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Concussion-Related Disruptions to Hub Connectivity in the Default Mode Network Are Related to Symptoms and Cognition

Heather C. Bouchard,[1,2,*] Kate L. Higgins,[1,3] Grace K. Amadon,[1,4] Julia M. Laing-Young,[1,2] Arthur Maerlender,[1] Seima Al-Momani,[1,2] Maital Neta,[1,2] Cary R. Savage,[1,2] and Douglas H. Schultz[1,2]

Abstract

Concussions present with a myriad of symptomatic and cognitive concerns; however, the relationship between these functional disruptions and the underlying changes in the brain are not yet well understood. Hubs, or brain regions that are connected to many different functional networks, may be specifically disrupted after concussion. Given the implications in concussion research, we quantified hub disruption within the default mode network (DMN) and between the DMN and other brain networks. We collected resting-state functional magnetic resonance imaging data from collegiate student-athletes ($n = 44$) at three time points: baseline (before beginning their athletic season), acute post-injury (approximately 48h after a diagnosed concussion), and recovery (after starting return-to-play progression, but before returning to contact). We used self-reported symptoms and computerized cognitive assessments collected across similar time points to link these functional connectivity changes to clinical outcomes. Concussion resulted in increased connectivity between regions within the DMN compared with baseline and recovery, and this post-injury connectivity was more positively related to symptoms and more negatively related to visual memory performance compared with baseline and recovery. Further, concussion led to decreased connectivity between DMN hubs and visual network non-hubs relative to baseline and recovery, and this post-injury connectivity was more negatively related to somatic symptoms and more positively related to visual memory performance compared with baseline and recovery. Relationships between functional connectivity, symptoms, and cognition were not significantly different at baseline versus recovery. These results highlight a unique relationship between self-reported symptoms, visual memory performance, and acute functional connectivity changes involving DMN hubs after concussion in athletes. This may provide evidence for a disrupted balance of within- and between-network communication highlighting possible network inefficiencies after concussion. These results aid in our understanding of the pathophysiological disruptions after concussion and inform our understanding of the associations between disruptions in brain connectivity and specific clinical presentations acutely post-injury.

Keywords: default mode network; functional connectivity; mild traumatic brain injury; network hub; neuroimaging; sport-related concussion

[1]Center for Brain, Biology and Behavior, Departments of [2]Psychology and [3]Athletics, University of Nebraska-Lincoln, Lincoln, Nebraska, USA.
[4]Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

*Address correspondence to: Heather C. Bouchard, MA, University of Nebraska-Lincoln, 328 Burnett Hall, Lincoln, NE 68588, USA E-mail: bbouchard2@huskers.unl.edu

Introduction

Approximately 3.8 million concussions occur each year within the United States[1]— approximately 300,000 of which are sports- or recreation-related[2]—and the incidence of sports-related concussions has been steadily increasing.[3,4] These increases in diagnosis may be because of increased awareness, changes in reporting requirements, changes in sport participation, and better recognition of concussion-related symptoms.[5]

Unfortunately, we still have limited understanding of the underlying brain pathophysiology resulting from a concussion and of the relationship between the clinical presentation of concussion and physiological brain changes that have been identified. The clinical presentation of concussions can include a variety of symptoms and changes in cognition, including somatic complaints (i.e., sensitivity to light or noise), cognitive deficits (i.e., difficulty concentrating or acute disruptions in memory), affective dysregulation (i.e., feeling more emotional), and sleep-related concerns (i.e., drowsiness).

The definition of a concussion and criteria for diagnosis can vary between practitioners, organizations, and consensus statements.[6] Typically, diagnoses are based on several clinical signs that represent a functional disturbance in the brain.[7] Evidence on standard clinical brain imaging (most commonly computed tomography [CT] or structural magnetic resonance imaging [MRI]) is not currently required for the diagnostic process because of lack of sensitivity to these mild brain-related changes.[7,8] Recent research using more advanced MRI techniques, however, has detected subtle changes in brain structural and functional connectivity, which has increased the understanding of the neurophysiological changes in the brain after concussion, specifically related to changes in axonal damage, inflammation, and cellular homeostasis.[9]

Reviews of the literature on functional MRI have reported both increases and decreases in functional connectivity post-concussion, evident globally and within a range of functional brain networks.[10,11] These inconsistencies have limited interpretation of these findings, which may be related to variability in measurement time lines post-injury. Given the heterogeneity of the literature and heterogeneity in the clinical presentation of concussions, it is unclear how the clinical presentation of a concussion relates to changes identified in brain function. Defining these connections may aid in mechanism-based interventions for concussion management.

Patients with moderate to severe traumatic brain injuries (TBIs) have disruptions in functional brain regions identified as ''hubs.''[12–15] Hubs are well-connected regions—evident in nearly all functional networks of the brain—that play an important role in brain organization as well as cognitive and behavioral functioning.[15-18] Specifically, hubs are involved in reducing the metabolic cost associated with communication across the brain and allow for greater global efficiency of the brain's communication.[19,20] Therefore, when hubs are disrupted through pathological processes, there is a disproportionate decrease in network efficiency compared with disruption of non-hubs. For example, lesions to regions identified as hubs can lead to long-term cognitive deficits,[21] and more subtle injuries, such as a concussion, may also result in a disruption to hubs.[22–25] This research on concussions (typically classified as mild TBIs) is limited, however, and only includes imaging data collected post-injury.

The default mode network (DMN) is thought to be central to concussion-related pathophysiology.[11,26-28] It plays a role in a wide variety of cognitive processes, including cognitive and emotional processing, monitoring of the environment, shifting between cognitive tasks, self-referential processing (i.e., remembering the past, planning the future, and self-reflection), and day dreaming,[29–31] many of which are impacted after a concussion. As a result, the DMN is one of the most investigated functional brain networks within the concussion literature.[11]

Reported changes to DMN functional connectivity after concussion have been variable, including findings of both hyperconnectivity and hypoconnectivity after injury.[11,27] Studies are heterogeneous in their neuroimaging preprocessing steps, analytical models, mechanism of injury, ages of participants, and timing of post-injury assessments. In addition, these studies did not include a measure of functional connectivity before injury.

Variability exists in baseline functional connectivity across people because of distinct individual-specific features of the brain's cortical organization. The previous inability to capture these intraindividual effects of concussion on the DMN may contribute to the heterogeneity of the literature.

An additional confound in understanding concussion-related physiological changes, such as functional connectivity disruptions, is the extended longevity of these changes. Often these changes persist past the point of recovery as defined by traditional clinical measures.[32] Time between concussion diagnosis and return-to-play for collegiate athletes occurs on average in 16 days.[33] Functional connectivity differences are still present up to 23 months after athletes returned-to-play.[32]

It is unclear why these physiological changes continue after clinical recovery. One explanation may be because of the brain's ability to compensate. Another explanation may be from comparing effects between groups (i.e., non-injured control group), because interindividual differences in cortical organization may complicate interpretations. Comparing post-injury functional connectivity patterns to an athlete's own baseline may resolve some heterogeneity in the literature.

This study aimed to explicate concussion-related changes to DMN functional connectivity, focusing on changes within and between DMN hubs, using a baseline comparison method. Collegiate student-athletes' functional connectivity at baseline (before the start of the season) was compared with connectivity approximately 48h after receiving a concussion diagnosis (post-injury), and after beginning their return-to-play progression, but before return to contact (recovery).

We hypothesized that functional connectivity of hubs *within* the DMN would be disrupted acutely post-injury compared with both baseline and recovery. Similarly, we hypothesized that as symptom reporting and cognitive performance return to baseline levels at recovery, so will functional connectivity differences. Last, for between-network functional connectivity, we predicted that functional connectivity *between* DMN hubs and other networks would be disrupted after a concussion and the degree of this disruption would be related to self-reported symptoms and cognitive performance. We did not expect, however, that all disruptions *between* the DMN and other networks will return to baseline levels at recovery, suggesting compensatory processes that allow for the appearance of clinical recovery while changes in the brain persist.

Methods

Participants

Forty National Collegiate Athletic Association (NCAA) men's football and four women's soccer student-athletes participated in the study. At baseline, participants ranged in age from 17 to 24 years (mean [M] = 19.75, standard deviation [SD] = 1.8). Participants completed an MRI scan during their baseline clinical evaluation before the start of their season. During the first year of data collection, however, a subset of participants (15 football; 2 soccer) had already been competing at the university, and MRI scans were conducted at the start of that season.

Acute post-injury scans were collected within approximately 48h of a diagnosed concussion (post-injury) and during the participants' return-to-play protocol immediately before returning to contact (recovery). Recovery time for participants ranged from 3-93 days (M = 11, SD = 14). Additional demographic information, including sample sizes because of missing clinical data at the three time points, can be found in Table 1.

Clinical data regarding concussion diagnosis, management, and clearance for return-to-play, including symptom reporting and cognitive performance, were collected in accordance with the Department of Athletics' concussion protocol at University of Nebraska-Lincoln (UNL). Concussions were diagnosed, managed, and cleared by the concussion management team in the Department of Athletics

Table 1. Sample Demographics

	Range			Mean (SD)
Age	17–24 years			19.8 (1.8)
Recovery time	3–93 days			10.5 (13.5)
	Women			**Men**
Gender	n = 4			n = 44
	White	**Black**	**Biracial**	**Unknown**
Race	n = 22	n = 12	n = 1	n = 4
	Zero	**One**	**Two**	**Three**
Concussion history	n = 22	n = 16	n = 4	n = 1
	Baseline	**Post-Injury**		**Recovery**
Participants with clinical data	n = 44	n = 40		n = 31
	Baseline-Post-Injury Mean (SD)	**Post-Injury-Recovery Mean (SD)**		**Baseline-Recovery Mean (SD)**
Days between MRI scans	265.1 (254.1)	10.5 (13.7)		275.7 (245.3)
	Min – Max	**Min – Max**		**Min – Max**
	19 – 1028 days	6 – 93 days		27 – 1034 days

SD, standard deviation; MRI, magnetic resonance imaging.

using a standardized protocol. Diagnoses were provided by the same clinicians, and return-to-play criteria included return to baseline symptom levels and clinical judgment. Most concussions were sport-related (n = 41), while three were not sport-related.

Most participants (n = 27) completed their clinical baseline assessments an average of 21 days (range 0–65 days) before their baseline MRI scan. A subset during the first year of data collection experienced a longer duration between the clinical baseline assessments and MRI scan with an average of 1.8 years (639 days, range 113 days–3.1 years). This was because of clinical baseline assessments being collected before the start of the neuroimaging study.

The clinical baseline measures represent normative function that is thought to be relatively stable over time. We included time in the regression models as a nuisance variable to account for potential variance, however. Clinical data, such as symptom reporting and cognitive performance assessed at baseline, were not missing for any participants, nor were MRI data at any of the three time points (i.e., baseline, post-injury, recovery). Because of clinical management procedures, however, clinical data used in this study for 15 participants were missing at either post-injury or recovery time points. All participants signed consent forms approved by the UNL Institutional Review Board to use their MRI scan and clinical data for research purposes.

Symptom reports and cognitive assessment

Self-reported symptoms and cognitive performance were assessed via Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT).[34] Self-report of 22 symptoms was collected via the ImPACT Post-Concussion Symptom Scale (PCSS)[35] at each time point and grouped into four symptom factors: cognitive, somatic, sleep, and affective.[36] ImPACT also creates four composite scores including reaction time, verbal memory, visual memory, and visual-motor speed and was administered at baseline, post-injury, and before clearance to begin return-to-play protocol (recovery) by clinicians in the Department of Athletics. To account for practice effects and regression to the mean, composite scores were converted to regression-based z-scores using a formula derived from a previously published sample of participants who also completed ImPACT across several time points.[37]

MRI acquisition

Data were collected on a 3T Siemens Skyra scanner housed within the Center for Brain, Biology, and Behavior at UNL. The T1-weighted anatomical (repetition time [TR] = 2530 msec, flip angle = 7 degrees, field of view [FOV] = 256 mm/100% phase, 176 slices, slice thickness = 1 mm) and multi-band echo-planar resting-state fMRI (TR/echo time [TE] = 1000/29.8 msec, flip angle = 60 degrees, FOV = 210 mm/100% phase, slice thickness = 2.5 mm, 51 interleaved slices, multi-band accel factor = 3) were acquired.

During resting-state fMRI, Framewise Integrated Real-Time MRI Monitoring (FIRMM) was used to assess real-time head motion of participants during their scan to improve data quality.[38] In the case of participant motion, scans were extended until we reached our goal of 30 min of low-motion data (framewise displacement <0.2 mm) or until allocated scan time was over (M [SD] scan time in minutes for baseline = 28.3 [4.6], post-injury = 29.6 [3.8], recovery = 30.8 [2.6]).

Resting-state fMRI pre-processing

Data were processed in Matlab (v.R2016b) with a previously established pipeline described elsewhere.[39] Pre-processing occurred with the Talairach atlas[40] space to register the mean intensity of the blood-oxygen-level-dependent (BOLD) signal with the T1-weighted image. Masks were created of the whole brain, white matter, and ventricles using Freesurfer recon-all command[41] (v5.3).

The following pre-processing steps all occurred in Matlab (v.R2016b). This involved slice-time correction, rigid body realignment, and normalization. Six motion estimates and their derivatives[42] were demeaned and detrended and were included as nuisance regressors along with global signal, white matter signal, and cere-bral spinal fluid signal. Frames with high motion (framewise displacement >0.2 mm) were removed. These scrubbed time points were replaced with interpolated data, using least squares spectral estimation, for the purposes of bandpass filtering but were excluded when calculating functional connectivity.[43] Next, temporal filtering was conducted with a bandpass filter between 0.009 to 0.08 Hz and spatially smoothed with a Gaussian filter of 6 mm.

After pre-processing steps were complete, the mean signal from 10 mm diameter spheres for each of 264 nodes[43] was extracted within Matlab (v.R2016b). Matrices representing the correlation (Pearson r) between each pair of nodes were calculated and Fisher z-transformed.

Hub identification

Participation coefficient[44] is a graph theoretic measure used to quantify the uniformity of node distribution within its own network or between other networks. We used participation coefficient to define hubs and non-hubs during participants' baseline scan in each of the 13 networks described by Power and colleagues[43] (the "uncertain network" was excluded from this analysis). The conventional participation coefficient measure assumes all networks are the same size, which is not the case in brain network connectivity. Therefore, a *normalized* participation coefficient value was used to reduce the influence of network size.[44]

Hubs in each network were identified as having a participation coefficient value in the top 25% of their network, while the remaining nodes in the network were identified as non-hubs. Figure 1 visualizes the average likelihood of a region being selected as a hub for two networks: DMN and visual network. Thresholds of 15% and 35% were also assessed and results are reported in Supplementary Text S1. Figure 2 represents a schematic of the within and between DMN functional connectivity described in the following, corresponding sections.

Within DMN functional connectivity

Next, we compared functional connectivity within the DMN at baseline, post-injury, and recovery time points. To produce a null distribution of functional connectivity, we also assessed 10,000 permutations of a randomized network with the same number of nodes (k = 58) as the DMN but excluding DMN nodes. Differences in functional connectivity at each time point within the DMN were compared with this null distribution. Given that this null distribution was created by using a random selection of nodes, each single permutation does not necessarily share the same characteristics as the DMN. This method was selected, however, as a more conservative approach to control for Type I errors. We also compared functional connectivity within DMN hubs, within DMN non-hubs, and between DMN hubs and non-hubs across time points.
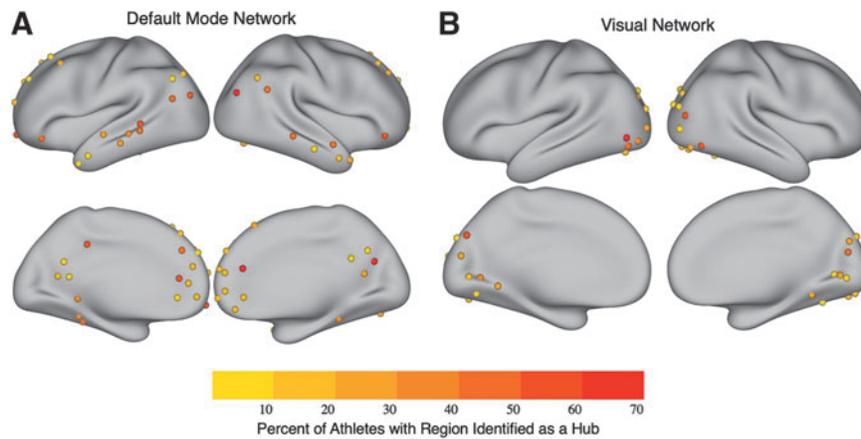
FIG. 1. Visualization of hubs. The average likelihood of a region to be identified as a hub across the 44 student-athletes is visualized across the (**A**) Default Mode Network and (**B**) Visual Network. Regions in red are more likely to be a hub for each participant compared with regions in yellow.

Hubs and non-hubs were also categorized in the 10,000 permutations of randomized networks. We then compared the functional connectivity within hubs, within non-hubs, and between hubs and non-hubs to obtain a null distribution of hub and non-hub connectivity. Differences in functional connectivity at each time point within DMN hubs, within DMN non-hubs, and between DMN hubs and non-hubs were compared with the null distribution of randomized networks within randomized hubs, within randomized non-hubs, and between randomized hubs and non-hubs. Significant findings were then related to symptom reporting and cognitive performance to examine the relationship between functional connectivity disruptions within the DMN and clinical presentation.

Between DMN functional connectivity

We assessed functional connectivity between DMN hubs and nodes in the remaining 12 networks across the three time points: baseline, post-injury, and recovery. These changes were compared with the connections between the permuted networks and the same nodes in the 12 non-DMN networks. For example, when assessing hubs in the DMN to the visual network, functional connectivity for this analysis was compared with permuted networks that excluded nodes in the DMN and visual network. Significant findings between DMN hubs and networks were then related to symptom reporting and cognitive performance to examine the relationship between functional connectivity disruptions and clinical presentation.

Statistical analysis

Statistical analyses of functional connectivity and clinical data were conducted in Matlab (v.R2020) using the *anova* and *fitlme* commands. Analysis of variance for linear mixed-effects models was used to account for the missing clinical data and because of their robustness to violations of distributional assumptions.[45] Models included time point (i.e., baseline, post-injury, or recovery) as a fixed effect and the random effect of participant ID.

Post-hoc tests across time points were analyzed using the *t-test* command in Matlab (v.R2020). To control for multiple comparisons, a false discovery rate (FDR) correction was used. Significant results are reported with adjusted p values for the within DMN analysis ($p_{adj} < 0.002$), between DMN and other networks ($p_{adj} < 0.013$), symptom clusters ($p_{adj} < 0.004$), and cognitive performance ($p_{adj} < 0.001$).

The relationship between functional connectivity and clinical data, such as symptom reporting and cognitive performance, was evaluated in Matlab (v.R2020) using a linear mixed effect model with the *fitlme* command to understand the interaction between time point (i.e., baseline, post-injury, or recovery) and functional connectivity to predict either symptom reporting or cognitive performance. Post-injury clinical and MRI data were compared with baseline and recovery data together. Given the exploratory nature of these comparisons, we did not implement FDR-correction.

Post-hoc analyses then compared baseline and recovery separately to understand the relationship to post-injury. In the model, we included the random effect of participant ID as well as time between baseline, post-injury, and recovery data collection to control for within-person effects and the variability in time between baseline assessments and when the concussion occurred.

Results

Symptom reports and cognitive assessment

The collegiate student-athletes who participated in this study returned-to-play across an expected recovery trajectory after sustaining their concussion. Student-athletes
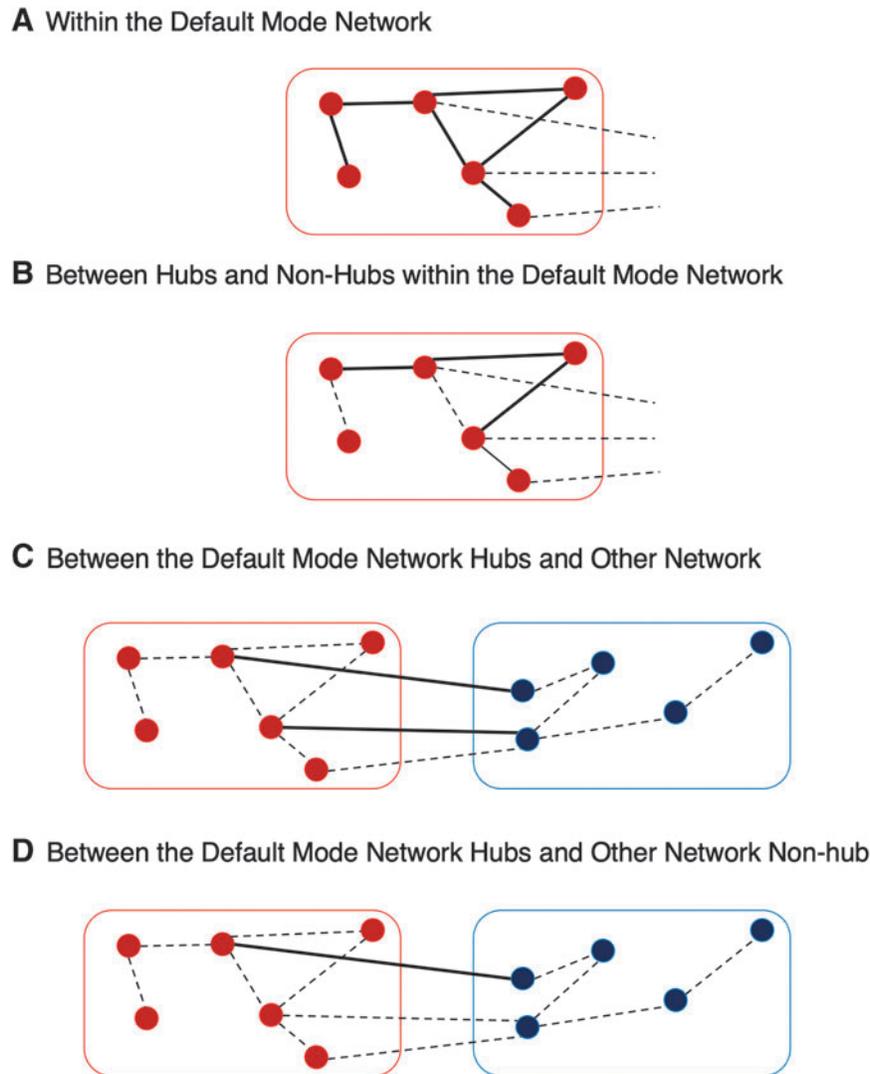
FIG. 2. Schematic of within and between Default Mode Network (DMN) analyses. Nodes are characterized as circles, and connections between nodes are characterized by lines. Red nodes represent brain regions within the DMN, while blue nodes represent brain regions in a non-DMN network. Hubs are represented as nodes with three or more connections, while non-hubs are represented as nodes with less than three connections. Solid lines depict connections that would have been included in the example analyses while connections represented as dotted lines would not have been included.

recovered an average of 11 days (median = 8 days). In addition, 91% of these student athletes recovered within 14 days, and all but one athlete (98%) recovered within 28 days, consistent with expected recovery.[46]

Table 2 reports findings for symptom factor and cognitive performance changes across time. Participants' self-reported total symptoms significantly differed across time points ($F(2, 112) = 22.233$, $p < 0.0001$), with more symptoms reported at post-injury than baseline ($t = -4.499$, $p < 0.0001$) and more symptoms reported at post-injury than recovery ($t = 5.355$, $p < 0.0001$). We observed differences across time points in affective symptoms ($F(2, 112) = 5.712$, $p = 0.004$), cognitive symptoms ($F(2, 112) = 17.219$, $p < 0.0001$), sleep symptoms ($F(2, 112) = 14.015$, $p < 0.0001$), and somatic symptoms ($F(2, 112) = 19.047$, $p < 0.0001$; Fig. 3A).

Student-athlete performance on ImPACT composite scores differed across time points for tasks assessing reaction time ($F(2, 110) = 343.370$, $p < 0.0001$), visual memory ($F(2, 110) = 9.193$, $p < 0.001$), and visual motor speed ($F(2, 110) = 7.254$, $p = 0.001$) performance, while verbal memory performance did not significantly change across time points ($F(2, 110) = 0.555$, $p = 0.576$; Fig. 3B).

Table 2. Statical Differences for Symptom Clusters and Cognitive Performance Across Baseline, Post-Injury, and Recovery Time Points

	Baseline - Post-injury		Post-injury - Recovery		Baseline - Recovery	
Symptom Clusters	**Statistical Differences for Symptom Clusters across Time (t-statistic, p-value)**					
Affective	$t = -1.956$	$p = 0.058$	$t = 3.610$	$p = 0.001**$	$t = 1.091$	$p = 0.284$
Cognitive	$t = -4.082$	$p < 0.001***$	$t = 4.570$	$p < 0.0001****$	$t = 0.496$	$p = 0.623$
Sleep	$t = -1.705$	$p = 0.096$	$t = 4.570$	$p < 0.0001****$	$t = 3.082$	$p < 0.001***$
Somatic	$t = -4.980$	$p < 0.0001****$	$t = 4.805$	$p < 0.0001****$	$t = 0.450$	$p = 0.656$
ImPACT Composites	**Statistical Differences for Cognitive Performance across Time (t-statistic, p-value)**					
Reaction time	$t = -25.701$	$p < 0.0001****$	$t = 14.253$	$p < 0.0001****$	$t = -3.701$	$p < 0.001***$
Visual memory	$t = 3.315$	$p = 0.002**$	$t = -3.826$	$p < 0.001***$	$t = 0.192$	$p = 0.849$
Visual motor speed	$t = 0.007$	$p = 0.995$	$t = -3.768$	$p < 0.001***$	$t = -4.597$	$p < 0.0001****$
Verbal memory	*Non-significant ANOVA*		*Non-significant ANOVA*		*Non-significant ANOVA*	

$*p < 0.05$; $**p < 0.01$; $***p < 0.001$; $****p < 0.0001$.

The initial analysis of variance (ANOVA) for linear mixed-effects models surpassed a false discovery rate (FDR) correction of $p_{adj} < 0.004$ for symptom clusters and $p_{adj} < 0.001$ for cognitive performance.
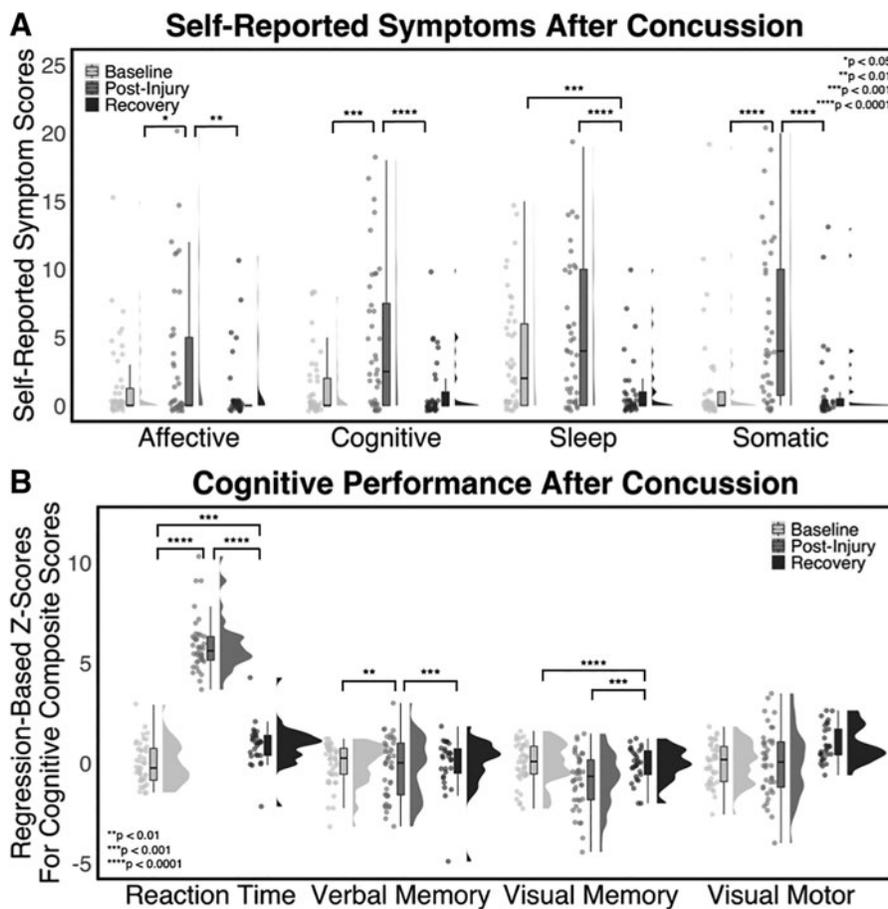
FIG. 3. Self-reported symptom and cognitive performance changes change post-concussion. (**A**) Changes in the four symptom factors over time. Affective, cognitive, and somatic symptoms factors increased from baseline to post-injury and then decreased from post-injury to recovery. Less sleep-related symptoms were reported at recovery compared with baseline and post-injury. (**B**) Cognitive performance assessed via the ImPACT compositive scores after conversion to regression-based z-scores. Reaction time slowed from baseline to post-injury and improved from post-injury to recovery, yet performance did not return to baseline levels. Visual memory performance was worse from baseline to post-injury and improved from post-injury to recovery. Visual motor performance was not significantly different between baseline and post-injury but did improve from baseline to recovery. Verbal memory performance did not significantly change across baseline, post-injury, and recovery.

Within DMN functional connectivity

Functional connectivity within the DMN did not significantly differ by time point ($F(2, 129) = 8.1$, $p = 0.070$), nor were there any significant differences across time for connectivity between DMN hubs ($F(2, 129) = 9.115$, $p = 0.079$) or between DMN non-hubs ($F(2, 129) = 4.336$, $p = 0.738$). Connectivity between DMN hubs and DMN non-hubs, however, did significantly differ by time point ($F(2, 129) = 13.656$, $p = 0.003$; Fig. 4), such that connectivity increased from baseline to post-injury ($t = -4.456$, $p < 0.0001$) and decreased from post-injury to recovery ($t = 3.129$, $p = 0.003$), but did not completely return to baseline at recovery (i.e., connectivity at recovery was greater than baseline; $t = -2.752$, $p = 0.009$). A schematic of these analyses is depicted in Figure 2A and Figure 2B. Significant *post-hoc* analyses are reported in Table 3.

Table 4 summarizes results from the linear mixed effect models linking this pattern of functional connectivity change with clinical outcomes. Specifically, greater functional connectivity post-injury was observed in participants reporting more cognitive symptoms post-injury resulting in a more positive relationship than the corresponding relationship at baseline and recovery ($t = 2.539$, $p = 0.012$), while the relationship at baseline and recovery was not significantly different from one another ($t = -0.576$, $p = 0.566$; Fig. 5A).

Similarly, greater functional connectivity post-injury was observed in participants reporting more somatic symptoms post-injury also resulting in a more positive relationship than the corresponding relationship at baseline and recovery ($t = 2.338$, $p = 0.021$), while the relationship at baseline and recovery was not significantly different from one another ($t = 0.017$, $p = 0.987$; Fig. 5B).

Greater functional connectivity post-injury was observed in participants with worse post-injury visual memory performance resulting in a more negative relationship than the corresponding relationship at baseline and recovery ($t = -2.793$, $p = 0.006$), while the relationship at baseline and recovery was not significantly different from one another ($t = -0.446$, $p = 0.657$; Fig. 5C).

Between DMN functional connectivity

Functional connectivity from DMN hubs to nodes in the remaining 12 networks were significantly different by time point for the cingulo-opercular network ($F(2, 129) = 8.499$, $p = 0.004$), dorsal attention network ($F(2, 129) = 4.972$, $p = 0.018$), salience network ($F(2, 129) = 6.274$, $p = 0.006$), somatomotor network ($F(2, 129) = 5.677$, $p = 0.019$), and visual network ($F(2, 129) = 13.762$, $p < 0.001$).

We next focused on connections between hubs in the DMN and non-hubs in the above networks because the connections between hubs and non-hubs within the DMN were specifically altered after concussion. Changes in these connectivity patterns over time were then related to clinical outcomes. A schematic of these analyses is depicted in Figure 2C and Figure 2D.

Functional connectivity differed across time point between DMN hubs and non-hubs in the cingulo-opercular network ($F(2, 129) = 7.605$ $p = 0.002$), dorsal attention network ($F(2, 129) = 3.981$, $p = 0.019$), salience network ($F(2, 129) = 4.980$, $p = 0.026$), somatomotor network ($F(2, 129) = 5.485$, $p = 0.023$), and visual network ($F(2, 129) = 12.861$, $p < 0.0001$; Fig. 6). Functional connectivity between DMN hubs and cingulo-opercular network non-hubs decreased from baseline to post-injury ($t = 3.194$, $p = 0.003$) and from baseline to recovery ($t = 2.481$, $p = 0.017$). Although functional connectivity
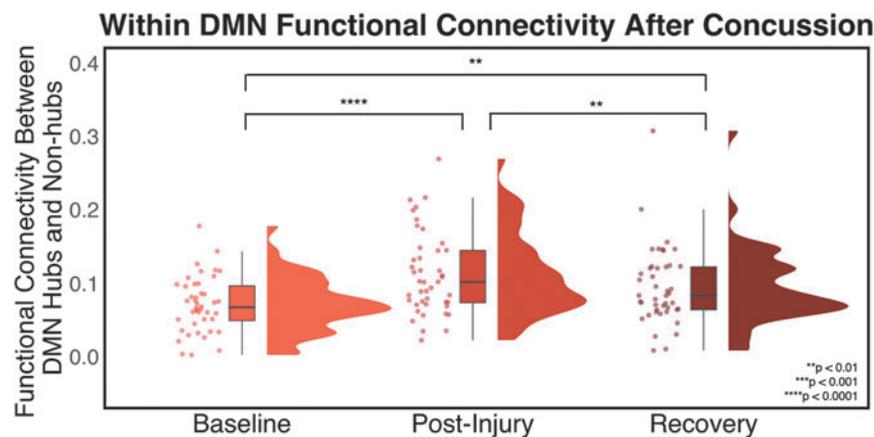
FIG. 4. Functional connectivity changes between Default Mode Network (DMN) hubs and non-hubs. Functional connectivity within the DMN between regions identified as hubs, and regions identified as non-hubs significantly increased from baseline to post-injury and significantly decreased from post-injury to recovery but did not return to baseline connectivity levels.

Table 3. Statistical Differences for Within and Between Default Mode Network Functional Connectivity Across Baseline, Post-Injury, and Recovery Time Points

	Baseline - Post-injury			Post-injury - Recovery			Baseline - Recovery		
Within DMN									
DMN hubs and DMN non-hubs	$t=-4.456$	$p<0.0001$****	↑	$t=3.129$	$p=0.003$**	↓	$t=-2.752$	$p=0.009$**	↑
Between DMN									
DMN hubs and somatomotor network non-hub	$t=3.010$	$p=0.026$*	↓	$t=0.738$	$p=0.465$		$t=2.738$	$p=0.009$**	↓
DMN hubs and cingulo-opercular network non-hub	$t=3.194$	$p=0.003$**	↓	$t=-1.493$	$p=0.143$		$t=2.481$	$p=0.017$*	↓
DMN hubs and visual network non-hub	$t=2.208$	$p=0.033$*	↓	$t=-2.700$	$p=0.010$**	↑	$t=2.847$	$p=0.007$**	↓
DMN hubs and salience network non-hub	$t=2.712$	$p=0.010$**	↓	$t=1.593$	$p=0.119$		$t=-1.888$	$p=0.066$	

*$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$.

The reported initial analysis of variance (ANOVA) for linear mixed-effects models surpassed a false discovery rate (FDR) correction of $p_{adj}<0.002$ for within default mode network (DMN) comparisons and $p_{adj}<0.013$ for comparisons between DMN and other networks.

between DMN hubs and dorsal attention network non-hubs differed, the pair-wise comparisons did not.

Functional connectivity between DMN hubs and the salience network non-hubs only significantly decreased from baseline to post-injury ($t=2.712$, $p=0.010$). Functional connectivity between DMN hubs and somatomotor network non-hubs decreased from baseline to post-injury ($t=2.310$, $p=0.026$) and from baseline to recovery ($t=2.738$, $p=0.009$). Functional connectivity between DMN hubs and visual network non-hubs decreased from baseline to post-injury ($t=2.208$, $p=0.033$), increased from post-injury to recovery ($t=-2.700$, $p=0.010$), and remained decreased from baseline to recovery ($t=2.847$, $p=0.007$). These significant *post-hoc* analyses are reported in Table 3.

Next, we related this pattern of changes in functional connectivity to symptoms and cognitive performance. The only significant relationship between functional connectivity and symptoms or cognitive performance was with the visual network. Somatic symptoms (Fig. 7A) and visual memory performance (Fig. 7B) were related to functional connectivity between DMN hubs and visual network non-hubs. Less functional connectivity between DMN hubs and visual network non-hubs at post-injury was observed in participants reporting more post-injury somatic symptoms resulting in a more negative relationship than the corresponding relationship at baseline and recovery ($t=-2.466$, $p=0.015$), while the relationship at baseline and recovery was not significantly different from one another ($t=-0.374$, $p=0.709$).

Similarly, for cognitive performance, less functional connectivity at post-injury was observed in participants with worse post-injury visual memory performance resulting in a more positive relationship than the

corresponding relationships at baseline and recovery ($t=2.901$, $p=0.004$), while the relationship at baseline and recovery was not significantly different from one another ($t=0.886$, $p=0.378$). The significant effects reported here are summarized in Table 5.

Discussion

Concussion disrupts multiple systems in the body, including functional organization of the brain. The present study examined the effect of concussion in 44 collegiate student-athletes on functional connectivity within and between the DMN and specified the relationship to clinical outcomes after concussion. Uniquely, the present study was able to obtain pre-injury baseline functional connectivity and clinical data in all 44 student-athletes. We found *increased* functional connectivity between hubs and non-hubs within the DMN during the acute period after concussion compared with baseline. At recovery, functional connectivity between DMN hubs and non-hubs *decreased* from post-injury but did not return to baseline levels.

In addition, functional connectivity between hubs in the DMN and non-hubs identified in several other brain networks decreased from baseline to post-injury. Results were variable between networks at recovery, however, with only some networks returning to baseline levels. Clinically, somatic and cognitive symptoms, and visual memory performance were the only measures related to these changes in brain organization post-injury.
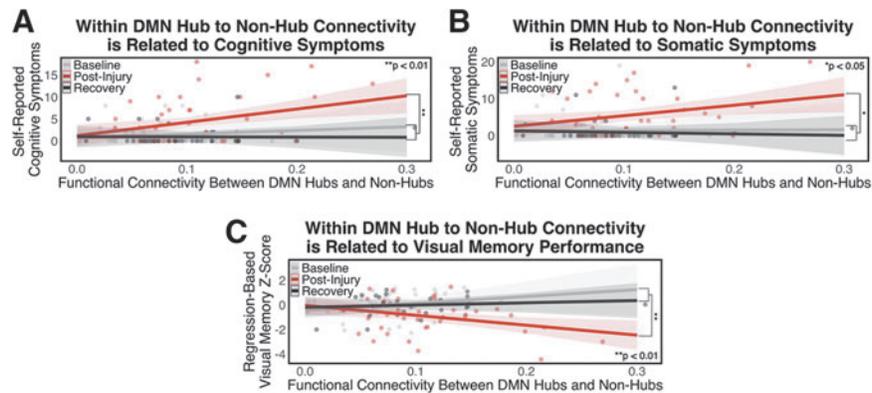
Within DMN functional connectivity

We found that post-injury functional connectivity between hubs and non-hubs within the DMN was significantly related to self-reported symptoms and cognitive

Table 4. Significant Relationship Between Post-Injury Clinical Outcomes and Functional Connectivity Between Default Mode Network Hubs and Non-Hubs

Clinical outcome	Estimate	Standard error	T-Statistic	Degree of freedom	p	Confidence interval	AIC	BIC
Cognitive symptoms	29.213	11.505	2.539	111	0.012*	6.416, 52.011	614.1	636.1
Somatic symptoms	34.285	14.663	2.338	111	0.021*	5.2291, 63.342	663.4	685.4
Visual memory	-10.995	3.937	-2.793	111	0.006**	-18.797, -3.1924	348.9	370.8

*$p<0.05$; **$p<0.01$. AIC, akaike information criterion; BIC, bayesian information criterion.

FIG. 5. Within Default Mode Network (DMN) connectivity, symptom reporting, and cognitive performance. There was a significantly stronger relationship between post-injury functional connectivity between DMN hubs and non-hubs and post-injury (**A**) cognitive symptoms, (**B**) somatic symptoms, and (**C**) visual memory performance than functional connectivity and clinical outcomes at baseline and recovery.

performance after concussion. Specifically, increased DMN hub and non-hub connectivity was associated with increased cognitive and somatic symptoms after a concussion. While these results are consistent with previous work,[22] we did not find evidence of a relationship with affective symptoms that has been demonstrated (based on depression-related symptoms) in other work.[23] Our findings of functional connectivity between DMN hubs and non-hubs and the relationship to symptomol-

ogy help expand the understanding of the pathophysiology of clustered symptoms after concussion.

Specifically related to cognition, Li and colleagues (2019)[22] found that hub metrics of frontal regions were associated with a brief measure of cognitive functioning after concussion. Similarly, our findings of DMN functional connectivity, which encompasses frontal regions of the brain, showed a significant relationship with visual memory performance. These results provide additional
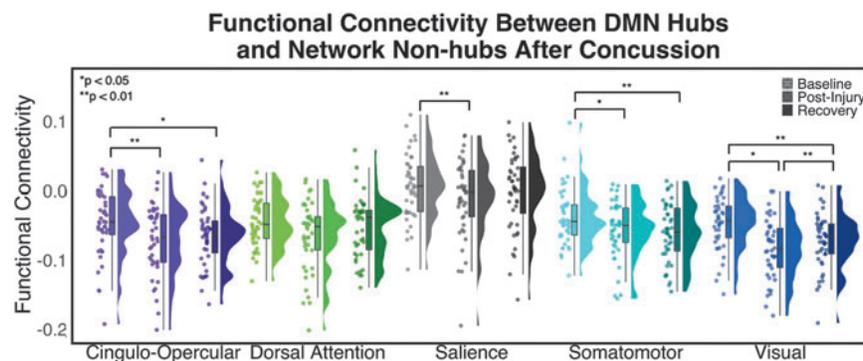
FIG. 6. Significant differences in functional connectivity between Default Mode Network (DMN) hubs and non-hubs in other networks. Functional connectivity was significantly different across time between DMN hubs to and non-hubs in five networks. Functional connectivity between DMN hubs and cingulo-opercular network non-hubs decreased from baseline to post-injury and recovery. While functional connectivity between DMN hubs and dorsal attention network non-hubs significantly changed across time, the pair-wise comparisons were not significantly different. Functional connectivity between DMN hubs and salience network non-hubs significantly decreased from baseline to post-injury. Functional connectivity between DMN hubs and somatomotor network non-hubs significantly decreased from baseline to post-injury and recovery. Functional connectivity between DMN hubs and visual network non-hubs significantly decreased from baseline to post-injury, increased from post-injury to recovery, and also decreased from baseline to recovery.
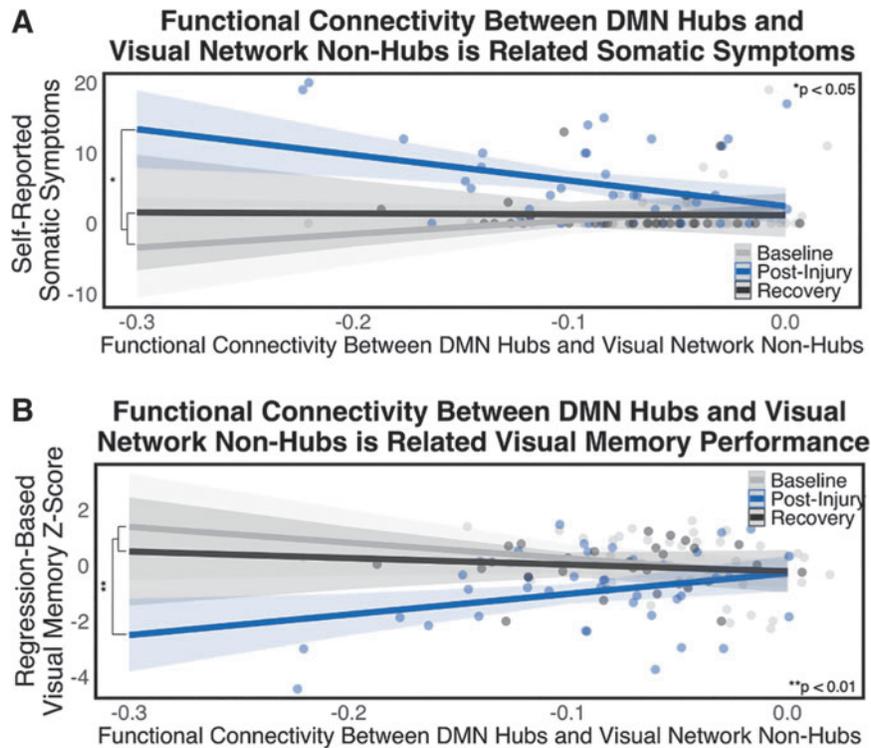
FIG. 7. Between Default Mode Network (DMN) and visual network connectivity, symptom reporting, and cognitive performance. (**A**) Functional connectivity between DMN hubs and visual network non-hubs displayed the only significant between network relationship to clinical outcomes such as symptom reporting and cognitive performance. Specifically, there was a stronger relationship between post-injury functional connectivity and post-injury somatic symptoms than measured at baseline and recovery. (**B**) Similarly, there was a stronger relationship between functional connectivity and visual memory performance at post-injury than at baseline and recovery.

evidence for the effect of pathophysiological changes in cognitive functioning during the acute stage of concussion recovery.

It is unclear, however, what role these changes in DMN hubs and non-hubs play specifically in visual memory performance, compared with the other cognitive domains assessed. One explanation relates to the medial prefrontal cortex (mPFC), a central hub of the DMN, and its role in memory.[47,48] Disruption to this hub after concussion may be associated with these acute disruptions to visual memory.

While we identified changes across time points between hubs and non-hubs within the DMN, we did not find significant differences by time point overall within the DMN. One explanation for the lack of post-concussion functional connectivity changes overall within DMN is that these disruptions may only occur to specialized regions within the network.

These more specific changes may primarily impact connectivity to regions that are critical in promoting network efficiency across the brain, such as hubs.[49]

Previous research has identified disruption to hubs across the brain in a concussed population,[22–25] but there is lack of consensus in the location of changes. Some studies found that a concussed population had on average a different set of brain regions identified as

Table 5. Significant Relationship Between Post-Injury Clinical Outcomes and Functional Connectivity Between Default Mode Network Hubs and Visual Network Non-Hubs

Clinical outcome	Estimate	Standard error	t-statistic	Degree of freedom	p	Confidence interval	AIC	BIC
Somatic symptoms	29.213	11.505	2.539	111	0.012*	-67.176, -7.313	663.1	685.1
Visual memory	11.600	3.998	2.901	111	0.004**	3.6759, 19.524	348.5	370.4

*$p < 0.05$; **$p < 0.01$. AIC, akaike information criterion; BIC, bayesian information criterion.

hubs compared with a non-concussed group and that this set of hubs differed throughout a 6-month recovery period.[22,25] Similarly, we identified that connectivity involving DMN hubs is disrupted after concussion and during recovery. This suggests that concussion results in a reorganization of network efficiency that fluctuates across time; however, it is unclear whether this change represents a positive, negative, or neutral change in brain functioning.

Previous studies were unable to compare post-injury changes with pre-injury organization of the brain. A significant contribution of the present study is that we can observe changes in hub connectivity post-injury compared with baseline brain network organization.

Hyperconnectivity

Considering the severity of brain injury, previous research studying the effects of moderate to severe TBI has identified hyperconnectivity (i.e., increased connectivity) after TBI in both longitudinal studies and in cross-sectional studies compared with healthy participants.[12,13,15,50-52] These studies suggest that after a more severe brain injury, hyperconnectivity may occur as an adaptive response to balance the brain's network cost and efficiency of brain hubs.[12–15]

Specifically related to clinical outcomes, hyperconnectivity of the DMN after moderate to severe TBI has been associated with faster reaction time and better performance on a working memory task.[51-53] A study of mild TBI patients with positive post-injury imaging findings (i.e., evidence of lesions) found that greater DMN connectivity within two weeks of injury was related to better performance on an assessment of attention and processing speed at six months post-injury,[54] suggesting a potential early compensatory mechanism for cognitive performance throughout recovery of those with more severe brain injuries such as complicated mild, moderate, or severe TBI.

While greater functional connectivity after these more severe injuries has been associated with better cognitive performance, in the present study we found that increased connectivity acutely post-injury, specifically with DMN hubs, was related to *more* cognitive and somatic symptoms, and *worse* visual memory performance. There may still be a potential adaptive mechanism after these less severe injuries; however, the compensation to balance cost and efficiency of brain hubs may occur to a lesser degree in concussion.

Although hyperconnectivity of the DMN has been identified across the TBI severity spectrum, most studies assessing functional connectivity of the DMN after mild TBI have identified variable results of hyperconnectivity and hypoconnectivity post-injury. Many of the studies identifying hypoconnectivity within the DMN compared functional connectivity with healthy control groups and

occurred across a range of time frames post-injury.[54–59] Some of these studies identified a relationship with clinical outcomes including an association between hypoconnectivity, cognitive symptoms,[57] and total symptoms,[55,59] while other studies did not find a significant relationship between DMN connectivity and symptom reporting.[56,60]

In addition, others have found both hypo- and hyperconnectivity between different regions in the DMN compared with healthy controls, where hyperconnectivity was related to poorer executive function and hypoconnectivity was associated with increased depression after mTBI.[60,61] Again, the inconsistencies in the literature are likely largely attributed to the lack of pre-injury baseline (i.e., comparing with a control group complicates interpretability given individual differences in cortical organization) and variability in the timeline of assessments.

In other concussion research that explores longitudinal changes in functional connectivity within the DMN, hyperconnectivity was consistently identified during acute recovery.[54.58.62] For example, hyperconnectivity within the DMN was evident within three days of injury but reduced after seven days when neurocognitive assessments had returned to baseline levels.[62] Increased connectivity within the DMN in the earlier stage of recovery was also related to visual and verbal memory performance in athletes.[58] These findings are consistent with the present study and highlight the importance of collecting neuroimaging data in the acute phase of an injury as well as measuring functional connectivity changes over time within participants.

These studies, using a longitudinal design to compare functional connectivity changes and clinical outcomes after concussion, clarify previously inconsistent results of hyperconnectivity identified within functional networks. In other words, although hyperconnectivity after moderate to severe TBI is consistently evident when compared with a control group, *mild* TBIs may produce more specific changes in the brain, discussed above, that are more reliant on a within-subjects approach. The understanding of DMN hyperconnectivity and its relationship to symptoms and cognition during recovery described here provides further insight into the brain's response to pathological changes after injury.

Between DMN functional connectivity

While changes within the DMN are compelling, this study also identified injury-related changes in functional connectivity between DMN hubs and several networks. Connectivity differences between the DMN and visual network were significantly related to somatic symptoms and cognitive performance. Specifically, at post-injury, there was a stronger relationship between functional

connectivity between DMN hubs and visual network non-hubs and visual memory performance, compared with baseline or recovery time points. Similar findings have been identified when comparing moderate TBI participants with healthy participants.[63]

In addition, another study focused on a hub within the visual network and found functional connectivity was specifically associated with sensitivity to light and noise in a concussed population.[22] Similarly, we also identified a stronger relationship with somatic symptoms, which encompasses light and noise sensitivity, and functional connectivity between DMN and visual network at post-injury. Therefore, future analyses should continue to explore hub and non-hub connectivity of the visual network after concussion to further our understanding of functional connectivity disruptions to this network and their relationship to symptom clusters.

Changes in network segregation versus integration

Overall, we observed increased post-injury connectivity within regions of the DMN as well as decreased connectivity between the DMN and multiple networks in the brain. This pattern of results is suggestive of a concussion-related imbalance of within and between network communication. In other words, a healthy brain relies on a balance of processing information globally (e.g., during higher order cognition) through the *integration* of networks as well as relatively specialized (e.g., visual) processing through the *segregation* of networks.[19] This organization allows the brain to efficiently transfer information, when necessary, but also supports functional specialization,[20] thus optimizing the metabolic cost of communicating information throughout the brain.[19] When the balance of integration and segregation is disrupted after injury, however, as evidenced here for concussion, it likely affects the functional output of the brain (as measured by symptom reporting and cognitive performance in this study).

Pre-clinical animal models studying the effects of mild TBI have suggested decreased network integration and increased network segregation for structural connectivity.[64] Similar findings of imbalances of structural connectivity have been identified in children after mild TBI.[65] Further, functional network segregation has also been associated with mild TBI-related fatigue.[66]

Clinically, concussion has been conceptualized as a disorder of multiple network disruptions stemming from changes in processes involving neurometabolic,[9] axonal,[67] cerebrovascular,[68] ocular-motor,[69,70] and vestibular systems.[69,70] The current results provide further evidence of disruption to multiple brain networks during the period after a concussion and lays the foundation to continue relating these network changes to functional outcomes, including specific clustered (e.g., cognitive and somatic) symptoms as well as cognitive difficulties particularly related to the visual system.

Strengths and limitations

While these results are informative, this study has several limitations. First, this analysis related functional connectivity findings to clinical outcomes (i.e., self-reported symptoms and cognitive performance) that were collected for clinical purposes. Therefore, we were unable to manage the timing of assessments, resulting in missing data at either post-injury or recovery time points for 15 participants. In addition, baseline clinical data for 17 participants during our first year of scanning, when the study first began, were collected approximately 1.8 years before their MRI scan.

To reduce the effects of both missing data and variable time between clinical and MRI assessments, however, we used a linear mixed effects model and included time between data collection as a random effect to help account for the variability in time between baseline assessments and when their concussion occurred. In addition, we did not have a sample of non-concussed student-athletes as a control group. Instead, we used a longitudinal approach that examined brain connectivity in an uninjured state (baseline), and compared it with the acute stage after concussion and after clearance to return to play.

Another strength of the study is that we collected approximately 30 min of resting-state fMRI data for each participant at each time point. There is strong evidence that this quantity of data provides reliable estimates of brain network connectivity.[71,72] Last, our sample of concussed student-athletes involved 40 men and four women. This sample restricted our ability to study gender-specific differences in functional connectivity and recovery, limiting the generalizability of these results to literature discerning differences in recovery for women post-concussion. Future work is necessary to explore these important gender-related differences.

Conclusion

These results highlight the relationships between acute concussion-related changes to functional connectivity of DMN hubs, visual memory performance, and self-reported cognitive and somatic symptoms, compared with the student-athletes' own baseline and recovery levels. Specifically, at the time of injury (compared with baseline and recovery), we found hyperconnectivity within regions of the DMN and hypoconnectivity between DMN hubs and distributed networks. These results provide evidence for a disrupted balance of within- and between-network communication, likely impacting network efficiency after concussion.

Moreover, these changes in cortical organization were uniquely related to poorer visual memory performance

and increased cognitive and somatic symptoms. Notably, some aspects of functional connectivity remained disrupted after clinical recovery, even when symptoms and cognitive performance returned to baseline levels, highlighting the importance of incorporating baseline functional connectivity levels. Understanding pre-injury organization of the brains of these athletes allows us to identify continued change in functional networks that may reflect the brain's ability to compensate after these changes in network inefficiency.

Transparency, Rigor, and Reproducibility Summary

This study was not formally registered nor was the analysis plan formally pre-registered. The sample was available from 336 collegiate men's football and women's soccer student-athletes who underwent baseline MRI scans starting in June 2018 for football and July 2019 for soccer. Of these participants, 50 experienced a concussion between their baseline scan and October 2021. The same team physician provided a diagnosis for all concussions. Five participants were removed from the analysis for missing either a post-injury or recovery scan and one was removed for excessive motion (> 70% of time points were removed due to motion). Thus, 44 participants were included in the analysis. All imaging data were collected using the same 3T Siemens Skyra scanner and preprocessed with the same pipeline. Complete imaging parameters are presented in the methods. Clinical outcomes were collected via ImPACT, a standard tool used for concussion evaluations in the sport setting, and composite scores were converted to regression-based z-scores to account for practice effects and regression to the mean. Fifteen participants were missing clinical outcome data. To account for missing clinical data and to address violations of distributional assumptions, specifically with symptom reports, analysis of variance for linear mixed-effects models were used. Further, a permutation method was selected as a more conservative approach to control for Type I errors when assessing changes in neuroimaging analyses. Replication of the current results is ongoing by the study group. Deidentified data from this study are not available in a public archive. Analytic code used to conduct the analyses presented in this study are not available in a public repository. Deidentified data from this study will be made available (as allowable according to institutional IRB standards) as well as analytic code by emailing the corresponding author. The authors provided the full content of the manuscript as a preprint as of 03/07/2023.

Acknowledgments

Authors' Contributions

Bouchard conducted analyses, conceptualization, visualization of data, and writing. Higgins provided supervision, resources, collection of clinical data, and contributions to reviewing and editing. Amadon visualized and synthesized data and provided contributions to reviewing and editing. Laing-Young preprocessed data and provided contributions to reviewing and editing. Maerlender provided conceptualization, resources, and contributions to reviewing and editing. Al-Momani preprocessed data and provided contributions to reviewing and editing. Neta provided supervision, methodology, funding, and contributions to reviewing and editing. Savage provided supervision, funding, and contributions to reviewing and editing. Schultz provided supervision, conceptualization, methodology, software and analyses support, and contributions to reviewing and editing.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Text S1

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