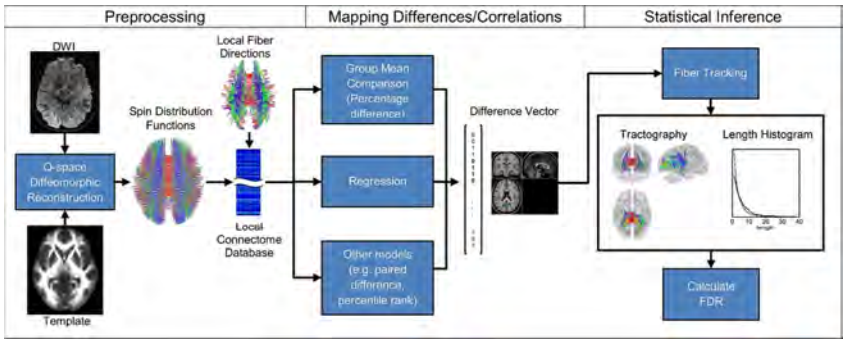

Fig. 1

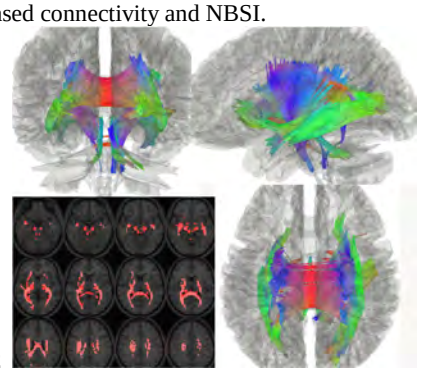

Fig. 2

Reference: 1. Yeh, F-C et al. (2013). Neuroimage: Clinical 2 (2013) 912-921. 2. Yeh, F-C et al. (2013). Neuroimage 58, 91-99 (2011). Neuroimage 58, 91-99 (2011). 3. Yeh, F-C et al. PLoS ONE 8(11): e80713). 4. Yeh, P-H et al (2014). HBM 35(6), 2652-2673.