The Dynamically Changing Default-Mode Network after Concussion in Sports: a Resting-State fMRI and DTI Integration Study

David C Zhu[1], Tracey Covassin[1], Sally Nogle[1], Scarlett Doyle[1], Doozie Russell[1], Randy Pearson[1], Jeffrey Monroe[1], Christine Liszewski[1], J. Kevin DeMarco[1], and David Kaufman[1]

[1]*Michigan State University, East Lansing, MI, United States*

TARGET AUDIENCE: Neuroimaging researchers/clinicians in concussion/traumatic brain injury

BACKGROUND: Current diagnosis and monitoring of concussion/mild traumatic brain injury (mTBI) rely on signs and symptoms, balance, vestibular, and neuropsychological examination. Conventional brain imaging often does not reveal abnormalities in concussed athletes. Recent work by Johnson et al. (1) demonstrated the alteration of default-mode network (DMN) with resting-state fMRI (rs-fMRI) in the sub-acute phase after concussion. To further understanding the recovery process, in this pilot work, we assessed the dynamic change of DMN connectivity with rs-fMRI and diffusion tensor imaging (DTI) on Days 1, 7 and 30 after concussion.

METHODS: Eight male intercollegiate concussed athletes (20 ± 1.3 years old, one repeated case) and 11 male control subjects (20.5 ± 1.8 years old) participated in this study. ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) was administered over the course of recovery. High-resolution 3D T_1-weighted, T_2*-weighted, DTI and rs-fMRI brain images were collected on a GE 3T Signa® HDx MR scanner from each subject within 1st day, on 7 ± 1 days and then 30 ± 1 days after concussion. The rs-fMRI included two 7-min resting-state (relax, eyes closed but staying awake) EPI datasets with the following parameters: 38 contiguous 3-mm axial slices, TE = 27.7 ms, TR = 2500 ms, flip angle = 80°, field of view (FOV) = 22 cm × 22 cm and matrix size = 64 × 64. DTI images were acquired with a dual spin-echo EPI sequence for 12 min and 6 sec with the following parameters: 48 contiguous 2.4-mm axial slices in an interleaved order, FOV = 22 cm × 22 cm, matrix size = 128 × 128, number of excitations = 2, TE = 77.5 ms, TR = 13.7 s, 25 diffusion gradient directions with b = 1000 s/mm^2, one volume with b = 0 and parallel imaging acceleration factor = 2. For each subject, correlation analyses of rs-fMRI were performed using AFNI (2). Slice-timing and motion corrections were applied. Baseline, linear and quadratic system trends were removed. Brain global, cerebral spinal fluid and white matter mean signals were modeled as nuisance variables and were removed from the time courses. Band-pass filter in the range of 0.009 Hz – 0.08 Hz was applied. Voxel-based correlation was done on every voxel of the brain against the time course from the average signal within a seed region. The right and left isthmi of cingulate cortex (ICCs), which are within the key hub regions of DMN (3), were defined with FreeSurfer (4) as seed regions. Correlation analysis results from individual subjects were warped to Talairach template for group analyses. In each group, full-brain ANOVAs were carried to compare the functional connectivity changes between the three time points. DTI was analyzed with FSL Diffusion Toolbox with the adjacent white-matter regions of ICCs as seeds (5). The anatomical images and DTI-based structural connectivity were reviewed for potential structural changes.

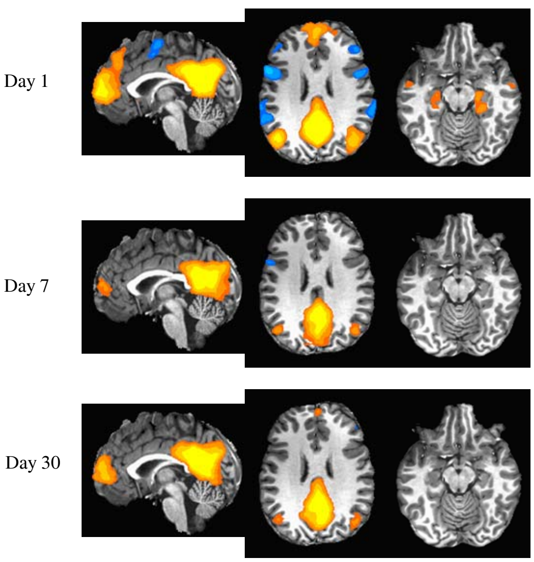

Fig.1. Mean functional connectivity to left isthmus of cingulate cortex (ICC) of the concussed group (correlation R > 0.25, n = 8).

RESULTS: ImPACT showed significant decline of cognitive scores across multiple categories and a significant increase of total symptom score on Day 1 following a concussion, with a full recovery after 5 ± 2.4 days. While the structural connectivity within DMN and gross anatomy appeared unchanged, a significantly reduced functional connectivity to ICCs within DMN from Day 1 to 7 was seen in the concussed group (P < 0.028, whole-brain corrected) based on the ANOVAs within the concussed group, notably around anterior cingulate, medial frontal, superior frontal, middle temporal/angular gyri and hippocampus/parahippocampal gyri (Fig. 1). This reduction trend was seen in eight of our nine concussion cases (Fig. 2). There was also a trend of improved DMN functional connectivity from Day 7 to 30. ANOVAs of the control group did not find significant brain alteration of DMN over the one-month period.

DISCUSSION AND CONCLUSION: There was a significantly higher functional connectivity within the DMN on Day 1 than Days 7 and 30. This phenomenon was even seen in individual concussed subjects. Equivalent analyses on the control group did not find the sequential alteration of DMN functional connectivity, suggesting that this alteration is specific to concussion. The high level of DMN functional connectivity on Day 1 seems to reflect the increase of alert level in monitoring the external environment (3). The lack of noticeable change in structural connectivity and gross anatomy confirmed that the concussions did not lead to severe structural damage. Based on our results, the functional connectivity of DMN measured with sequential rs-fMRI can potentially serve as a biomarker to monitor the dynamically changing brain function after sports-related concussion.

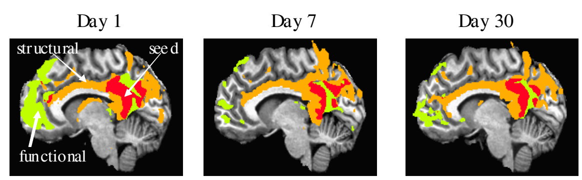

Fig.2. Case study: The functional (in green and red) and structural (in orange and red) connectivity to left isthmus of cingulate cortex of a concussed subject over one month (correlation R > 0.4 and connectivity distribution > 1000). Red: overlap regions.

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