

# Neuroimaging Biomarkers of Mild Traumatic Brain Injury (mTBI) and its Recovery: A Preliminary Study in Acute Setting

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## Introduction:

Patients with mild Traumatic Brain Injury (mTBI) have been largely reported to develop post-concussion symptoms (PCS) and cognitive sequelae in working memory, speed of information processing, attention, executive function at one month post injury [1-2]. However, most symptomatic mTBI patients have normal findings in clinical computed tomography (CT) and conventional magnetic resonance imaging (MRI) [3]. There is lack of imaging biomarkers that are sensitive enough to differentiate mTBI patients from normal healthy controls in acute setting and to predict their recovery. Few studies focused on acute changes (within 24 hours) in neurovascular structure and neural functions that are susceptible to injury. Advanced MRI technique such as Susceptibility Weighted Imaging and resting-state functional connectivity MRI may well be poised to provide complimentary information for ER physicians to facilitate their decision-making process in evaluation and management of patients. The objective of this study was to evaluate whether application of two advanced MRI methods will reveal both anatomical and functional disruption in mTBI patients and its recovery in association with clinical outcome measures.

## Methods:

10 mTBI adult patients (mean age $\pm$  std = 31.8 $\pm$  10.2 years, 6 females) with GCS (Glasgow Coma Scale) score 15 treated at Detroit Receiving Hospital ER were enrolled and followed up in the study from April 2010 through March 2011. 18 healthy age-matched controls were enrolled in the study to provide baseline measurement. Patients received evaluation in acute setting (within 26 hours) and were followed up sub-acutely (within one to three months). GCS and head CT of the patients was primarily evaluated. Standardized Assessment of Concussion (SAC) was administered for both patient visits. Advanced MRI scans (SWI and rs-fcMRI) were performed to patients for both time points and to healthy controls as well. The scan was performed on 3.0T Siemens VERIO scanner (Siemens, Germany). In each visit, an 8-minute resting-state fMRI scan was acquired using EPI sequence (33 slices; voxel size: 3 x 3 x 3.5 mm<sup>3</sup>; matrix size: 64 x 64; repetition time = 2000 ms; echo time = 30 ms; flip angle = 90; field of view = 200 mm). Two other anatomical imaging were performed using Susceptibility Weighted Imaging (SWI) sequence and High resolution 3D T1W MPRAGE in the same session.

Data analysis was carried out using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for Resting-State fMRI (DPARSF) V2.0 Basic Edition (Yan and Zang, 2010). The seed ROI was selected in the PCC (MNI coordinates: x=-5, y=-53, z=41) to identify Default Mode Network (DMN) and FC between other brain regions and the seed region was calculated and mapped. The cross correlation between 90 brain regions, defined by AAL Atlas, was calculated and the correlation matrix was generated. The one-sample t-test connectivity maps of patients and control group, as well as the two-sample t-test comparison of these two groups were performed.

## Results:

Four of ten patients were lost to follow-up. All patients had a GCS score of 15 and indicated as normal in head CT results. The average SAC score at acute stage was 24.8 and 27.3 at follow-up stage (Total score=30). Patients were significantly better over the time ( $p<.05$ ), which is consistent with MRI results as Figure 1 indicated. The brain function connectivity, defined as the correlation between signals of all 90 brain regions, increased from acute stage (26 hours) to sub-acute stage (one to three months). Patients have also demonstrated different level of FC within DMN in middle temporal gyrus, middle frontal gyrus, superior temporal gyrus, cuneus, inferior parietal lobule, superior frontal gyrus, inferior frontal gyrus compared to controls.

No conspicuous trauma related lesions or microbleeds were observed in anatomical images (SWI and T1 MPRAGE) in these mTBI patients. However, in majority of patients, subtle medullary veins were involved as shown on SWI (9 out of 10 patients) and T1 images (yellow arrows) indicated frontal medullary vein damage post injury (see Figure 2 for a representative case).

## Discussion:

Taken together, both clinical outcome and MRI results indicate a recovery process in mTBI patients post injury. mTBI patients showing frontal medullary vein damage at acute stage opens the door to understanding why there may be perfusion deficits in these patients. The correlational matrix in the patient at acute stage demonstrated a distinctive pattern compared to the healthy control and the matrix at one to three-month follow-up started to approximate the normal level. These subtle neurovascular damage indicated by SWI, together with the changes in patients' functional connectivity over time shows these advanced MRI indices will be imaging biomarkers complimentary to routine clinical evaluation of mTBI patients.

## Reference:

[1-2] Bazarian JJ et al, 2005; 2008; [3] Belanger HG et al J Neuropsychiatry Clin Neurosci., 2007.

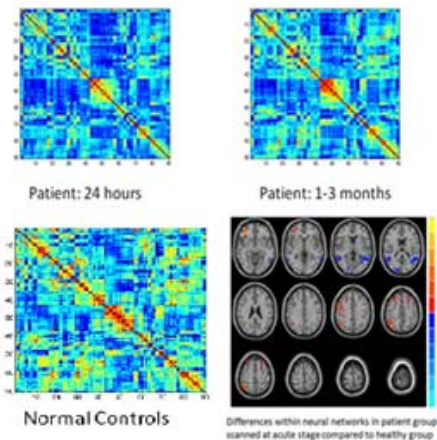


Figure 1. Changes in functional connectivity of patients compared to normal controls.

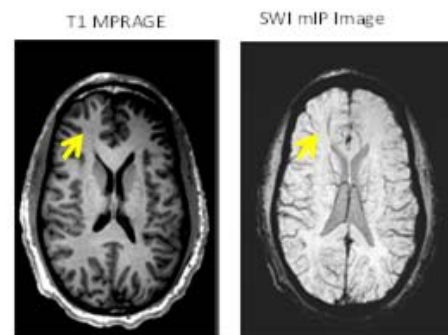


Figure 2. Medullary vein involvement in one mTBI case