Voxel-Based Diffusion Tensor Imaging Study of Mild Traumatic Brain Injury

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Introduction: Mild Brain Traumatic Injury (MTBI) disrupts the healthy linear structure of axonal bundles with axonal swelling or even demyelination, leading to a change of free space for water motion. It thus reduces the water diffusivity proportionally. In the free water, diffusivity is uniformly distributed in all directions. In the presence of restriction from microstructures such as axonal or myelin, water diffusivity perpendicular to axon bundle is much lower than that along the axon bundle. Diffusion Tensor Imaging is an MRI technique sensitive to diffusion of water, and therefore is an ideal in-vivo technique for measuring the MTBI induced change in diffusivities. In principle the whole brain should be affected with the impact of mild brain traumatic injury, but due to difference in plasticity and durability, some tissues are more vulnerable than others. In the present study, we used a voxel-based analysis to investigate the common vulnerable regions with group unpaired t-tests on diffusivity. Furthermore, the surrounding tissue and mechanism of injury also may affect the injury distribution in the brain, and the pattern of distribution may in turn determine cognitive, affective and somatic symptoms. In another words, finding regions with diffusivities highly correlated to outcomes reveals additional regions that may be particularly vulnerable to MTBI.

Material and Methods: The current study included ten mild brain traumatic injury patients, with mean age 15.70±1.18 years (range 14-17), and ten demographically- matched healthy volunteers with mean age 15.70±1.83 years (range 14-19). All MTBI patients included in this study had no positive findings on CT scan. All subjects including both MTBIs and controls were right-handed and had no previous history of neurological and psychological dysfunction. This research protocol was approved by institutional review board at Baylor College of Medicine. Informed consent was obtained from each subject before performing the study. The MRI image data was acquired using the same Philips 3.0T Achieva scanner (Philips, Cleveland, Ohio) at Texas Children's Hospital with a sensitivity encoding (SENSE) 8-channel head coil. In addition to the conventional MRI scans, the diffusion tensor imaging (DTI) was performed to measure the integrity of white matter with parameters: axial, single-short multiple-slice, spin echo, echo planar imaging (EPI) sequence with thirty diffusion encoding directions [Jones DK 1999], 224 FOV, acquisition voxel size 2×2×2 mm3, reconstruction voxel size 1.75×1.75×2.0 mm3, 6318.0 ms TR, 51 ms TE, AP foldover, SENSE reduction factor of 2, two b-factor with 0 sec/mm2 low-b and 1000/mm2 high-b), and two acquisitions for averaging.

The DTI data went through motion and eddy current correction using Philips DTI registration tool, following by DTI index map calculation using DTIstudio (Radiology Department, Johns Hopkins University). The DTI index maps of three eigenvalues, apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were exported. The axial diffusivity measures water movement along the axonal bundle direction, represented by the largest eigenvalue, while the radial diffusivity measures movement of water molecules perpendicular to the axonal bundle direction, computed by average of the secondary and tertiary eigenvalues. Due to its susceptibility to TBI, white matter is the target region in the present VBA analysis. It is important to use the image with high white matter contrast over other tissues to serve as reference in registration to achieve a good white matter inter-subject registration. As matter of fact, the FA map itself is a good candidate with high intensity on WM and low on GM and CSF, except that the skull portion of the FA image is noisy. To remove signal outside the brain, the binary brain masks were applied to its correspondent FA images to generate FA images of isolated brains. Before statistical analyses, the data preparation took three steps: (1) register and average FA images in one healthy subject space, (2) transform the averaged FA map into MNI space using a segmented B0 image as reference, resulting in a FA template in MNI space, (3) normalize all images into MNI space using the FA image as reference, and smoothing with FWHM of 8 mm.

The student unpaired t-test in SPM2 was performed between patient and control groups to evaluate any ADC difference (ADC-GRP analysis). In addition, the linear regression model in SPM2 was also used to investigate the respective relationship between the following two pairs of variables: (1) ADCs and Rivermead Post Concussion Symptoms Questionnaire (ADC-RPCSQ analysis), (2) ADCs and Brief Symptom Inventory (ADC-BSI analysis). The whole brain mask was used to exclude anything outside of the brain, but the whole brain was included in the evaluation. All statistically significant regions revealed in the voxel-based statistic analysis were exported using Marsbar toolbox as regions, then was used subsequently in a refined region-based statistic analysis, which analyzed the relationship of the mean ADC on regions identified by the voxel-based analyses against clinical or psychological outcomes.

Result and Discussions: The voxel-based ADC-GRP analysis in Figure 1 reveals six significant regions [T(18)=3.6, P<0.001] and demonstrated more injury-related difference on the left side than the right. The voxel based ADC-RPCSQ analysis reveals seven regions [T(18)=3.3, P<0.002] while the voxel based ADC-BSI analysis reveals seven regions [T(18)=3.4, P<0.002]. The region-based analyses overcome the information dilution from smoothing and demonstrate more significant results, illustrated in table 1. All injury-affected regions show a drop in radial diffusivity [2] and no detectable change in axial diffusivity, consistent with the mechanism of axonal swelling. Table 1 showed that the apparent diffusivity coefficient (ADC) on injury-affected regions strongly correlated with psychological test outcomes on measures of post-concussive symptoms.

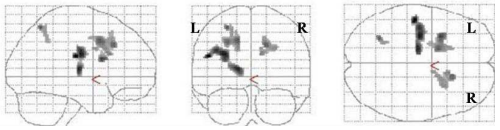

Figure 1: Regions identified by SPM2 T-test of ADC between patients and controls.

Table 1. The statistical result of the region-based analyses, where R is linear Pearson correlation coefficient, and Bdp: slope (10^{-9} mm^2/sec/RPCSQ), Bfp: slope (10^{-3}/RPCSQ), Bdb: slope (10^{-9} mm^2/sec/BSI), Bfb: slope (10^{-3}/BSI)

	ADC		Axial Diffusivity		Radial Diffusivity	
Unpaired t-test	T score	P Value	T score	P Value	T score	P Value
	-7.14	0.000	-1.72	0.102	-7.08	0.000
Linear correlation between ADC and RPCSQ on regions in combination	R	Bdp	R	Bdp	R	Bdp
	-0.94	-1.370	-0.08	-0.163	-0.90	-2.317
Linear correlation between ADC and BSI on regions in combination	R	Bdb	R	Bdb	R	Bdb
	-0.91	-2.850	-0.45	-1.550	-0.88	-3.500

Conclusion: The present study showed that the voxel-based statistical analysis is capable of identifying the diffuse axonal injury-prone regions that are invisible to CT and conventional MRI. The subsequent region-based statistical analysis furthermore quantifies the degree of the injury, helping to predict possible post-morbid neurological and psychological deficits. Moreover, the analysis elucidates the underlying mechanism of MTBI pathology.

Reference:

1. Jones DK, et al, Magn Reson Med 1999;42:515-525.
2. Wilde EA,et al,Neurology, (in press, 2007)