DTI parametric lesion load is a better surrogate marker when regional analysis is insensitive to distinguish between control and TBI population.

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Introduction: In general population, mild Traumatic Brain Injury (mTBI) is a major public healthcare burden that causes a constellation of physical, cognitive, and emotional symptoms that significantly impact the patients' quality of life and cost the nation more than $60 billion each year in terms of direct medical costs and indirect costs like loss of productivity. The cause of mTBI especially non-combat related injuries is diversified and the most common causes are from falls, motor vehicle accidents, sports-recreation related injuries, injuries from assault and use of fire arms. mTBI usually results in primary and secondary injuries, primary injuries being the direct result of the traumatic impact and the secondary injuries are from complex biochemical cascade of events that is being triggered by the primary traumatic event. Recent animal studies, neuropathological findings and computer modeling have shown various potential mechanisms of injury because of high strain effects in traditional coup and contrecoup regions and high stress effects in white matter regions leading to diffuse axonal injury (DAI)[1]. Conventional, clinical imaging is insensitive to identify the lesions or microscopic white matter abnormalities as a result of TBI. Advanced magnetic resonance techniques like, diffusion tensor imaging (DTI) has been shown to detect TBI pathologies and functional impairments that underlie patient's cognitive symptoms as well as alteration in axonal integrity occurring including TBI[2]. The purpose of this study is to determine what kind of role does DTI–MRI quantitative parameters namely axial diffusivity (AD), radial diffusivity(RD), apparent diffusion coefficient(ADC) and trace(Tr) play in driving fractional anisotropy (FA) changes in terms of lesion load that serve as good predictors of tissue damage or pathology and guide in improving therapeutic and rehabilitative efforts.

Materials and Methods: Thirty seven healthy control subjects (age range = 19-57 yrs; 29 ± 10 M±SD) and twenty seven mTBI subjects (GCS of 13-15; age range = 19-63 yrs; 38 ± 14 M±SD underwent trauma imaging scanning protocol on a 3T Siemens Verio system with 32-channel head coil. DTI in 30 directions (resolution = 1.3x1.3x2mm; 60 axial slices; TR/TE = 13300/124 ms, and b values of 0 and 1000 sec/mm^2) was part of the TBI protocol that was used for both the control and mTBI group. All the mTBI subjects were recruited from Emergency Department of Detroit Medical Level 1 Trauma Center. All the mTBI subjects were scanned within 48 hrs of emergency visit.

Processing: DTI studio was used to create DTI parametric maps from DTI-MRI images. Brain extraction tool from Mricro was used to skull strip the no diffusion weighted B0 image and was used as a mask over the DTI maps to skull strip the images. These skull stripped FA images were spatially normalized (nonlinearly) in SPM8 using FA as white matter weighting image to a FA template that was created using the same control group. All other DTI parametric maps like AD,RD,ADC and Tr were shadow transformed to the standard space using the transformation matrix generated during the process of normalization. Age correction for all the DTI maps was done by using a slope map created from DTI parameter vs age regression plot. Automated segmentation using SPM8 produced tissue-class probability maps for each subjects FA image. A WM binary mask was created by weighting the FA maps with the product of white matter probabilistic maps and the control group standard deviation map; this helped in masking out the nonwhite matter voxels. A composite mask resulting from the product of thresholded white matter segmented images from the control group as well as the TBI subject was used to mask out the voxels that have been resulted because of mis-registration. An atlas based white matter parcellation map comprising of forty eight regions in ICBM_MNI space was used to do the regional analysis. A voxel was only included for analysis if it was included in an ROI mask and in subject's WM-only FA image. For each ROI, we extracted the mean number of voxels for all subjects, the FA mean and standard deviation. For each mTBI subject, a Z-score map was created for all the DTI parameter maps by using the controls mean map and standard deviation map. To investigate the diagnostic values of quantitative diffusion tensor imaging parameters in detecting abnormalities in white matter of TBI subjects, we have measured and compared their absolute values against a group of healthy controls and also measured the total number of voxels in all of the DTI quantitative parameters z score maps that are 3 or 4 standard deviations below or above the mean of the control population and considered them as abnormal voxels and termed the same as "lesion load (LL)".

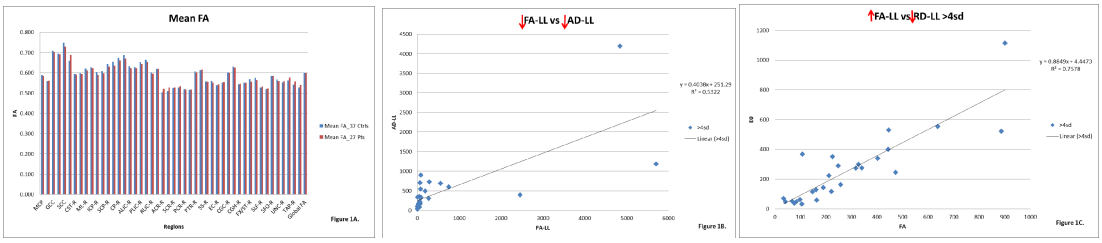

Figure A. Regional analysis of mean FA between controls and mTBI Figure B. Plot showing decreased FA-LL and decreased AD-LL Figure C. Plot showing increased FA-LL and decreased RD-LL

Results: Regional analysis of all the DTI parametric maps revealed no significant difference for any of the white matter regions between the control group and mTBI group (Figure 1A). For all the DTI parametric maps lesion load analysis, the lesion load in the mTBI group was significantly different (p<0.01) when compared to the lesion load in the control group. A correlation analysis was also done for all the DTI parametric maps against the FA to find out which diffusion parametric map drives the FA changes. A strong positive correlation is found between the decreased FA-LL and decreased AD-LL(r=0.73) (Figure 1B). A strong positive correlation is found between the increased FA-LL and decreased RD-LL(r=0.87) (Figure 1C). A strong positive correlation is found between the decreased FA-LL and increased ADC-LL(r=0.50). A strong positive correlation is found between the decreased FA-LL and increased Tr-LL(r=0.50) (Figure 1C).

Discussion and conclusion: TBI is heterogeneous with different injury pathology and injury locations suggestive of lesions in the white matter tracts that are only sensitive to DTI and might go unnoticed in other classic conventional MR sequences or CT scans. These results suggest that there is a clear indication of increased lesion load of reduced FA in the TBI patient group and this can be attributed by the decreased axial diffusivity and increased radial diffusivity. These different associations might give us better understanding behind the strong driving forces in predicting the FA white matter changes. This study also exposes the fact that when regional analysis fails to be sensitive in identifying the abnormal regions then lesion load can be a strong surrogate marker in establishing associations between diagnostic or prognostic tools and patient clinical outcomes that can help in diagnosis or neurological deficits in the TBI population.

References: 1. Huisman, T.A., et al., *Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury.* AJNR Am J Neuroradiol, 2004. **25**(3): p. 370.**2.** Benson, R.R., et al., *Global white matter analysis of diffusion tensor images is predictive of injury severity in traumatic brain injury.* J Neurotrauma, 2007. **24**(3): p. 446-59.