A Longitudinal Study of Thalamic and White Matter Damage in Mild Traumatic Brain Injury Using Diffusional Kurtosis Imaging and Arterial Spin Labeling

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Introduction: Mild traumatic brain injury (MTBI) is one of the most significant public health problems facing the modern world but remains difficult to assess because conventional imaging fails to detect damage that can account for long-term or permanently disabling cognitive impairment associated with this condition **(1)**. In previous cross-sectional studies we reported diffusion tensor imaging (DTI), diffusional kurtosis imaging (DKI), and arterial spin labeling (ASL) can supply complimentary information that may serve as a sensitive marker for possible early detection of injury in the thalamus and white matter (WM) regions of MTBI patients **(2-4)**. The purpose of this study was to conduct a longitudinal investigation of structural and physiological changes in the thalamus and WM regions of MTBI patients using DTI, DKI, and ASL to ascertain if these measures can be predictive of outcome. This is the first study to examine MTBI longitudinally using DKI which, unlike DTI, measures non-Gaussian water movement and therefore provides unique information unattainable with DTI about tissue microstructural organization **(5)**. This is also the first study to examine MTBI longitudinally using a new ASL sequence we have developed to measure perfusion in deep gray matter (DGM) at a high spatial resolution **(6)**. Very few longitudinal studies of MTBI have been conducted using diffusion imaging and none using perfusion imaging. Furthermore, the thalamus has only been infrequently studied in MTBI despite its influence over many neural pathways which if impaired could produce much of the clinical non-focalized sequelae observed in patients.

Brain Region	Measure	Controls Mean ± SE	MTBI Mean ± SE	Controls vs MTBI p-values
Thalamus	MK	0.893 ± 0.014	0.746 ± 0.012	< 0.001
	FA	0.304 ± 0.006	0.253 ± 0.004	< 0.001
	MD	0.861 ± 0.016	0.966 ± 0.019	< 0.001
Internal Capsule	MK	1.130 ± 0.020	1.038 ± 0.021	0.003
	FA	0.508 ± 0.007	0.483 ± 0.004	0.002
	MD	0.712 ± 0.005	0.733 ± 0.006	0.009
External Capsule	MK	0.853 ± 0.014	0.794 ± 0.015	0.009
	FA	0.336 ± 0.006	0.310 ± 0.004	0.001
	MD	0.728 ± 0.004	0.744 ± 0.006	0.028
Optic Radiations	MK	1.060 ± 0.015	1.003 ± 0.018	0.015
	FA	0.487 ± 0.007	0.464 ± 0.006	0.015
	MD	0.758 ± 0.007	0.778 ± 0.008	0.044
Corpus Callosum Splenium	MK	1.203 ± 0.017	1.101 ± 0.017	< 0.001
	FA	0.705 ± 0.008	0.679 ± 0.008	0.016
	MD	0.779 ± 0.007	0.824 ± 0.010	< 0.001
Cingulum	MK	1.031 ± 0.016	0.925 ± 0.021	< 0.001
	FA	0.426 ± 0.008	0.396 ± 0.007	0.009
	MD	0.730 ± 0.006	0.763 ± 0.007	< 0.001
Centrum Semiovale	MK	1.086 ± 0.018	0.990 ± 0.023	0.001
	FA	0.414 ± 0.007	0.388 ± 0.006	0.002
	MD	0.730 ± 0.007	0.758 ± 0.006	0.003
Total DGM	MK	0.740 ± 0.032	0.692 ± 0.017	< 0.001
	FA	0.223 ± 0.016	0.207 ± 0.009	< 0.001
	MD	0.879 ± 0.024	0.915 ± 0.025	0.047
Total WM	MK	1.074 ± 0.030	0.994 ± 0.026	< 0.001
	FA	0.526 ± 0.003	0.498 ± 0.027	0.002
	MD	0.774 ± 0.030	0.812 ± 0.019	< 0.001

Table 1. DTI and DKI measurements with standard errors (SE) in regions where MTBI patients displayed significant differences from controls during first examination. P-values have been adjusted for age and gender.

Methods: Twenty adult patients with MTBI (16 male, 4 female; mean age 34.8 yrs ± 10.7) were recruited for examination within an average of 22.1 days ± 15.4 following injury in accordance with diagnostic criteria of the American Congress of Rehabilitative Medicine **(7)** along with 16 gender and age matched controls (13 male, 3 female; mean age 35.1 yrs ± 11.9). Ten patients (8 male, 2 female, mean age 37.8 yrs ± 9.3) returned for a second examination within an average of 369.6 days ± 112.1 following first examination. The study was IRB approved and all participants provided informed written consent. All subjects underwent testing for diagnostic measures of postconcussion syndrome and MRI which was conducted on a Siemens 3T whole-body MR scanner (Magnetom Trio, A Tim System) using DKI and ASL parameters previously discussed elsewhere **(3)**. DKI data was preprocessed using 3D motion correction and spatial smoothing with a Gaussian filter (FWHM = 3.875 mm) and mean kurtosis (MK), fractional anisotropy (FA), and mean diffusivity (MD) maps were generated. DKI metrics in DGM regions were estimated from the mean value of voxels contained in uniformly sized ROIs placed bilaterally on three consecutive slices in the thalamus, putamen, and caudate. DKI metrics in WM regions were estimated by applying tract-based spatial statistics (TBSS) **(8)** using a threshold of $p < 0.05$ at 2,000 iterations. ASL metrics in DGM regions were estimated from the mean value of voxels contained in uniformly sized ROIs placed bilaterally on one slice in the thalamus, putamen, and caudate, and absolute perfusion was calculated by applying a general kinetic model **(9).**

Brain Region	Measure	Controls Mean ± SE	MTBI Mean ± SE	Controls vs MTBI p-values
Thalamus	MK	0.890 ± 0.0193	0.779 ± 0.010	< 0.001
Optic Radiations	MK	1.027 ± 0.015	0.985 ± 0.008	0.020
Corpus Callosum Splenium	MK	1.171 ± 0.020	1.089 ± 0.015	0.004
Cingulum	MK	1.010 ± 0.017	0.929 ± 0.026	0.018
Centrum Semiovale	MK	1.015 ± 0.013	0.957 ± 0.016	0.011
Total DGM	MK	0.742 ± 0.039	0.702 ± 0.022	0.007
Total WM	MK	1.072 ± 0.025	1.005 ± 0.023	0.002

Table 2. DTI and DKI measurements with standard errors (SE) in regions where MTBI patients displayed significant differences from controls during second examination. P-values have been adjusted for age and gender.

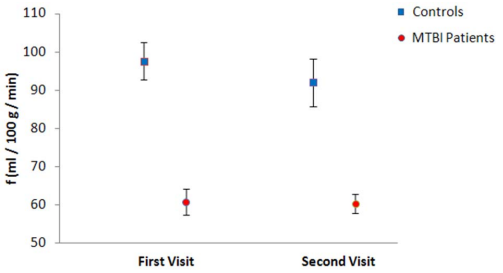

Fig 1. Means and standard errors for perfusion measured in the thalamus of MTBI patients compared to controls during first and second examinations in both of which $p < 0.001$ adjusted for age and gender.

Results: DTI and DKI measurements in regions where patients displayed significant differences from controls during first and second examinations are reported in Tables 1 and 2. DGM regions where patients displayed significant differences in perfusion from controls during first and second examinations are reported in Fig.1; this included only the thalamus. Regression analyses showed significant correlations in patients during first examination between MK and MD in the thalamus with FA in total WM ($r = 0.481$, $p = 0.018$ and $r = -0.475$, $p = 0.038$) and ASL in thalamus with MK in total WM ($r = 0.577$, $p = 0.012$). There was also a trend towards significant correlation in patients during first examination between MK in the thalamus and the postconcussion symptoms scale ($r = - 0.394$, $p = 0.085$). Patients exhibited significant improvement in FA and MD for the thalamus (FA: $p < 0.001$; MD: $p < 0.001$), the internal capsule (MD: $p = 0.015$), the splenium of corpus callosum (MD: $p < 0.001$) and total WM (MD: $p < 0.001$) between first and second examinations, but not in MK.

Conclusions: These preliminary results demonstrate the feasibility of using DTI, DKI, and ASL to investigate longitudinal changes in the thalamus and WM regions of MTBI patients. DKI provides information that is both additional and complementary to DTI concerning the degree of diffusional heterogeneity in tissue. Damage sustained to the thalamus and several WM regions of patients within one month of injury may lead to significant differences in MK compared to controls lasting more than one year, suggesting the use of this metric in evaluating these structures might be important to identifying individuals at high risk of developing a complex persistent long-term condition. Alterations of structure and perfusion in the thalamus were associated in part with structural changes in total WM suggesting changes in this region may be of both primary and secondary origin related to direct injury as well as damage to cortical axons that innervate blood vessels and Wallerian degeneration. These results are part of an ongoing study in which changes in DTI, DKI, and ASL will be examined with respect to diagnostic measures for postconcussion syndrome and neurocognitive performance.

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References: 1. Report to Congress on mild traumatic brain injury in the United States, Atlanta, GA:CDC;2003; **2.** Grossman EJ, et al, J Neurotrauma, in press;DOI:10.1089/ neu.2011.1763; **3.** Grossman EJ, et al, Proc ISMRM 2011;19:4205; **4.** Grossman EJ, et al, Proc ISMRM 2010;18:4484; **5.** Jensen JH, et al, NMR Biomed 2010;23:698-710; **6.** Grossman EJ, et al, JMRI 2009;29:1425-1431; **7.** Esselman PC, et al, Brain Injury 1995;9:417-424; **8.** Smith et al, Neuroimage;31:1487-1505; **9.** Buxton RB, et al, MRM 1998;40:383-96.