Identify Potentially Vulnerable Functional Networks to Concussion in Sports: a Resting-State fMRI Longitudinal Study

David C Zhu[1], Sally Nogle[1], Scarlett Doyle[1], Doozie Russell[1], Tracey Covassin[1], Randolph L Pearson[1], J Kevin DeMarco[1], and David I Kaufman[1]
[1]*Michigan State University, East Lansing, Michigan, United States*

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

PURPOSE: 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. Recently we demonstrated a dynamic change of default-mode network (DMN) functional connectivity with resting-state fMRI (rs-fMRI) on Days 1, 7 and 30 after concussion (1). While the structural connectivity within DMN and gross anatomy appeared unchanged, a significantly reduced functional connectivity within DMN from Day 1 to 7 was found in the concussed subjects. In this pilot work, we attempted to systematically identify all potentially vulnerable networks, beyond DMN.

METHODS: Data were collected from 11 cases (one repeated case) of concussion from 10 male collegiate football student-athletes. ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) was administered over the course of recovery. High-resolution 3D T_1-weighted, T_2*-weighted, T_2 FLAIR (on some subjects), and rs-fMRI brain images were collected on a GE 3T Signa® HDx MR scanner from each subject within the 1st day, on 7 ± 1 days and then 30 ± 2 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 = 28 ms, TR = 2500 ms, flip angle = 80°, field of view (FOV) = 22 cm × 22 cm and matrix size = 64 × 64. In rs-fMRI pre-processing, 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. For each subject, the cortical nodes of the 17 networks produced by Yeo et al. (2) based on rs-fMRI datasets from 1,000 healthy young adults were identified in the native space through FreeSurfer (3). Correlation analyses of rs-fMRI time courses between the nodes of each network were performed using AFNI (4). The mean correlation of all node-pairs in a network was calculated. To prepare for group analyses, the correlation coefficients were converted to Z values through Fisher's Z-transformation. We performed repeated measure ANOVA on the connectivity of each network to assess whether there was significant change over time, followed with post-hoc 2-tail paired *t* tests between each pair of measurement time points. The anatomical images were reviewed for potential structural changes.

RESULTS: The repeated measure ANOVAs concluded that six of the 17 networks had uncorrected $p < 0.05$ (Table 1). The effect sizes between two time points were shown by *Hedges' g* values. The gross anatomy appeared unchanged over time.

Table 1. Changes of connectivity on different networks from Days 1 to 30 after concussion

Days		DMN A	DMN C	Salience/Ventral Attention A	Somatomotor B	Temporal-Parietal	Visual Peripheral
Day 1	Correlation *R*	0.450 ± 0.125	0.420 ± 0.143	0.514 ± 0.089	0.536 ± 0.084	0.610 ± 0.142	0.628 ± 0.096
Day 7	Correlation *R*	0.335 ± 0.151	0.298 ± 0.086	0.394 ± 0.159	0.452 ± 0.113	0.666 ± 0.167	0.690 ± 0.105
Day 30	Correlation *R*	0.369 ± 0.118	0.336 ± 0.111	0.432 ± 0.101	0.514 ± 0.098	0.711 ± 0.143	0.737 ± 0.095
ANOVA	*p* value	0.043*	0.039*	0.050*	0.017*	0.009*	0.030*
	F statistics	3.692	3.817	3.497	5.032	6.027	4.216
Day 1 vs. Day 7	*p* value	0.034*	0.039*	0.054	0.013*	0.127	0.156
	Hedges' g	0.765	0.972	0.862	0.773	-0.421	-0.638
Day 7 vs. Day 30	*p* value	0.023*	0.117	0.029*	0.426	0.004*	0.007*
	Hedges' g	0.664	0.647	0.850	0.211	-0.720	-1.140
Day 1 vs. Day 30	*p* value	0.584	0.289	0.536	0.052	0.106	0.257
	Hedges' g	-0.204	-0.373	-0.226	-0.541	-0.267	-0.487

*Uncorrected *p* value < 0.05 are indicated. The comparisons did not survive Bonferroni correction for 17 networks.

DISCUSSION AND CONCLUSION: In this pilot study, within the 17 functional networks, we found six networks (DMN A and C, Salience/Ventral Attention A, Somatomotor B, Temporal-Parietal and Visual Peripheral) relatively more prone to the impact of concussion. Although the connectivity on these six networks did not survive the conservative Bonferroni correction, the relatively large effect sizes (Hedges' g > 0.75) on almost all the comparisons with $p < 0.05$ on Table 1 suggest the likelihood of significant changes with a large sample size. We are continuing to collect more data from concussed collegiate student-athletes.

REFERENCES:

1. Zhu DC, Covassin T, Nogle S, Doyle S, Russell D, Pearson RL, Monroe J, Liszewski CM, DeMarco JK, Kaufman DI. A Potential Biomarker in Sports-Related Concussion: Brain Functional Connectivity Alteration of the Default-Mode Network Measured with Longitudinal Resting-State fMRI over 30 Days. J Neurotrauma 2014. In Press.
2. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, Fischl B, Liu H, Buckner RL. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011;106(3):1125-1165.
3. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33(3):341-355.
4. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 1996;29(3):162-173.