

Global diffusion kurtosis parameter changes in mild traumatic brain injury patients with persistent symptoms at six months

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Introduction: Patients with mild traumatic brain injury (mTBI) are hard to diagnose because a majority of them have negative findings on CT or conventional MRI¹. Although most of mTBI patients recover fully, a majority of them experience post concussive symptoms and cognitive deficits acutely, and some report persistent problems years later^{2,3}. The lack of a measurable neurological signature severely limits diagnosis eventually leading to sub-optimal intervention. In this study, we use diffusion kurtosis imaging to study global white and gray matter changes following mTBI at sub-acute (1 month) and chronic (6 months) stages following TBI and examine their relationship to post concussive symptoms and cognitive status.

Methods: 26 mTBI patients (age: 37.0±14.6) and 26 age-matched (age: 37.4±15.6) healthy controls were included in this study as part of the ongoing MagNeT study (Magnetic Resonance Imaging of Neuro Trauma). Each patient underwent MRI evaluation at the sub-acute (1 month) and chronic (6 months) stages post injury. Neurocognitive tests using the American Neurological Assessment Metrics (ANAM) and the Rivermead post-concussion symptom Questionnaire (RPCSQ) were administrated at each visit. Based on their RPCSQ ratings at the chronic stage, the patients were further partitioned to the low RPCSQ group (N = 14, RPCSQ < 4, and included 5 patients with positive CT or MRI findings) and the high RPCSQ group (N = 12, RPCSQ ≥ 4), and included 8 patients with positive CT or MRI findings. Diffusion weighted images were obtained with b = 1000, 2000 s/mm² at 30 diffusion directions, 6 volumes at b = 0 s/mm², 2 averages, resolution = 2.7mm³, TE/TR = 93ms/6000ms. Motion and eddy correction, brain extraction, and smoothing (kernel size = 3mm) were performed. Fractional anisotropy (FA), mean, radial and axial diffusivity (MD, RD, AD) and kurtosis (MK, RK, AK) maps were generated offline⁴. A high resolution T1-weighted-MPRAGE sequence (TE=3.44ms, TR=2250ms, TI=900ms, flip angle=9°, resolution = 0.9×0.9×1.5mm³) was acquired for anatomic reference. MPRAGE image was segmented using SPM8 for gray (GM) and white matter (WM) masks, which was then co-registered to the DKI maps to extract whole brain GM and WM mean values.

Results: For all mTBI patients as a whole, significantly reduced WM FA (p = 0.0097) and increased RD (p = 0.027) were observed at the sub-acute stage, which showed recovery at chronic stage with only WM FA still reduced (p = 0.026). No significant differences were found in the ANAM scores between the mTBI patients and control subjects, although a trend towards reduced performance was observed at the sub-acute stage (p=0.09).

When further partitioning the patients based on symptom ratings, the low RPCSQ mTBI patients did not show any changes in DKI parameters, or ANAM scores at any time points (Fig. 1-3). However in the high RPCSQ group, significantly reduced WM FA (p = 0.0018) and increased WM MD (p = 0.032) and RD (p = 0.023) (Fig. 1), as well as ANAM scores (p = 0.028) were observed at the acute stage compared to controls (Fig. 2). These measures were also significantly different between the two groups (p < 0.05). At the chronic stage, although no differences in the ANAM scores of the high RPCSQ group was observed (p = 0.25) compared to control subjects, reduction in WM FA (p = 0.0008) while increase in MD (p = 0.011) and RD (p = 0.0027) were still observed. There also appeared to be a widening in the gap in WM measures between the low and high RPCSQ groups, with a more significant difference (p < 0.005) between the two groups, which also extends to AD (p = 0.037). At the chronic stage a significant increase in MK within the gray matter among the high RPCSQ group compared to controls (p = 0.031) was observed (Fig. 3). This increase in MK was also significant between the two groups of patients (p = 0.013). At the sub-acute stage WM MK and RK values were found to be significantly correlated with the sub-acute ANAM scores after adjusting for age (WM MK: r = 0.707, p = 0.010; WM RK: r = 0.711, p = 0.010) and the chronic ANAM scores (WM MK: r = 0.610, p = 0.035; WM RK: r = 0.684, p = 0.014).

Discussion: The reduction in FA and increase in MD and RD in high RPCSQ mTBI patients are consistent with axonal degeneration post TBI. The increase in MK in the gray matter possibly indicates increased glial cell activity that contributes to the repair mechanism following TBI⁴, or an increased cortical packing density due to cortical thinning⁵ post injury, both of which will increase the diffusion heterogeneity. Kurtosis has also been shown to be more sensitive to intra- and extra- axonal exchange rate than diffusion coefficient⁶. Based on the observed correlation between

kurtosis parameters and ANAM scores, a higher MK or RK may indicate better myelin integrity, which might result in higher cognitive performances.

Conclusion: mTBI patients with persistent post concussive symptoms showed greater changes in global white and gray matter microstructures at the sub-acute stage. Such changes persist into the chronic stage even when they experienced cognitive recovery. DKI parameters are sensitive to gray matter changes and myelin integrity hence may complement DTI parameters in evaluating TBI.

References: [1] Kraus and Nourjan, 1988; [2] Binder et al., 1997; [3] Alexander, 1995; [4] Zhuo et al., 2012; [5] Falangola et al., 2008; [6] Jensen and Helpern, 2010

Fig. 1 Whole Brain White Matter Changes

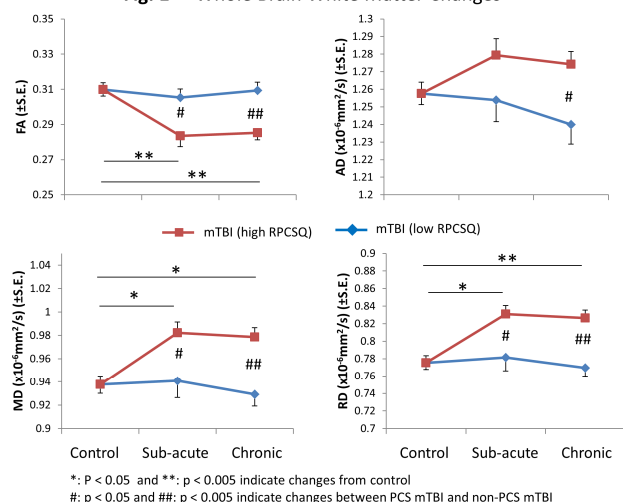


Fig. 2 Cognitive Performance Changes

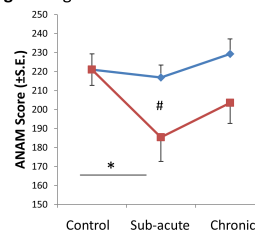


Fig. 3 Whole Brain Gray Matter Changes

