NeuroImage: Clinical 36 (2022) 103211

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Adolescents with a concussion have altered brain network functional connectivity one month following injury when compared to adolescents with orthopedic injuries

Katherine Healey [a,e], Zhuo Fang [b], Andra Smith [b], Roger Zemek [a,c], Andrée-Anne Ledoux [a,b,d,e,*]

[a] Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
[b] School of Psychology, University of Ottawa, Ottawa, Ontario, Canada
[c] Department of Pediatrics, Division of Emergency Medicine, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada
[d] Department of Cellular Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
[e] Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada

ARTICLE INFO

Keywords:
Pediatric concussion
Resting-state functional magnetic resonance imaging
Functional connectivity
Default mode network
Salience network
Central executive network

ABSTRACT

Concussion is a mild traumatic brain injury (mTBI) with increasing prevalence among children and adolescents. Functional connectivity (FC) within and between the default mode network (DMN), central executive network (CEN) and salience network (SN) has been shown to be altered post-concussion. Few studies have investigated connectivity within and between these 3 networks following a pediatric concussion. The present study explored whether within and between-network FC differs between a pediatric concussion and orthopedic injury (OI) group aged 10–18. Participants underwent a resting-state functional magnetic resonance imaging (rs-fMRI) scan at 4 weeks post-injury. One-way ANCOVA analyses were conducted between groups with the seed-based FC of the 3 networks. A total of 55 concussion and 27 OI participants were included in the analyses. Increased within-network FC of the CEN and decreased between-network FC of the DMN-CEN was found in the concussion group when compared to the OI group. Secondary analyses using spherical SN regions of interest revealed increased within-network FC of the SN and increased between-network FC of the DMN-SN and CEN-SN in the concussion group when compared to the OI group. This study identified differential connectivity patterns following a pediatric concussion as compared to an OI 4 weeks post-injury. These differences indicate potential adaptive brain mechanisms that may provide insight into recovery trajectories and appropriate timing of treatment within the first month following a concussion.

1. Introduction

Concussion is a mild traumatic brain injury (mTBI) with increasing prevalence among children and adolescents (Zemek et al., 2017). The neurobiological mechanism implicated in concussion injury and repair is not fully understood. In addition to axonal injuries due to shearing forces, cortical, neurochemical, metabolic, cerebral blood flow, and mitochondrial dysfunctions have also been associated with concussion pathophysiology (Giza and Hovda, 2001). Insults to cerebrovascular control (cerebral blood flow mechanisms) likely contribute to concussion symptoms. Cerebral blood flow impairments may contribute to changes in brain activity and connectivity within and between functional brain networks. Understanding network connectivity in pediatric concussion may improve our understanding of associated symptoms and recovery trajectories, helping to establish the most appropriate type and timing of treatment intervention.

A pathophysiological network studied in concussion is the default mode network (DMN). The DMN—sometimes referred to as the task-negative network—is a group of structures that are consistently active during tasks that are internally-focused or in the absence of outwardly

Abbreviations: CEN, central executive network; dACC, dorsal anterior cingulate cortex; DMN, default mode network; dlPFC, dorsolateral prefrontal cortex; ED, emergency department; FC, functional connectivity; FIC, frontoinsular cortex; GCS, Glasgow coma scale; HBI, Health and Behavior Inventory; mPFC, medial prefrontal cortex; mTBI, mild traumatic brain injury; OI, orthopedic injury; PCC, posterior cingulate cortex; pPC, posterior parietal cortex; rs-fMRI, resting-state magnetic resonance imaging; SN, salience network; zFC, functional connectivity z-scores.

* Corresponding author.
E-mail address: aledoux@cheo.on.ca (A.-A. Ledoux).

https://doi.org/10.1016/j.nicl.2022.103211
Received 9 March 2022; Received in revised form 15 September 2022; Accepted 26 September 2022
Available online 27 September 2022
2213-1582/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

engaging tasks (Buckner et al., 2008). The DMN is comprised of the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC), temporoparietal areas, and regions of the medial temporal lobe (Andrews-Hanna et al., 2014). The PCC is thought to be responsible for coordinating representations of the self while the mPFC filters and selects the relevant representations into conscious thought (Davey et al., 2016).

Despite the well-documented presence of changes post-concussion, findings of DMN FC vary considerably in both adults and adolescents following concussion. Increases in functional connectivity (FC) within the DMN have been associated with rumination in adults (van der Horn et al., 2016a,b) and it has been speculated that ongoing increases in FC within the DMN may impede recovery following an mTBI due to persistent thoughts about present injury state and future consequences (van der Horn et al., 2017a,b). However, findings of both increased and decreased connectivity have been observed in adults in the months following a concussion (van der Horn et al., 2017a,b; van der Horn et al., 2016a,b). In children and young adults, patterns of decreased DMN connectivity in the acute and chronic phases of concussion have been observed across adolescence (Iyer et al., 2019a,c; Plourde et al., 2020) and have corresponded to increased sleep and cognitive disturbances (Iyer et al., 2019a,c). However, based on the research to date, a trend towards increased DMN connectivity appears to be most prevalent in concussed adolescents (Abbas et al., 2015; Newsome et al., 2016a; Orr et al., 2016). Studies have noted increased connectivity within 30 days and up to a year following concussion in both symptomatic and asymptomatic youth in comparison to participants with no history of concussion or suffering from an OI (Abbas et al., 2015; Newsome et al., 2016a; Orr et al., 2016). Due to the variability of the findings, further research is needed to better understand the FC patterns of the DMN following a concussion in youth.

While the DMN is described as the task-negative network, the central executive network (CEN) can be described as the task-positive network or the frontoparietal control network (Vincent et al., 2008). This network appears to be anticorrelated with the DMN and is activated during external tasks requiring executive control and function (Sridharan et al., 2008). Its main hub regions include the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (pPC) which have been shown to contribute to sustained attention and working memory (Seeley, 2019). Following concussion, the CEN has been shown to be irregular when measured in a resting-state in comparison to controls in both adolescence and adulthood. Similar to the DMN, the CEN appears to demonstrate primarily increased connectivity in youth following a concussion (Borich et al., 2015) but studies investigating the role of the CEN in pediatric concussion are limited. Given that children and youth with concussion have demonstrated deficits in attentional control and executive function in the subacute (<2 weeks) and chronic (>1 month) phase (Broadway et al., 2019; Howell et al., 2013), pediatric CEN functional activity requires further attention.

Another network with demonstrated involvement with the DMN and CEN is the salience network (SN). The role of the SN involves the perception, integration, and filtration of emotional and interoceptive cues (Liu et al., 2020). Its main hub regions include the dorsal anterior cingulate cortex (dACC) and frontoinsular cortex (FIC) (Seeley et al., 2007; Seeley, 2019). The SN provides crucial control of executive behavior through its modulation of CEN activity (van der Horn et al., 2016a,b) and control over cognitive functions through its modulation of DMN activity (Bonnelle et al., 2012). Resting-state FC increases within the SN have been found in adults 7 days following an mTBI in comparison to controls (Liu et al., 2020) and these within-network increases have been associated with increased symptoms of anxiety (Seeley, 2019). In adolescence, strong FC between the main SN hub regions has been observed (Marusak et al., 2017) and negative correlations were found between trait anxiety and FC of the left and right anterior insula and right dACC (Geng et al., 2016). However, studies investigating the role of SN FC following a pediatric concussion are lacking. Due to its apparent control over the DMN and CEN in adulthood, the SN's connectivity patterns following pediatric concussion also require more attention.

Correlated activity between the 3 networks has been observed in adults following concussion. The SN has been shown to modulate the relationship between the DMN and the CEN, including exerting control over the switch between the task-on and task-off states (Chand et al., 2017; Goulden et al., 2014; Jilka et al., 2014). Recently, further evidence implicated the FIC (also referred to as the anterior insula) as a key site for mediating the balance between the DMN and attention/executive control networks using task-based functional magnetic resonance imaging (fMRI) (Huang et al., 2021). Decreased segregation between the DMN and CEN, and increased connectivity between the DMN and SN, has been observed in the acute and chronic stages of concussion and have been associated with increased cognitive complaints (Iraji et al., 2015; Liu et al., 2020; Sours et al., 2018; van der Horn et al., 2017a,b). In addition, higher FC between the CEN and SN has been associated with decreased post-mTBI cognitive complaints and depression symptoms (van der Horn et al., 2016a,b). This evidence supports the assumption that when SN function becomes dysregulated, DMN activity interferes with CEN function resulting in cognitive and attention deficits (van der Horn et al., 2016a,b).

Although much of the research has been conducted with adults, correlated activity between the 3 networks has also been observed throughout childhood and adolescence (Sherman et al., 2014). Connectivity between the CEN and DMN, as well as the CEN and SN, appears to become anticorrelated throughout childhood, with significant anticorrelation noted as early as 7 years old (Marusak et al., 2017; Sherman et al., 2014). Further, reduced FC between regions of the SN and DMN were found to be associated with higher trait anxiety in adolescents (Geng et al., 2016). Contrary to research in adults, a study investigating a pediatric sample found no significant differences in DMN and CEN interconnectivity between concussion and control participants (Iyer et al., 2019a,c). To our knowledge, studies have yet to investigate the interactions between the 3 networks in pediatric concussion. Further research is needed to better understand connectivity changes between these brain networks following a pediatric concussion.

The following study investigated the intraconnectivity of the DMN and its interconnectivity with the CEN and SN at 1 month following a pediatric concussion in comparison to an age and sex-matched orthopedic injury (OI) group. The inclusion of the OI group allowed conclusions to be made regarding the influence of being in an injured state, for example, the experience of pain or initial pause in regular activities (Mathias et al., 2013; Stancin et al., 1998; Wilde et al., 2019). In addition, this study investigated connectivity at a point in time when the majority of adolescents have typically recovered from concussion symptoms (Ledoux et al., 2019) to highlight if differential connectivity persists. It was hypothesized that intraconnectivity within the DMN would be increased in concussion participants in comparison to OI participants at 4 weeks post-injury. In addition, it was hypothesized that increased interconnectivity between the DMN and CEN and increased SN intraconnectivity in the concussion group would be observed at 4 weeks post-injury.

2. Materials and methods

2.1. Study participants

A total of 92 participants with a concussion and 46 participants with an OI were enrolled as part of the Pediatric Concussion Assessment of Rest and Exertion with MRI (PedCARE^{+MRI}) study, an adjunct study to the multicentre randomized clinical trial PedCARE (Ledoux et al., 2019), from May 2018 to January 2020. All participants were enrolled at the Children's Hospital of Eastern Ontario (CHEO) emergency department (ED) and underwent an MRI at < 72 h and 4 weeks post-injury. Participants and parent/guardian provided written informed consent and/or

assent as appropriate. Of those enrolled in the study, 15 concussion and 16 OI participants did not complete the full MRI protocol and were either excluded or withdrew. Further, 17 concussion and 3 OI participants were excluded from the FC analysis due to excessive motion (>3 mm) in their rs-fMRI scans. An additional 3 concussion participants were excluded despite complete MRI data due to significant incidental findings. No participants were excluded for excess motion in their structural scans. A total of 55 concussion and 27 OI participants remained for the rs-fMRI analyses. For a complete enrolment breakdown, see Supplemental 1. The study was approved by the Research Ethics Board at CHEO and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Although the PedCARE trial randomized concussion participants to either resume non-contact, aerobic physical activity at 72 h post-concussion or rest until asymptomatic, the concussion participants were regrouped and the randomization was broken for the purposes of this study as both groups completed similar levels of physical activity (Ledoux et al., 2021). The study herein is a cross sectional design of the data collected for PedCARE^{+MRI}. The inclusion of the age and sex-matched orthopedically injured group further contributed to the cross-sectional design as recruitment in the same ED allowed for the control of enrolment in a hospital setting, pain, injury-related stress and pre-morbid characteristics (Mathias et al., 2013; Stancin et al., 1998; Wilde et al., 2019).

2.1.1. Concussion participants

Inclusion criteria was as follows: aged 10–17.99 years old; had a concussion as defined by the Berlin consensus statement; head injury was acquired within 48 h of ED visit; and proficiency in English. An adapted version of the CDC tiered framework (Peterson et al., 2021) was used to increase the chances of enrolling patients with a true concussion. Patients were included if they presented with either: 1 symptom within the highest level of certainty (e.g., amnesia; loss of consciousness); or 2 symptoms within the higher level of certainty immediately or within 1 h of injury (e.g., nausea or vomiting; headache; clumsiness or balance problems). Participants were excluded if they had: a Glasgow coma scale (GCS) rating of $\leq$ 13 or below at ED presentation as determined by the treating physician; neuroimaging abnormalities; neurosurgical intervention, intubation, or intensive care admission; multi-system injuries requiring hospitalization; severe chronic neurological developmental delay with communication difficulties; intoxication; absence of trauma history; previous enrolment; unable to provide informed consent; previous neurological or neurodevelopmental disorder; previously hospitalized for psychiatric disorders; administered sedation medication before or during ED visit; unable to attend MRI follow-ups; or any reason that prevented undergoing an MRI.

2.1.2. Orthopedic injury participants

Inclusion criteria was as follows: aged 10–17.99 years; had an isolated upper extremity OI due to blunt force or physical trauma; injury was acquired within 48 h of ED visit; and proficiency in English. Participants were excluded if they had: a concussion upon presentation or a previous concussion or traumatic brain injury within the last year; closed reduction procedural sedation or surgical management at time of ED visit; severe chronic neurological developmental delay with communication difficulties; intoxication; absence of trauma history; previous enrolment; unable to provide informed consent; previous neurological or neurodevelopmental disorder; previously hospitalized for psychiatric disorders; administered sedation medication before or during ED visit; unable to attend MRI follow-ups; or any reason that prevented undergoing an MRI.

2.2. Clinical and demographic data

Participant demographics and diagnostic history (including age, sex, handedness, number of previous concussions and prior diagnosis of ADHD, anxiety, depression, and learning disabilities) were collected due to their adverse effects on concussion recovery, psychophysiology and pathophysiology (Iaccarino et al., 2018; Iverson et al., 2017). Clinical and demographic data were collected during enrolment in the ED. When collection was not possible in the ED, data was collected either 72 h post-injury or retroactively post-study completion (if not collected at 72 h). Degree of concussion symptoms were also measured using the validated and reliable Health and Behaviour Inventory (HBI) (Ayr et al., 2009), a 20-item questionnaire that includes a total score and measurements of cognitive and somatic symptoms. The HBI is recommended as a NIH core common data element for concussion (Broglio et al., 2018). The questionnaire requires the participant to self-report the frequency of each symptom over the past week. Symptoms are rated on a 4-point scale (0, 1, 2, or 3 points) with the options ranging from “never” to “often” for a total score range of 0 to 60. The HBI was completed at 72 h and 4 weeks post-injury for the concussed and OI groups. Only the total scores of the 4-week assessments were included in this study.

Demographics and clinical data were compared to identify differences between groups (concussion and OI). Independent two-sample t-tests (for continuous variables) and Pearson Chi-square tests (for categorical variables) were conducted using IBM Statistical Package for the Social Sciences (SPSS), version 26.0 for Macintosh. Variables that did not meet the assumptions for parametric testing were analyzed using the Mann-Whitney U test. Significance was defined by $p < 0.05$.

2.3. Magnetic resonance imaging

The 3-Tesla Siemens PET-MRI system equipped with a 12-channel head coil at the Royal Ottawa Mental Health Centre’s Brain Imaging Centre was used for the acquisition of neuroimaging data. The protocol included a resting-state functional magnetic resonance imaging (rs-fMRI) sequence and acquired a T1-weighted anatomical image for each participant at 4 weeks post-injury. During the rs-fMRI sequence, a crosshair was placed at the centre of the viewing screen. Participants were instructed to keep their eyes open, relax, try not to move, look straight ahead at the crosshair, and try not to think of anything specific. Slice planes were prescribed at 20–25° from the AC-PC line such that a slice plane passed along the base of the front of the brain and the base of the cerebellum, approximately, ensuring whole brain coverage. The gradient-echo echoplanar pulse sequence was acquired with the following parameters: TR (repetition time) = 2 s; TE (echo time) = 30 ms; 241 measurements; flip angle = 70°; FOV (field of view) = 230 mm; 36 slices, 3.6 mm thick; voxel size = 3.6 × 3.6 × 3.6 mm; acquisition length = 8 min 10 s. The high-resolution T1-weighted images were acquired along the AC-PC, ensuring whole head coverage, with the following parameters: TE = 2.21, 4.09, 5.97, 7.85 ms; TR = 2.3 s; TI (inversion time) = 1.16 s; 8° flip angle; slice thickness = 1 mm; voxel size = 0.9 × 0.9 × 1 mm^3; FOV = 230 mm; resolution = 230 × 230 × 176 mm; acquisition length = 5 min 52 s.

2.4. Neuroimaging data analysis

fMRI data analysis was performed using the Statistical Parametric Mapping software (SPM12, Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) and the Data Processing Assistant for Resting-State fMRI-Advanced Edition (DPARSFA), a software within DPABI (Yan et al., 2016), carried out using Matlab 9.8 (R2020a, MathWorks). DICOM images (generated by the SIEMENS scanner) were converted to 4D NIfTI files using the program MRIcron (Rorden and Brett, 2000).

2.4.1. Preprocessing

Using DPARSFA (Chao-Gan & Yu-Feng, 2010; Yan et al., 2021), rs-fMRI images were corrected for slice timing and realigned to correct for motion. At this point, participants with >3 mm of absolute motion in their scans were excluded from the analysis (Sours et al., 2015; Stephens

et al., 2018a,b). Next, the rs-fMRI images were skull-stripped and co-registered with the structural image for each individual. Using the diffeomorphic nonlinear registration tool (DARTEL) (Ashburner, 2007), T1 images were segmented and used later for normalization. Next, nuisance covariates including white matter signal, cerebrospinal fluid signal, six head motion parameters (using Friston 24), and global mean signal were regressed out. The decision to regress out the global signal was based on the findings that global signal regression facilitates better removal of respiratory, cardiac, and motion signals (Madhavan et al., 2019; Power et al., 2014). Head motion scrubbing regressors were implemented to regress out the frame-wise displacements (FD) exceeding a threshold of 0.5 mm, including the volume proceeding and 2 following (Iyer et al., 2019a,c; Power et al., 2014). Regressing out the volumes containing excessive micromovements has been demonstrated to account for motion artifacts without reducing power by scrubbing (Orr et al., 2016). In addition, the FD values were not considered significant between groups (Concussion group mean[SD] = 0.069[0.135], OI group mean[SD] = 0.079[0.076]; Mann-Whitney U Test p = 0.083) so were not included as covariates in the group-level analysis. To reduce high-frequency cardiac and respiratory noise and low-frequency drift, functional volumes were bandpass filtered between 0.01 and 0.1 Hz. Next, the images were normalized (3.6 mm^3) and smoothed (using a 6 mm full width at half maximum Gaussian kernel) using DARTEL. DARTEL was used because it creates a template that models the shape of each brain to improve the accuracy of inter-subject alignment of grey and white matter (Ashburner, 2007), especially important considering the differences in developmental stages within the targeted age group.

2.4.2. Functional connectivity analysis

Seed-based FC analysis was performed using DPARSFA. Regions of interest (ROI) masks (seed regions) were created using the SPM toolbox WFU_Pickatlas (https://www.nitrc.org/projects/wfu_pickatlas/). Seed ROIs were defined for each of the 3 networks being studied. The regions included bilateral PCC and mPFC of the DMN, bilateral dlPFC and pPC of the CEN, and bilateral dACC and FIC of the SN. In pediatric and adult concussion research, the PCC and mPFC have been consistently studied and shown to play an important role in DMN function (Abbas et al., 2015; Borich et al., 2015; Iyer et al., 2019a; Johnson et al., 2012; Sharp et al., 2011; Stephens et al., 2018b). The dACC and FIC of the SN were chosen as these regions have consistently shown to be functionally linked to exert a level of cognitive control (Geng et al., 2016; Ham et al., 2014; Seeley et al., 2007; Seeley, 2019). Finally, the dlPFC and the pPC of the CEN have been identified as functionally active contributors to sustained attention and working memory (Mayer et al., 2011; Seeley, 2019).

The PCC, mPFC, dlPFC, and the pPC were defined with the AAL1 atlas. The dACC and the FIC were defined using the Human Brainnetome Atlas (Fan et al., 2016).

To measure intra- and interconnectivity between the networks, FC was measured within and between the 3 networks. To calculate FC per participant, the mean blood-oxygen-level dependent (BOLD) signal time series was extracted for each individual seed-region. Then, the Pearson correlation coefficients between the BOLD time series of each seed region and the whole brain were grouped into FC maps. The FC maps were then converted into z-scores for normality and used for the statistical analysis.

2.4.3. Between group differences in FC within the DMN, CEN and SN

First, one-way ANCOVAs were conducted with the z-transformed FC maps to determine if differences exist in connectivity within the DMN, CEN and SN (between internal hub regions) between the concussion and OI groups.

Specifically, SPM second-level analysis and the WFU_Pickatlas toolbox were used to perform region-specific analyses of FC. The concussion and OI z-transformed FC maps of a hub region (for example, the left PCC) were uploaded into the design matrix and another region was specified as the ROI (for example, the left mPFC for within-network analyses). FC between the hub region and the selected ROI were then computed from the z-transformed FC map while adjusting for the smaller volume of the ROI and compared between groups. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016a,b). A cluster threshold of $p < 0.05$ with family-wise error (FWE) correcting for multiple comparisons (Stephens et al., 2018a,b) with an extent threshold of 10 voxels (Lieberman and Cunningham, 2009) was considered significant. Visual brain maps illustrating clusters within an ROI (visualized) that significantly differed between groups in FC with the hub region (not visualized) were generated. Scatterplots representing the spread of average FC z-score (zFC) values (extracted from the z-transformed FC maps) were generated with SPSS for significant regions.

As per the guidelines for reporting fMRI studies, a crude and adjusted analysis were conducted (Poldrack et al., 2008). The adjusted ANCOVA analyses included age, sex, handedness, randomization group, and a composite diagnostic score (based on self-reported diagnoses of a learning disability, ADHD, anxiety, depression, and number of previous concussions) as covariates.

Due to the variation in FC strength throughout adolescence, age was included as a covariate in all analyses (Sherman et al., 2014). Sex was also covaried as reduced connectivity post-concussion was recently identified in females within and between multiple regions (Shafi et al., 2020). To account for the possibility of group differences between the physical activity and rest concussion groups [despite no significant activity level differences (Ledoux et al., 2021)], assigned groups were added as covariates. For the purposes of this analysis, each participant was assigned a composite diagnostic score that was the sum of: 1 point per prior diagnosis of ADHD, anxiety, depression or learning disability; and total number of previous concussions. A recent study found that age, sex, and inattention symptoms may be less significant in influencing DMN FC than the number of previous concussions (Plourde et al., 2020), therefore, number of previous concussions were included in the covaried composite score. ADHD was included in the composite score due to the demonstrated associations between ADHD symptoms and DMN connectivity (as well as connectivity within and between the DMN and other networks including the CEN and SN) (Hilger and Fiebach, 2019). Anxiety and depression were included in the composite score because mental health history has been associated with worse recovery outcomes (Iverson et al., 2017). In addition, anxiety has been associated with increased FC within the SN (van der Horn et al., 2016a,b), and the presence of depression symptoms has been demonstrated to alter connectivity within the DMN and CEN 1 month after a mTBI (van der Horn et al., 2017a,b). Finally, handedness was included as a covariate as it has been demonstrated to have significant effects on FC (Raemaekers et al., 2018; Wiberg et al., 2019).

2.4.4. Between group FC differences between the DMN, CEN and SN

One-way ANCOVAs were conducted with the z-transformed FC maps to determine if differences exist between the main hub regions of the DMN-CEN (the PCC and dlPFC, respectively), DMN-SN (the PCC and FIC, and mPFC and FIC, respectively), and CEN-SN (the dlPFC and FIC, respectively). The PCC was chosen as the main hub region of the DMN because it appears to play a role in alternating between brain networks [such as between the DMN and CEN (Mayer et al., 2011; Mary R. Newsome et al., 2016; Sours et al., 2015), and between the DMN and SN (Jilka et al., 2014)] and mental states (van der Horn et al., 2016a,b). Similarly, the FIC of the SN has been shown to be robustly functionally linked with the PCC of the DMN during internal cognitive activity (Jilka et al., 2014; Sours et al., 2015). Finally, the dlPFC was chosen as the main hub region of the CEN because of its demonstrated functional connectivity with the PCC following concussion (Sours et al., 2015). An additional analysis was performed between the FIC and the mPFC due to the evidence that the two may be functionally connected following a concussion (Liu et al., 2020).

The same methods were employed as the within-network analyses to conduct the between-network analyses. SPM second-level analysis and the WFU_Pickatlas toolbox were used to compute FC between the hub region and the selected ROI from the z-transformed FC map while adjusting for the smaller volume of the ROI and compared between groups. The adjusted ANCOVA analyses used the same covariates as defined for the within-network ANCOVA analyses. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016a,b). A cluster threshold of $p < 0.05$ with FWE correcting for multiple comparisons (Stephens et al., 2018a,b) with an extent threshold of 10 voxels (Lieberman and Cunningham, 2009) was considered significant. Visual brain maps illustrating clusters within an ROI (visualized) that significantly differed between groups in FC with the hub region (not visualized) were generated. Scatterplots representing the spread of average FC z-score (zFC) values (extracted from the z-transformed FC maps) were generated with SPSS for significant regions.

2.4.5. Secondary FC analysis within and between the SN

An additional functional connectivity analysis was performed employing the same methods as the within- and between-network analyses but with the incorporation of spherical ROIs for SN regions. As in the previous analyses, the PCC, mPFC, and the dlPFC were defined with the AAL1 atlas. The left and right dACC were created with spheres with MNI coordinates defined by Fang et al. (2015) (left x: −6 y: 45 z: 9; right x: 8 y: 45 z: 9; radius: 8 mm). The left and right FIC were created with spheres with MNI coordinates defined by Sridharan et al. (2008) (left x: −32 y: 24 z: −6; right x: 37 y: 25 z: −4; radius: 8 mm). We chose a priori spheres in addition to the analysis conducted with the Brainnetome structural regions due to the small size of the regions in question and individual variability in age and size of the participants. It has been suggested that spheres (as long as they are a reasonable size) are more accurate when attempting to define smaller regions at the group level as they may accommodate some of the individual variability (Sohn et al., 2015) considering the younger age group of the current sample population. We attempted to compensate for this in our spherically defined ROIs by increasing the size without adding unnecessary voxels thereby decreasing the true representation of the regions.

3. Results

3.1. Clinical and demographic data

Demographic and clinical characteristics can be found in Table 1. The concussion group median age was 12.87 (IQR: 11.68–14.36; 47.3 % female) and the OI group was 12.54 (IQR: 11.25–14.02, 37 % female). No significant differences were found between concussion and OI groups in age, sex, handedness, time between injury and MRI, or number of previous concussions ($p > 0.05$). The groups did not differ significantly on pre-existing diagnoses of learning disabilities, ADHD, other developmental disorders, anxiety, depression, sleep disorders, or other psychiatric disorders as well as in composite diagnostic score ($p > 0.05$). Finally, the groups did not differ in their degree of concussion symptoms as measured using the HBI ($p > 0.05$).

Table 1
Participant Demographics.

Variable	Concussion Participants (N = 55)	Orthopedic injury (OI) Participants (N = 27)	*P* Value[a]
Median age (IQR), in years	12.87 (11.68–14.36)	12.54 (11.25–14.02)	0.361
Female (%)	26 (47.3 %)	10 (37 %)	0.380
Right handedness (%)	47 (85.5 %)	19 (73.1 %)	0.181
Randomization group Group A (Rest Group) Group B (Experimental Group)	25 (45.5 %)30 (54.5 %)	N/A	N/A
Median Time (IQR) Between Injury and 4-Week MRI, in days (OI group n = 26)	30.23 (28.21–32.08)	29.98 (25.92–32.10)	0.160
Median gcs score (iqr)	15 (15–15)	N/A	N/A
Median number of previous concussions (iqr) (concussion group n = 54)	0 (0–1)	0 (0–0)	0.309
Diagnostic history: (concussion group n = 53)			
Learning disabilities (%)	6 (11.3 %)	2 (7.4 %)	0.581
Adhd (%)	10 (18.9 %)	4 (14.8 %)	0.652
Other developmental disorder (specify):	2 (3.8 %)	0 (%)	0.316
Anxiety (%)	11 (20.8 %)	3 (11.1 %)	0.283
Depression (%)	4 (7.5 %)	1 (3.7 %)	0.502
Sleep disorder (%)	2 (3.8 %)	1 (3.7 %)	0.988
Other psychiatric disorder (%)	0 (0 %)	1 (3.7 %)	0.159
Median composite diagnostic score (iqr) (number of previous concussions, adhd, anxiety, depression, and learning disabilities)	1 (0–2)	0 (0–1)	0.084
Median hbi score at 4 weeks (iqr) (concussion group n = 53)	12.00 (4.00–19.00)	8 (3.00–18.00)	0.572
Mechanism of injury (%)			
Sport:	32 (58.2 %)		
Hockey	7 (12.7 %)		
Soccer	11 (20.0 %)		
Recreational play (gym, recess)	4 (7.3 %)		
Skating	1 (1.8 %)		
Football	2 (3.6 %)		
Basketball	1 (1.8 %)		
Badminton	2 (3.6 %)		
Dodgeball	1 (1.8 %)		
Rugby	2 (3.6 %)		
Four-square	1 (1.8 %)		
Ran into stationary object	5 (9.1 %)		
Fall from standing/walking/running	7 (12.7 %)		
Fall from elevation	1 (1.8 %)		
Fall down stairs	2 (3.6 %)		
Other mechanisms	8 (14.5 %)		

[a] Continuous variables (age and time between injury and MRI) were analyzed with two-sample t-tests. Variables with non-normal distributions (number of previous concussion, composite diagnostic score, and HBI score) were analyzed with Mann-Whitney U tests. Categorical variables (sex, handedness, and diagnostic history) were analyzed with the Pearson Chi-square test. Significance was defined by $p < 0.05$.

3.2. Between group differences in FC within the DMN, CEN and SN

3.2.1. DMN Within-Network analyses

Both the crude and adjusted analyses revealed no significant differences in DMN within-network FC (between the bilateral PCC and mPFC) between the concussion and OI group at the whole brain level threshold of $p_{uncorr} < 0.001$.

3.2.2. CEN Within-Network analyses

The crude and adjusted analysis of the CEN found increased FC in the concussion group compared to the OI group. The crude analysis revealed a cluster in the right pPC ($p_{FWE} = 0.020$; 37 voxels) of the concussion group with significantly increased FC with the right dlPFC at a whole brain level threshold of $p_{uncorr} < 0.001$. The adjusted analysis replicated and strengthened the crude finding increasing the size and significance of the cluster in the right pPC ($p_{FWE} = 0.001$; 145 voxels). See Table 2 and Fig. 1 for complete ANCOVA cluster results.

3.2.3. SN Within-Network analyses

Both the crude and adjusted analyses revealed no significant differences in SN within-network FC (between the bilateral FIC and dACC) between the concussion and OI group at the whole brain level threshold of $p_{uncorr} < 0.001$.

Table 2
Adjusted Within-Network FC Differences in the Concussion Group Compared to the OI Group.

Network	FC ↑ or ↓[a]	Seed Region	Significant Region	Cluster-size (voxels[b])	Peak MNI coordinates x	y	z	P_{FWE} value (cluster)
CEN	↑	Right dlPFC	Right pPC	145	45	−48	51	0.001

Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. CEN = central executive network; dlPFC = dorsolateral prefrontal cortex; pPC = posterior parietal cortex.
[a] ↑ and ↓ denote increased or decreased FC, respectively, in the concussion compared to the OI group.
[b] Voxel size = 3.6 mm × 3.6 mm × 3.6 mm.

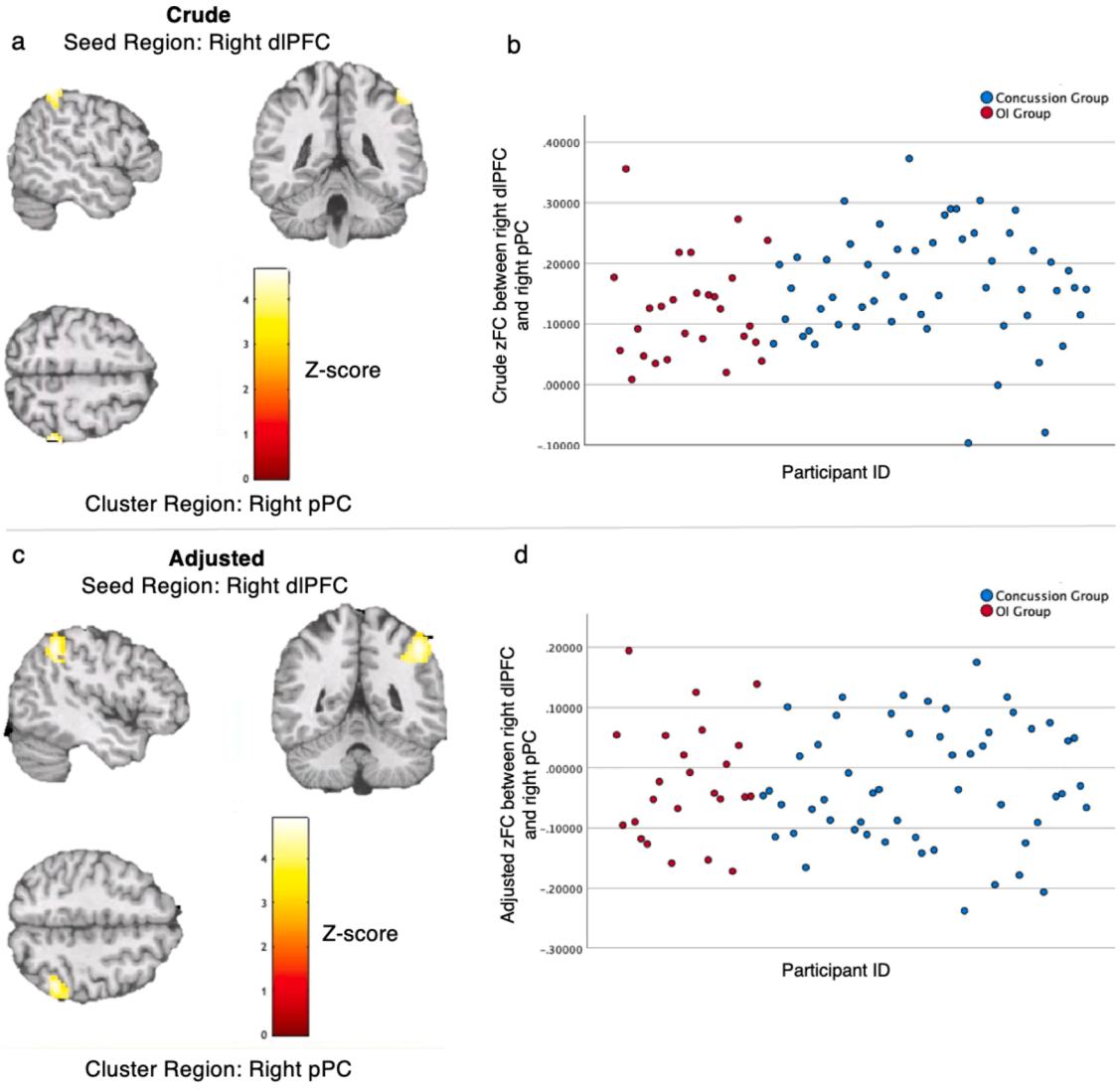

Fig. 1. Crude and adjusted ANCOVA analyses (1a and 1c; contrast = Concussion > OI) revealed a cluster within the right pPC (visualized) found to have significantly increased FC with the right dlPFC (not visualized) in the concussion group (n = 55) compared to the OI group (n = 27). Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. The scatterplots (1b and 1d) represent the spread of the crude and adjusted average zFC values between the right dlPFC and right pPC in the concussion group (n = 55) and the OI group (n = 27). CEN = central executive network; dlPFC = dorsolateral prefrontal cortex; pPC = posterior parietal cortex; zFC = functional connectivity z-scores.

3.3. Between group differences in FC between the DMN, CEN and SN

No significant clusters were found in the crude analyses between networks. Adjusted analyses revealed that a cluster in the left PCC (p_{FWE} = 0.006; 25 voxels) of the DMN had significantly decreased FC with the right dlPFC of the CEN in the concussion group (see Fig. 2). Cluster results can be found in Table 3. No significant clusters were found in the adjusted analyses between the DMN-SN or the CEN-SN.

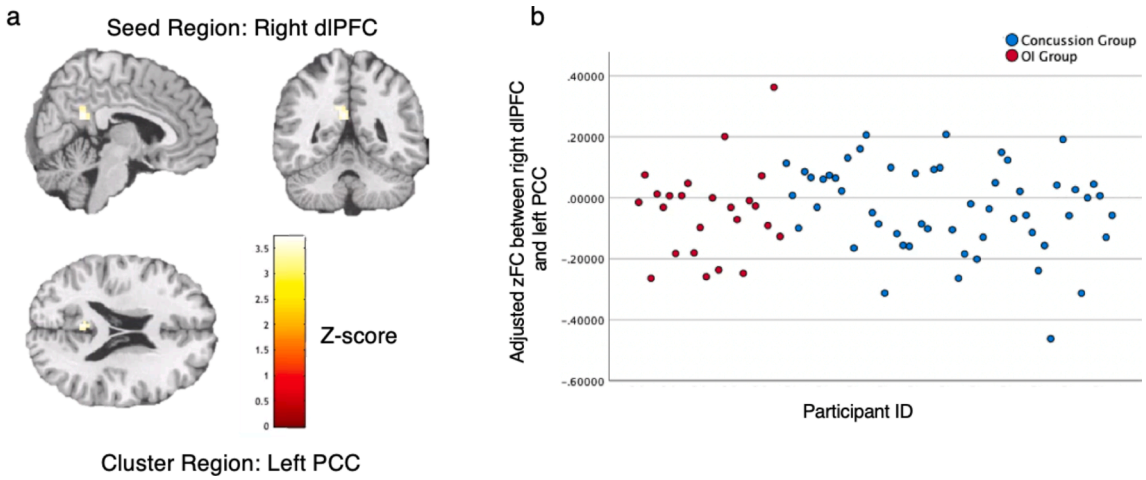

Fig. 2. Adjusted ANCOVA analyses (2a; contrast = OI > Concussion) revealed a cluster within the left PCC (visualized) with significantly decreased FC with the right dlPFC (not visualized) in the concussion group (n = 55) compared to the OI group (n = 27). Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. The scatterplot (2b) represents the spread of the adjusted average zFC values between the right dlPFC and left PCC in the concussion group (n = 55) and the OI group (n = 27). CEN = central executive network; dlPFC = dorsolateral prefrontal cortex; DMN = default mode network; PCC = posterior cingulate cortex; zFC = functional connectivity z-scores.

Table 3
Adjusted Between-network FC Differences in the Concussion Group Compared to the OI Group.

Network(s)	FC ↑ or ↓[a]	Seed Region	Significant Region	Cluster-size (voxels[b])	Peak MNI coordinates			P_{FWE} Value (cluster)
					x	y	z	
CEN-DMN	↓	Right dlPFC	Left PCC	25	−6	−48	21	0.006

Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. CEN = central executive network; dlPFC = dorsolateral prefrontal cortex; DMN = default mode network; PCC = posterior cingulate cortex.

[a] ↑ and ↓ denote increased or decreased FC, respectively, in the concussion compared to the OI group.

[b] Voxel size = 3.6 mm × 3.6 mm × 3.6 mm.

3.4. Secondary FC analysis with spherical ROIs

3.4.1. Between group differences in FC within the SN

No significant clusters were found in the crude analysis of SN intraconnectivity. The adjusted analysis of SN intraconnectivity found increased FC in the concussion group compared to the OI group between the right FIC and the bilateral dACC. Clusters within the left dACC (p_{FWE} = 0.001; 61 voxels) and right dACC (p_{FWE} = 0.002; 41 voxels) had significantly increased FC with the right FIC in the concussion group compared to the OI group [see Table 4 and Fig. 3].

3.4.2. Between group differences in FC between the DMN, CEN and SN

No significant clusters were found in the crude analyses between networks. Adjusted analyses revealed increased FC in the concussion group compared to the OI group between the sN-DMN and sN-CEN. More specifically, clusters in the left PCC (p_{FWE} = 0.001; 84 voxels), right PCC (p_{FWE} = 0.002; 56 voxels), left mPFC (p_{FWE} = 0.000; 580 voxels) and right mPFC (p_{FWE} = 0.000; 490 voxels) of the DMN had significantly increased FC with the right FIC of the SN in the concussion group (see Fig. 4). Clusters in the left dlPFC (p_{FWE} = 0.007; 81 voxels) and right dlPFC (p_{FWE} = 0.004; 107 voxels) of the CEN also had significantly increased FC with the right FIC in the concussion group (see Fig. 5). Complete cluster results can be found in Table 5.

4. Discussion

The present study investigated differences in FC within and between the 3 functional brain networks thought to be responsible for internally and externally directed attention between concussed youth and youth who sustained an OI 4 weeks following injury.

Table 4
Adjusted Within-Network FC Differences in the Concussion Group Compared to the OI Group.

Network	FC ↑ or ↓[a]	Seed Region	Significant Region	Cluster-size (voxels[b])	Peak MNI coordinates			P_{FWE} value (cluster)
					x	y	z	
SN	↑	Right FIC	Left dACC	61	0	48	15	0.001
			Right dACC	41	3	45	15	0.002

Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. dACC = dorsal anterior cingulate cortex; FIC = frontoinsular cortex; SN = salience network.

[a] ↑ and ↓ denote increased or decreased FC, respectively, in the concussion compared to the OI group.

[b] Voxel size = 3.6 mm × 3.6 mm × 3.6 mm.

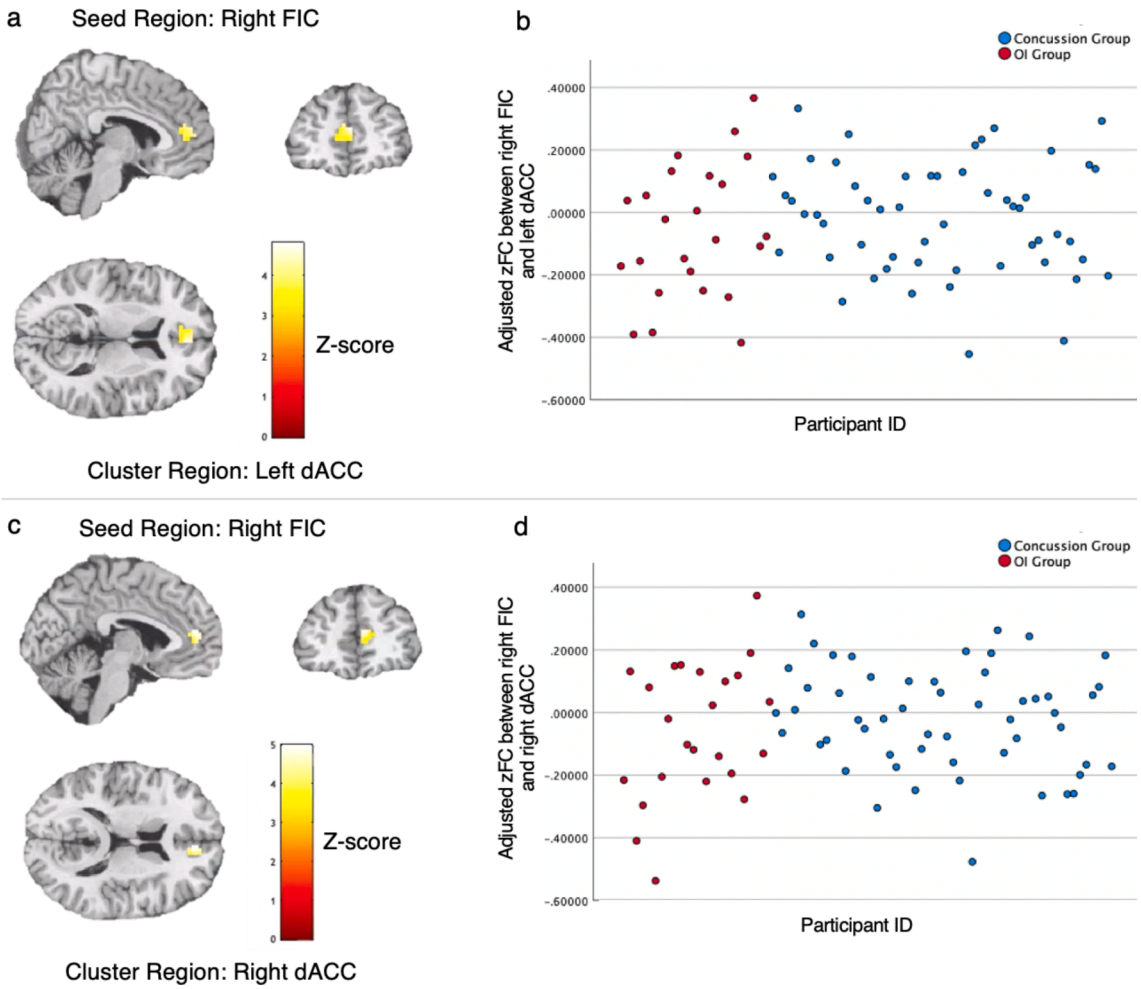

Fig. 3. Adjusted ANCOVA analyses (3a and 3c; contrast = Concussion > OI) revealed clusters within the bilateral dACC (visualized) found to have significantly increased FC with the right FIC (not visualized) in the concussion group (n = 55) compared to the OI group (n = 27). Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. The scatterplots (3b and 3d) represent the spread of the adjusted average zFC values between the right FIC and bilateral dACC in the concussion group (n = 55) and the OI group (n = 27). dACC = dorsal anterior cingulate cortex; FIC = frontoinsular cortex; SN = salience network; zFC = functional connectivity z-scores.

4.1. Within-network connectivity

No significant differences in within-network DMN and SN FC were found between the concussion and OI group in the initial analyses. However, increased within-network FC of the CEN (between the right pPC and dlPFC) were present in the concussion group. Our finding of within-network CEN hyperconnectivity in the concussion group aligns with CEN connectivity findings in a study conducted in adolescents within 2 months of head injury (Borich et al., 2015). These researchers suggest increased CEN connectivity in the chronic phase may be occurring to compensate for any microstructural damages to connectivity that could have occurred during the initial injury (Borich et al., 2015). Within-network CEN hyperconnectivity was also observed in adults with mTBI compared to healthy controls but was associated with worse post-concussive complaints at approximately 1 month post-injury (van der Horn et al., 2016a,b). Sullivan et al. (2018), who studied brain connectivity during cognitive control tasks in adults with blast-related mTBI in the later chronic stage (2 + years post-injury), found that CEN hyperconnectivity was positively associated with a measurement of cognitive control. This suggests increased connectivity within this network may be compensatory during cognitive tasks and may compensate for reduced network connectivity coupling between the CEN and DMN (Sullivan et al., 2018).

Secondary analyses using spherical ROIs of the SN regions revealed increased within-network FC of the SN (between clusters in the bilateral dACC and the right FIC). Findings of increased SN intraconnectivity have been demonstrated in adults with moderate to severe TBI within 3 and 6 months following injury in comparison to healthy controls (Hillary et al., 2014). These increases, however, did not significantly correlate with neuropsychological measures of cognition, suggesting the timing of measurement and intersubject variability (i.e. stage of recovery) may have influenced the results at the group level (Hillary et al., 2014). FC between the bilateral FIC and dACC of the SN has been found to be negatively correlated with trait anxiety in healthy adolescents (Geng et al., 2016). This suggests that the increases in our concussion sample (found between the right FIC and bilateral dACC) may reflect a compensatory mechanism to improve cognitive control during recovery due to the importance of the SN in the initiation of executive control (Sridharan et al., 2008). Alternatively, this could represent a different response entirely in the pediatric concussed brain. To our knowledge, no studies to date have investigated within-network FC in the SN in the pediatric concussion population. Further research is needed to investigate the associations of this intra-connectivity with cognitive symptomology post-concussion.

Our finding of no differences in within-network DMN connectivity was partially supported by prior research. In pediatric concussion

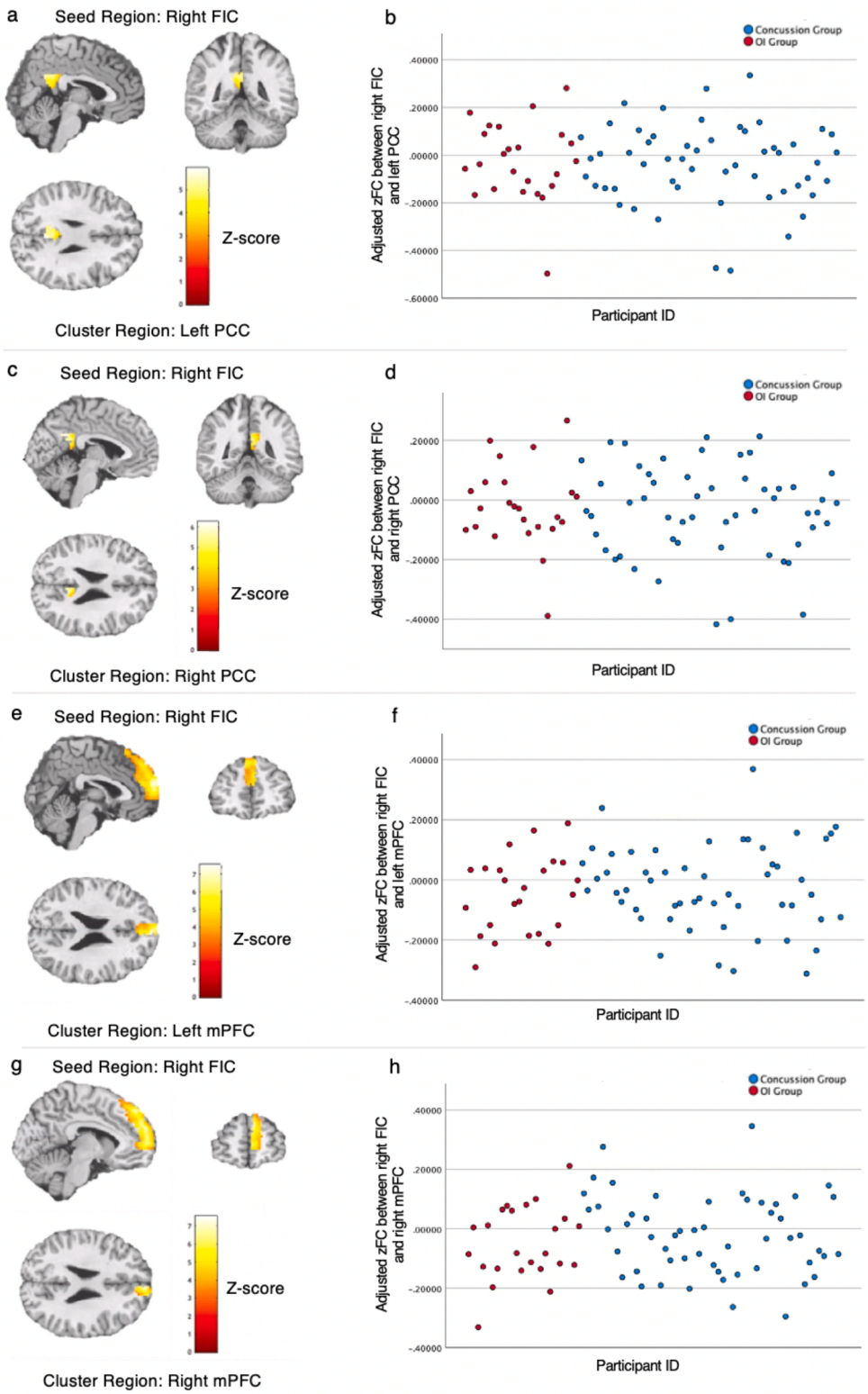

Fig. 4. Adjusted ANCOVA analyses revealed clusters within the bilateral PCC (4a and 4c; contrast = Concussion > OI; visualized) and mPFC (4e and 4 g; contrast = Concussion > OI; visualized) with significantly increased FC with the right FIC (not visualized) in the concussion group (n = 55) compared to the OI group (n = 27). Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. The scatterplots represent the spread of the adjusted average zFC values between the right FIC and bilateral PCC (4b and 4d) and bilateral mPFC (4f and 4 h) in the concussion group (n = 55) and the OI group (n = 27). DMN = default mode network; FIC = frontoinsular cortex; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; SN = salience network; zFC = functional connectivity z-scores.

groups compared to healthy controls, studies have shown no differences in within-network DMN FC (Iyer et al., 2019a,c), as well as increased posterior DMN and decreased anterior DMN FC (Borich et al., 2015) at 1 month post-injury. A study by Iyer et al. (2020) found that adolescents who were still experiencing symptoms at 4 weeks post-injury had increased anterior DMN FC compared to those who had recovered, suggesting further that incidences of hypo and hyperconnectivity may be dependent on recovery state. As suggested by Zhu et al. (2015), many of the changes in DMN connectivity may be occurring within the first 7 days following a head injury. This would suggest that our measurement may have captured within-network DMN connectivity while normalizing. This observation is supported by the recovery status of our concussion group. When comparing the preinjury symptom scores (recorded retrospectively in the ED) to the symptom scores at 4 weeks,

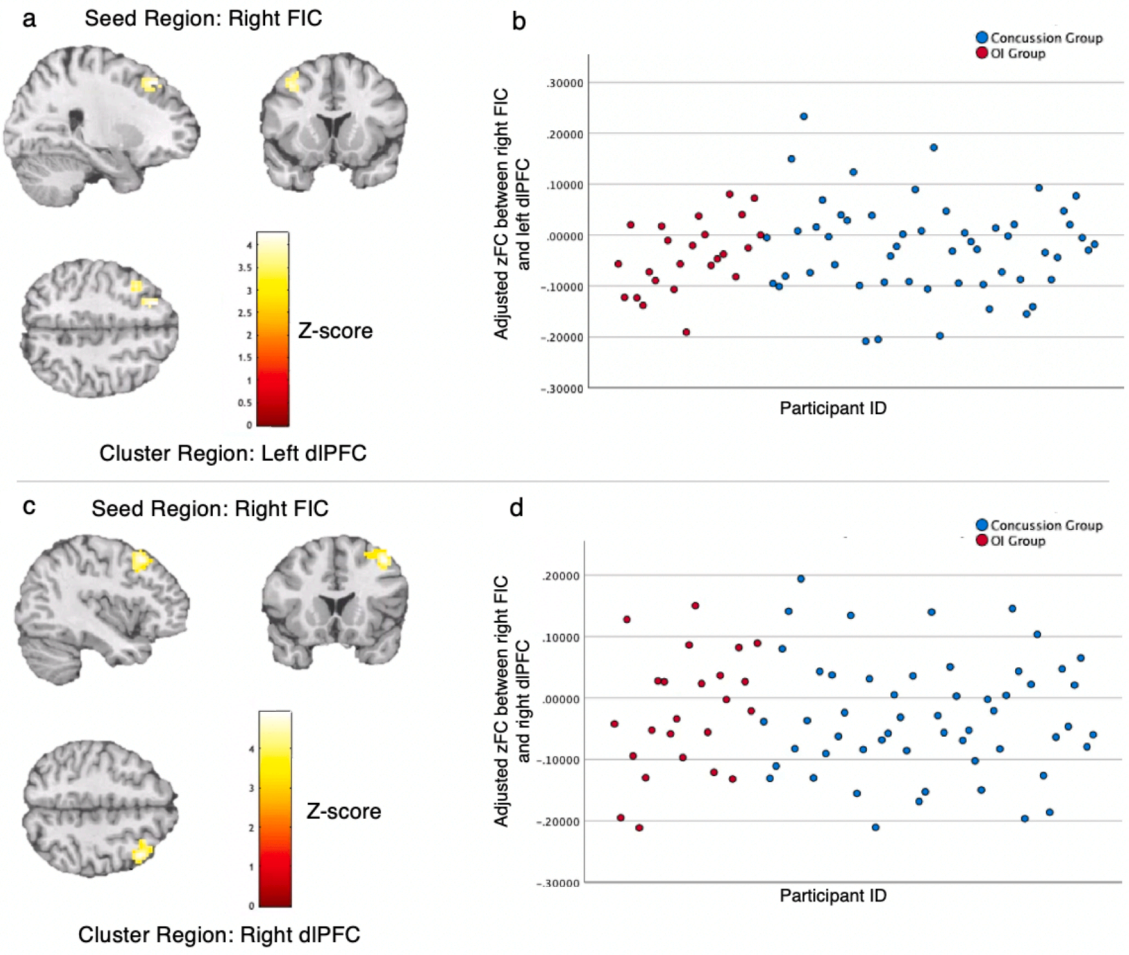

Fig. 5. Adjusted ANCOVA analyses (5a and 5c; contrast = Concussion > OI) revealed clusters within the bilateral dlPFC (visualized) found to have significantly increased FC with the right FIC (not visualized) in the concussion group (n = 55) compared to the OI group (n = 27). Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. The scatterplots (5b and 5d) represent the spread of the adjusted average zFC values between the right FIC and bilateral dlPFC in the concussion group (n = 55) and the OI group (n = 27). CEN = central executive network; dlPFC = dorsolateral prefrontal cortex; FIC = frontoinsular cortex; SN = salience network; zFC = functional connectivity z-scores.

Table 5
Adjusted Between-network FC Differences in the Concussion Group Compared to the OI Group.

Network(s)	FC ↑ or ↓[a]	Seed Region	Significant Region	Cluster-size (voxels[b])	Peak MNI coordinates			P_{FWE} Value (cluster)
					x	y	z	
SN-DMN	↑	Right FIC	Left PCC	84	0	−54	30	0.001
			Right PCC	56	3	−54	30	0.002
			Left mPFC	580	−3	63	18	0.000
			Right mPFC	490	3	60	24	0.000
SN-CEN	↑	Right FIC	Left dlPFC	81	−24	30	48	0.007
			Right dlPFC	107	39	18	51	0.004

Age, sex, handedness, randomization group, and composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were added as covariates. P < 0.001 (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. CEN = central executive network; dACC = dorsal anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; DMN = default mode network; FIC = frontoinsular cortex; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; SN = salience network.

[a] ↑ and ↓ denote increased or decreased FC, respectively, in the concussion compared to the OI group.

[b] Voxel size = 3.6 mm × 3.6 mm × 3.6 mm.

69.8 % of the concussion group were considered recovered (i.e., had no symptoms at 4 weeks relative to preinjury scores). Further analyses comparing acute stage scans to the 4-week scans may shed more light on the recovery timeline of the DMN following a pediatric concussion.

4.2. *Between-network connectivity findings*

Our finding of hypoconnectivity between the right dlPFC of the CEN and left PCC of the DMN in the concussion group is in contrast to the

hypotheses and to other concussion studies performed in both pediatric and adult populations. Iyer et al. (2019) found no differences in FC at 4 weeks post-injury between the DMN and CEN in adolescents who suffered a concussion and healthy controls. A pilot study investigating FC in adolescent athletes 30 days post-injury found a cluster within the right ventral lateral prefrontal cortex with increased connectivity to the PCC in comparison to an OI group (Newsome et al., 2016a). Increased connectivity was also found between the DMN and inferior parietal lobule in adolescents 1 year post-TBI in comparison to uninjured controls and this increase in connectivity was correlated with decreased response inhibition (Stephens et al., 2018). Sours et al. (2015), who found no differences in FC in adults between the DMN and CEN at 1 month post-injury but found increased connectivity in the concussed group between the DMN and left dlPFC at approximately 6 months post-injury, suggests that differences in reported connectivity at 1 month post-injury may be due to differences in clinical recovery of the participants at that timepoint. These differences in recovery trajectory have been noted in other research (Cairncross et al., 2021; Doroszkiewicz et al., 2021; Iaccarino et al., 2018; Iverson et al., 2017; Ledoux et al., 2019; Losoi et al., 2016; Taubman et al., 2016), such as the fact that approximately 30 % of adolescents still experience symptoms at 4 weeks (Zemek et al., 2016). This supports the need to further investigate recovery status, especially considering pre-existing diagnoses, such as mental illness and ADHD, have been demonstrated to prolong recovery (Cairncross et al., 2021; Iaccarino et al., 2018; Iverson et al., 2017).

4.3. Secondary analyses Between-network connectivity findings

The initial analyses using structurally defined ROIs within the SN revealed no significant clusters between this network and the DMN and CEN. The right FIC of the SN, however, was found to have increased connectivity in the spherical ROI analyses between the bilateral dlPFC of the CEN, and the PCC and mPFC of the DMN. Although studied in adults with concussion (Iraji et al., 2015; Liu et al., 2020; Sours et al., 2015; van der Horn et al., 2016a,b), between-network connectivity of the DMN and SN, as well as the CEN and SN, has not previously been investigated in a pediatric sample.

Current research implicates the SN as an important modulatory network of the DMN and CEN, providing control over individual responses of emotion, affect, attention, and cognition (Chand et al., 2017; Goulden et al., 2014; Jilka et al., 2014; Seeley, 2019). The FIC (or anterior insula) has been further implicated to play a key role in the mediation of attention and executive control between the DMN and CEN (Huang et al., 2021) and is suggested to play a crucial part in affective and emotional processes due to its extensive connections with limbic and paralimbic structures (Chand et al., 2017). Based on our findings, the FIC (particularly the right FIC) appears to play a significant role in connectivity following pediatric concussion.

The hyperconnectivity between the DMN and SN found in our concussion group has been echoed in adult studies in the acute (within 7 days of injury) and chronic (>6 months) phase of concussion. Sours et al. (2015) found increased connectivity between the PCC and both the dACC and the insula in concussed adults>6 months following concussion. Liu et al. (2020) found increased FC between the mPFC and both the dACC and FIC in concussed adults within 7 days of injury and these increases were positively correlated with a cognitive measure of executive function. Liu et al. (2020) hypothesized that this initial increase could be compensatory, acting as a mechanism to meet cognitive demands and balance the dysfunction of the other networks. Sours et al. (2015) echoed this sentiment in the chronic phase, suggesting the hyperconnectivity may be due to an increased need for SN modulation of residual dysregulation of the other functional networks following concussion, such as the DMN and CEN. This may suggest that, in the chronic phase, SN compensation may contribute to increased instances of cognitive fatigue and associated pathologies following a TBI (Ponsford, 2013), suggesting that a once compensatory mechanism may become maladaptive. It is also possible these differences in connectivity were present pre-injury due to pre-existing characteristics, however, the concussion and OI groups did not significantly differ in clinical history and important prognostic variables were added as covariates in the analyses.

Our finding of hyperconnectivity between the SN and CEN has also been found in adults 1 month after mTBI. van der Horn et al. (2016) found that connectivity between regions in the right CEN and SN was significantly higher in participants experiencing post-concussive complaints compared to those no longer experiencing complaints. In addition, right CEN-SN connectivity was positively correlated with depression symptoms (van der Horn et al., 2016a,b). In more severe TBI, Ham et al. (2014) found increased activity of the FIC in those who made errors on a task of self-awareness, suggesting this increased connectivity may have adverse effects on cognitive control. In our sample, further investigation is warranted into the associations between sN-CEN connectivity and cognitive complaints.

4.4. Potential influence of differential duration of recovery

Based on our findings and supporting research (Iverson et al., 2017; Ledoux et al., 2019; van der Horn et al., 2017a,b; Zemek et al., 2016), the differential duration of recovery of our concussed sample may be preventing us from identifying group differences in comparison to the OI group. Our finding that 70 % of the concussion group had recovered by 4 weeks suggests future analyses should compare connectivity within those still symptomatic versus those asymptomatic. However, it is important to note that imaging differences are still found in asymptomatic patients. Despite our sample being almost 70 % recovered, significant FC differences were still found in the concussion group compared to the OI group suggesting network compensation and dysfunction may still be in effect. Further, concussion studies have found connectivity differences between asymptomatic concussion participants and healthy controls using rs-fMRI (Johnson et al., 2012; Newsome et al., 2016a; Orr et al., 2016) and have noted differences in cerebral blood flow (CBF) using arterial spin labelling (Barlow et al., 2017; Brooks et al., 2019; Hamer et al., 2020).

Due to the neurovascular coupling and uncoupling of the BOLD signal and CBF following a concussion, similarities in recovery patterns between FC and CBF research may provide further evidence for the potential network connectivity recovery patterns observed in our study sample. Similar to our findings of CEN hyperconnectivity, children and adolescents still experiencing symptoms at approximately 40 days post-injury demonstrated higher CBF in the inferior frontal gyrus compared to healthy controls (Barlow et al., 2017). In adults at 1 month post-injury, perfusion in the frontal lobes was positively correlated with symptom severity (Lin et al., 2016). Further, Sours et al. (2015) found that participants experiencing chronic symptoms at 6 months post-injury had increased CEN perfusion at 1 week, 1 month and 6 months compared to concussed individuals without symptoms suggesting a potential biomarker for long-term symptomology. Similar to our finding of SN hyperconnectivity, Stephens et al., (2018) showed that concussed adolescents had higher regional perfusion within the SN in comparison to controls at 2 weeks post-injury (in the left FIC and dACC) and at 6 weeks post-injury (in the left dACC). In addition, those still experiencing symptoms at the 6-week follow-up had higher regional CBF in the left dACC than both controls and asymptomatic concussed participants (Stephens et al., 2018a,b). Further investigation of CBF recovery patterns of our sample may strengthen our FC findings.

4.5. Novelty of connectivity differences in pediatric concussion

Although the proposed hypotheses were only partially confirmed, this study discovered novel findings in the realm of pediatric concussion FC research. To our knowledge, no studies to date have investigated within-network FC in the SN in the pediatric concussion population and

our secondary analyses found increased connectivity within the SN in the concussion group compared to the OI group. Although studied in adults with concussion (Iraji et al., 2015; Liu et al., 2020; Sours et al., 2015; van der Horn et al., 2016a,b), between-network connectivity of the DMN and SN, as well as the CEN and SN, has not previously been investigated in a pediatric sample. Our secondary analyses found significantly increased connectivity between the SN and DMN, and SN and CEN, in the concussion group compared to the OI group.

FC within the pediatric brain has been shown to significantly differ from that of the adult brain. A longitudinal study of FC within and between the DMN and CEN found that children at the age of 10 and again at the age of 13 demonstrated similar connectivity patterns (increased within-network and reduced between-network connectivity) when compared to adult participants from a previous study (Sherman et al., 2014). Another study reported significantly weaker connections within the DMN in children aged 7–9 potentially identifying a time period of significant functional maturation (Fair et al., 2008; Sherman et al., 2014). The biggest FC shift identified in children aged 10 and over appears to be the weakening of DMN and CEN "hub" region interconnectivity and strengthening of their respective intraconnectivity (Sherman et al., 2014). These findings were supported with resting-state FC data of healthy children (mean age of 12.28) showing strong within-network DMN connectivity and DMN-CEN anticorrelation as well as increasing variability in FC with age (Marusak et al., 2017). Despite the variability brought on by these changes throughout adolescence, the basic functional connectome of the default mode hub regions is established and comparable to adults but differs in regards to strength of connection (Sherman et al., 2014). This variability in connection strength throughout development may help to explain the increased variability in FC response following a concussion and points to the importance of considering age in concussion research.

This study has numerous strengths. First, the timing of the MRI scan (4 weeks post-injury) was a crucial time for identifying and measuring objective recovery since children and adolescents (with the exception of adolescent females) typically recover within the first month (Ledoux et al., 2019). It has also been suggested that imaging biomarkers within the first month of recovery may be the most beneficial for predicting concussion outcomes (Puig et al., 2020). Second, in comparison to many pediatric and adult concussion studies with neuroimaging, our sample size of concussed (n = 55) and OI (n = 27) participants was relatively large. In addition, the inclusion of an age and sex-matched orthopedically injured group recruited in the same ED controlled for enrolment in an ED setting and allowed us to make conclusions regarding the influence of being in an injured state (e.g., experiencing pain or initial pause in regular activities). Third, this study provides objective evidence of altered brain network connectivity following a pediatric concussion that can augment and bring additional information to the subjective clinical recovery measurements.

Despite its strengths, this study also has its limitations. For instance, our ROIs were not subject-specific. Less connectivity is observed when using standardized ROIs rather than subject-specific ROIs due to the intersubject variability of brain region locations. This could have contributed to missing optimum nodes in some participants. In addition, this can cause problems with misrepresenting networks, where correlations cannot definitively be said to be within that network for every person in the analysis (Sohn et al., 2015). However, another study did not find differences in results generated from standardized and participant-specific regions (Marrelec and Fransson, 2011). Our initial analyses included only structurally defined regions of interest. In our secondary analyses we attempted to compensate for individual variation with spherically defined ROIs by increasing the size without adding unnecessary voxels thereby decreasing the true representation of the regions. Based on other concussion studies in the literature, 8 mm was used (Iyer et al., 2019a,c; Sridharan et al., 2008). In addition, the use of a task-based fMRI protocol paired with a resting-state protocol would have been preferable to fully capture clusters of significant connectivity between networks, especially between the CEN and SN. However, many studies in the field of concussion (Bharath et al., 2015; D'Souza et al., 2020; Liu et al., 2020; Shafi et al., 2020), development and aging (Chand et al., 2017; Li and Tian, 2014; Sherman et al., 2014; Vincent et al., 2008), neural mechanisms (Sridharan et al., 2008), and various sleep (Wei et al., 2020) and mental health disorders (Geng et al., 2016; Gong et al., 2019) use rs-fMRI to evaluate connectivity between networks most active during external cognitive control. In addition, rs-fMRI is reliable in a pediatric population since it removes the burden of having to perform a task while in the MRI machine (especially following concussion) and prevents added micromovements from producing artifacts in the images (Roland et al., 2017). Our sample might represent the more severe cases of concussion since recruitment took place in the ED rather than in a community-based setting. Further, inclusion of an uninjured control group in addition to the OI group would have validated our findings outside of the clinical population. Although age was covaried, it can have significant effects on network connectivity and recovery. Additional grouping of smaller age ranges may help identify age-specific results. Finally, since no biomarker currently exists to definitively diagnose a concussion, we cannot be certain all participants had a concussion. However, the adapted version of the CDC tiered framework (Peterson et al., 2021) used to screen eligible participants has robust diagnostic capabilities to increase the chances of enrolling patients with a true concussion.

To our knowledge, this is the first study to investigate FC within and between all 3 networks during a resting-state in a pediatric population. Our findings suggest persisting connectivity differences 1 month following injury that could be both compensatory and maladaptive. Within and between-network connectivity of the SN may be increased to manage some of the dysfunction between the CEN and DMN. Decreased connectivity between the CEN and DMN may be associated with improved recovery outcomes. Future analyses are needed to assess these network connectivity characteristics based on recovery status and their associations with specific pre-existing diagnoses and cognition. Overall, our findings provide evidence for adaptive network mechanisms that may provide insight into recovery trajectories and help to inform best practice for timing of treatment interventions within the first month following a concussion.

CRediT authorship contribution statement

Katherine Healey: Conceptualization, Investigation, Methodology, Writing – original draft. **Zhuo Fang:** Methodology, Writing – review & editing. **Andra Smith:** Conceptualization, Writing – review & editing. **Roger Zemek:** Conceptualization, Writing – review & editing. **Andrée-Anne Ledoux:** Conceptualization, Investigation, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgements

This work was supported by the IMPACT OSSU Award; the PSI Foundation; and graduate student funding by the Canadian Institutes of Health Research (CIHR).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103211.

References

Abbas, K., Shenk, T.E., Poole, V.N., Breedlove, E.L., Leverenz, L.J., Nauman, E.A., Talavage, T.M., Robinson, M.E., 2015. Alteration of default mode network in high school football athletes due to repetitive subconcussive mild traumatic brain injury: a resting-state functional magnetic resonance imaging study. Brain Connect. 5, 91–101. https://doi.org/10.1089/brain.2014.0279.

Andrews-Hanna, J.R., Smallwood, J., Spreng, R.N., 2014. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Ann. N. Y. Acad. Sci. 1316, 29–52. https://doi.org/10.1111/nyas.12360.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Ayr, L.K., Yeates, K.O., Gerry Taylor, H., Browne, M., 2009. Dimensions of postconcussive symptoms in children with mild traumatic brain injuries. https://doi.org/10.1017/S1355617708090188.

Barlow, K.M., Marcil, L.D., Dewey, D., Carlson, H.L., Macmaster, F.P., Brooks, B.L., Lebel, R.M., 2017. Cerebral perfusion changes in post-concussion syndrome: a prospective controlled cohort study. J. Neurotrauma 34, 996–1004. https://doi.org/10.1089/neu.2016.4634.

Bharath, R.D., Munivenkatappa, A., Gohel, S., Panda, R., Saini, J., Rajeswaran, J., Shukla, D., Bhagavatula, I.D., Biswal, B.B., 2015. Recovery of resting brain connectivity ensuing mild traumatic brain injury. Front. Hum. Neurosci. 9, 513. https://doi.org/10.3389/fnhum.2015.00513.

Bonnelle, V., Ham, T.E., Leech, R., Kinnunen, K.M., Mehta, M.A., Greenwood, R.J., Sharp, D.J., 2012. Salience network integrity predicts default mode network function after traumatic brain injury. Proc. Natl. Acad. Sci. U. S. A. 109, 4690–4695. https://doi.org/10.1073/pnas.1113455109.

Borich, M., Babul, A.-N., Yuan, P.H., Boyd, L., Virji-Babul, N., 2015. Alterations in resting-state brain networks in concussed adolescent athletes. J. Neurotrauma 32, 265–271. https://doi.org/10.1089/neu.2013.3269.

Broadway, J.M., Rieger, R.E., Campbell, R.A., Quinn, D.K., Mayer, A.R., Yeo, R.A., Wilson, J.K., Gill, D., Fratzke, V., Cavanagh, J.F., 2019. Executive function predictors of delayed memory deficits after mild traumatic brain injury. Cortex 120, 240–248. https://doi.org/10.1016/j.cortex.2019.06.011.

Broglio, S.P., Kontos, A.P., Levin, H., Schneider, K., Wilde, E.A., Cantu, R.C., Feddermann-Demont, N., Fuller, G.W., Gagnon, I., Gioia, G.A., Giza, C., Griesbach, G.S., Leddy, J.J., Lipton, M.L., Mayer, A.R., McAllister, T.W., McCrea, M., McKenzie, L.B., Putukian, M., Signoretti, S., Suskauer, S.J., Tamburro, R., Turner, M., Yeates, K.O., Zemek, R., Ala', I.S., Esterlitz, J., Gay, K., Bellgowan, P.S.F., Joseph, K., 2018. National institute of neurological disorders and stroke and department of defense sport-related concussion common data elements version 1.0 recommendations. J. Neurotrauma 35, 2776–2783. https://doi.org/10.1089/neu.2018.5643.

Brooks, B.L., Low, T.A., Plourde, V., Virani, S., Jadavji, Z., MacMaster, F.P., Barlow, K.M., Lebel, R.M., Yeates, K.O., 2019. Cerebral blood flow in children and adolescents several years after concussion. Brain Inj. 33, 233–241. https://doi.org/10.1080/02699052.2018.1540798.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. https://doi.org/10.1196/annals.1440.011.

Cairncross, M., Brooks, B.L., Virani, S., Silverberg, N.D., 2021. Fear avoidance behavior in youth with poor recovery from concussion: measurement properties and correlates of a new scale. Child Neuropsychol. 1–11 https://doi.org/10.1080/09297049.2021.1908533.

Chand, G.B., Wu, J., Hajjar, I., Qiu, D., 2017. Interactions of the salience network and its subsystems with the default-mode and the central-executive networks in normal aging and mild cognitive impairment. Brain Connect. 7, 401–412. https://doi.org/10.1089/brain.2017.0509.

Chao-Gan, Y., Yu-Feng, Z., 2010. DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. Front. Syst. Neurosci. 4 https://doi.org/10.3389/fnsys.2010.00013.

D'Souza, M.M., Kumar, M., Choudhary, A., Kaur, P., Kumar, P., Rana, P., Trivedi, R., Sekhri, T., Singh, A.K., 2020. Alterations of connectivity patterns in functional brain networks in patients with mild traumatic brain injury: a longitudinal resting-state functional magnetic resonance imaging study. Neuroradiol. J. 33, 186–197. https://doi.org/10.1177/1971400920901706.

Davey, C.G., Pujol, J., Harrison, B.J., 2016. Mapping the self in the brain's default mode network. Neuroimage 132, 390–397. https://doi.org/10.1016/j.neuroimage.2016.02.022.

Doroszkiewicz, C., Gold, D., Green, R., Tartaglia, M.C., Ma, J., Tator, C.H., 2021. Anxiety, depression, and quality of life: a long-term follow-up study of patients with persisting concussion symptoms. J. Neurotrauma 38, 493–505. https://doi.org/10.1089/neu.2020.7313.

Fair, D.A., Cohen, A.L., Dosenbach, N.U.F., Church, J.A., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L., 2008. The maturing architecture of the brain's default network. Proc. Natl. Acad. Sci. U. S. A. 105, 4028–4032. https://doi.org/10.1073/pnas.0800376105.

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb. Cortex 26, 3508–3526. https://doi.org/10.1093/cercor/bhw157.

Geng, H., Li, Xuebing, Chen, J., Li, Xinying, Gu, R., 2016. Decreased intra- and inter-salience network functional connectivity is related to trait anxiety in adolescents. Front. Behav. Neurosci. 9, 350. https://doi.org/10.3389/fnbeh.2015.00350.

Giza, C.C., Hovda, D.A., 2001. The neurometabolic cascade of concussion. J. Athl. Train. 36, 228–235.

Gong, J.Y., Chen, G., Jia, Y., Zhong, S., Zhao, L., Luo, X., Qiu, S., Lai, S., Qi, Z., Huang, L., Wang, Y., 2019. Disrupted functional connectivity within the default mode network and salience network in unmedicated bipolar II disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 88, 11–18. https://doi.org/10.1016/j.pnpbp.2018.06.012.

Goulden, N., Khusnulina, A., Davis, N.J., Bracewell, R.M., Bokde, A.L., McNulty, J.P., Mullins, P.G., 2014. The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM. Neuroimage 99, 180–190. https://doi.org/10.1016/j.neuroimage.2014.05.052.

Ham, T.E., Bonnelle, V., Hellyer, P., Jilka, S., Robertson, I.H., Leech, R., Sharp, D.J., 2014. The neural basis of impaired self-awareness after traumatic brain injury. Brain 137, 586–597. https://doi.org/10.1093/brain/awt350.

Hamer, J., Churchill, N.W., Hutchison, M.G., Graham, S.J., Schweizer, T.A., 2020. Sex differences in cerebral blood flow associated with a history of concussion. J. Neurotrauma 37, 1197–1203. https://doi.org/10.1089/neu.2019.6800.

Hilger, K., Fiebach, C.J., 2019. ADHD symptoms are associated with the modular structure of intrinsic brain networks in a representative sample of healthy adults. Netw. Neurosci. 3, 567–588. https://doi.org/10.1162/netn_a_00083.

Hillary, F.G., Rajtmajer, S.M., Roman, C.A., Medaglia, J.D., Slocomb-Dluzen, J.E., Calhoun, V.D., Good, D.C., Wylie, G.R., 2014. The rich get richer: brain injury elicits hyperconnectivity in core subnetworks. PLoS One 9, 104021. https://doi.org/10.1371/journal.pone.0104021.

Howell, D., Osternig, L., Van Donkelaar, P., Mayr, U., Chou, L.-S., 2013. Effects of concussion on attention and executive function in adolescents. Med. Sci. Sport. Exerc. 45, 1030–1037. https://doi.org/10.1249/MSS.0b013e3182814595.

Huang, Z., Tarnal, V., Vlisides, P.E., Janke, E.L., McKinney, A.M., Picton, P., Mashour, G. A., Hudetz, A.G., 2021. Anterior insula regulates brain network transitions that gate conscious access. Cell Rep. 35, 109081 https://doi.org/10.1016/j.celrep.2021.109081.

Iaccarino, M.A., Fitzgerald, M., Pulli, A., Yvonne Woodworth, K., Spencer, T.J., Zafonte, R., Biederman, J., 2018. Sport concussion and attention deficit hyperactivity disorder in student athletes: a cohort study. Neurol. Clin. Pract. 8, 403–411. https://doi.org/10.1212/CPJ.0000000000000525.

Iraji, A., Benson, R.R., Welch, R.D., O'Neil, B.J., Woodard, J.L., Ayaz, S.I., Kulek, A., Mika, V., Medado, P., Soltanian-Zadeh, H., Liu, T., Haacke, E.M., Kou, Z., 2015. Resting state functional connectivity in mild traumatic brain injury at the acute stage: independent component and seed-based analyses. J. Neurotrauma 32, 1031–1045. https://doi.org/10.1089/neu.2014.3610.

Iverson, G.L., Gardner, A.J., Terry, D.P., Ponsford, J.L., Sills, A.K., Broshek, D.K., Solomon, G.S., 2017. Predictors of clinical recovery from concussion: a systematic review. Br. J. Sports Med. https://doi.org/10.1136/bjsports-2017-097729.

Iyer, Kartik K., Barlow, K.M., Brooks, B., Ofoghi, Z., Zalesky, A., Cocchi, L., 2019a. Relating brain connectivity with persistent symptoms in pediatric concussion. Ann. Clin. Transl. Neurol. 6, 954–961. https://doi.org/10.1002/acn3.764.

Iyer, Kartik K., Zalesky, A., Barlow, K.M., Cocchi, L., 2019c. Default mode network anatomy and function is linked to pediatric concussion recovery. Ann. Clin. Transl. Neurol. 6, 2544–2554. https://doi.org/10.1002/acn3.50951.

Iyer, K.K., Zalesky, A., Cocchi, L., Barlow, K.M., 2020. Neural correlates of sleep recovery following melatonin treatment for pediatric concussion: a randomized controlled trial. J. Neurotrauma 37, 2647–2655. https://doi.org/10.1089/neu.2020.7200.

Jilka, S.R., Scott, G., Ham, T., Pickering, A., Bonnelle, V., Braga, R.M., Leech, R., Sharp, D.J., 2014. Damage to the salience network and interactions with the default mode network. J. Neurosci. 34, 10798–10807. https://doi.org/10.1523/JNEUROSCI.0518-14.2014.

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., Slobounov, S., 2012. Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. Neuroimage 59, 511–518. https://doi.org/10.1016/j.neuroimage.2011.07.081.

Ledoux, A.-A., Barrowman, N.J., Boutis, K., Davis, A., Reid, S., Sangha, G., Farion, K.J., Belanger, K., Tremblay, M.S., Yeates, K.O., DeMatteo, C., Reed, N., Zemek, R., 2019. Multicentre, randomised clinical trial of paediatric concussion assessment of rest and exertion (PedCARE): a study to determine when to resume physical activities following concussion in children. Br. J. Sports Med. 53, 195. https://doi.org/10.1136/bjsports-2017-097981.

Ledoux, A.-A., Tang, K., Yeates, K.O., Pusic, M.V., Boutis, K., Craig, W.R., Gravel, J., Freedman, S.B., Gagnon, I., Gioia, G.A., Osmond, M.H., Zemek, R.L., 2019. Natural progression of symptom change and recovery from concussion in a pediatric population. JAMA Pediatr. 173, e183820 https://doi.org/10.1001/jamapediatrics.2018.3820.

Ledoux, A.-A., Barrowman, N., Bijelić, V., Borghese, M.M., Davis, A., Reid, S., Sangha, G., Yeates, K.O., Tremblay, M.S., Mcgahern, C., Belanger, K., Barnes, J.D., Farion, K.J., Dematteo, C.A., Reed, N., Zemek, R., 2021. Is early activity resumption after paediatric concussion safe and does it reduce symptom burden at 2 weeks post injury? The Pediatric Concussion Assessment of Rest and Exertion (PedCARE) multicentre randomised clinical trial. Br. J. Sport. Med. 1–8. https://doi.org/10.1136/bjsports-2021-105030.

Li, C., Tian, L., 2014. Association between resting-state coactivation in the parieto-frontal network and intelligence during late childhood and adolescence. Am. J. Neuroradiol. 35, 1150–1156. https://doi.org/10.3174/ajnr.A3850.

Lieberman, M.D., Cunningham, W.A., 2009. Type I and type II error concerns in fMRI research: re-balancing the scale. Soc. Cogn. Affect. Neurosci. 4, 423–428. https://doi.org/10.1093/scan/nsp052.
Lin, C.M., Tseng, Y.C., Hsu, H.L., Chen, C.J., Chen, D.Y.T., Yan, F.X., Chiu, W.T., 2016. Arterial spin labeling perfusion study in the patients with subacute mild traumatic brain injury. PLoS One 11. https://doi.org/10.1371/journal.pone.0149109.
Liu, Y., Wu, W., Chen, X., Wu, M., Hu, G., Zhou, G., Wang, Z., Chen, R., 2020. Aberrant correlation between the default mode and salience networks in mild traumatic brain injury. Front. Comput. Neurosci. 14, 1–11. https://doi.org/10.3389/fncom.2020.00068.
Losoi, H., Silverberg, N.D., Wäljas, M., Turunen, S., Rosti-Otajärvi, E., Helminen, M., Luoto, T.M., Julkunen, J., Öhman, J., Iverson, G.L., 2016. Recovery from mild traumatic brain injury in previously healthy adults. J. Neurotrauma 33, 766–776. https://doi.org/10.1089/neu.2015.4070.
Madhavan, R., Joel, S.E., Mullick, R., Cogsil, T., Niogi, S.N., Tsiouris, A.J., Mukherjee, P., Masdeu, J.C., Marinelli, L., Shetty, T., 2019. Longitudinal resting state functional connectivity predicts clinical outcome in mild traumatic brain injury. J. Neurotrauma 36, 650–660. https://doi.org/10.1089/neu.2018.5739.
Marrelec, G., Fransson, P., 2011. Assessing the influence of different ROI selection strategies on functional connectivity analyses of fmri data acquired during steady-state conditions. PLoS One 6, 14788. https://doi.org/10.1371/journal.pone.0014788.
Marusak, H.A., Calhoun, V.D., Brown, S., Crespo, L.M., Sala-Hamrick, K., Gotlib, I.H., Thomason, M.E., 2017. Dynamic functional connectivity of neurocognitive networks in children. Hum. Brain Mapp. 38, 97–108. https://doi.org/10.1002/hbm.23346.
Mathias, J.L., Dennington, V., Bowden, S.C., Bigler, E.D., 2013. Community versus orthopaedic controls in traumatic brain injury research: how comparable are they? Brain Inj. 27, 887–895. https://doi.org/10.3109/02699052.2013.793398.
Mayer, A.R., Mannell, M.V., Ling, J., Gasparovic, C., Yeo, R.A., 2011. Functional connectivity in mild traumatic brain injury. Hum. Brain Mapp. 32, 1825–1835. https://doi.org/10.1002/hbm.21151.
Newsome, Mary R., Li, X., Lin, X., Wilde, E.A., Ott, S., Biekman, B., Hunter, J.V., Dash, P. K., Taylor, B.A., Levin, H.S., 2016a. Functional connectivity is altered in concussed adolescent athletes despite medical clearance to return to play: a preliminary report. Front. Neurol. 7, 1–9. https://doi.org/10.3389/fneur.2016.00116.
Orr, C.A., Albaugh, M.D., Watts, R., Garavan, H., Andrews, T., Nickerson, J.P., Gonyea, J., Hipko, S., Zweber, C., Logan, K., Hudziak, J.J., 2016. Neuroimaging biomarkers of a history of concussion observed in asymptomatic young athletes. J. Neurotrauma 33, 803–810. https://doi.org/10.1089/neu.2014.3721.
Peterson, A., Gabella, B.A., Johnson, J., Hume, B., Liu, A., Costich, J.F., Hathaway, J., Slavova, S., Johnson, R., Breiding, M., 2021. Multisite medical record review of emergency department visits for unspecified injury of head following the ICD-10-CM coding transition. Inj. Prev. 27, i13–i18. https://doi.org/10.1136/injuryprev-2019-043517.
Plourde, V., Rohr, C.S., Virani, S., Bray, S., Yeates, K.O., Brooks, B.L., 2020. Default mode network functional connectivity after multiple concussions in children and adolescents. Arch. Clin. Neuropsychol. 35, 302–311. https://doi.org/10.1093/arclin/acz073.
Poldrack, R.A., Fletcher, P.C., Henson, R.N., Worsley, K.J., Brett, M., Nichols, T.E., 2008. Guidelines for reporting an fMRI study. Neuroimage. https://doi.org/10.1016/j.neuroimage.2007.11.048.
Ponsford, J., 2013. Factors contributing to outcome following traumatic brain injury. NeuroRehabilitation 32, 803–815. https://doi.org/10.3233/NRE-130904.
Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI NIH Public Access. Neuroimage 84. https://doi.org/10.1016/j.neuroimage.2013.08.048.
Puig, J., Ellis, M.J., Kornelsen, J., Figley, T.D., Figley, C.R., Daunis-I-Estadella, P., Mutch, W.A.C., Essig, M., 2020. Magnetic resonance imaging biomarkers of brain connectivity in predicting outcome after mild traumatic brain injury: a systematic review. J. Neurotrauma. https://doi.org/10.1089/neu.2019.6623.
Raemaekers, M., Schellekens, W., Petridou, N., Ramsey, N.F., 2018. Knowing left from right: asymmetric functional connectivity during resting state. Brain Struct. Funct. 223, 1909–1922. https://doi.org/10.1007/s00429-017-1604-y.
Roland, J.L., Griffin, N., Hacker, C.D., Vellimana, A.K., Akbari, S.H., Shimony, J.S., Smyth, M.D., Leuthardt, E.C., Limbrick, D.D., 2017. Resting-state functional magnetic resonance imaging for surgical planning in pediatric patients: a preliminary experience. J. Neurosurg. Pediatr. 20, 583–590. https://doi.org/10.3171/2017.6.PEDS1711.
Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. Behav. Neurol. 12, 191–200.
Seeley, William W, 2019. The salience network: a neural system for perceiving and responding to homeostatic demands. J. Neurosci. 39, 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007.
Shafi, R., Crawley, A.P., Tartaglia, M.C., Tator, C.H., Green, R.E., Mikulis, D.J., Colantonio, A., 2020. Sex-specific differences in resting-state functional connectivity of large-scale networks in postconcussion syndrome. Sci. Rep. 10 https://doi.org/10.1038/s41598-020-77137-4.
Sharp, D.J., Beckmann, C.F., Greenwood, R., Kinnunen, K.M., Bonnelle, V., De Boissezon, X., Powell, J.H., Counsell, S.J., Patel, M.C., Leech, R., 2011. Default mode network functional and structural connectivity after traumatic brain injury. Brain 134, 2233–2247. https://doi.org/10.1093/brain/awr175.
Sherman, L.E., Rudie, J.D., Pfeifer, J.H., Masten, C.L., McNealy, K., Dapretto, M., 2014. Development of the default mode and central executive networks across early adolescence: a longitudinal study. Dev. Cogn. Neurosci. 10, 148–159. https://doi.org/10.1016/j.dcn.2014.08.002.
Sohn, W.S., Yoo, K., Lee, Y.-B., Seo, S.W., Na, D.L., Jeong, Y., 2015. Influence of ROI selection on resting state functional connectivity: an individualized approach for resting state fMRI analysis. Front. Neurosci. 9, 1–10. https://doi.org/10.3389/fnins.2015.00280.
Sours, C., Zhuo, J., Roys, S., Shanmuganathan, K., Gullapalli, R.P., 2015. Disruptions in resting state functional connectivity and cerebral blood flow in mild traumatic brain injury patients. PLoS One 10. https://doi.org/10.1371/journal.pone.0134019.
Sours, C., Kinnison, J., Padmala, S., Gullapalli, R.P., Pessoa, L., 2018. Altered segregation between task-positive and task-negative regions in mild traumatic brain injury. Brain Imaging Behav. 12, 697–709. https://doi.org/10.1007/s11682-017-9724-9.
Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc. Natl. Acad. Sci. U. S. A. 105, 12569–12574. https://doi.org/10.1073/pnas.0800005105.
Stancin, T., Taylor, H.G., Thompson, G.H., Wade, S., Drotar, D., Yeates, K.O., 1998. Acute psychosocial impact of pediatric orthopedic trauma with and without accompanying brain injuries. J. Trauma 45, 1031–1038. https://doi.org/10.1097/00005373-199812000-00010.
Stephens, J.A., Liu, P., Lu, H., Suskauer, S.J., 2018a. Cerebral blood flow after mild traumatic brain injury: associations between symptoms and post-injury perfusion. J. Neurotrauma 35, 241–248. https://doi.org/10.1089/neu.2017.5237.
Stephens, J.A., Salorio, C.F., Barber, A.D., Risen, S.R., Mostofsky, S.H., Suskauer, S.J., 2018b. Preliminary findings of altered functional connectivity of the default mode network linked to functional outcomes one year after pediatric traumatic brain injury. Dev. Neurorehabil. 21, 423–430. https://doi.org/10.1080/17518423.2017.1338777.
Sullivan, D.R., Hayes, J.P., Lafleche, G., Salat, D.H., Verfaellie, M., 2018. Functional brain alterations associated with cognitive control in blast-related mild traumatic brain injury. J. Int. Neuropsychol. Soc. 24, 662–672. https://doi.org/10.1017/S1355617718000279.
Taubman, B., McHugh, J., Rosen, F., Elci, O.U., 2016. Repeat concussion and recovery time in a primary care pediatric office. J. Child Neurol. 31, 1607–1610. https://doi.org/10.1177/0883073816667194.
van der Horn, H.J., Liemburg, E.J., Aleman, A., Spikman, J.M., van der Naalt, J., 2016a. Brain networks subserving emotion regulation and adaptation after mild traumatic brain injury. J. Neurotrauma 33, 1–9. https://doi.org/10.1089/neu.2015.3905.
van der Horn, H.J., Liemburg, E.J., Scheenen, M.E., de Koning, M.E., Marsman, J.B.C., Spikman, J.M., van der Naalt, J., 2016b. Brain network dysregulation, emotion, and complaints after mild traumatic brain injury. Hum. Brain Mapp. 37, 1645–1654. https://doi.org/10.1002/hbm.23126.
van der Horn, H.J., Scheenen, M.E., de Koning, M.E., Liemburg, E.J., Spikman, J.M., van der Naalt, J., 2017. The default mode network as a biomarker of persistent complaints after mild traumatic brain injury: a longitudinal functional magnetic resonance imaging study. J. Neurotrauma 34, 3262–3269. https://doi.org/10.1089/neu.2017.5185.
Van Der Horn, H.J., Liemburg, E.J., Scheenen, M.E., De Koning, M.E., Spikman, J.M., Der Van Naalt, J., 2017. Graph analysis of functional brain networks in patients with mild traumatic brain injury. PLoS One 12. https://doi.org/10.1371/journal.pone.0171031.
Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J. Neurophysiol. 100, 3328–3342. https://doi.org/10.1152/jn.90355.2008.
Wei, Y., Leerssen, J., Wassing, R., Stoffers, D., Perrier, J., Van Someren, E.J.W., 2020. Reduced dynamic functional connectivity between salience and executive brain networks in insomnia disorder. J. Sleep Res. 29 https://doi.org/10.1111/jsr.12953.
Wiberg, A., Ng, M., Omran, Y. Al, Alfaro-Almagro, F., McCarthy, P., Marchini, J., Bennett, D.L., Smith, S., Douaud, G., Furniss, D., 2019. Handedness, language areas and neuropsychiatric diseases: Insights from brain imaging and genetics. Brain 142, 2938–2947. https://doi.org/10.1093/brain/awz257.
Wilde, E.A., Ware, A.L., Li, X., Wu, T.C., McCauley, S.R., Barnes, A., Newsome, M.R., Biekman, B.D., Hunter, J.V., Chu, Z.D., Levin, H.S., 2019. Orthopedic injured versus uninjured comparison groups for neuroimaging research in mild traumatic brain injury. J. Neurotrauma 36, 239–249. https://doi.org/10.1089/NEU.2017.5513.
Yan, C.G., Wang, X.D., Zuo, X.N., Zang, Y.F., 2016. DPABI: data processing & analysis for (resting-state) brain imaging. Neuroinformatics 14, 339–351.
Yan, C.-G., Wang, X.-D., Zuo, X.-N., Zang, Y.-F., 2021. DPABI: data processing & analysis for (resting-state) brain imaging. Neuroinformatics. https://doi.org/10.1007/s12021-016-9299-4.
Zemek, R., Barrowman, N., Freedman, S.B., Gravel, J., Gagnon, I., McGahern, C., Aglipay, M., Sangha, G., Boutis, K., Beer, D., Craig, W., Burns, E., Farion, K.J., Mikrogianakis, A., Barlow, K., Dubrovsky, A.S., Meeuwisse, W., Gioia, G., Meehan, W.P., Beauchamp, M.H., Kamil, Y., Grool, A.M., Hoshizaki, B., Anderson, P., Brooks, B.L., Yeates, K.O., Vassilyadi, M., Klassen, T., Keightley, M., Richer, L., DeMatteo, C., Osmond, M.H., 2016. Clinical risk score for persistent postconcussion symptoms among children with acute concussion in the ED. JAMA 315, 1014. https://doi.org/10.1001/jama.2016.1203.
Zemek, R.L., Grool, A.M., Rodriguez Duque, D., DeMatteo, C., Rothman, L., Benchimol, E.I., Guttmann, A., Macpherson, A.K., 2017. Annual and seasonal trends in ambulatory visits for pediatric concussion in ontario between 2003 and 2013. J. Pediatr. 181, 222–228. https://doi.org/10.1016/j.jpeds.2016.10.067.
Zhu, D.C., Covassin, T., Nogle, S., Doyle, S., Russell, D., Pearson, R.L., Monroe, J., Liszewski, C.M., DeMarco, J.K., 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. https://doi.org/10.1089/neu.2014.3413.