Longitudinal Changes of DTI Parameters During Acute and Sub-acute Phase Following Mild Traumatic Brain Injury Using Tract-Based Spatial Statistics Analysis: the Preliminary Results

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Introduction: Traumatic brain injury (TBI) accounts for approximately 40% of all deaths from acute injuries in the United States and affects approximately 1.2 million Americans annually [1]. To overcome the under-diagnosis of symptom-based clinical routine and insensitivity of conventional MRI and CT, recent development in the diffusion tensor imaging (DTI) technique has been applied to achieve more robust early detections of axonal injuries with mild TBI. DTI studies of both human mTBI subjects [2,3,4] and animal TBI models [5] have shown different alteration patterns of tensor derived parameters, such as fractional anisotropy (FA), axial and radial diffusivity, with the evolution of neurological impairments following initial concussions. In this study, we performed a prospective longitudinal study of mTBI patients and healthy controls. Three DTI scans were acquired for each subject to characterize the acute, late acute and sub-acute phase following mTBI. The tract-based spatial statistics (TBSS) was then performed [6] to achieve voxelwise statistical comparisons of longitudinal changes of DTI.

Method: *Subjects:* The study is ongoing and so far 13 mTBI patients and 21 age- and gender-matched controls were analyzed. For all patients, the initial Glasgow Coma Scale (GCS) were within 13-15. No extra- and intra-cranial injuries were observed in CT scans. No other neurological disorders were founded with all subjects investigated. For each mTBI subject, three DTI scans were acquired within 24 hrs, 1 week and 1 month following the initial concussion. The same acquisition scheme was applied to each control subject. *Image acquisition:* DTI scans were performed on a 3T Siemens scanner and a 3T GE scanner with parameters: TR/TE=10s/100ms, isotropic 2x2x2 mm voxel, acceleration factor=2, 60 diffusion gradient directions with b=700 s/mm^2 and one average, b=0 images with 10 averages. While longitudinal scans of the same subject were acquired on the same scanner, assignments of scanners for different subjects were randomized to minimize scanner bias. Dual-echo GRE images were also acquired for susceptibility corrections. *TBSS analysis*: All image processing steps and statistical analyses were performed using FSL package (FMRIB, Oxford, UK). Image distortions due to eddy-current and susceptibility artifacts were corrected before tensor calculations and all FA maps were fed to the TBSS toolbox to generate the mean FA skeleton that represents the white matter tracts common to all subjects. Longitudinal changes of four DTI derived parameters, FA, MD, axial diffusivity and radial diffusivity, were then characterized with non-parametric permutation tests using the Randomize toolbox [7] in FSL. Voxelwise comparisons were carried out to perform paired permutation t-tests among longitudinal DTI scans of the same group of mTBI subjects and unpaired permutation tests between the mTBI group and the control group at the same time point. Multiple comparison issue was corrected using the threshold-free cluster enhancement (TFCE) approach [8] in FSL. For each DTI parameter, two contrasts, increased and decreased trends, were tested.

Results: Although none of the comparisons reach statistically significant level with corrected p value <0.05, there are clear trends of longitudinal changes of DTI parameters following mTBI (**Tab.1**). With comparison to control, voxels with decreased FA at the acute phase (within 24 hrs) of the mTBI group were observed at the anterior corona radiata (ACR) and the genu corpus callosum (GCC), approaching significance (corrected p<0.1). This trend tends to be normalized with time. No trend in changes of other three DTI parameters was observed between the mTBI and control group. For comparisons between longitudinal datasets of same mTBI subjects, TBSS identified multiple regions in white matter tracts with increased radial diffusivity (corrected p<0.1), decreased FA (corrected p<0.1) and increased MD (corrected p<0.15) at the acute stage (with 24 hrs) with comparison to the late acute (1 week) and sub-acute phase (1 month). Regions with corrected p values smaller than 0.082 (**Fig.1** & **Tab.2**) include the genu and body corpus callosum (GCC & BCC), anterior, superior and posterior corona radiata (ACR, SCR and PCR), external and internal capsule (EC & IC), cingulum (CING) and the cerebral peduncle. Voxels with decreased FA and increased radial diffusivity tend to be in clusters at same structures spatially (**Fig. 1**).

Discussion: Our experimental design of monitoring longitudinal DTI changes within 24hrs, at 1 week and after 1 month following mTBI provides invaluable insights into the pathological evolution at the acute and sub-acute phase of axonal injuries. Similar to the study from Arfanakis et al [2] which also focused on the acute changes in selected regions, we observed decreased FA and increased radial diffusivity in several major white matter tracts such as GCC and IC, although our findings so far are only approaching significance (p<0.1) due to the small number of subjects and subtle DTI changes with mTBI. The application of the fully automated TBSS approach also enables detections of DTI changes within the whole white matter tracts, such as changes in the cerebral peduncle. Different from increased radial diffusivity in the recovery phase (9-15 months) of TBI [9] due to demyelination, increased radial diffusivity and consequently decreased FA in the acute phase of mTBI are consistent with the possibility of neurofilament misalignment to create projections of the principal diffusivity onto the transverse plane [2]. Confound pathological and physiological changes follow initial concussions with mTBI, such as neurofilament misalignments, cellular edema and demyelination. Consequently, these pathomorphological changes alter the diffusive characteristics of the white matter mirco-structures in a time-dependent and confound manner. As an ongoing project, we expect further validations of reported longitudinal DTI changes with more data acquired in the future.

Table 1. Comparisons of longitudinal changes of DTI parameters following mTBI. (the minimum corrected p values of each comparison are listed)

DTI Parameters	Con-trast	24hrs (A) vs. 1 week (B)	24 hrs (A) vs. 1 month (B)	1 week (A) vs. 1 month (B)
FA	A>B	0.795	0.903	0.481
	A<B	**0.100**	**0.060**	0.374
MD	A>B	0.344	**0.136**	0.316
	A<B	0.832	0.9552	0.750
Axial_D	A>B	0.820	0.380	0.282
	A<B	0.520	0.942	0.936
Radial_D	A>B	0.264	**0.080**	0.271
	A<B	0.750	0.942	0.713

Table 2. Typical regions with decreased FA and increased Radial_D in mTBI within 24 hrs vs. same mTBI subjects after 1 month.

White matter Tracts	#Voxel in TFCE clusters	Talairach coordinates of voxel with the minimum p			
		P_{min}	X(mm)	Y(mm)	Z(mm)
ACR and GCC	3472	0.060	19	38	0
Posterior limb of IC	304	0.076	25	-10	17
Cerebral Peduncle	188	0.080	19	-16	-7
SCR	95	0.080	23	10	20
EC	151	0.082	34	1	1

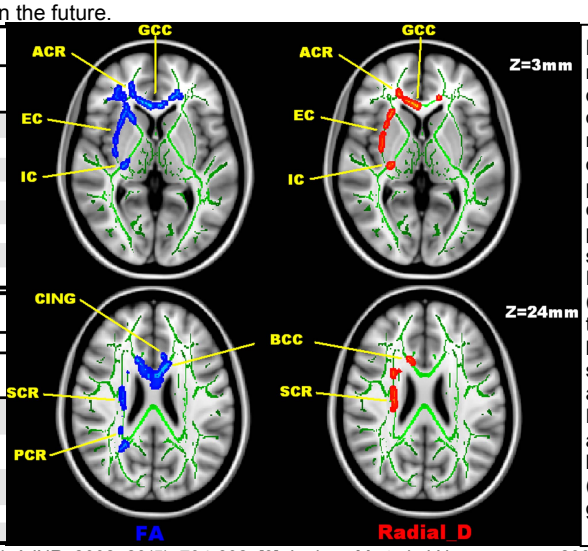

Fig.1. Typical white matter regions identified with decreased FA (blue patches on the left) and increased radial diffusivity (red patches on the right) in the acute phase of mTBI (within 24hrs), comparing to the sub-acute phase (one month), superimposing on the mean FA skeleton map of the study (green) and the MNI152_T1 template. All regions displayed have corrected p values smaller than 0.082, approaching significance. Detailed information of the abovementioned regions are listed in **Tab. 2**.

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Reference: [1]. CDC. Report to congress, 2003. [2]. Arfanakis K et al. AJNR, 2002; 23(5): 794-802; [3]. Inglese M et al. J Neurosurgery, 2005; 103(2): 298-303; [4]. Bazarian J. et al., J Neurotrauma, 2007; 24:1447-1459. [5]. Mac Donald et al., J Neurosci, 2007:27(44)11869-11876. [6]. Smith SM et al., Neuroimage, 2006;31:1487-1505. [7]. Nichols TE., et al., Human brain mapping, 2001;15:1-25. [8].Smith SM et al., Neuroimage, 2009;44(1):83-98. [9].Sidaros A et al., Brain, 131:559-572.