Abnormal resting state functional connectivity as a marker for diagnosing and predicting recovery in mild traumatic brain injury

G. chen[1], T. Hammeke[2], G. chen[1], M. McCrea[2], B. D. Ward[1], S. Miller[3], and S-J. Li[1,4]

[1]Biophysics, Medical College of Wisconsin, milwaukee, wisconsin, United States, [2]Department of Neurology, Medical College of Wisconsin, milwaukee, wisconsin, United States, [3]St. Mary's Regional Medical Center, St. Mary's Regional Medical Center, Enid, Oklahoma, United States, [4]Psychiatry and Behavioral Medicine, Medical College of Wisconsin, milwaukee, wisconsin, United States

Introduction: While impairments in memory and postural steadiness are common early after mild traumatic brain injury (mTBI), abnormalities on standard anatomical neural imaging are rare. It is hypothesized that regional analyses of large scale neural networks from resting state fMRI data can detect abnormalities in functional connectivity between brain regions and provide a marker for clinical diagnosis in acute (1 day after injury) mTBI and predict its recovery (7 weeks after injury).

Materials and Methods: ***Subjects and Imaging acquisition***: Thirty-four high school football players (17 with mTBI and 17 sex, age and education matched controls) were recruited. Imaging was performed using a whole-body 1.5T GE scanner. Sagittal resting-state functional MRI (fMRI) datasets of the whole brain were obtained in five minutes (150 points) with a single-shot gradient echo-planar imaging pulse sequence. The fMRI imaging parameters were: TE of 40 ms, TR of 2.5 s, flip angle of 90º; 22 slices were obtained without gap; slice thickness was 6 mm with a matrix size of 64×64 and field of view of 24×24 cm. High-resolution SPGR 3D axial images were acquired for anatomical reference. ***Behavioral Scores***: Subjects completed memory (Hopkins Verbal Learning Test) and postural steadiness (Balance Error Scoring System) on the day after injury and again seven weeks later. ***Regional Functional Connectivity***: Common preprocessing steps using the Analysis of Functional NeuroImages (AFNI) software were completed, including: T1-equilibration effects; slice-acquisition-dependent time shifts correction; despiking; motion correction; detrending; white matter, CSF and global signal correction; and low-frequency band-pass filtering. Each subject's functional image was automatically parcellated in to 116 regions[1]. The functional connectivity between the 116 whole-brain regions was assessed by the Pearson product-moment correlation coefficient (CC). ***Classification and Prediction***: Data driven analyses were used in large scale network analyses[2] to classify the two groups from significant differences in functional connections. The Leave-One-Out (LOO) error estimate method and nonparametric rank-sum test were used to identify regions of increased and decreased regional functional connections between groups. The area under curve value (AUC) of receiver operation characteristics (ROC) curves for this set was used at both the session on the day of injury and seven weeks after injury to predict TBI diagnosis and recovery outcome. Larger AUC values indicate greater deviation from control values and imply a more severe injury.

Results and Discussion: Figures A and B show the classification ROC curves of different recovery stages (A: Session 1--one day after injury; B: Session 2-- 7 weeks after injury). The AUC value for Session 1 was 0.82, which declines to 0.73 in Session 2. The classification sensitivity and accuracy declined from Session 1 to Session 2, which is consistent with recovery in injured players. In Session 1, the classification algorithm found 14 regions with significantly ($P<0.005$) different functional connections between the groups (Figure C), most of which represented connections between the cerebral cortex and cerebellum. In Session 2, 13 of the 14 regions no longer showed a significant difference between the mTBI and control groups, which is consistent with the recovery of functional brain connections in mTBI subjects to normal levels. Only the connection between the left middle cingulate gyrus (L MCC) and the right inferior frontal gyrus (R IFG) was still significantly different between the mTBI and control groups in Session 2. Among the 14 connections in session 1, the connections between the left hippocampus (L HIP) and right dorsal lateral superior frontal gyrus (R DLSFC); the left parahippocampal gyrus (L PHP) and right lobule VIII of cerebellar hemisphere; right amygdala (R AMY) and left lobule VIII of cerebellar hemisphere were significantly correlated with the balance score (Figure E, F, G). Also, the connection of right amygdala (R AMY) and left lobule VIII of cerebellar hemisphere was also correlated with memory score (Figure H). These results suggest that resting state functional connectivity MRI is a promising technology for the study of recovery from mTBI, and connections between the cortex and the cerebellum may be particularly vulnerable to acceleration-deceleration forces in closed head injury.

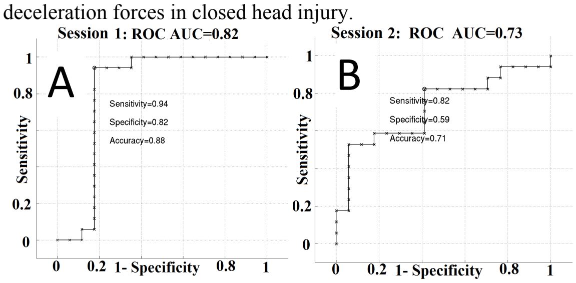
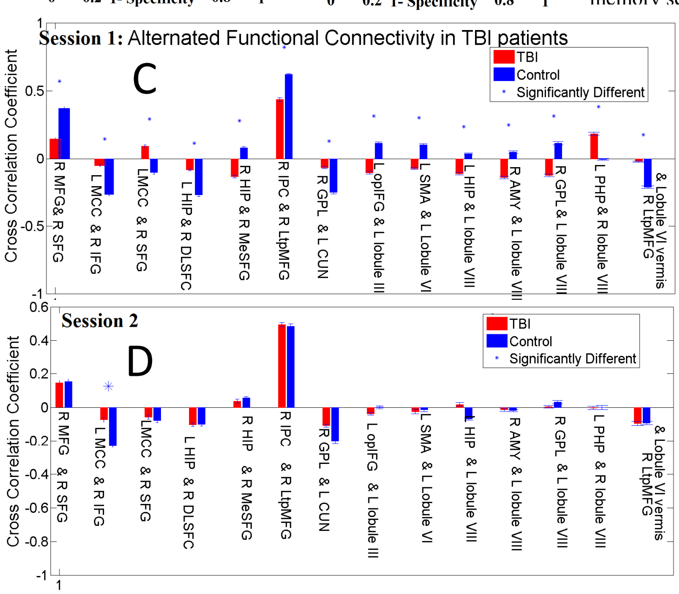
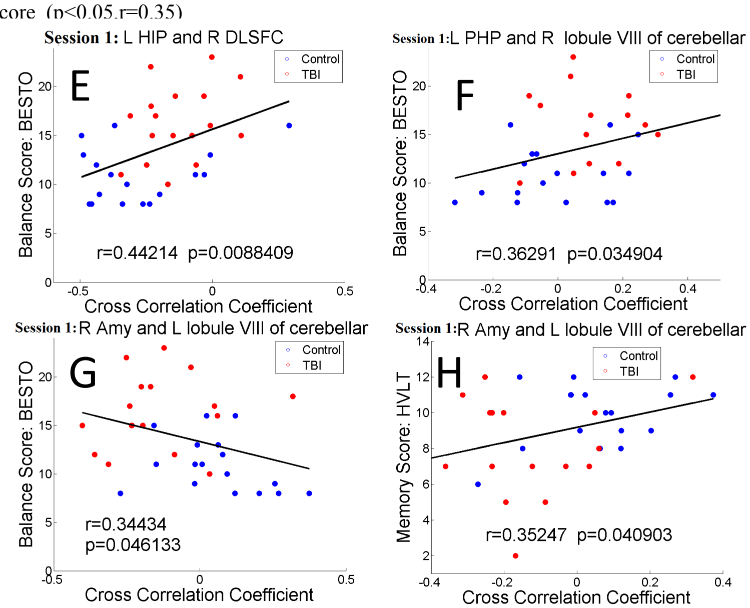


Figure A: ROC curve of Session 1. Figure B. ROC curve of Session 2. Figure C.: 14 connections were significantly different between mTBI (red) and Controls (blue) at Session 1. Figure D: results of same 14 connections in C between mTBI and Controls (blue) during Session 2 : only one connection was significantly different. Figure E: functional connectivity between L HIP and R DLSFC were significantly correlated with the Balance score ($p<0.01, r=0.44$). Figure F: functional connectivity between L PHP and R Lobule VIII of the cerebellum was significantly correlated with Balance score ($p<0.05, r=0.36$). Figure G: functional connectivity between R Amy and L lobule VIII was significantly correlated with Balance score ($p<0.05, r=-0.34$). Figure H: functional connectivity between R Amy and L lobule VIII was significantly correlated with memory score ($p<0.05, r=0.35$)





References:1.Tzourio-Mazoyer N, et al. Neuroimage. 2002;15(1):273-89. 2. Chen et al., Radiology. In press (2010)