Title

Resting-State fMRI Metrics in Acute Sport-Related Concussion and Their Association with Clinical Recovery: A Study from the NCAA-DOD CARE Consortium

Journal

Journal of Neurotrauma, 37(1)

ISSN

0897-7151

Authors

Meier, Timothy B
Giraldo-Chica, Monica
España, Lezlie Y
et al.

Publication Date

2020

DOI

10.1089/neu.2019.6471

Peer reviewed

JOURNAL OF NEUROTRAUMA 37:152–162 (January 1, 2020)

DOI: 10.1089/neu.2019.6471

Resting-State fMRI Metrics in Acute Sport-Related Concussion and Their Association with Clinical Recovery: A Study from the NCAA-DOD CARE Consortium

Timothy B. Meier,[1–3] Monica Giraldo-Chica,[1] Lezlie Y. España,[1] Andrew R. Mayer,[4] Jaroslaw Harezlak,[5] Andrew S. Nencka,[6] Yang Wang,[6] Kevin M. Koch,[6] Yu-Chien Wu,[7] Andrew J. Saykin,[7] Christopher C. Giza,[8] Joshua Goldman,[9,10] John P. DiFiori,[11] Kevin M. Guskiewicz,[12] Jason P. Mihalik,[12] Alison Brooks,[13] Steven P. Broglio,[14] Thomas McAllister,[15] and Michael A. McCrea[1]

Abstract

There has been a recent call for longitudinal cohort studies to track the physiological recovery of sport-related concussion (SRC) and its relationship with clinical recovery. Resting-state functional magnetic resonance imaging (rs-fMRI) has shown potential for detecting subtle changes in brain function after SRC. We investigated the effects of SRC on rs-fMRI metrics assessing local connectivity (regional homogeneity; REHO), global connectivity (average nodal strength), and the relative amplitude of slow oscillations of rs-fMRI (fractional amplitude of low-frequency fluctuations; fALFF).
Athletes diagnosed with SRC ($n = 92$) completed visits with neuroimaging at 24–48 h post-injury (24 h), after clearance to begin the return-to-play (RTP) progression (asymptomatic), and 7 days following unrestricted RTP (post-RTP). Non-injured athletes ($n = 82$) completed visits yoked to the schedule of matched injured athletes and served as controls. Concussed athletes had elevated symptoms, worse neurocognitive performance, greater balance deficits, and elevated psychological symptoms at the 24-h visit relative to controls.These deficits were largely recovered by the asymptomatic visit. Concussed athletes still reported elevated psychological symptoms at the asymptomatic visit relative to controls. Concussed athletes also had elevated REHO in the right middle and superior frontal gyri at the 24-h visit that returned to normal levels by the asymptomatic visit. Additionally, REHO in these regions at 24 h predicted psychological symptoms at the asymptomatic visit in concussed athletes. Current results suggest that SRC is associated with an acute alteration in local connectivity that follows a similar time course as clinical recovery. Our results do not indicate strong evidence that concussion-related alterations in rs-fMRI persist beyond clinical recovery.

Keywords: functional connectivity; magnetic resonance imaging; mild traumatic brain injury; resting state; sport-related concussion

Introduction

Sport-related concussion (SRC) is a major public health concern that is estimated to affect millions of individuals every year.[1] Currently, decisions regarding diagnosis and recovery after SRC are based on clinical judgment largely informed by athlete self-report of symptoms as well as cognitive and additional assessments.[2] The underlying pathophysiological recovery trajectory remains largely unknown. Results from pre-clinical research suggest there is a window of vulnerability following concussion that is

[1]Department of Neurosurgery, [2]Department of Cell Biology, Neurobiology and Anatomy, [3]Department of Biomedical Engineering, [6]Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin.
[4]The Mind Research Network/Lovelace Biomedical and Environmental Research Institute, Neurology and Psychiatry Departments, University of New Mexico School of Medicine, Department of Psychology, University of New Mexico, Albuquerque, New Mexico.
[5]Department of Epidemiology and Biostatistics, Indiana University, Bloomington, Indiana.
[7]Department of Radiology and Imaging Sciences, [15]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana.
[8]Departments of Pediatrics and Neurosurgery, [9]Departments of Family Medicine and Orthopaedic Surgery, University of California Los Angeles, Los Angeles, California.
[10]Center for Sports Medicine, Orthopaedic Institute for Children, Los Angeles, California.
[11]Hospital for Special Surgery, Primary Sports Medicine Service, New York, New York.
[12]Department of Exercise and Sport Science, University of North Carolina, Chapel Hill, North Carolina.
[13]Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.
[14]School of Kinesiology, University of Michigan, Ann Arbor, Michigan.

associated with increased risk for an additional concussion with worse behavioral and physiological consequences.[3,4] This has raised the concern that clearing athletes to return-to-play (RTP) before complete physiological recovery may put them at risk for a subsequent, more severe injury. Thus, there is a need to identify reliable biomarkers of SRC that have both diagnostic and prognostic value in determining an athlete's true level of recovery and readiness to RTP after injury.

A recent systematic review of biomarker studies of SRC reported several physiological measures with post-injury abnormalities that appear to extend beyond the time frame of clinical recovery.[5] Several of these studies focused on metrics derived from low-frequency fluctuations of the blood oxygen-level dependent (BOLD) signal collected at rest (i.e., resting-state functional magnetic resonance imaging; rs-fMRI) due to its ability to detect subtle differences in brain function.[6,7] For example, multiple prior studies have reported differences in resting-state metrics in asymptomatic athletes at post-injury time-points ranging from initial clearance to RTP up to multiple months post-concussion.[8–12] As highlighted by recent systematic reviews, however, much of the work in SRC to date has included small sample sizes, been predominately cross-sectional in design, and/or focused primarily on male athletes.[5,7]

The National Collegiate Athletic Association (NCAA) – Department of Defense (DoD) Grand Alliance: Concussion Assessment, Research and Education (CARE) Consortium is a large-scale, multi-site study of the natural history of concussion.[13] Advanced MRI data, including rs-fMRI, are collected from a subset of collegiate athletes at multiple visits in concussed athletes including 24 to 48 h post-injury (24-h), time of symptom resolution when cleared to start the RTP progression (asymptomatic), 7 days after their RTP (post-RTP), and 6 months post-injury. Matched controls are studied at similar intervals allowing examination of the extent to which any physiological abnormalities following SRC persist beyond clinical recovery.

In the current study, we investigated the effects of SRC in collegiate athletes on multiple complementary resting-state metrics previously shown to be sensitive to SRC or mild traumatic brain injury (mTBI) in other cohorts. Specifically, we focused on fMRI metrics that do not require the selection of specific regions or networks of interest for analysis: regional homogeneity (REHO), a measure of local connectivity between a voxel and its adjacent voxels[12,14,15]; fractional amplitude of low-frequency fluctuations (fALFF), an estimate of the relative amplitude of slow oscillations of the BOLD signal typically associated with rs-fMRI[16,17]; and average nodal strength of connectivity, a measure capturing the global connectivity strength of the brain.[18,19] Importantly, these rs-fMRI metrics have been shown to have fair to excellent test-retest reliability in gray matter within participants across multiple imaging sessions.[20–23] In addition to traditional group analyses, we conducted analyses of subject-specific abnormalities to account for potentially heterogeneous injury locations.[24–26] We tested the hypothesis that concussion would result in REHO, fALFF, and global nodal strength abnormalities that persist beyond the time frame of clinical recovery (i.e., abnormalities evident at asymptomatic and post-RTP visits).

Methods

Participants

This study was approved by the Medical College of Wisconsin Institutional Review Board and the Human Research Protection Office (HRPO). All participants provided written informed consent. The study design and methods of the NCAA-DoD CARE Consortium have been described elsewhere.[13]

The current report focuses on athletes that completed a 10-min resting-state scan (i.e., without presentation of visual or auditory stimuli) collected on a 32-channel head coil at three of the four CARE sites (University of North Carolina at Chapel Hill, UNC; University of Wisconsin-Madison, UW; University of California Los Angeles, UCLA) participating in the Advanced Research Core (ARC). For data consistency, data from the fourth site (Virginia Tech) are not included in this report because they were not collected on a 32-channel head coil. Contact sport athletes were enrolled at pre-season. Athletes who sustained a concussion completed multiple follow-up visits that included multi-modal neuroimaging data collection: 24–48 h post-injury (24-h), following clearance to begin the RTP progression (asymptomatic), 7 days following unrestricted RTP (post-RTP), and 6 months post-injury. Concussions were diagnosed by research and medical staff of each participating institution based on the following definition: ''A change in brain function following a force to the head, which may be accompanied by temporary loss of consciousness, but is identified in awake individuals with measures of neurologic and cognitive dysfunction.''[27]

Non-injured contact sport athletes participated in multiple visits yoked to the schedule of demographically matched injured athletes. A matching algorithm was used to match control athletes to concussed athletes based on variables of institution, sport, gender, race/ethnicity, estimate of pre-morbid verbal intellectual functioning, concussion history, years of participation, status as a starter, and head impact exposure estimate or data if available. The current study focuses on the acute and sub-acute effects of concussion; thus, only data from the 24-h, asymptomatic, and post-RTP time-points are presented. A total of 93 concussed athletes and 82 control athletes met the criteria for this study. One injured athlete was determined to have acute, injury-related pathology based on a non-diagnostic clinical read of structural MRI scans and was excluded to limit analyses to typical SRC (i.e., without acute injury-related MR findings),[28] resulting in a final total of 92 concussed athletes. Data sets from athletes participating in the protocol for multiple injuries ($n=10$) or as a control and then subsequently as an injured athlete ($n=7$) are treated as independent data sets. Sensitivity analyses showed that findings from analyses with these excluded subjects were identical to those in the complete data set (see Supplementary Appendix S1 and Supplementary Tables S1 and S2). The final number of participants at each visit is reported in Table 1.

Clinical battery

Detailed demographic and health history information were collected at baseline along with an extensive clinical battery. The Wechsler Test of Adult Reading (WTAR) was used as an estimate of pre-morbid intelligence.[29] The clinical battery for this report focuses on measures of symptom severity (Sport Concussion Assessment Tool – 3rd Edition symptom checklist; SCAT),[30] psychological symptoms (Brief Symptom Inventory-18 Global Severity Index, BSI-GSI),[31] postural stability (Balance Error Scoring System; BESS),[32] and cognition (Standardized Assessment of Concussion; SAC).[33] The WTAR was performed at the baseline visit only; all other measures were repeated at all visits.

Imaging parameters and processing

MRI data were acquired with 32-channel head coils on either Siemens MAGNETOM Prisma (UCLA or UNC), Siemens MAGNETOM Trio (UCLA or UNC), or General Electric (GE) MR750 3T (UW) scanners. A gradient-echo echo-planar image (EPI) sequence was used to collect approximately 10-min resting-state scans on each system, during which athletes were instructed to keep

Table 1. Sample Characteristics

Demographics	*Control athletes*	*Concussed athletes*	*Statistic*
Total no.	82	92	
Sex (% male)	81.71	84.78	$X^2(1) = 0.30$, $p = 0.59$
Race			$X^2(3) = 1.67$, $p = 0.64$
Black or African-American (%)	25.61	29.35	
White (%)	64.63	58.70	
Other (%)	4.88	8.70	
Unknown/NR (%)	4.88	3.26	
Age at baseline	19.18 (1.16)	19.20 (0.90)	$t(172) = -0.11$, $p = 0.91$
Years education	12.59 (1.02)	12.49 (0.79)	$t(166) = 0.70$, $p = 0.48$
Body mass index	26.46 (3.97)	27.53 (5.08)	$t(171) = -1.53$, $p = 0.13$
WTAR standard score	108.54 (13.07)	108.03 (12.56)	$t(170) = 0.26$, $p = 0.80$
Years participation	10.71 (3.15)	10.34 (3.14)	$t(167) = 0.78$, $p = 0.44$
Median no. previous concussion (interquartile range)	0 [0-1]	1.0 [0-1]	*$U = 4652.5$, $p = 0.002$*
Sport			$X^2(3) = 0.72$, $p = 0.87$
Football	64.63	65.22	
Ice hockey	3.66	5.43	
Lacrosse	6.10	7.61	
Soccer	25.61	21.74	
Scanner and site combination			$X^2(3) = 1.12$, $p = 0.77$
% UW GE MR750	31.71	31.52	
% UNC Siemens Trio	15.85	17.39	
% UNC Siemens Prisma	25.61	30.43	
% UCLA Siemens Prisma	26.83	20.65	
Health history	*Control athletes*	*Concussed athletes*	*Statistic*
ADHD+ (%)	9.76	18.48	$X^2(1) = 2.68$, $p = 0.10$
Migraines+ (%)	7.32	7.61	$X^2(1) = 0.01$, $p = 0.94$
Psychiatric disorder + (%)	2.44	5.43	$X^2(1) = 1.01$, $p = 0.32$
Vision or hearing problem+ (%)	2.44	3.26	$X^2(1) = 0.10$, $p = 0.75$
Memory disorder+ (%)	1.22	2.17	$X^2(1) = 0.23$, $p = 0.63$
Learning disorder+ (%)	1.22	1.09	$X^2(1) = 0.01$, $p = 0.94$
Meningitis+ (%)	2.44	0	$X^2(1) = 2.27$, $p = 0.13$
Sleep disorder+ (%)	0	2.17	$X^2(1) = 1.80$, $p = 0.18$
Prior moderate-severe TBI+ (%)	0	1.09	$X^2(1) = 0.90$, $p = 0.34$
Seizure disorder+ (%)	0	1.09	$X^2(1) = 0.90$, $p = 0.34$
Diabetes+ (%)	0	1.09	$X^2(1) = 0.90$, $p = 0.34$
MRI visit information	*24-h/Asymp./Post-RTP*	*24-h/Asymp./Post-RTP*	*Statistic*
Available rs-fMRI	75/79/75	73/72/53	NA
Usable rs-fMRI	70/71/65	70/69/50	NA

Significant differences at $p < 0.05$ are underlined and italicized.

24-h, 24–48 h visit; ADHD, attention deficit hyperactivity disorder; Asymp., asymptomatic visit; no., number; GE, General Electric; NA, not applicable; NR, not reported; Post-RTP, post-return-to-play visit; rs-fMRI, resting-state functional magnetic resonance imaging; TBI, traumatic brain injury; UCLA, University of California Los Angeles; UNC, University of North Carolina; UW, University of Wisconsin; WTAR, Wechsler Test of Adult Reading.

their eyes open. The GE MR750 EPI had the following parameters: repetition time [TR]/echo time [TE] = 2000/33 msec, flip angle = 90 degrees, field of view [FOV] = 256 mm, matrix = 64 × 64, slice thickness = 4 mm, 36 axial slices. EPI collected on the Siemens Trio had the following parameters: TR/TE = 2250/27 msec, flip angle = 90 degrees, FOV = 245 mm, matrix = 70 × 70, slice thickness = 3.5 mm, 45 axial slices. EPI collected on the Siemens Prisma scanner had the following parameters: TR/TE = 2300/27 msec, flip angle = 90 degrees, FOV = 245 mm, matrix = 70 × 70, slice thickness = 3.5 mm, 45 axial slices. Scanner and EPI parameters were constant for each individual participant across visits. High-resolution T_1-weighted images (1 mm × 1 mm × 1 mm) were collected during each scan for anatomical reference (see Supplementary Appendix S1).

Image processing was performed using Analysis of Functional NeuroImages (AFNI) programs unless otherwise indicated.[34] Anatomical images were skull stripped using segmentations generated from SPM12 and subsequently registered to the MNI-152 template using affine registration with correlation cost ratio function and trilinear interpolation followed by non-linear warp using FSL.[35] Initial EPI volumes were removed to allow for stabilization of longitudinal magnetization. Signal spike artifacts were removed from time series data sets by interpolation of data from neighboring time-points. Following slice time correction, head motion correction was performed by registering each volume to the first volume using cubic polynomial interpolation. A 6 degrees-of-freedom registration of the first EPI volume to the native-space anatomical

scan was calculated using FSL FLIRT with the boundary-based registration cost-function.[35,36] This transformation was concatenated with the anatomical-to-MNI-152 matrix, and the resulting matrix was applied with a non-linear warp to spatially normalize the motion corrected data to standard space with 2 mm isotropic resolution.

The six motion parameters and their derivatives, the zero through third-order polynomial trends, and the average cerebrospinal fluid (CSF) and white matter signals were regressed from the spatially normalized data as signals of no-interest. Average white matter and CSF signals were obtained from masks derived from MNI-152 tissue priors provided by FSL. Volumes for which the Euclidian norm of the motion parameters was greater than 0.30 were censored along with the preceding volume and replaced using interpolation on a subject-by-subject basis. The AFNI program 3dRSFC was used to bandpass filter (0.01 to 0.10 Hz) and to calculate fALFF.[16,37] REHO was calculated across a neighborhood of 27 voxels in resampled space using the bandpass filtered output of 3dRSFC.[14,37] The calculations of fALFF and REHO were limited to gray matter using a masked derived from the gray matter tissue prior in template space provided by FSL. fALFF and REHO maps were then spatially smoothed within the gray matter mask with varying smoothing kernels (approximately 3.5 to 6 mm full-width at half-maximum kernels; FWHM) until the smoothness of the residual data set reached 10 mm FWHM to account for intrinsic smoothness differences due to vendor and sequence, consistent with recommendations from the Function Biomedical Informatics Research Network (FBIRN).[38,39] The smoothed fALFF and REHO maps were converted to z-scores by subtracting the mean global metric and dividing by the standard deviation of the mean at each voxel.

Average nodal strength was calculated from the unsmoothed bandpass filtered data in regions of interest (ROIs) identified from the whole-brain Craddock r 2-level 200 region parcellation using a combination of 3dNetCorr and the BRain Analysis using the graPH theory Matlab program (BRAPH) as previously described.[19,40,41] Briefly, average strength was calculated as the sum of all positive Pearson correlations to each individual ROI (i.e., node) averaged across all ROIs in the matrix.

In addition, subject-specific abnormalities in fALFF and REHO were quantified using previously described methods.[24–26] Voxel-wise data from SRC athletes at all visits and controls at the first visit were transformed to z-scores with the mean and standard deviation of the control group at visit 1 serving as the reference group. Z-scores were distribution-corrected based on the number of participants in the reference group to control for known bias. A leave-one-out approach was used to z-score controls at the asymptomatic and post-RTP visits relative to their first visit. The number and volume of clusters with abnormally increased or decreased fALFF or REHO were calculated. Abnormal clusters were defined as clusters with a minimum size of 500 μL with $z < 2$ (negative) or $z > 2$ (positive) following distribution correction.

All data were visually inspected for artifacts at multiple processing stages. Scans in which the Euclidean norm of motion parameter was greater than 0.2 or more than 30% of time-points were censored and excluded from analyses to minimize effects of motion on group analyses.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 24 (Armonk, NY) unless otherwise indicated. Independent samples *t* tests, Mann-Whitney U tests, and chi-square tests were used to compare demographic variables between groups. Generalized linear mixed models were used to assess differences in variables (e.g., clinical, motion parameters, non-voxel-wise imaging metrics) with the fixed factor of group (SRC vs. controls), visit modeled as a repeated factor across participants (i.e., 24-h, asymptomatic, post-RTP), and the group by visit interaction. Continuous data were modeled with normal distributions; count data were modeled with Poisson or negative binomial distributions as appropriate. Degrees of freedom were estimated using the Satterthwaite approximation and robust covariance estimation was used. The primary analyses of the current work focused on the effects of group and potential group by visit interactions; main effects of visit are not reported and will be the focus of subsequent work. Because concussed athletes reported significantly more prior concussions than controls (see Results), the number of prior concussions was included as a covariate in analyses of clinical and rs-fMRI metrics of interest. For all analyses of rs-fMRI metrics a single variable was created and used as a factor of no-interest to account for potential site, scanner, and sequence differences (i.e., UW/GE-MR750/TR = 2, UNC/Trio/TR = 2.25, UNC/Prisma/TR = 2.3, UCLA/Prisma/TR = 2.3; Table 1). Post hoc testing with Bonferroni correction was conducted for significant interactions at $p < 0.05$.

Voxel-wise linear mixed effects (LME) models were performed for fALFF and REHO using the AFNI program 3dLME as described above.[42] For cluster-wise correction, the smoothness of the spatially smoothed residuals was estimated using a non-Gaussian, spherically symmetric auto-correlation function.[43] Monte Carlo simulations (10,000 iterations) were conducted in native voxel space (3.5 mm isotropic, corresponding to Siemens data sets), limited to the interpolated gray matter mask, to determine the necessary correction for a familywise error rate of $p < 0.05$ (smoothness parameters = 0.48, 5.39, and 15.78, effective FWHM = 15.19, voxel *p*-value 0.001, minimum cluster volume = 978 μL for $p < 0.05$). The updated Automated Anatomical Labeling atlas (AAL2)[44,45] and the online Neurosynth database[46] were used to localize and define clusters. Voxel-wise statistical analyses were limited to gray matter where all subjects had coverage. Finally, generalized linear models using normal, Poisson, or negative binomial distributions, as appropriate, and robust covariance estimation were performed to determine the relationship between rs-fMRI metrics and clinical variables that were significantly associated with SRC, controlling for the number of prior concussions and scanner/site.

Results

Baseline demographic information and injury characteristics

Groups were closely matched on demographic and baseline variables with the exception of number of prior concussions, which was higher in concussed athletes ($p < 0.05$; Table 1).

Post-injury visits occurred on average 2.25 ± 1.43 (median 2 [interquartile range (IQR) 2–2]), 10.43 ± 7.52 (median 9 [IQR 6–12]), and 26.49 ± 14.26 (median 23 [18–31]) days after injury. Three concussed athletes self-reported loss of consciousness, 2 had witnessed loss of consciousness, 14 reported post-traumatic amnesia, and 9 reported retrograde amnesia. The average number of days until concussed athletes were asymptomatic was 10.57 ± 9.27 (median 7.73 [IQR 5.65–11.99]), whereas the average number of days to complete RTP was 16.23 ± 12.48 (median 12.93 [IQR 8.99–18.37]).

Clinical data

Group main effects and interactions for clinical variables are presented in Table 2; simple effects are presented in Table 3. Follow-up testing demonstrated that concussed athletes had elevated symptoms, greater balance deficits, worse neurocognitive performance, and greater psychological symptoms at the 24-h visit relative to controls ($ps \leq 0.001$; Fig. 1). Clinical deficits in concussed athletes were also present at the 24-h visit relative to their

Table 2. Main Effects for Clinical and Imaging Data

Measure	Group			Group by visit		
Clinical data	*df*	*F*	p	*df*	*F*	p
SAC total score	1, 174	4.10	*0.044*	3, 386	3.70	*0.012*
BESS total errors	1, 145	6.79	*0.01*	3, 347	5.76	*0.001*
BSI-GSI	1, 134	2.70	0.10	3, 367	10.28	*<0.001*
SCAT3 sym. sev.	1, 156	0.00	0.99	3, 312	28.95	*<0.001*
rs-fMRI motion	*df*	*F*	p	*df*	*F*	p
Head motion	1, 148	0.22	0.64	2, 208	1.46	0.24
% non-censored volumes	1, 152	0.04	0.84	2, 215	0.41	0.66
rs-fMRI metrics	*df*	*F*	p	*df*	*F*	p
Nodal strength	1, 143	1.09	0.30	2, 239	0.25	0.78
No. pos. REHO abnor.	1, 142	0.01	0.91	2, 252	0.13	0.88
Vol. pos. REHO abnor.	1, 122	1.32	0.25	2, 177	0.60	0.55
No. neg. REHO abnor.	1, 134	0.25	0.62	2, 258	1.05	0.35
Vol. neg. REHO abnor.	1, 122	1.84	0.18	2, 233	0.10	0.90
No. pos. fALFF abnor.	1, 140	0.38	0.54	2, 267	0.34	0.71
Vol. pos. fALFF abnor.	1, 123	0.01	0.92	2, 231	0.18	0.83
No. neg. fALFF abnor.	1, 152	0.06	0.80	2, 228	1.59	0.21
Vol. neg. fALFF abnor.	1, 87	0.05	0.83	2, 243	0.92	0.40

Significant effects at $p < 0.05$ are underlined and italicized.

BESS, Balance Error Scoring System; BSI-GSI, Brief Symptom Inventory-18 Global Severity Index; df, numerator and denominator degrees of freedom; fALFF, fractional amplitude of low frequency fluctuations; neg., negative; No., number; pos, positive; REHO, regional homogeneity; SAC, Standardized Assessment of Concussion; SCAT3, Sport Concussion Assessment Tool – 3rd Edition; sev., severity; sym., symptom; Vol., volume.

own baseline, asymptomatic, and post-RTP visits ($ps < 0.001$), with the exception of balance deficits, which were not significantly elevated at 24 h relative to baseline ($p > 0.10$). All measures had returned to or exceeded control levels and pre-season baseline levels at the asymptomatic and post-RTP visits with the exception of psychological symptoms (BSI-GSI), which was still significantly higher at the asymptomatic visit relative to the post-RTP levels and compared with control levels at the asymptomatic visit ($ps < 0.005$). A complete description of results from post hoc testing for clinical and imaging measures can be found in Supplementary Table S1.

Imaging data—group

There were no significant group differences in REHO, fALFF, or average nodal strength ($ps > 0.05$; Fig. 2) with appropriate correction for multiple comparisons. In addition, there were no group differences in subject-specific abnormalities including the number and volume of either positive or negative clusters of fALFF or REHO ($ps > 0.10$; Fig. 3).

Imaging data—group by visit

There was a significant interaction in REHO in a cluster in the right superior and middle frontal gyri (1472 μL; peak voxel MNI coordinates 26, 38, 46). Post hoc analyses demonstrated that concussed athletes had higher REHO at the 24-h visit relative to asymptomatic and post-RTP visits as well as relative to controls ($ps < 0.001$; Fig. 2). There were no group by visit interactions in fALFF or nodal strength ($ps > 0.10$), or in the number of volume or positive or negative subject-specific abnormalities in fALFF or REHO ($ps > 0.10$; Fig. 3).

Relationship with symptoms and outcome

Generalized linear models were conducted in concussed athletes to determine if REHO in the middle and superior frontal gyri at the acute 24-h visit was associated with clinical measures at the same time-point, the number of days until athletes were asymptomatic, or psychological symptoms at the asymptomatic visit. Concussed

Table 3. Simple Effects for Clinical and Imaging Data with Significant Group by Visit Interactions

	Visit at group		Group at visit			
Clinical data	*Concussed*	*Control*	*BL*	*24-h*	*Asymp.*	*Post-RTP*
SAC total score	F(3,384) = 17.16 *p < 0.001*	F(3,444) = 10.86 *p < 0.001*	F(1,565) = 0.61 p = 0.44	F(1,210) = 11.42 *p = 0.001*	F(1,511) = 0.007 p = 0.93	F(1,585) = 0.95 p = 0.33
BESS total errors	F(3,390) = 11.16 *p < 0.001*	F(3,421) = 2.90 *p = 0.035*	F(1,363) = 2.11 p = 0.15	F(1,195) = 15.43 *p < 0.001*	F(1,265) = 2.60 p = 0.11	F(1,341) = 0.73 p = 0.39
BSI-GSI	F(3,306) = 34.35 *p < 0.001*	F(3,408) = 6.67 *p < 0.001*	F(1,366) = 0.22 p = 0.64	F(1,356) = 34.96 *p < 0.001*	F(1,355) = 9.02 *p = 0.003*	F(1,165) = 1.70 p = 0.19
SCAT3 sym. sev.	F(3,574) = 32.19 *p < 0.001*	F(3,468) = 4.39 *p = 0.005*	F(1,277) = 1.62 p = 0.20	F(1,584) = 48.90 *p < 0.001*	F(1,263) = 2.78 p = 0.10	F(1,363) = 13.11 *p < 0.001*
Imaging data	*Concussed*	*Control*	*BL*	*24-h*	*Asymp.*	*Post-RTP*
REHO MFG/SFG[a]	F(2,259) = 15.57 *p < 0.001*	F(2,233) = 2.71 p = 0.07	NA	F(1,234) = 14.21 *p < 0.001*	F(1,240) = 0.23 p = 0.63	F(1,267) = 0.58 p = 0.45

[a]Indicates follow-up testing on significant voxel-wise cluster. Significant effects at $p < 0.05$ are underlined and italicized.

24-h, 24–48 h visit; Asymp., asymptomatic visit; BESS, Balance Error Scoring System; BSI-GSI, Brief Symptom Inventory-18 Global Severity Index; BL, baseline visit; MFG, middle frontal gyrus; post-RTP, post-return-to-play visit; REHO, regional homogeneity; SAC, Standardized Assessment of Concussion; SCAT3, Sport Concussion Assessment Tool – 3rd Edition; sev., severity; SFG, superior frontal gyrus; sym., symptom.

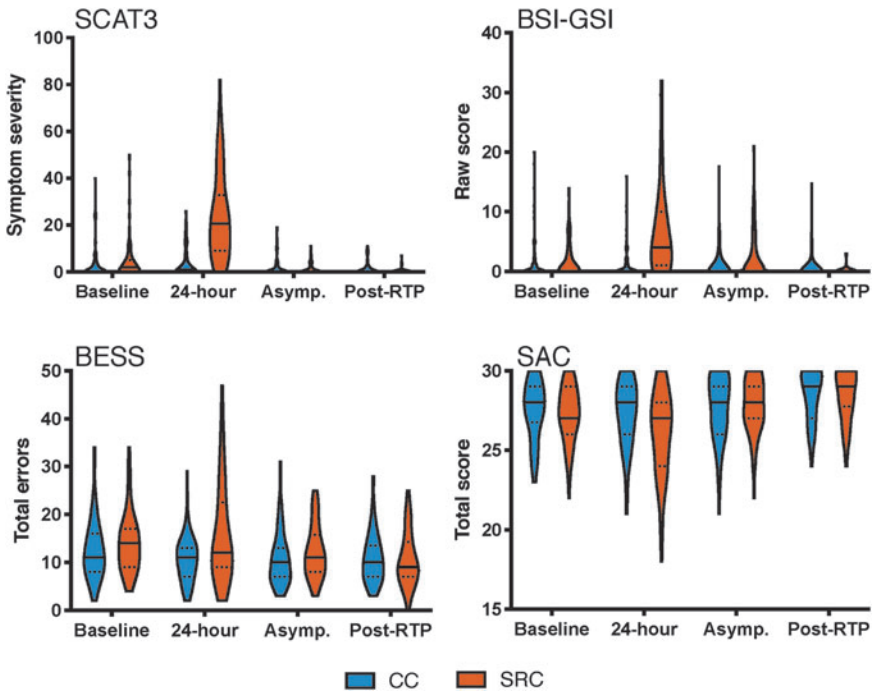

FIG. 1. Clinical data. Shown are violin plots for clinical measures in athletes with sport-related concussion (SRC) and contact sport controls (CC) at the baseline, 24-h, asymptomatic (Asymp.), and post-return-to-play (post-RTP) visits. Solid lines denote medians, dotted lines denote quartiles. BESS, Balance Error Scoring System; BSI-GSI, Brief Symptom Inventory-18 Global Severity Index; SAC, Standardized Assessment of Concussion; SCAT3, Sport Concussion Assessment Tool – 3rd Edition. Color image is available online.

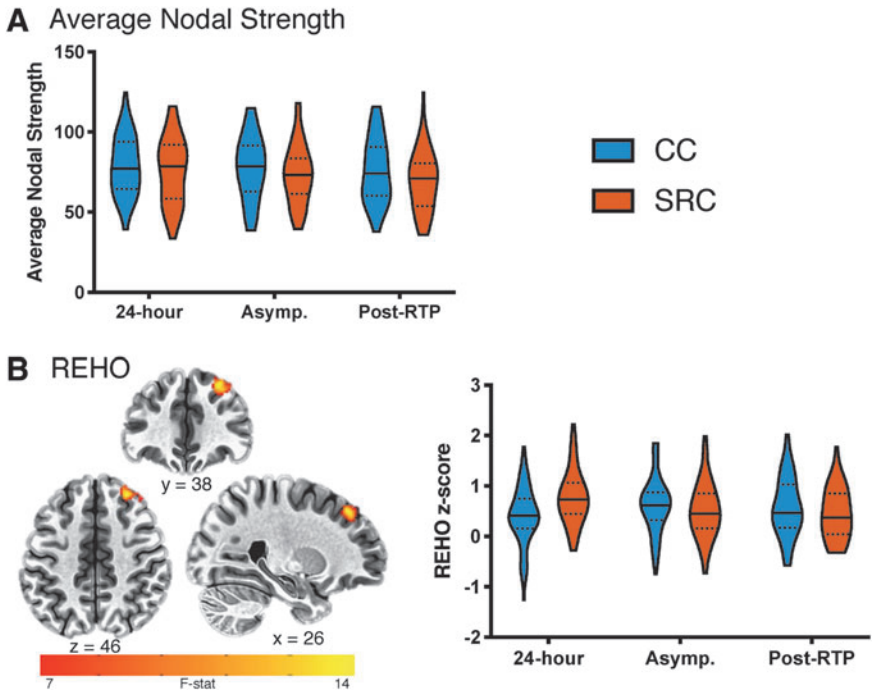

FIG. 2. Average nodal strength and voxel-wise imaging data. **(A)** Shown are violin plots for average nodal strength in athletes with sport-related concussion (SRC) and contact sport controls (CC) at the 24-h, asymptomatic (Asymp.), and post-return-to-play (post-RTP) visits. **(B)** Shown is the cluster where there was a significant group by visit interaction for regional homogeneity (REHO; left), along with violin plots of the mean REHO in this region across visits in each group. Solid lines denote medians, dotted lines denote quartiles. Right = right. Color image is available online.

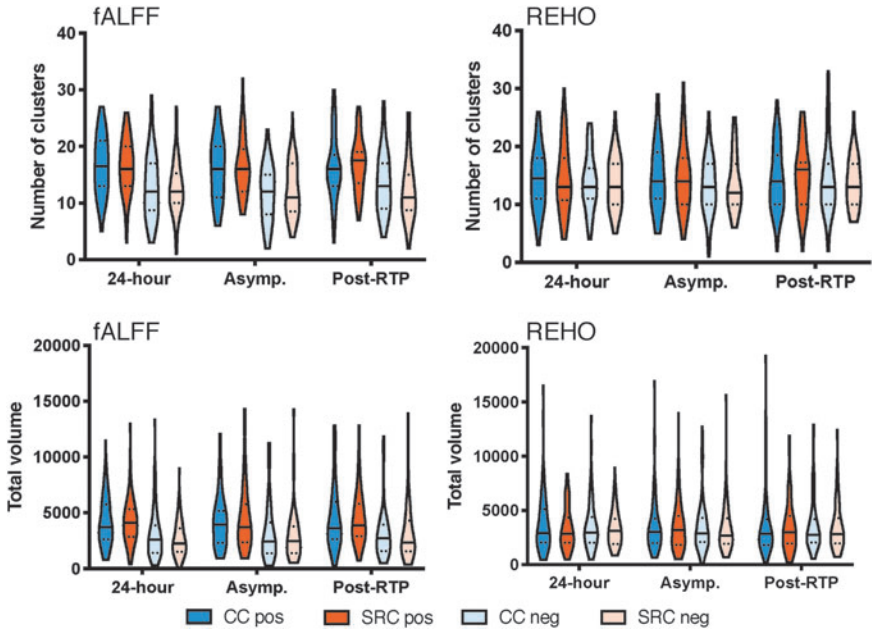

FIG. 3. Subject-specific abnormalities.Shown are violin plots of the total volume and number of clusters of positive (pos) or negative (neg) abnormalities in regional homogeneity (REHO) or fractional amplitude of low-frequency fluctuations (fALFF) in athletes with sport-related concussion (SRC) and contact sport controls (CC) at the 24-h, asymptomatic (Asymp.), and post-return-to-play (post-RTP) visits. Solid lines denote medians, dotted lines denote quartiles. Color image is available online.

athletes with greater REHO in the middle and superior frontal gyri at 24 h had significantly greater psychological symptoms at the asymptomatic visit ($B = 1.41$, $Wald = 10.67$, $p = 0.001$). An exploratory analysis showed that this association was still significant when controlling for the presence of pre-morbid attention deficit hyperactivity disorder (ADHD) and psychiatric disorders ($B = 1.17$, $Wald = 7.67$, $p = 0.006$). There were no significant associations between REHO and clinical measures at 24 h or the number of days until asymptomatic ($ps > 0.05$; Supplementary Table S2).

Discussion

This large-scale, prospective study in male and female collegiate athletes addresses recent calls to characterize the time course of the acute physiological effects of SRC and their relationship with clinical recovery.[5] Multiple rs-fMRI metrics that have been shown to be sensitive to SRC and/or mTBI were assessed using both traditional and subject-specific analyses that can capture spatially heterogenous effects. Concussed athletes had elevated local connectivity in the right middle and superior frontal gyri at the 24-h visit that returned to normal levels by the asymptomatic (average 10.43 days post-concussion) and post-RTP (average 26.49 days post-concussion) visits. Moreover, elevated local connectivity in the middle and superior frontal gyri at the 24-h visit in concussed athletes was associated with elevated psychological symptoms at the time-point at which athletes were cleared to start their RTP progression (i.e., asymptomatic visit). Significant differences in rs-fMRI were not observed in any metric at the asymptomatic and post-RTP visits. Collectively, these results suggest that SRC is associated with an acute alteration in local connectivity that follows a similar time course as clinical recovery in athletes who ultimately recover. Current results do not indicate evidence of prolonged abnormalities in multiple rs-fMRI metrics persisting beyond resolution of concussion symptoms, neurocognitive deficits, or balance deficits observed in typical cases of concussion.

The observed clinical results are consistent with prior literature and the design of the study, with concussion resulting in acute elevations in concussion symptoms, psychological symptoms, cognitive dysfunction, and balance deficits that recover by the asymptomatic time-point.[47,48] It is noteworthy, however, that psychological symptoms were still elevated in concussed athletes relative to controls at the asymptomatic time-point. We have previously reported elevated scores on the Hamilton Rating Scale for Depression in an independent cohort of collegiate athletes up to 1 month following concussion despite recovery of self-report symptoms and neurocognitive testing deficits by 1 week.[49,50] Thus, it is possible that post-injury psychological symptoms, such as mood dysfunction, are slower to recover relative to self-reported concussion symptoms and neurocognitive deficits. It is important to note that the asymptomatic time-point for the current study was defined as the time that athletes are cleared to begin the RTP progression, largely based on the resolution of SCAT3 symptoms.[13] This is consistent with the current state of clinical management of concussion, which is based on clinical judgement largely dependent on self-reported concussion symptoms and other assessments. Additional research is needed to determine the clinical utility of psychological assessment following concussion and its potential role in decisions regarding athlete recovery.

The acute increase in local connectivity observed in the current study was localized to a region in the right middle and superior frontal gyri that is typically associated with the default mode network (DMN). Multiple previous studies have observed abnormalities in functional connectivity of the DMN, which mediates internally oriented processing,[51] at various time-points following SRC and mTBI.[6,7] For example, altered DMN connectivity has been reported following SRC acutely (i.e., approximately 1 day post-injury),[52] within the first week,[53] approximately 10 days post-injury,[10] and approximately 1 month post-injury in both adolescent[54] and collegiate athletes,[12,50] although the direction of reported results has varied. The fact that the DMN is one of the most

functionally connected networks in the brain might make it more susceptible to brain injury.[55,56] In addition, the observation that the anterior portion of the DMN was affected in the current study is consistent with the known susceptibility of the frontal cortex to brain injury.[57–59]

Additional analyses demonstrated that the acute elevation in local connectivity in the middle and superior frontal gyri was associated with elevated psychological symptoms at the asymptomatic visit. Functional connectivity of the DMN has been repeatedly shown to be associated with psychological or emotional distress in psychiatric samples (e.g., depression, anxiety),[60] with recent studies demonstrating associations between DMN connectivity and psychological symptoms following mTBI or SRC.[50,61,62] DMN abnormalities in psychiatric disease have been proposed to reflect rumination and negative self-referential thought.[60,63] The current results were not driven by pre-morbid psychiatric disorders or ADHD; thus, they possibly reflect alterations in internally oriented processing following concussion (e.g., rumination or fixation of symptoms). Additional research is needed to test this hypothesis. Nevertheless, our results demonstrate that acute increases in local connectivity of the frontal cortex is a potential biomarker for prolonged psychological symptoms following SRC.

The underlying pathophysiology of the observed acute differences in local connectivity cannot be definitively established using existing methodologies. Differences in regional homogeneity could reflect an acute alteration in neuronal synchronicity. There are, however, several other aspects of the known neurometabolic cascade of concussion that could conceivably affect functional connectivity, including alterations in cerebral blood flow, glucose metabolism, neurotransmission, and white matter integrity.[64] For example, prior work from the CARE Consortium has demonstrated alterations in white matter and cerebral blood flow in sub-samples of the present cohort.[65,66] Future studies by the CARE Consortium will focus on the integration of multi-modal neuroimaging to better characterize the pathophysiology of SRC in collegiate athletes.

Importantly, no significant signal abnormalities were observed at either the asymptomatic or post-RTP time-points in any of the selected rs-fMRI metrics. There is growing concern that current RTP guidelines may allow the medical clearance of athletes before complete physiological recovery of their injury, with pre-clinical evidence supporting the notion that these athletes may be at risk for a more severe subsequent injury.[3–5] Our results, however, suggest that the effects of SRC on multiple rs-fMRI metrics follow a similar time course of recovery to that of concussion symptoms, neurocognitive deficits, and balance deficits. This is consistent with a recent report from our group from an independent, large-scale prospective study of concussion in high school and local football players in which whole-brain differences in global connectivity were only observed in athletes whom were still symptomatic at 8 days post-concussion.[19] Thus, the current work represents the second large-scale study to observe no rs-fMRI abnormalities beyond the resolution of self-reported symptoms or after unrestricted RTP following SRC and extends these results to non-football players and female athletes.

The fact that no significant differences were observed following clinical recovery in the rs-fMRI metrics selected for this study does not rule out the possibility that other metrics might have persistent abnormalities in asymptomatic or cleared athletes. In fact, multiple prior studies have documented persistent differences in rs-fMRI metrics following SRC.[9–11] As previously reviewed, however, much of the prior work has been limited by relatively small sample sizes and/or cross-sectional designs.[5,7] Additional factors, such as age (e.g., youth vs. high school vs. college) or differing clinical definitions of concussions could also explain variation across studies. Nevertheless, it is possible that targeted analyses focusing on abnormalities in specific seed-regions or resting-state networks would show persistent or prolonged effects. For example, future studies could investigate functional connectivity abnormalities of affective regions in athletes who still report psychological symptoms despite being cleared as ''asymptomatic.'' Finally, the neurometabolic cascade of concussion is complex, and it is likely that different aspects of the cascade have different time courses of recovery. Thus, it is possible that other neuroimaging modalities capture pathology with more prolonged recovery trajectories, such as white matter abnormalities.[67,68]

Limitations and future directions

This study has several strengths, including the prospective design, matching of control participants, and the large number of participants. There are, however, limitations that should be considered. First, although our study included both men and women, the total number of female athletes included in the study was still relatively small. Future studies with more female athletes are required to determine the potential moderating effect of sex on rs-fMRI metrics after concussion. Second, by design, this study only included athletes that ultimately recovered from their injury. Therefore, current results may not generalize to other samples that show persistent concussion symptoms (e.g., athletes that report to concussion clinics). There were scanner and sequence variation across sites. However, scanning parameters were constant for individual athletes across their multiple visits and the proportion of concussed and control athletes scanned with each set of parameters did not differ. Moreover, scanning differences were accounted for in the statistical analyses.

We have also previously demonstrated that the variability between athletes in MR metrics is equal to or greater than cross-site variability.[69] This study focused on rs-fMRI metrics that have been shown to be sensitive to brain injury and that do not require the selection of specific networks or regions of interest for analysis. Nevertheless, there are several other rs-fMRI metrics that may ultimately be sensitive to concussion. Prior concussion is a risk factor for subsequent concussion,[70] and the injured group in the current study reported more prior concussions relative to controls; however, the number of prior concussions was included as a covariate. The number of prior concussions was also based on participant self-report, which may over- or under-estimate actual number of prior concussions. It is noteworthy that the median number of prior concussions in each group is consistent with recent work in an independent sample of concussed athletes.[19] In addition, control athletes may have experienced repetitive head impacts below the threshold of concussion due to contact sport exposure (i.e., ''subconcussive'' impacts). It has been hypothesized that these head impacts are associated with negative physiological consequences[71,72] and it is possible that the sub-concussive impacts affected the rs-fMRI metrics in the current study. Future research will focus on potential longitudinal changes (e.g., across a single season) in rs-fMRI metrics associated with this exposure compared with athletes participating in non-contact sports.

Conclusion

This large-scale, multi-site study found no evidence that abnormalities in the selected rs-fMRI metrics extend beyond the time course of symptom recovery or after clearance for unrestricted RTP

in recovered athletes.These results suggest that recovery of the physiological effects of concussion captured by these rs-fMRI metrics is linked with clinical recovery based on commonly implemented clinical concussion assessment metrics. However, acute physiological abnormalities in functional connectivity following typical SRC may be predictive of psychological symptoms at later time-points.

Acknowledgments

The authors would like to thank Jody Harland, Janetta Matesan, and Larry Riggen (Indiana University); Ashley Rettmann (University of Michigan); Melissa Koschnitzke and Brad Swearingen (Medical College of Wisconsin); Michael Jarrett, Vibeke Brinck, and Bianca Byrne (Quesgen); Thomas Dompier, Melissa Niceley Baker, and Sara Dalton (Datalys Center for Sports Injury Research and Prevention); and the research and medical staff at each participating site. We are grateful for the participation of the student athletes without whom this research would not be possible.

Funding Information

This project was funded with support from the Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium, funded, in part by the National Collegiate Athletic Association (NCAA) and the Department of Defense (DoD). The U.S. Army Medical Research Acquisition Activity (820 Chandler Street, Fort Detrick, MD 21702-5014) is the awarding and administering acquisition office. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Psychological Health and Traumatic Brain Injury Program under Award Number W81XWH-14-2-0151. The REDCap electronic database used for this project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, Award Number UL1TR001436. This research was completed in part with computational resources and technical support provided by the Research Computing Center at the Medical College of Wisconsin.

Author Disclosure Statement

No competing financial interests exist.

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense (DHP funds).

Supplementary Material

Supplementary Appendix S1
Supplementary Table S1
Supplementary Table S2

References

1. Langlois, J.A., Rutland-Brown, W., and Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. J. Head Trauma Rehabil. 21, 375–378.
2. McCrory, P., Meeuwisse, W., Dvorak, J., Aubry, M., Bailes, J., Broglio, S., Cantu, R.C., Cassidy, D., Echemendia, R.J., Castellani, R.J., Davis, G.A., Ellenbogen, R., Emery, C., Engebretsen, L., Feddermann-Demont, N., Giza, C.C., Guskiewicz, K.M., Herring, S., Iverson, G.L., Johnston, K.M., Kissick, J., Kutcher, J., Leddy, J.J., Maddocks, D., Makdissi, M., Manley, G.T., McCrea, M., Meehan, W.P., Nagahiro, S., Patricios, J., Putukian, M., Schneider, K.J., Sills, A., Tator, C.H., Turner, M., and Vos, P.E. (2017). Consensus statement on concussion in sport—the 5(th) International Conference on Concussion in Sport held in Berlin, October 2016. Br. J. Sport. Med. 51, 838–847.
3. Prins, M.L., Alexander, D., Giza, C.C., and Hovda, D.A. (2013). Repeated mild traumatic brain injury: mechanisms of cerebral vulnerability. J. Neurotrauma 30, 30–38.
4. Longhi, L., Saatman, K.E., Fujimoto, S., Raghupathi, R., Meaney, D.F., Davis, J., McMillan, B.S.A., Conte, V., Laurer, H.L., Stein, S., Stocchetti, N., and McIntosh, T.K. (2005). Temporal window of vulnerability to repetitive experimental concussive brain injury. Neurosurgery 56, 364–374.
5. Kamins, J., Bigler, E., Covassin, T., Henry, L., Kemp, S., Leddy, J.J., Mayer, A., McCrea, M., Prins, M., Schneider, K.J., McLeod, T.C.V., Zemek, R., and Giza, C.C. (2017). What is the physiological time to recovery after concussion? A systematic review. Br. J. Sports Med. 51, 935–940.
6. Mayer, A.R., Bellgowan, P.S., and Hanlon, F.M. (2015). Functional magnetic resonance imaging of mild traumatic brain injury. Neurosci. Biobehav. Rev. 49, 8–18.
7. McCrea, M., Meier, T., Huber, D., Ptito, A., Bigler, E., Debert, C.T., Manley, G., Menon, D., Chen, J.K., Wall, R., Schneider, K.J., and McAllister, T. (2017). Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review. Br. J. Sport. Med. 51, 919–929.
8. Churchill, N.W., Hutchison, M.G., Richards, D., Leung, G., Graham, S.J., and Schweizer, T.A. (2017). Neuroimaging of sport concussion: persistent alterations in brain structure and function at medical clearance. Sci. Rep. 7, 8297.
9. Manning, K.Y., Schranz, A., Bartha, R., Dekaban, G.A., Barreira, C., Brown, A., Fischer, L., Asem, K., Doherty, T.J., Fraser, D.D., Holmes, J., and Menon, R.S. (2017). Multiparametric MRI changes persist beyond recovery in concussed adolescent hockey players. Neurology 89, 2157–2166.
10. Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., and Slobounov, S. (2012). Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. Neuroimage 59, 511–518.
11. Czerniak, S.M., Sikoglu, E.M., Liso Navarro, A.A., McCafferty, J., Eisenstock, J., Stevenson, J.H., King, J.A., and Moore, C.M. (2015). A resting state functional magnetic resonance imaging study of concussion in collegiate athletes. Brain Imaging Behav. 9, 323–332.
12. Meier, T.B., Bellgowan, P.S.F., and Mayer, A.R. (2017). Longitudinal assessment of local and global functional connectivity following sports-related concussion. Brain Imaging Behav. 11, 129–140.
13. Broglio, S.P., McCrea, M., McAllister, T., Harezlak, J., Katz, B., Hack, D., Hainline, B., and CARE Consortium Investigators. (2017). A National Study on the Effects of Concussion in Collegiate Athletes and U.S. Military Service Academy Members: The NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium Structure and Methods. Sport. Med 47, 1437–1451.
14. Zang, Y., Jiang, T., Lu, Y., He, Y., and Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. Neuroimage 22, 394–400.
15. Zhan, J., Gao, L., Zhou, F., Kuang, H., Zhao, J., Wang, S., He, L., Zeng, X., and Gong, H. (2015). Decreased regional homogeneity in patients with acute mild traumatic brain injury: a resting-state fMRI study. J. Nerv. Ment. Dis. 203, 786–791.
16. Zou, Q.H., Zhu, C.Z., Yang, Y., Zuo, X.N., Long, X.Y., Cao, Q.J., Wang, Y.F., and Zang, Y.F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J. Neurosci. Methods 172, 137–141.
17. Madhavan, R., Joel, S.E., Mullick, R., Cogsil, T., Niogi, S.N., Tsiouris, A.J., Mukherjee, P., Masdeu, J.C., Marinelli, L., and Shetty, T. (2019). Longitudinal resting state functional connectivity predicts clinical outcome in mild traumatic brain injury. J. Neurotrauma 36, 650–660.
18. Rubinov, M., and Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069.
19. Kaushal, M., España, L.Y., Nencka, A.S., Wang, Y., Nelson, L.D., McCrea, M.A., and Meier, T.B. (2019). Resting-state functional connectivity after concussion is associated with clinical recovery. Hum. Brain Mapp. 40, 1211–1220.
20. Zuo, X.N., Di Martino, A., Kelly, C., Shehzad, Z.E., Gee, D.G., Klein, D.F., Castellanos, F.X., Biswal, B.B., and Milham, M.P. (2010). The oscillating brain: complex and reliable. Neuroimage 49, 1432–1445.

21. Zuo, X.N., Xu, T., Jiang, L., Yang, Z., Cao, X.Y., He, Y., Zang, Y.F., Castellanos, F.X., and Milham, M.P. (2013). Toward reliable characterization of functional homogeneity in the human brain: preprocessing, scan duration, imaging resolution and computational space. Neuroimage 65, 374–386.
22. Guo, C.C., Kurth, F., Zhou, J., Mayer, E.A., Eickhoff, S.B., Kramer, J.H., and Seeley, W.W. (2012). One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. Neuroimage 61, 1471–1483.
23. Schwarz, A.J., and McGonigle, J. (2011). Negative edges and soft thresholding in complex network analysis of resting state functional connectivity data. Neuroimage 55, 1132–1146.
24. Dodd, A.B., Ling, J.M., Bedrick, E.J., Meier, T.B., and Mayer, A.R. (2018). Spatial distribution bias in subject-specific abnormalities analyses. Brain Imaging Behav. 12, 1828–1834.
25. Mayer, A.R., Bedrick, E.J., Ling, J.M., Toulouse, T., and Dodd, A. (2014). Methods for identifying subject-specific abnormalities in neuroimaging data. Hum. Brain Mapp. 35, 5457–5470.
26. Mayer, A.R., Dodd, A.B., Ling, J.M., Wertz, C.J., Shaff, N.A., Bedrick, E.J., and Viamonte, C. (2018). An evaluation of Z-transform algorithms for identifying subject-specific abnormalities in neuroimaging data. Brain Imaging Behav. 12, 437–448.
27. Carney, N., Ghajar, J., Jagoda, A., Bedrick, S., Davis-O'Reilly, C., du Coudray, H., Hack, D., Helfand, N., Huddleston, A., Nettleton, T., and Riggio, S. (2014). Concussion Guidelines Step 1. Neurosurgery 75, S3–S15.
28. Klein, A.P., Tetzlaff, J.E., Bonis, J.M., Nelson, L.D., Mayer, A.R., Huber, D.L., Harezlak, J., Mathews, V.P., Ulmer, J.L., Sinson, G.P., Nencka, A.S., Koch, K.M., Wu, Y.-C., Saykin, A.J., DiFiori, J.P., Giza, C.C., Goldman, J., Guskiewicz, K.M., Mihalik, J.P., Duma, S.M., Rowson, S., Brooks, A., Broglio, S.P., McAllister, T., McCrea, M.A., and Meier, T.B. (2019). Prevalence of potentially clinically significant magnetic resonance imaging findings in athletes with and without sport-related concussion. J. Neurotrauma 11, 1776–1785.
29. Wechsler, D. (2001). Wechsler Test of Adult Reading: WTAR. San Antonio, TX: The Psychological Corp.
30. McCrory, P., Meeuwisse, W.H., Aubry, M., Cantu, B., Dvorak, J., Echemendia, R.J., Engebretsen, L., Johnston, K., Kutcher, J.S., Raftery, M., Sills, A., Benson, B.W., Davis, G.A., Ellenbogen, R.G., Guskiewicz, K., Herring, S.A., Iverson, G.L., Jordan, B.D., Kissick, J., McCrea, M., McIntosh, A.S., Maddocks, D., Makdissi, M., Purcell, L., Putukian, M., Schneider, K., Tator, C.H., and Turner, M. (2013). Consensus statement on concussion in sport—the 4th International Conference on Concussion in Sport held in Zurich, November 2012. Br. J. Sport. Med. 47, 250–258.
31. Derogatis, L.R. (2001). *Brief Symptom Inventory 18 (BSI-18): Administration, Scoring, and Procedures Manual*. Pearson: Minneapolis, MN.
32. Riemann, B.L., and Guskiewicz, K.M. (2000). Effects of mild head injury on postural stability as measured through clinical balance testing. . Athl. Train. 35, 19–25.
33. McCrea, M., Kelly, J.P., Kluge, J., Ackley, B., and Randolph, C. (1997). Standardized assessment of concussion in football players. Neurology 48, 586–588.
34. Cox, R.W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.
35. Jenkinson, M., Bannister, P., Brady, M., and Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.
36. Greve, D.N., and Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. Neuroimage 48, 63–72.
37. Taylor, P.A., and Saad, Z.S. (2013). FATCAT: (an efficient) Functional and Tractographic Connectivity Analysis Toolbox. Brain Connect. 3, 523–535.
38. Glover, G.H., Mueller, B.A., Turner, J.A., van Erp, T.G., Liu, T.T., Greve, D.N., Voyvodic, J.T., Rasmussen, J., Brown, G.G., Keator, D.B., Calhoun, V.D., Lee, H.J., Ford, J.M., Mathalon, D.H., Diaz, M., O'Leary, D.S., Gadde, S., Preda, A., Lim, K.O., Wible, C.G., Stern, H.S., Belger, A., McCarthy, G., Ozyurt, B., and Potkin, S.G. (2012). Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. J. Magn. Reson. Imaging 36, 39–54.
39. Friedman, L., Glover, G.H., Krenz, D., Magnotta, V., and First, B. (2006). Reducing inter-scanner variability of activation in a multicenter fMRI study: role of smoothness equalization. Neuroimage 32, 1656–1668.
40. Mijalkov, M., Kakaei, E., Pereira, J.B., Westman, E., Volpe, G., and Alzheimer's Disease Neuroimaging Initiative. (2017). BRAPH: a graph theory software for the analysis of brain connectivity. PLoS One 12, e0178798.
41. Craddock, R.C., James, G.A., Holtzheimer, P.E., Hu, X.P.P., and Mayberg, H.S. (2012). A whole brain fMRI atlas generated via spatially constrained spectral clustering. Hum. Brain Mapp. 33, 1914–1928.
42. Chen, G., Saad, Z.S., Britton, J.C., Pine, D.S., and Cox, R.W. (2013). Linear mixed-effects modeling approach to FMRI group analysis. Neuroimage 73, 176–190.
43. Cox, R.W., Chen, G., Glen, D.R., Reynolds, R.C., and Taylor, P.A. (2017). FMRI clustering in AFNI: false-positive rates redux. Brain Connect. 7, 152–171.
44. Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., and Joliot, M. (2002). Automated anatomical labeling 90ROIs. Neuroimage 15, 273–289.
45. Rolls, E.T., Joliot, M., and Tzourio-Mazoyer, N. (2015). Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. Neuroimage 122, 1–5.
46. Yarkoni, T., Poldrack, R.A., Nichols, T.E., Van Essen, D.C., and Wager, T.D. (2011). Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods 8, 665–670.
47. Williams, R.M., Puetz, T.W., Giza, C.C., and Broglio, S.P. (2015). Concussion recovery time among high school and collegiate athletes: a systematic review and meta-analysis. Sport. Med. 45, 893–903.
48. McCrea, M., Guskiewicz, K.M., Marshall, S.W., Barr, W., Randolph, C., Cantu, R.C., Onate, J.A., Yang, J., and Kelly, J.P. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. JAMA 290, 2556–2563.
49. Meier, T.B., Bellgowan, P.S., Singh, R., Kuplicki, R., Polanski, D.W., and Mayer, A.R. (2015). Recovery of cerebral blood flow following sports-related concussion. JAMA Neurol 72, 530–538.
50. McCuddy, W.T., Espana, L.Y., Nelson, L.D., Birn, R.M., Mayer, A.R., and Meier, T.B. (2018). Association of acute depressive symptoms and functional connectivity of emotional processing regions following sport-related concussion. Neuroimage Clin. 19, 434–442.
51. Buckner, R.L., Andrews-Hanna, J.R., and Schacter, D.L. (2008). The brain's default network: anatomy, function, and relevance to disease. Ann. N Y Acad. Sci. 1124, 1–38.
52. Zhu, D.C., Covassin, T., Nogle, S., Doyle, S., Russell, D., Pearson, R.L., Monroe, J., Liszewski, C.M., DeMarco, J.K., and Kaufman, D.I. (2015). A potential biomarker in sports-related concussion: brain functional connectivity alteration of the default-mode network measured with longitudinal resting-state fMRI over thirty days. J. Neurotrauma 32, 327–341.
53. Militana, A.R., Donahue, M.J., Sills, A.K., Solomon, G.S., Gregory, A.J., Strother, M.K., and Morgan, V.L. (2016). Alterations in default-mode network connectivity may be influenced by cerebrovascular changes within 1 week of sports related concussion in college varsity athletes: a pilot study. Brain Imaging Behav. 10, 559–568.
54. Borich, M., Babul, A.N., Yuan, P.H., Boyd, L., and Virji-Babul, N. (2015). Alterations in resting-state brain networks in concussed adolescent athletes. J. Neurotrauma 32, 265–271.
55. Cole, M.W., Pathak, S., and Schneider, W. (2010). Identifying the brain's most globally connected regions. Neuroimage 49, 3132–3148.
56. Sepulcre, J., Liu, H., Talukdar, T., Martincorena, I., Yeo, B.T., and Buckner, R.L. (2010). The organization of local and distant functional connectivity in the human brain. PLoS Comput. Biol. 6, e1000808.
57. Bigler, E.D. (2007). Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology 21, 515–531.
58. Eierud, C., Craddock, R.C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., and LaConte, S.M. (2014). Neuroimaging after mild traumatic brain injury: review and meta-analysis. Neuroimage Clin. 4, 283–294.
59. Bayly, P.V, Cohen, T.S., Leister, E.P., Ajo, D., Leuthardt, E.C., and Genin, G.M. (2005). Deformation of the human brain induced by mild acceleration. J. Neurotrauma 22, 845–856.
60. Hamilton, J.P., Farmer, M., Fogelman, P., and Gotlib, I.H. (2015). Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. Biol. Psychiatry 78, 224–230.

61. Zhou, Y., Milham, M.P., Lui, Y.W., Miles, L., Reaume, J., Sodickson, D.K., Grossman, R.I., and Ge, Y. (2012). Default-mode network disruption in mild traumatic brain injury. Radiology 265, 882–892.
62. van der Horn, H.J., Liemburg, E.J., Scheenen, M.E., de Koning, M.E., Marsman, J.B., Spikman, J.M., and van der Naalt, J. (2016). Brain network dysregulation, emotion, and complaints after mild traumatic brain injury. Hum. Brain Mapp. 37, 1645–1654.
63. Beck, A.T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. Am. J. Psychiatry 165, 969–977.
64. Giza, C.C., and Hovda, D.A. (2014). The new neurometabolic cascade of concussion. Neurosurgery 75, Suppl. 4, S24–S33.
65. Wang, Y., Nencka, A.S., Meier, T.B., Guskiewicz, K., Mihalik, J.P., Alison Brooks, M., Saykin, A.J., Koch, K.M., Wu, Y.-C., Nelson, L.D., McAllister, T.W., Broglio, S.P., and McCrea, M.A. (2018). Cerebral blood flow in acute concussion: preliminary ASL findings from the NCAA-DoD CARE consortium. Brain Imaging Behav., 1–11.
66. Mustafi, S.M., Harezlak, J., Koch, K.M., Nencka, A.S., Meier, T.B., West, J.D., Giza, C.C., DiFiori, J.P., Guskiewicz, K.M., Mihalik, J.P., LaConte, S.M., Duma, S.M., Broglio, S.P., Saykin, A.J., McCrea, M., McAllister, T.W., and Wu, Y.-C. (2018). Acute white-matter abnormalities in sports-related concussion: a diffusion tensor imaging study from the NCAA-DoD CARE Consortium. J. Neurotrauma 35, 2653–2664.
67. Meier, T.B., Bergamino, M., Bellgowan, P.S.F., Teague, T.K., Ling, J.M., Jeromin, A., and Mayer, A.R. (2016). Longitudinal assessment of white matter abnormalities following sports-related concussion. Hum. Brain Mapp. 37, 833–845.
68. Lancaster, M.A., Meier, T.B., Olson, D.V, McCrea, M.A., Nelson, L.D., and Muftuler, L.T. (2018). Chronic differences in white matter integrity following sport-related concussion as measured by diffusion MRI: 6-month follow-up. Hum. Brain Mapp. 39, 4276–4289.
69. Nencka, A.S., Meier, T.B., Wang, Y., Muftuler, L.T., Wu, Y.C., Saykin, A.J., Harezlak, J., Brooks, M.A., Giza, C.C., Difiori, J., Guskiewicz, K.M., Mihalik, J.P., LaConte, S.M., Duma, S.M., Broglio, S., McAllister, T., McCrea, M.A., and Koch, K.M. (2018). Stability of MRI metrics in the advanced research core of the NCAA-DoD concussion assessment, research and education (CARE) consortium. Brain Imaging Behav. 12, 1121–1140.
70. Guskiewicz, K.M., McCrea, M., Marshall, S.W., Cantu, R.C., Randolph, C., Barr, W., Onate, J.A., and Kelly, J.P. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. JAMA 290, 2549–2555.
71. Reynolds, B.B., Stanton, A.N., Soldozy, S., Goodkin, H.P., Wintermark, M., and Druzgal, T.J. (2018). Investigating the effects of subconcussion on functional connectivity using mass-univariate and multivariate approaches. Brain Imaging Behav. 12, 1332–1345.
72. Johnson, B., Neuberger, T., Gay, M., Hallett, M., and Slobounov, S. (2014). Effects of subconcussive head trauma on the default mode network of the brain. J. Neurotrauma 31, 1907–1913.

Address correspondence to:
Timothy B. Meier, PhD
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226

E-mail: tmeier@mcw.edu