Voxel-based DTI of longitudinal changes post pediatric TBI compared with age-matched developing controls

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Introduction:
Traumatic brain injury (TBI) is a leading cause of death and disability during childhood. Previous quantitative diffusion tensor imaging (DTI) reports using metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial and radial diffusivities, $\lambda_{//}$ and $\lambda_{\perp}$ revealed subtle differences of grey matter (GM) and white matter (WM) during recovery from TBI [1]. However, there is no systematic whole brain study on the longitudinal evolution of GM and WM diffusion abnormalities during recovery from pediatric TBI patients. In this work, we perform a longitudinal study of 25 pediatric TBI patients who sustained moderate and severe TBI and 21 age-matched pediatric orthopedic comparison subjects. DTI was acquired 3 months after injury for each participant. DTI scans were repeated at 24 months after injury for both groups to examine recovery in the TBI group in relation to normal neurodevelopment changes during childhood and adolescence [2]. Voxel based morphometry (VBM) [3] is adopted for longitudinal data analysis for its unbiased approach and comprehensive assessment of differences throughout the whole brain [4]. An optimal VBM procedure using the recently available DARTEL technique in SPM8 is developed to minimize misregistration. The VBM results for FA, MD maps of GM and FA, $\lambda_{//}$ and $\lambda_{\perp}$ maps of WM are shown in Fig.1 and Fig.2 respectively.

Methods:
Twenty-five pediatric TBI patients with moderate to severe TBI (20 boys & 5 girls, age = 11.3 ± 4.9 years {mean ± SD}, Glasgow Coma Scale 3-13) and twenty-one age-matched children with orthopedic injuries not involving the head were imaged using a Philips 3.0T Intera system with a SENSE parallel imaging receive head coil. The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the well-balanced Icosa21 encoding scheme, b=1000sec/mm^2, TR/TE = 6100/84msec. The Field-of-view = 240 × 240mm^2, and voxel volume = 0.9375x0.9375x3 mm^3. DTI acquisition time was approximately 7 minutes. The same scan was repeated at 24 month following the injury for all participants. The FA, MD, λ// and $\lambda_{\perp}$ maps were computed [5] for each subject and were normalized to the International Corstium for Brain Mapping (ICBM) atlas using SPM8. Tissue segmentation was then completed for the resulting FA and MD maps using the segmentation tools in SPM8. Both segmented FA and MD maps of GM were imported to DARTEL tool in SPM8 for optimal normalization. The template in DARTEL is created iteratively based on the entire data subsets in analysis. Then Jacobian-scaled warped images are generated using a single velocity flow fields which parameterize the deformations to the template. The end result volumes are smoothed by a Gaussian filter with size of 8. Statistical analysis of FA and MD values was performed with a two sided t-test. A p-value of less than 0.001 for longitudinal study and a p-value of less than 0.05 for group difference study were considered significant and the corresponding area is displayed on ICBM atlas in Fig.1 and Fig2 using software MRIcroN for GM and WM respectively. The results in Fig.1and Fig.2 are displayed using corresponding t values (P<0.001 corresponds to t>3.7 or t<-3.7 while P<0.05 corresponds to t>2.3 or t<-2.0).

Results:
Group Differences at the initial scan relative to the comparison group: FA and MD of GM in the TBI group were found to be decreased in the thalamus, putamen, pallidum, cerebellar hemispheres, and mid temporal regions; MD of GM was also decreased in the caudate, vermis, hippocampus, and orbital frontal regions; FA of WM in the TBI group was decreased at fornix, splenium of the corpsu callosum (sCC) and temporal cortx; $\lambda_{//}$ of WM in the TBI group was increased at The genu and splenium of the CC, respectively. Increased $\lambda_{\perp}$ of WM in the TBI group was found in cingulum, anterior limb of internal capsule (alIC), frontal, parietal, temporal and occipital cortex and deceased $\lambda_{\perp}$ of WM only in fornix. **Group Differences at the follow-up scan relative to the comparison group**: FA of GM in the TBI group was reduced at more clusters in the thalamus, putamen, pallidum; in the vermis and cerebellar hemispheres and in cortical regions including calcarine, fusiform, cingulum, precentral, lingual, superior motor, mid frontal and right mid temporal regions. MD of GM in the TBI group was increased in in the putamen, cerebellar hemispheres, left lingual, left calcarine, and right postcentral regions. Also MD in the TBI group was decreased in thalamus and vermis as compared with controls. FA of WM in the TBI group was decreased at SCC, fornix, temporal and paritel cortex; $\lambda_{//}$ of WM in the TBI group was increased at allC, brain stem, parietal, temporal and frontal cortex; $\lambda_{\perp}$ of WM in the TBI group was increased at cingulum, frontal, parietal, temporal, occipital cortex and decreased at SCC and fornix. **Changes over Time in the comparison group**: Relative to the initial scan, FA of GM from the follow-up scan was reduced in vermis and lingual regions and increased in left pallidum, left thalamus, left calcarine and right precuneus regions; MD of GM was increased only in the calcarine region. Relative to the initial scan, FA of WM from the follow-up scan was increased in CC, ALIC, Frontal, parietal, occipital, and temporal cortex; $\lambda_{//}$ of WM was decreased in frontal, temporal parietal cortex; $\lambda_{\perp}$ of WM of controls increases at GCC, ALIC, frontal, parietal and occipital cortex. **Change over Time in the TBI group**: Compared to the control group, there were considerably more clusters with longitudinal changes identified in FA and MD maps of GM over 24 month period. Relative to the initial scan, FA of GM from the follow-up scan was decreased in calcarine, cingulum, left caudate, precuneus, fusiform, cerebellar hemispheres, lingual and mid temporal regions; MD of GM from the follow-up scan was decreased in caudate, thalamus, putamen, calcarine, fusiform, hippocampus and lingual regions. There were less longitudinal changes in FA, $\lambda_{//}$ and $\lambda_{\perp}$ maps of WM over 24 month period. FA of WM from follow-up scans was increased in cingulum, fornix, alIC, frontal, parietal and temporal cortex. There are no significant longitudinal changes of $\lambda_{//}$ and $\lambda_{\perp}$ except an increased $\lambda_{\perp}$ found in small area at parietal cortex.

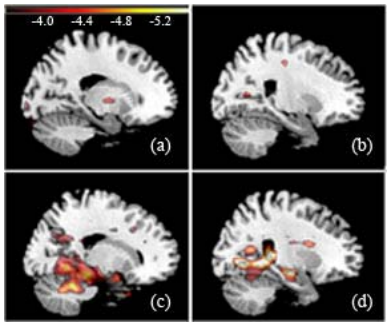

Fig.1. VBM results of GM longitudinal changes in the comparison group (FA (a) and MD (b)) and TBI group (FA (c) and MD (d)).

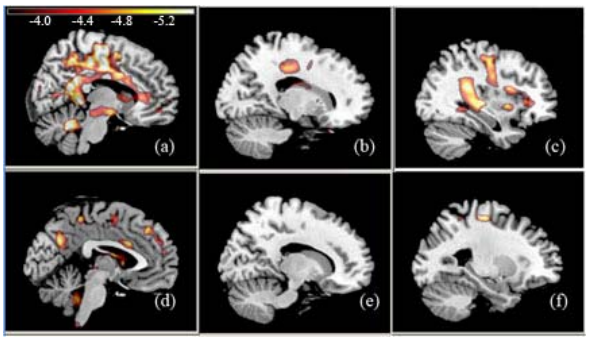

Fig.2. VBM results of WM longitudinal changes in the comparison (FA (a), $\lambda_{//}$ (b) and $\lambda_{\perp}$ (c)) and TBI group (FA (d), $\lambda_{//}$ (e) and $\lambda_{\perp}$ (f)).

Discussion: The 2-year follow-up scan of 25 child TBI patients and 21 pediatric controls reveal different longitudinal changes in both GM and WM during the first two years following moderate and severe pediatric TBI compared with normal neurodevelopment changes during childhood and adolescence. There were significantly more longitudinal GM changes and less WM development in TBI patient cortical and subcortical structures. Along with the group difference characterized by widespread reduction in anisotropy and diffusivity, increase in axial and radial diffusivity in local structures, the VBM result of this study provide insight into the significant impact of TBI on GM and WM. The identified regions should be correlated with behavior scores in future studies.

Reference:
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