Diffusional Kurtosis Imaging of Deep Gray Matter in Mild Traumatic Brain Injury

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Introduction: Mild traumatic brain injury (MTBI) is a major public health problem **(1)** for which conventional imaging approaches have failed to detect any evidence of cerebral damage that can account for its potentially serious long-term or permanently disabling impairments **(2)**. Recently, a number of investigations have applied diffusion tensor imaging (DTI) to the evaluation of white matter in MTBI patients and reported evidence of diffuse axonal injury (DAI) **(3-5)**. The purpose of the current study is to assess whether diffusional kurtosis imaging (DKI) **(6-7)**, a newly developed technique for measuring non-Gaussian water diffusion that can provide an index of diffusional heterogeneity, is capable of supplying additional or complimentary information about pathology that could be used as an early prognostic measure of subsequent brain damage. We have employed both DKI and DTI to examine not only white matter regions but also the thalamus and functionally related deep gray matter structures. The thalamus influences many diverse neural pathways and, if impaired, could produce much of the clinical non-focalized sequelae associated with MTBI **(8)**.

Methods: A total of 22 adult patients with MTBI (14 male, 8 female; mean age 38.2 yrs ± 11.7; age range 21-60 yrs) were recruited in accordance with diagnostic criteria of the American Congress of Rehabilitative Medicine **(9)**. Patients were categorized into two groups, seven acute and 15 chronic, that underwent MR imaging within a mean interval of 0.18 yrs (range 0.04-0.59 yrs) and 3.9 yrs (range 1.33-9.58 yrs), respectively, after their traumatic incident. The same scanning protocol was administered to 14 age and gender matched healthy controls (9 male, 5 female; mean age 36.5 yrs ± 12.3; age range 19-62 yrs). The study was IRB approved and all participants provided proper informed written consent. Experiments were conducted on a Siemens 3T whole-body MR scanner (Magnetom Trio, A Tim System). DKI was performed by means of a twice-refocused spin echo diffusion sequence **(10)** with 30 different diffusion encoding directions using an optimized sampling strategy **(11, 12)**. For each direction six b-values (0, 500, 1000, 1500, 2000, and 2500 s/mm^2) were employed. Thirteen oblique axial slices centered at the AC-PC line were obtained using the following imaging parameters: TR = 2000 ms, TE = 108 ms, FOV = 320 x 320 mm^2, matrix = 128 x 128, SENSE factor = 2, NEX = 2, slice thickness = 2.5 mm, voxel size = 2.5 x 2.5 x 2.5 mm^3. Three-dimensional motion correction and spatial smoothing using a Gaussian filter (FWHM = 3 mm) was applied to the data and fractional anisotropy (FA), mean diffusivity (MD), and mean kurtosis (MK) maps were generated. Diffusion metrics were estimated from the mean value of voxels contained in uniformly sized ROIs placed in the same position on three consecutive slices by a single reader blinded to subject group. Regions measured included various white matter (anterior limb, genu, and posterior limb of internal capsule, splenium and genu of corpus callosum, and right and left centrum semiovale and frontal white matter) and deep gray matter (right and left thalamus, putamen, and caudate) landmarks. Nonparametric analyses were conducted in which patient and control subject groups were compared in terms of individual MR measures in each brain region adjusted for age and gender using ANCOVA based on ranks.

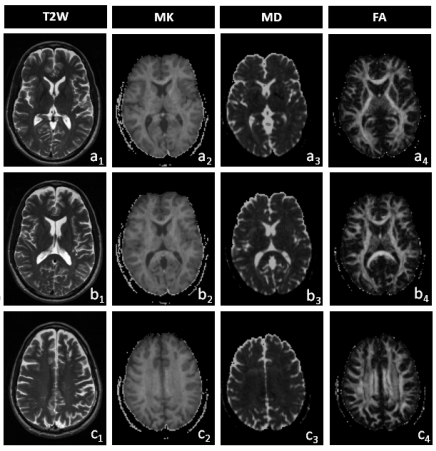

Figure 1. MK, MD, and FA maps acquired from three different axial slices (a, b, and c) in one MTBI patient with a T2W structural scan for reference.

Results: Figure 1 shows an example of MK, MD, and FA maps acquired in three different axial slices (a, b, and c) of one MTBI patient with a corresponding T2W structural scan for anatomical reference. Table 1 is a summary of regions where significant results were obtained for acute and chronic MTBI subjects and shows the combined bilateral mean and standard deviations for each diffusion metric with its corresponding p-value in both patient groups with respect to controls. Evidence for injury is present in the thalamus (acute: $p = 0.04$ and $p < 0.01$ for MK and FA; chronic: $p < 0.01$ for both acute MK and FA) and posterior internal capsule (acute: $p < 0.01$ for MK, MD, and FA; chronic: $p = 0.01$ and $p = 0.02$ in FA and MD) at both early and late time points following injury, suggesting that these regions may be important to early prediction of long-term brain damage.

Regions	Measures	Controls	Acute MTBI	p-values Controls vs Acute MTBI	Chronic MTBI	p-values Controls vs Chronic MTBI
Thalamus	MK	1.26 ± 0.08	1.24 ± 0.06	**0.04**	1.23 ± 0.07	**< 0.01**
	MD	0.83 ± 0.03	0.83 ± 0.03	0.51	0.84 ± 0.03	0.06
	FA	0.32 ± 0.04	0.30 ± 0.03	**< 0.01**	0.30 ± 0.03	**< 0.01**
Posterior Internal Capsule	MK	1.37 ± 0.06	1.33 ± 0.06	**< 0.01**	1.35 ± 0.09	**0.01**
	MD	0.83 ± 0.04	0.85 ± 0.04	**< 0.01**	0.84 ± 0.05	**0.02**
	FA	0.70 ± 0.05	0.66 ± 0.05	**< 0.01**	0.68 ± 0.07	0.15
Splenium of Corpus Callosum	MK	1.42 ± 0.09	1.46 ± 0.05	0.21	1.37 ± 0.13	0.44
	MD	1.00 ± 0.09	0.96 ± 0.08	0.48	1.10 ± 0.15	**0.01**
	FA	0.74 ± 0.05	0.74 ± 0.04	0.76	0.70 ± 0.09	0.08
Centrum Semiovale	MK	1.37 ± 0.04	1.36 ± 0.03	0.4	1.33 ± 0.06	**< 0.01**
	MD	0.82 ± 0.03	0.82 ± 0.02	0.82	0.84 ± 0.04	**< 0.01**
	FA	0.50 ± 0.09	0.52 ± 0.07	0.48	0.47 ± 0.07	**0.02**
Frontal White Matter	MK	1.27 ± 0.06	1.25 ± 0.07	0.72	1.25 ± 0.09	**< 0.05**
	MD	0.90 ± 0.04	0.92 ± 0.06	0.51	0.93 ± 0.06	**< 0.01**
	FA	0.42 ± 0.07	0.42 ± 0.10	0.74	0.41 ± 0.10	0.63

Table 1. DKI and DTI measurements in regions where acute and chronic MTBI patients showed a significant difference from controls.

Conclusions: We have shown the feasibility of using DKI to investigate tissue damage in acute and chronic MTBI. Our preliminary results suggest that DKI might provide additional and complementary information to DTI about the degree of difffusional heterogeneity in tissue. While DKI and DTI reveal significant differences between patients and controls in sites with a predilection for DAI, in the thalamus and posterior internal capsule they show evidence of injury in both acute and chronic MTBI, suggesting that these regions may be important to identifying individuals at high risk of developing a complex persistent long-term condition. We plan to further evaluate these results with respect to diagnostic measures of post-concussion syndrome and neurocognitive performance.

References: **(1)** Report to Congress on mild traumatic brain injury in the United States, Atlanta, GA: CDC; 2003; **(2)** Hammoud DA, et al, Neuroimaging Clin N Am 2002;12:205-216; **(3)** Arfanakis K, et al, AJNR 2002;23:794-802; **(4)** Inglese M, et al, J Neurosurg 2005;103:298-303; **(5)** Miles L, et al, Brain Injury 2008;22:115-122; **(6)** Jensen JH, et al, MRM 2005;53:1432-1440; **(7)** Lu H, et al, NMR Biomed 2006;19:236-247; **(8)** Sherman SM, et al, J Neurophysiol 1996;76:1367-1395; **(9)** Esselman PC, et al, MRM 2003;49:177-182; **(10)** Reese TG, et al, MRM 2003;49:177-182; **(11)** Jones DK, et al, MRM 1999;42:515-525; **(12)** Skare S, et al, JMR 2000;147:340-352.