NeuroImage: Clinical 19 (2018) 434–442

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Association of acute depressive symptoms and functional connectivity of emotional processing regions following sport-related concussion

William T. McCuddy[a], Lezlie Y. España[a], Lindsay D. Nelson[a,b], Rasmus M. Birn[c,d], Andrew R. Mayer[e,f,g], Timothy B. Meier[a,h,i,*]

[a] Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, United States
[b] Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, United States
[c] Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States
[d] Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States
[e] The Mind Research Network/Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, United States
[f] Neurology Department, University of New Mexico School of Medicine, Albuquerque, NM, United States
[g] Department of Psychology, University of New Mexico, Albuquerque, NM, United States
[h] Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI, United States
[i] Laureate Institute for Brain Research, Tulsa, OK, United States

ARTICLE INFO

Keywords:
Resting state fMRI
Concussion
Mild traumatic brain injury (mTBI)
Depression
Connectivity

ABSTRACT

Acute mood disturbance following sport-related concussion is common and is known to adversely affect post-concussion symptoms and recovery. The physiological underpinnings of depressive symptoms following concussion, however, are relatively understudied. We hypothesized that functional connectivity of the emotional processing network would be altered in concussed athletes and associated with the severity of depressive symptoms following concussion. Forty-three concussed collegiate athletes were assessed at approximately one day ($N = 34$), one week ($N = 34$), and one month post-concussion ($N = 30$). Fifty-one healthy contact-sport athletes served as controls and completed a single visit. The Hamilton Rating Scale for Depression (HAM-D) was used to measure depressive symptoms. Resting state fMRI data was collected on a 3 T scanner (TR = 2 s) and functional connectivity was calculated in a meta-analytically derived network of regions associated with emotional processing. Concussed athletes had elevated depressive symptoms across the first month post-concussion relative to control athletes, but showed partial recovery by one month relative to more acute visits ($ps < 0.05$). Concussed athletes had significantly different connectivity in regions associated with emotional processing at one month post-concussion relative to one day post-concussion ($p = 0.002$) and relative to controls ($p = 0.003$), with higher connectivity between default mode and attention regions being common across analyses. Additionally, depressive symptoms in concussed athletes at one day ($p = 0.003$) and one week post-concussion ($p = 7 \times 10^{-8}$) were inversely correlated with connectivity between attention (e.g., right anterior insula) and default mode regions (e.g., medial prefrontal cortex). Finally, the relationships with HAM-D scores were not driven by a general increase in somatic complaints captured by the HAM-D, but were strongly associated with mood-specific HAM-D items. These results suggest that connectivity of emotional processing regions is associated with acute mood disturbance following sport-related concussion. Increased connectivity between attention and default mode regions may reflect compensatory mechanisms.

1. Introduction

Sport-related concussions (SRCs) are a major public health issue, with an estimated 1.6–3.8 million occurring in the United States every year (Langlois et al., 2006). Mood disturbance, a common consequence of brain injury, occurs in up to 50% of athletes following SRC (Kontos et al., 2012; Ellis et al., 2015). While previous work suggests that persistent depressive symptoms following SRC are associated with neural abnormalities consistent with the limbic-frontal model of depression (Chen et al., 2008), the precise physiological underpinnings of mood disturbance following *acute* brain injury remain unknown.

A better understanding of the physiological underpinnings of acute depressive symptoms following SRC is particularly important given evidence that depression adversely affects post-concussive symptoms

* Corresponding author at: Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, United States.
E-mail address: tmeier@mcw.edu (T.B. Meier).

https://doi.org/10.1016/j.nicl.2018.05.011
Received 29 December 2017; Received in revised form 20 April 2018; Accepted 8 May 2018
Available online 09 May 2018

and recovery. For example, emergency room patients with mild traumatic brain injury (mTBI) who developed major depressive disorder (MDD) acutely following injury experienced higher levels of post-concussive symptoms and worse behavioral outcomes (Rapoport et al., 2003). In similar samples, MDD following mild to moderate TBI was associated with increased disability and cognitive impairment (Levin et al., 2001) and significantly reduced functional outcome and health-related quality of life (Haagsma et al., 2015). Thus, isolating the relationships between neurophysiology and depressive symptoms following mTBI may provide novel prognostic information.

Resting state functional magnetic resonance imaging (rs-fMRI) has emerged as a popular method to assess neurophysiological changes brought on by mTBI. This method allows for the indirect study of large scale neural networks by measuring correlated fluctuations in the blood-oxygen-level dependent (BOLD) signal in the absence of external task demands. Although rs-fMRI may develop into a viable biomarker candidate, previous investigations regarding functional connectivity following SRC have yielded mixed results (McCrea et al., 2017). Such discrepant findings are likely the product of methodological differences, limited sample sizes, and variations in assessment timelines. Additionally, the natural heterogeneity of concussion sequelae, particularly as it pertains to mood disturbance, may account for the observed inconsistencies across studies (McCrory et al., 2017). Efforts to categorize this heterogeneity have led to attempts at identifying specific symptom clusters describing and predicting unique clinical trajectories (Collins et al., 2014). Identifying the physiological signatures of specific SRC indicators may eventually lead to the development of objective diagnostic or prognostic biomarkers for symptoms that largely depend on subjective self-report (e.g., depressive mood symptoms).

The present study sought to determine the extent to which depressive symptoms following SRC are associated with physiological abnormalities in brain regions associated with emotional processing. Specifically, we investigated patterns of functional connectivity between regions of interest (ROI) comprising a meta-analytically derived emotion network in collegiate athletes with SRC across the acute and sub-acute phase of injury. We hypothesized that: 1) SRC would be associated with disrupted resting state connectivity in regions associated with emotional processing relative to healthy contact sport athletes; and 2) greater post-concussion depressive symptoms would be associated with greater disruption of functional connectivity in regions associated with emotional processing.

2. Method

2.1. Participants and behavioral data

Data from this sample have been previously reported (Meier et al., 2017). This study was approved by an institutional review board. A total of 94 NCAA Division I student-athletes were referred by sports medicine professionals and provided written informed consent. From this sample, 43 concussed athletes completed at least one visit following SRC that occurred at one day (T1: 1.74 ± 0.93 days; $N = 34$), one week (T2: 8.44 ± 2.15 days; $N = 34$), and one month (T3: 32.47 ± 4.68 days $N = 30$) post-concussion. Of the 43 concussed athletes, 19 participated in all three visits and 36 participated in at least two visits. Concussions were diagnosed independent of the study at the time of injury by physicians trained in sports medicine following recommended guidelines (McCrory et al., 2013). Diagnosis was based on a clinical exam assessing symptoms, manual muscle testing for strength deficits, a cranial nerve check, on-field cognitive testing, the King-Devick test, and the Rhomberg's test for balance deficits. Fifty-one non-injured collegiate contact sport athletes served as healthy controls (HA). No participants reported past or current mood disorders, anxiety disorders, or alcohol/substance abuse.

For the purposes of this study, depressive symptoms were quantified using a structured interview for the Hamilton Depression Rating Scale (HAM-D) collected at each study visit. Sample characteristics are presented in Table 1.

Table 1
Sample characteristics.

	Healthy athletes ($N = 51$) Mean (*SD*)	Concussed athletes ($N = 43$) Mean (*SD*)
Demographics		
Gender (male/female)	35/16	34/9
Age	20.26 (1.44)	20.29 (1.31)
Education	13.31 (1.29)	13.12 (0.98)
Previous concussions	0.59 (1.10)	0.93 (1.14)
Concussion information		
Post-traumatic amnesia (# of athletes)	NA	1 of 37
Retrograde amnesia (# of athletes)	NA	6 of 37
Loss of consciousness (# of athletes)	NA	4 of 37
Sport		
Basketball	0	6
Football	31	31
Volleyball	0	1
Rowing	0	1
Soccer	20	4
Final n of usable data	HA	T1/T2/T3
Enrolled	51	34/34/30
HAM-D	50	34/34/30
Rs-fMRI	50	28/29/26

HAM-D = Hamilton Depression Rating Scale, HA = healthy athletes, T1 = one day post-concussion, T2 = one week post-concussion, T3 = one month post-concussion, NA = not applicable.

2.2. MRI parameters

Imaging data were collected on a General Electric Healthcare Discovery MR750 3-Tesla whole body scanner and a brain-dedicated receive-only 32-element coil array (Nova Medical, Inc.). T_1-weighted structural images were obtained using a parallelized magnetization-prepared rapid gradient-echo sequence with sensitivity encoding, FOV = 240 mm, 130 1.1 mm axial slices, image matrix 256 × 256, TR = 5 ms, TE = 1.948 ms, TI = 725 ms, acceleration factor R = 2, flip angle = 8°, sampling bandwidth 32.25 kHz, and voxel size = 0.9375 × 0.9375 × 1.1 mm. 180 volumes of rs-fMRI data were collected in a six-minute gradient-echo echo-planar image (EPI) during which participants were instructed to fixate on a cross. Rs-fMRI data had the following parameters: TR = 2 s, TE = 30 ms, flip angle = 90°, sampling bandwidth = 250 kHz, acceleration factor R = 2, FOV = 240 mm, acquisition matrix = 96 × 96, 37 axial slices, slice thickness = 3 mm, inter-slice spacing = 0.2 mm acquired voxel size 2.5 × 2.5 × 3.2 mm interpolated to 1.875 × 1.875 × 3.2 mm.

2.3. MRI processing

Image processing for these data has been previously described (Meier et al., 2017). T_1-weighted images were skull stripped and transformed to the TT_N27 template available in the Analysis of Functional NeuroImages software package (AFNI) (Cox, 1996) by applying a 12-parameter affine transformation followed by a non-linear warp as implemented in the Advanced Normalization Tools (ANTS; Avants et al., 2011). An eroded white matter mask was created following tissue segmentation. FreeSurfer segmentation v5 (Fischl et al., 2002) was used to create a bilateral lateral ventricle mask in native space, which was transformed to standard space and eroded to exclude non-CSF voxels.

The first four EPI volumes were removed, anomalous time-series data were replaced using AFNI's despike program, and images were slice-time corrected. EPI volumes were registered to the first volume to account for head motion using a 6-degree of freedom transformation. Motion-corrected volumes were then aligned to the TT_N27 template