

Investigating the Associations between Brain Network Functional Connectivity and
Health-Related Quality of Life following a Pediatric Concussion

by

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Abstract

Concussions negatively affect the health-related quality of life (HRQoL) of children and youth for months post-injury. In addition, connectivity 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 and none have assessed its associations with HRQoL. The present study explored whether within and between-network functional connectivity (FC) differs between a pediatric concussion and orthopedic injury (OI) group aged 10-18. In the concussion group, associations between FC of these networks and HRQoL 4 weeks post-injury were also assessed. Participants underwent a resting-state functional magnetic resonance imaging (rs-fMRI) scan and HRQoL was measured with the Pediatric Quality of Life Inventory (PedsQL) at 4 weeks post-injury. One-way ANCOVA analyses were conducted between groups with the seed-based FC of the 3 networks. Multivariate linear regressions were conducted to assess the association between connectivity of the 3 networks and HRQoL. A total of 55/72 concussion and 27/30 OI participants were included in the analyses. Increased within-network FC of the CEN and SN, increased between-network FC of the DMN-SN and CEN-SN, and decreased between-network FC of the DMN-CEN was found in the concussion group when compared to the OI group. No significant associations were found between HRQoL and FC within and between the DMN, CEN and SN 4 weeks after concussion. When compared to OI, differential connectivity patterns are present following a pediatric concussion at 4-weeks post-injury, however, these network differences are not associated with HRQoL.

Keywords: Pediatric concussion, resting-state functional connectivity, health-related quality of life, default mode network, salience network, central executive network

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Table of Contents

Abstract ii

Acknowledgements iii

List of Abbreviations vi

List of Tables viii

List of Figures ix

List of Appendices x

Investigating the Associations between Brain Network Functional Connectivity and Health-Related Quality of Life following a Pediatric Concussion 1

 Measuring Connectivity in Concussion 3

BOLD signal 3

 Brain Networks Associated with Concussion 5

Default mode network 5

 Default mode network in youth with concussion. 6

Central executive network 8

 Central executive network in concussion. 9

Saliency network 9

How the three networks interact 10

 How the three networks interact in concussion. 11

 Health-related Quality of Life in Pediatric Concussion 11

Health-related quality of life and concussion 11

Health-related quality of life and network connectivity 12

 Study Objectives and Hypothesis 12

Methods 14

 Study Design and Setting 14

 Participants 14

Inclusion - Exclusion Criteria 14

 Concussion participants 15

 Orthopedic injury participants 16

Incentives 16

 Measures 17

Clinical data 17

 Health-related Quality of Life. 17

 Degree of Symptoms. 17

 Diagnostic History 18

Magnetic resonance imaging data 18

 Procedure 19

 Data analysis 20

MRI data analysis 20

 Initial T1 motion mitigation. 20

 Preprocessing. 21

 Processing. 22

 Statistical Analysis 24

<i>Assessing the Importance of Physical Activity Levels in Concussion Subgroups</i>	24
<i>Demographic and Clinical Characteristics</i>	25
<i>Primary Functional Connectivity Analysis Within the DMN</i>	25
Between Group Differences in FC Within the DMN.	25
Association Between HRQoL and FC Within the DMN.....	26
Post-hoc Power Analysis.....	28
<i>Secondary Analysis of FC Within and Between the DMN, CEN and SN</i>	28
Between Group Differences in FC Within the CEN and SN.....	28
Between Group Differences in FC Between the DMN, CEN and SN.....	29
Association Between HRQoL and FC Within the CEN and SN.....	29
Association Between HRQoL and FC Between the DMN, CEN and SN.....	30
<i>Results</i>	31
Participant Enrolment and Characteristics.....	31
<i>Assessing the Importance of Physical Activity Levels in Concussion Subgroups</i>	31
<i>Demographic and Clinical Characteristics</i>	32
Primary Functional Connectivity Analysis Within the DMN	34
<i>Between Group Differences in FC Within the DMN</i>	34
<i>Association Between HRQoL and FC Within the DMN</i>	34
Post-hoc Power Analysis.....	37
Secondary Analysis of FC Within and Between the DMN, CEN and SN	37
<i>Between Group Differences in FC Within the CEN and SN</i>	37
CEN Within-Network Analyses.....	37
<i>Between Group Differences in FC Between the DMN, CEN and SN</i>	40
<i>Association Between HRQoL and FC Within and Between the DMN, CEN and SN</i>	44
Within-Network Analyses.....	44
Between-Network Analyses.....	45
<i>Discussion</i>	49
Summary of Findings	49
<i>Novel Findings in Connectivity 1 Month after Pediatric Concussion</i>	51
Interpretation of Results	52
<i>Increased SN Connectivity in Concussion: Within and Between Networks</i>	52
<i>Differential CEN Connectivity in Concussion: Within and Between Networks</i>	54
<i>No Differences in Within-Network DMN Connectivity 1 Month after Concussion</i>	56
<i>Potential Influence of Differential Duration of Recovery</i>	57
<i>No Associations Found Between FC and HRQoL 1 Month after Concussion</i>	58
<i>Potential Influence of Image Processing Methodology</i>	60
Strengths	60
Limitations.....	61
Future Directions	62
Conclusion	64
<i>References</i>	65

List of Abbreviations

AC-PC	Anterior commissure - posterior commissure
BOLD	Blood-oxygen-level-dependent
CBF	Cerebral blood flow
CEN	Central executive network
CHEO	Children's Hospital of Eastern Ontario
dACC	Dorsal anterior cingulate cortex
DARTEL	Diffeomorphic nonlinear registration tool
dIPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DPARSFA	Data Processing Assistant for Resting-State fMRI-Advanced Edition
eCHIRPP	Electronic Canadian Hospitals Injury Reporting and Prevention program
ED	Emergency department
FC	Functional connectivity
FD	Frame-wise displacements
FIC	Frontoinsular cortex
FOV	Field of view
FWE	Family-wise error
GCS	Glasgow Coma Scale
HBI	Health and Behaviour Inventory
HRQoL	Health-related quality of life
ICA	Independent component analysis
IQR	Interquartile range
LPA	Light-intensity physical activity
MNI	Montreal Neurological Institute
MPA	Moderate-intensity physical activity
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
MVPA	Moderate- to vigorous-intensity physical activity
OI	Orthopedic injury
PA	Physical activity

PCC	Posterior cingulate cortex
PedCARE	Pediatric Concussion Assessment of Rest and Exertion study
PedCARE ^{+MRI}	Pediatric Concussion Assessment of Rest and Exertion with MRI study
PedsQL	Pediatric Quality of Life Inventory
pPC	Posterior parietal cortex
QoL	Quality of life
REDCap	Research Electronic Data Capture
ROI	Region of interest
rs-fMRI	Resting-state functional magnetic resonance imaging
SN	Salience network
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
TBI	Traumatic brain injury
TE	Echo time
TR	Repetition time
VPA	Vigorous-intensity physical activity

List of Tables

Table 1: Participant Demographics.....	32
Table 2: Clinical Measure Results	34
Table 3: DMN FC Associated with Age.....	35
Table 4: Within-Network FC Group Differences	39
Table 5: Between-network FC Group Differences	41
Table 6: FC Associated with Age, Sex and Composite Diagnostic Score.....	46

List of Figures

Figure 1: Functional Network Seed Regions Defined for the FC Analysis..... 23

Figure 2: FC Within the DMN of the Concussion Group Positively Associated with Age 36

Figure 3: Increased FC Within the CEN Identified in the Concussion Group 38

Figure 4: Increased FC Within the SN Identified in the Concussion Group 40

Figure 5: Increased FC Between the SN and DMN Identified in the Concussion Group 42

Figure 6: Increased FC Between the SN and CEN Identified in the Concussion Group..... 43

Figure 7: Decreased FC Between the CEN and DMN Identified in the Concussion Group 44

Figure 8: FC Within the CEN of the Concussion Group Positively Associated with Age..... 45

Figure 9: FC Between the SN and DMN of the Concussion Group Positively Associated with
Composite Diagnostic Score 47

Figure 10: FC Between the CEN and DMN of the Concussion Group Positively Associated with
Composite Diagnostic Score 48

Figure 11: FC Between the SN and DMN of the Concussion Group Positively Associated with
Sex (Female) 49

List of Appendices

Appendix A: Clinical Measures..... 83

Appendix B: Enrolment Breakdown of the Concussion and OI Groups 85

Appendix C: Average Daily Physical Activity Levels of the PA Group and Rest Group..... 87

Investigating the Associations between Brain Network Functional Connectivity and Health-Related Quality of Life following a Pediatric Concussion

Concussion is a mild traumatic brain injury with increasing prevalence among children and adolescents. In Ontario, from the years 2003 to 2013, visits to emergency departments and physicians' offices for pediatric concussions saw a 4-fold increase (Zemek et al., 2017), highlighting the need for better assessment and treatment measures. In addition, the Electronic Canadian Hospitals Injury Reporting and Prevention program (eCHIRPP) recently reported that 80% of adolescent sport- and recreation-related head injuries presenting to the emergency department (ED) are brain injuries, 93% of which are concussions (Government of Canada, 2018).

A concussion is characterized as an injury to brain tissue without apparent macroscopic damage, as the result of a jolt, blow, or impact causing biomechanical changes to the brain (Giza & Hovda, 2001). This can result in impairments to glucose metabolism in an effort to restore homeostasis, swelling to the regions affected by the impact, and microstructural damage to neurons and glia (Giza & Hovda, 2001). More specifically, it can result in irregular ionic flux, reduced cerebral blood flow, impairments in neurotransmission and mitochondrial function (i.e., catalyst of the Krebs cycle), overactivation of microglia, and dysfunction of the cytoskeleton, dendrites, axons, and astrocytes (Giza & Hovda, 2014). Altered mitochondrial metabolism and changes in cerebral blood flow can cause an uncoupling of the energy supply and demand (Giza & Hovda, 2014), and the blood-oxygen-level-dependent (BOLD) response—an indirect measure of brain activity—is dependent on this coupling (Hillman, 2014). This suggests that cerebral blood flow impairments may contribute to significant changes in brain activity and brain network connectivity.

Approximately 30% of children with a pediatric concussion will suffer from persistent post-concussive symptoms at 1-month post-injury (Zemek et al., 2016). Abnormal brain activity has been linked to persistent symptoms following concussion (Iyer et al., 2019) and persistent symptoms have been shown to negatively affect health-related quality of life (HRQoL) of concussed children and youth, affecting their physical, emotional, social, and educational domains (Novak et al., 2016). However, reduced HRQoL has been shown to persist even after the resolution of concussion symptoms, especially in the realm of academic performance (Novak et al., 2016). This points to a need for objective measures of brain activity associated with these deficits.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a method used to measure the BOLD response and has been utilized in many concussion studies to demonstrate irregularities. Functional connectivity (FC), a measure of the interconnectivity or synchrony of activity between brain regions (Chao-Gan & Yu-Feng, 2010), is one of the possible ways to quantify this data and has been used in past concussion analysis. In addition, FC can be compared within and between the main networks of the brain that have been demonstrated to be altered in concussion in the acute phase (1-7 days post-injury) and in the chronic phase (30+ days post-injury) (Borich et al., 2015; Churchill et al., 2017; van der Horn et al., 2016). A primary network studied in concussion is the default mode network (DMN). The DMN has been shown to be abnormal in the post-concussed brain (Churchill et al., 2018) and normal function in the DMN has been associated with increased HRQoL in healthy adults (Kraft et al., 2018). In addition, the DMN has demonstrated irregular FC with other brain networks following concussion including the salience network (SN; a network shown to be crucial in coordinating brain activity) (Seeley, 2019) and the central-executive network (CEN; a network shown to be

active during tasks involving executive function) (Seeley et al., 2007). The SN has been shown to modulate some of the relationship between the DMN and the CEN (Chand et al., 2017). Following concussion in adults, the DMN has been shown to be less segregated from the CEN or task-positive network (a network typically found to be anti-correlated with the DMN) responsible for cognitively-taxing tasks demonstrating its overactivation in the face of cognitive demands (Sours et al., 2018). This suggests, due to the SN's modulation of the connection between the DMN and CEN, that the SN may play a part in this altered connection.

To date, few studies have investigated the intraconnectivity of the DMN and its interconnectivity with the CEN and SN in pediatric concussion, and no pediatric concussion study has looked at the associations between these network connectivities and HRQoL. Therefore, a more complete picture of the impact of pediatric concussion on brain connectivity and HRQoL is warranted. The following study investigated the intraconnectivity of the DMN and its interconnectivity with the CEN and SN, as well as the associations between DMN, CEN and SN connectivity and HRQoL at 1 month following a pediatric concussion. First, we will outline the current research to date on connectivity of these networks and on HRQoL.

Measuring Connectivity in Concussion

BOLD signal

Resting-state functional magnetic resonance imaging (rs-fMRI) is a neuroimaging technique used to measure the BOLD signal in the brain at rest. To understand the MRI BOLD signal and its relation to concussion there must first be an understanding of neurovascular coupling. In response to the oxygen and glucose demands of neural activity, vasculature, glia and neurons supply blood to independent regions by working together as a neurovascular unit (Tan et al., 2014). This increase in cerebral blood flow (CBF) paired with the cerebral metabolic rate is

referred to as neurovascular coupling (Tan et al., 2014). Coupling is thought to occur due to changes in vasodilation mediated by activity-related neurotransmission, shifts in ion content, changes in energy substrate levels, and astrocyte and interneuron secretions through direct contact with the endothelial-cell lining (Tan et al., 2014). Following a traumatic brain injury (TBI), damage to the endothelium lining of the brain vasculature and white matter tracts can occur due to the shearing forces of soft brain tissue colliding with the skull (Wilson & Matschinsky, 2020). These damages can directly and indirectly impact blood flow through arterial wall tearing and reduced vasodilation control due to axonal damage, respectively. This results in decreased CBF in the immediate regions and compensatory CBF increases in surrounding regions causing a neurovascular uncoupling (Tan et al., 2014; Wilson & Matschinsky, 2020). The imbalance in energy supply and demand creates changes in the MRI BOLD signal because it is detected through differences in magnetism between oxygenated and deoxygenated hemoglobin in the blood (Gauthier & Fan, 2019). In its deoxygenated state, hemoglobin is paramagnetic causing a decrease in T2*-weighted signal of the surrounding tissue (the signal used in fMRI imaging) (Gauthier & Fan, 2019). When brain regions are active, deoxygenated hemoglobin levels increase as oxygen is consumed (Gauthier & Fan, 2019). This causes increases in the localized flow of blood containing oxygenated hemoglobin (Gauthier & Fan, 2019). As the deoxygenated hemoglobin levels change and become more diluted, the BOLD signal increases (Gauthier & Fan, 2019). In rs-fMRI analysis, the BOLD signal is assumed to be an indirect measure of brain activity because of the correlations found between signal changes and neural activity (Gauthier & Fan, 2019). The BOLD signal time-series collected with rs-fMRI can be analysed in multiple ways, one of which being through measurements of FC. FC measures the interconnectivity or degree of synchrony of the BOLD time-series between brain

regions (Chao-Gan & Yu-Feng, 2010) and has become a useful tool for measuring connectivity differences within and between brain networks following a concussion.

Brain Networks Associated with Concussion

Default mode network

The default mode network (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 engaging tasks (Buckner et al., 2008). The network includes the medial prefrontal cortex (mPFC), the lateral frontal cortex, the medial parietal cortex [including the posterior cingulate cortex (PCC) and retrosplenial cortex], the medial temporal lobe, the lateral parietal cortex, and the lateral temporal cortex (Andrews-Hanna et al., 2014). The regions within the network have shown to be intrinsically functionally connected and these connections have correlated with specific functions, such as self-reflection and mental exploration (Buckner et al., 2008).

Through the regions' connections with the hypothalamus and midbrain autonomic control centres, the DMN is thought to influence both behavioural and emotional response to internal and external events (Davey & Harrison, 2018). These responses are then integrated into cognitive self-awareness and awareness of the body itself (Davey & Harrison, 2018). Increases in FC within the DMN have also been associated with rumination (van der Horn et al., 2016) and it has been speculated that ongoing increases in FC within this region may impede recovery following an mTBI due to poor coping mechanisms (Cairncross et al., 2021), such as persistent thoughts about present injury state and future consequences (van der Horn et al., 2017). Contrastingly, acute reductions in FC within the DMN in adults have been observed less than 7 days after concussion (Iraji et al., 2015) and over the span of 3 weeks to 5 months following

concussion (Mayer et al., 2011), and have been associated with symptom severity (Churchill et al., 2018; D'Souza et al., 2020; Madhavan et al., 2019). Disruptions in FC within and between the DMN and frontal executive regions following mTBI have been demonstrated less than 3 weeks and 3-5 months post-injury (Mayer et al., 2011) and have been shown to persist even after symptom resolution (Johnson et al., 2012).

The most robust set of regions in the DMN—consistently referred to as the “hub” regions of the network—are the mPFC and the PCC (Buckner et al., 2008; Davey & Harrison, 2018). 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). The PCC also appears to play a role in alternating between brain networks (such as between the DMN and the central executive network) and mental states (van der Horn et al., 2016). Within the first 2 months after mTBI, decreased mPFC and PCC FC in adults has been associated with negative cognitive and posttraumatic symptoms (including mood, fatigue and concussion symptoms) (Zhou et al., 2012). Although less studied, DMN FC differences have also been observed in youth following concussion.

Default mode network in youth with concussion. Despite the pattern of reduced FC within the DMN of adults following concussion, FC appears to be less predictable in children and young adults. 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.

Patterns of decreased connectivity have been observed across adolescence. One study found that children aged 8-19 with a history of multiple concussions showed decreased FC within the anterior DMN in comparison to children with a history of a single concussion or an orthopedic injury (Plourde et al., 2020). In addition, decreased DMN FC corresponded to increased sleep disturbances and cognitive difficulties in children aged 10-17 with persistent symptoms following a concussion (Iyer et al., 2019). The same researchers demonstrated that children aged 8-18 who reported higher sleep disturbances 1 month following a concussion had reduced FC between the PCC and mPFC (Iyer et al., 2019).

Findings demonstrating increased connectivity have also been noted. High school football players monitored and scanned throughout the preseason, regular season, and postseason were found to have significant hyperconnectivity within the DMN at all timepoints in comparison to non-collision athletes (Abbas et al., 2015). In addition, whereas non-collision athletes did not show significant changes in connectivity across the season, the football players

had increased variability throughout the season (Abbas et al., 2015). Recently concussed (30 days post-injury) but asymptomatic high-school athletes had greater FC between the PCC and the right ventrolateral PFC in comparison to high school athletes with orthopedic injuries (Newsome et al., 2016). A study comparing adolescent hockey players with a history of concussion (more than 3 months prior) to their teammates with no history of concussion found that the players with concussions had increased posterior DMN FC within the DMN and increased anterior DMN FC with the inferior frontal lobe (Orr et al., 2016). In adolescents aged 10-17 1 year after a mild to moderate TBI, increased FC was found between the DMN and the right Brodmann Area 40 (part of the inferior parietal lobe—considered a task-positive brain region) in comparison to healthy controls (Stephens et al., 2018). These increases were correlated with worse performance on response inhibition tasks (Stephens et al., 2018).

Patterns of differential activity have also been observed. Athletes aged 14-17 who sustained a concussion within 2 months of scanning were shown to have increased connectivity in the PCC and decreased connectivity in the frontal and parietal cortices within the DMN in comparison to healthy controls (Borich et al., 2015).

Based on the research to date, a trend towards increased DMN connectivity appears to be most prevalent in adolescents following a concussion. However, 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.

Central executive network

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). Increased within-network connectivity of the CEN has been associated with increased IQ scores in late childhood and adolescence (Li & Tian, 2014). 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 et al., 2007).

Central executive network in concussion. 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. A study with athletes aged 14-17 found increased FC in the frontal poles of the executive network within 2 months of sustaining a concussion in comparison to controls (Borich et al., 2015). Increased FC within the right lateral CEN was found in adults with mTBI (Shumskaya et al., 2012). In contrast, decreased FC within the CEN has been observed within 7 days of an mTBI in adults and restorative increases were noted after 6 months (D'Souza et al., 2020). Similar to the DMN, the CEN appears to demonstrate primarily increased connectivity in youth following a concussion 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 following a concussion (Broadway et al., 2019; Howell et al., 2013), pediatric CEN functional activity requires further attention.

Saliency network

The role of the salience network (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 frontoinsula cortex (FIC) (Seeley, 2019; Seeley et al., 2007). The SN provides crucial control of executive behavior through its modulation of CEN

activity (van der Horn et al., 2016) 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 require more attention.

How the three networks interact

Although much of the research has been conducted with adults, correlated activity between the 3 networks has 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, 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 fMRI (Huang et al., 2021). Reduced FC between regions of the SN and DMN were found to be associated with higher trait anxiety in adolescents (Geng et al., 2016). 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., 2016).

How the three networks interact in concussion. In the chronic stage of concussion in adults (on average 210 days post-injury), the DMN was shown to be less segregated from the CEN while performing a cognitive task (Sours et al., 2018) and FC was increased between the PCC and the dACC, bilateral insular cortex and the left dlPFC in a resting state (Sours et al., 2015). Adults with an acute mTBI (< 7 days) showed increased resting-state FC between the PCC and the frontal lobe regions of the CEN (Iraji et al., 2015) and between anterior regions of the DMN and the SN (Liu et al., 2020) in comparison to controls. In addition, increased resting-state FC between the DMN and CEN after concussion has been associated with cognitive complaints (van der Horn et al., 2016). Finally, higher FC between the CEN and SN in adults has been associated with decreased post-mTBI cognitive complaints and depression symptoms (van der Horn et al., 2016). In pediatric populations, no significant differences in DMN and CEN interconnectivity were found between concussion and control participants (Iyer et al., 2019). 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. In addition, altered connectivity within and between these 3 networks may contribute to poor quality of life after sustaining a concussion.

Health-related Quality of Life in Pediatric Concussion

Health-related quality of life and concussion

Health-related quality of life (HRQoL) is a conceptual measure of the effects of a person's health on their perceived mental, physical, and social well-being (Fineblit et al., 2016).

Following pediatric concussion, HRQoL has shown to be reduced in children with and without post-concussive symptoms, with overall deficits (as well as deficits in emotional, social, physical and school QoL) appearing acutely and lasting for months (Doroszkiewicz et al., 2021; Fineblit et al., 2016; Howell et al., 2019; McLeod et al., 2019; Novak et al., 2016; Russell et al., 2017, 2019). In addition, cognitive and somatic symptoms following concussion have been associated with worse HRQoL outcomes (Fineblit et al., 2016).

Health-related quality of life and network connectivity

Normal function of the DMN has been associated with increased HRQoL (Kraft et al., 2018) and increased FC within the anterior and posterior regions of the DMN have been associated with eudaimonic and hedonic well-being (Luo et al., 2017). In addition, functions within the hub regions of the DMN are thought to be responsible for unconscious self-perceptions of bodily and cognitive well-being and for bringing the most relevant self-perceptions to the forefront (Buckner et al., 2008). These functions are crucial for perceiving and reporting well-being. Due to the associations that have been found between FC and post-concussive symptoms (Iyer et al., 2019), as well as the associations found between symptoms and total, emotional, school, social and physical HRQoL in pediatrics (Novak et al., 2016; Russell et al., 2017), more research is necessary to establish how HRQoL relates to network connectivity within the DMN and between the DMN, CEN, and SN following a pediatric concussion. If deficits in HRQoL were to be associated with altered FC, treatments targeting the improvement of both connectivity deficits and mood symptoms [such as mindfulness based interventions (Mak et al., 2018; Simon & Engström, 2015)] may help to improve QoL in those experiencing long lasting symptoms post-concussion.

Study Objectives and Hypothesis

The present study explored 1) network FC differences between a pediatric concussion group and orthopedic injury (OI) group aged 10-18, and 2) whether an association exists between FC and HRQoL after a pediatric concussion.

The primary objective was to examine if FC within the DMN differs between those who suffered a concussion and those who suffered an OI at 4 weeks post-injury. Specifically, a region of interest (ROI) analysis was conducted with the relevant hub regions of the DMN. Based on the literature, these hub regions were defined as the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC) (Buckner et al., 2008; Davey & Harrison, 2018). Next, the association between total HRQoL (as well as the subdomains of physical, emotional, social, and school HRQoL) and FC within the DMN was investigated in those who sustained a concussion, at 4 weeks post-injury.

The secondary objective was to examine if FC within the CEN and SN, and between the DMN, CEN and SN, differs between those who suffered a concussion and those who suffered an OI at 4 weeks post-injury. An ROI analysis was conducted with the relevant hub regions of each network. Based on the literature, these hub regions were defined as the PCC of the DMN, the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (pPC) of the CEN (Seeley et al., 2007), and the dorsal anterior cingulate cortex (dACC) and frontoinsula cortex (FIC) of the SN (Seeley, 2019; Seeley et al., 2007). Next, the association between HRQoL (as well as the subdomains of physical, emotional, social, and school HRQoL) and FC between the DMN, CEN, and SN, and within the CEN and SN, was investigated in those who sustained a concussion, at 4 weeks post-injury.

Due to overall increases in DMN FC following pediatric concussion, it was hypothesized that intraconnectivity within the DMN would be increased in concussion participants in

comparison to OI participants, and that increased DMN intraconnectivity within the concussion group would be associated with reduced HRQoL at 4 weeks post-injury. For the secondary analysis, it was hypothesized that decreased segregation between the DMN and CEN (i.e., increased interconnectivity) and increased SN intraconnectivity in the concussion group would be associated with reduced HRQoL at 4 weeks post-injury.

Methods

Study Design and Setting

The Pediatric Concussion Assessment of Rest and Exertion with MRI (PedCARE^{+MRI}) study is an adjunct study to the multicentre randomized clinical trial PedCARE (Ledoux et al., 2017). The study investigated whether early reintroduction of non-contact physical activity (PA) at 72 hours post-injury improves neurophysiological measures at 4 weeks following a pediatric concussion. Concussion participants were randomized to either resume non-contact, aerobic PA at 72 hours post-concussion or rest until asymptomatic. Participants who suffered an OI were also recruited to serve as a control group for the neurophysiological measures. All participants were enrolled at the Children's Hospital of Eastern Ontario (CHEO) ED.

The study herein is a cross sectional design of the data collected for PedCARE^{+MRI}. For the purpose of this study, the concussion participants were regrouped and the randomization (to either the PA or rest until asymptomatic group) was broken.

Participants

92 participants with a concussion and 46 participants with an OI were enrolled as part of the PedCARE^{+MRI} study.

Inclusion - Exclusion Criteria

Concussion participants. To be included in the PedCARE^{+MRI} study, the concussion participants had to be between the ages of 10-17.99 years old; have a concussion, as defined by the Zurich and Berlin consensus statement; have acquired the head injury within 48 hours of their ED visit; and had to be proficient in English. Considering that no biomarker exists for diagnosing a concussion, 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, which included being dazed, confused or having trouble thinking within minutes after the event, difficulty remembering what happened just before or minutes before the event or loss of consciousness; or 2 symptoms within the higher level of certainty immediately or within 1 hour of injury, which included nausea or vomiting, headache, dizziness, clumsiness or balance problems, blurred/double/change in vision, difficulty concentrating or sensitivity to light or noise.

Participants were excluded if they had a Glasgow coma scale (GCS) rating of 13 or below; had any abnormalities on neuroimaging studies; if neurosurgical operative intervention, intubation, or intensive care was required; if they had to be admitted to the hospital, operating room, or procedural sedation in the ED due to multi-system injuries; if they presented with any severe chronic neurological developmental delay that impeded their ability to communicate; if they didn't have the ability to return to PA; if they were intoxicated at their ED visit; if the cause of the injury wasn't due to a trauma (such as a seizure, syncope, or migraine); if they were previously enrolled in the study; if they were unable to provide informed consent; if their legal guardian wasn't present; if they had a previous neurological or neurodevelopmental disorder (such as epilepsy or autism); if they'd been previously hospitalized for psychiatric disorders; if

they were administered sedation medication either before or during their ED visit; if they were not able to attend either of the 2 MRI appointments within the appropriate time periods (72 hours +/- 48 hours and 4 weeks +/- 5 days); or if the participant had any reason that prevented them from undergoing an MRI (such as pregnancy, claustrophobia, braces, or other metal implants).

Orthopedic injury participants. To be included in the PedCARE^{+MRI} study, the OI participants had to be between the ages of 10-17.99 years old; have an isolated upper extremity OI due to blunt force or physical trauma (such as a sprain, fracture or strain); have acquired the injury within 48 hours of their ED visit; and had to be proficient in English. Participants were excluded if they had a previous concussion or traumatic brain injury within the last year; if their injury required closed reduction procedural sedation or surgical management; if they presented with any severe chronic neurological developmental delay that impeded their ability to communicate; if they had a previous neurological or neurodevelopmental disorder (such as epilepsy or autism); if they'd been previously hospitalized for psychiatric disorders; if they didn't have the ability to return to PA; if they were intoxicated at their ED visit; if they were unable to provide informed consent; if their legal guardian wasn't present; if they were administered sedation medication either before or during their ED visit; if they were not able to attend either of the 2 MRI appointments within the appropriate time periods (72 hours +/- 48 hours and 4 weeks +/- 5 days); or if the participant had any reason that prevented them from undergoing an MRI (such as pregnancy, claustrophobia, braces, or other metal implants).

Incentives

Participants were given a gift card of \$25 for each MRI follow-up (total of two). A prepaid parking pass was also provided while attending the MRIs.

The study was approved by the Research Ethics Board at the Children's Hospital of Eastern Ontario.

Measures

Clinical data

Health-related Quality of Life. The Pediatric Quality of Life Inventory version 4.0 (PedsQL-4.0) (Varni et al., 2003) was used to assess health-related quality of life (HRQoL; see Appendix A1). The PedsQL is a 23-item valid and reliable measure covering four domains: physical, emotional, social, and school. The PedsQL is recommended as a NIH core common data element for concussion (Broglia et al., 2018). For the PedCARE^{+MRI} study, the child's version (ages 8-12) and adolescent's version (ages 13-18) were used. The PedsQL was completed by participants at 72 hours and 4 weeks post-injury for the concussion and OI groups. A higher score indicates a higher quality of life. For the purposes of this analysis, only the 4-week assessments were used.

Degree of Symptoms. Symptoms were 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 (see Appendix A2). The HBI is recommended as a NIH core common data element for concussion (Broglia 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 hours and 4 weeks post-injury for the concussed and OI groups. For the purposes of this analysis, only the total scores of the 4-week assessments were used.

Diagnostic History. Participant diagnostic history (including number of previous concussions and prior diagnosis of ADHD, anxiety, depression, and learning disabilities) were collected (see Appendix A3) due to their adverse effects on concussion recovery, psychophysiology and pathophysiology (Cairncross et al., 2021; Iaccarino et al., 2018; Iverson et al., 2017). Prior clinical and psychiatric diagnoses were collected from OI participants and number of previous concussions were collected from concussion and OI participants during enrolment in the ED. Prior clinical and psychiatric diagnoses were collected from concussion participants either 72 hours post-injury or retroactively post-study completion (if not collected at 72 hours). 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.

Magnetic resonance imaging data

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 72 hours and 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 degrees 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. 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 x 0.9 x 1 mm³; FOV = 230 mm; resolution = 230 × 230 x 176 mm.

Procedure

An experimental, a control group, and an OI group were included in the PedCARE^{+MRI} study to assess the impact of early resumption of PA post-concussion on neurophysiological data. The experimental group was randomly assigned to resume non-contact, aerobic PA at 72 hours post-concussion. The control group was randomly assigned to rest until fully asymptomatic. The OI group was instructed to resume regular activity whenever was comfortable and safe to do so with their OI.

Once the participant was deemed eligible in the ED, participants and parents signed an informed consent and an assent if needed. Both concussion and OI participants completed demographic and health history forms which included reporting the number of previous concussions and OI participants completed forms collecting clinical and psychiatric diagnostic history. The treating physician also completed a form that allowed the participant to proceed with the study.

Subsequently, concussion participants were randomized using the Research Electronic Data Capture (REDCap) data management system to 1 of the 2 study groups (experimental or control). The participants were given a standardized letter to physicians, an instruction booklet based on their assigned condition, and an accelerometer. They were then discharged by the physician and sent home. OI participants were not randomized into a study arm and were not

given an accelerometer or information about any treatment outside of their injury treatment from the physician. The following day, participants were called to book 2 MRIs.

The first MRI appointment took place at 72 +/- 48 hours post-injury. HRQoL and symptom data, as well as clinical and psychiatric diagnostic history data (for the concussion group), were collected at this time. The second MRI appointment took place at 4 weeks +/- 5 days post-injury and followed the same protocol as the first MRI (including the collection of HRQoL and symptom data). For the purposes of this analysis, only the 4-week MRI and clinical data were used with the exception of diagnostic history. Participants with incomplete diagnostic history were retroactively sent an electronic survey collecting this information post-study completion.

Data analysis

MRI 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 & Brett, 2000).

Initial T1 motion mitigation. In order to identify any structural T1 images with high motion that have the potential to cause artifacts during co-registration with the fMRI data, a structural image check was developed based on the quality control guidelines laid out by Backhausen et al. (2016). The check rated images on 4 motion components: image sharpness, ringing, and contrast to noise ratio in the subcortical structures and in the gray and white matter.

Each image was then given a final rating based on the scores of the 4 components; either a pass, check (for later review), or fail. If a participant received a final rating of fail on both MRI 1 and 2, they were excluded from the study. If they received a check on 1 or both MRI's, the better of the 2 will be used for preprocessing and processing.

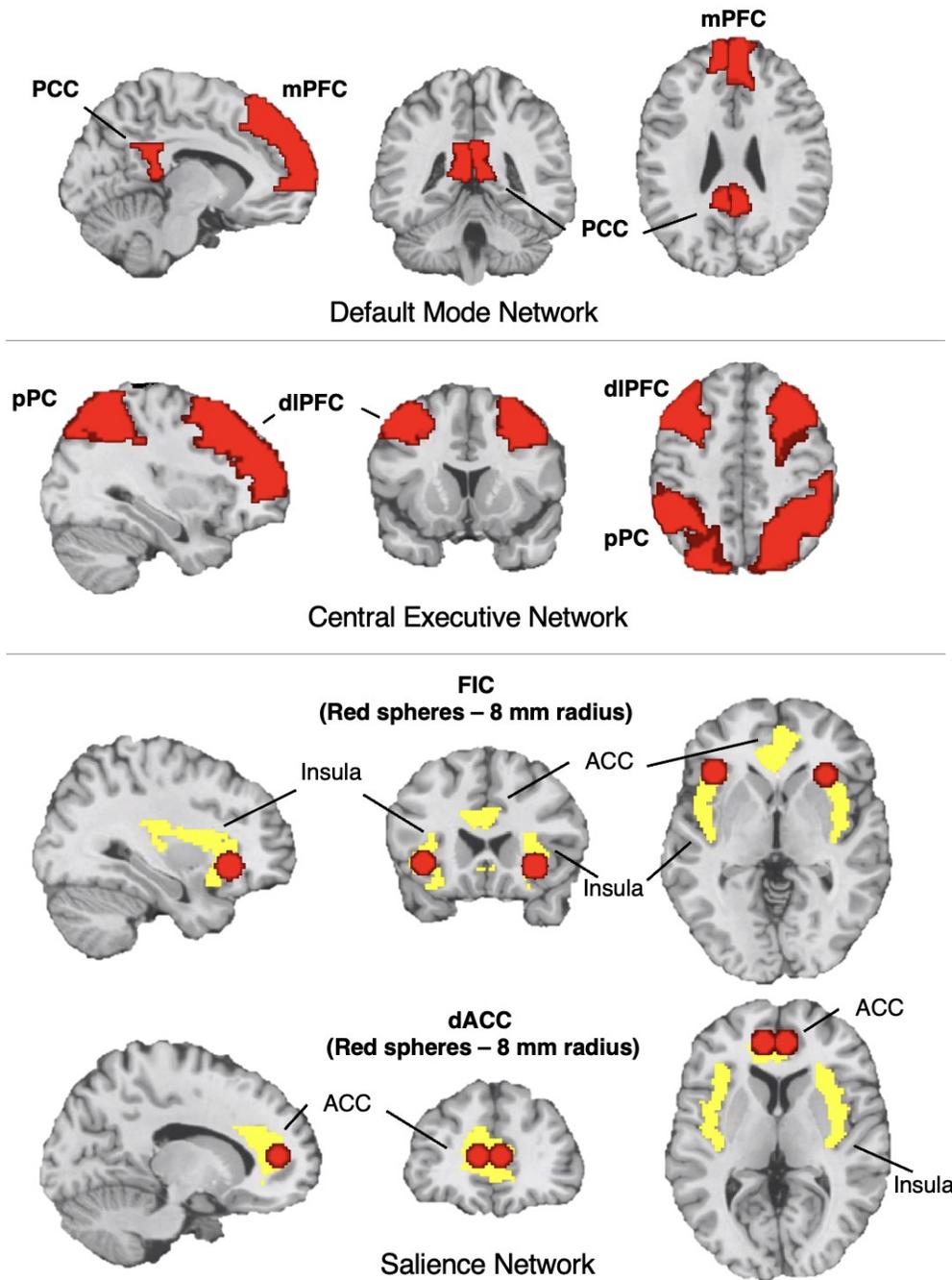
Preprocessing. Using DPARSFA, rs-fMRI images were corrected for slice timing and realigned to correct for motion. At this point, participants with more than 3 mm of absolute motion in their scans were excluded from the analysis (Sours et al., 2015; Stephens et al., 2018). Next, the rs-fMRI images were 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). In addition, head motion scrubbing regressors were implemented to regress out the frame-wise displacements (FD) exceeding a threshold of 0.5 mm, including the volume preceding and 2 following (Iyer et al., 2019; 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). To reduce high-frequency cardiac and respiratory noise and low-frequency drift, functional volumes were bandpass filtered between 0.01-0.1 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.

Processing. 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 the PCC and mPFC of the DMN, the dlPFC and pPC of the CEN, and the dACC and FIC of the SN. The PCC, mPFC, dlPFC, and the pPC were defined with the aal 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). See Figure 1 for the defined regions.

Figure 1

Functional Network Seed Regions Defined for the FC Analysis



Note. dACC=dorsal anterior cingulate cortex; dIPFC=dorsolateral prefrontal cortex; FIC=frontoinsulaar cortex; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex; pPC=posterior parietal cortex

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

Statistical Analysis

The statistical analysis was performed using SPM12 and IBM Statistical Package for the Social Sciences (SPSS), version 26.0 for Macintosh.

Assessing the Importance of Physical Activity Levels in Concussion Subgroups

Given that the design of the original parent study was a randomized clinical trial assessing PA as a treatment, PA levels were assessed between randomization groups to determine if they should be added as a covariate in the analyses. Based on the parent study main results, both the experimental and control group had low adherence to their assigned protocols. Adherence was assessed based on days 4 and 7 of the 14 days participants were assigned to wear the accelerometer. To be considered adherent, participants required 1 valid Actical day (meaning the accelerometer was worn) between days 1-3 and between days 5-6. In addition, participants must have completed a minimum of 1 daily symptom-log between days 1-3 and days 5-6. In order to determine the design of the current study, independent two-sample t-tests were performed in SPSS between the experimental and control MRI concussion groups. Variables that did not meet the assumptions for parametric testing were analyzed using the Mann-Whitney U test. If the groups demonstrated significant differences in PA data collected by the accelerometer for 14 days at all levels of activity (mild to vigorous), PA activity would be covaried. Significance was defined by $p < 0.05$.

Demographic and Clinical Characteristics

Demographics 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 SPSS where applicable. Variables that did not meet the assumptions for parametric testing were analyzed using the Mann-Whitney U test.

Significance was defined by $p < 0.05$.

Primary Functional Connectivity Analysis Within the DMN

Between Group Differences in FC Within the DMN. First, one-way ANCOVAs were conducted with the z-transformed FC maps to determine if differences exist in connectivity within the DMN between the concussion and OI groups. More specifically, FC between the bilateral PCC and mPFC were compared between groups. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). A cluster threshold of $p < 0.05$ with family-wise error (FWE) correcting for multiple comparisons (Stephens et al., 2018) with an extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant. Visual brain maps indicating regions with differences were generated.

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, 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 PA and rest concussion groups, assigned groups were covaried. 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 & 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., 2016), and the presence of depression symptoms has been demonstrated to alter connectivity within the DMN and CEN 1 month after a mild traumatic brain injury (Van Der Horn et al., 2017). Finally, handedness has been demonstrated to have significant effects on FC (Raemaekers et al., 2018; Wiberg et al., 2019).

Association Between HRQoL and FC Within the DMN. Next, the association between HRQoL and FC within the DMN in the concussion group was explored with multivariate linear regressions in SPM. The regression analyses were conducted with the total PedsQL score at 4 weeks post-injury as the independent variable and FC between the bilateral PCC and mPFC as the dependent variable. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). A cluster threshold of $p < 0.05$ with FWE correcting for multiple comparisons (Stephens et al., 2018) with an extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant.

Both crude linear regression and adjusted multivariate linear regression analyses were computed. The covariates used for the adjusted regression analyses included age (Sherman et al., 2014), sex (Shafi et al., 2020), randomization group (experimental or rest group), a composite diagnostic score (based on self-reported diagnoses of a learning disability, ADHD (Hilger & Fiebach, 2019), anxiety (Iverson et al., 2017; van der Horn et al., 2016), depression (Iverson et al., 2017; van der Horn et al., 2017) and number of previous concussions (Plourde et al., 2020) and HBI total scores. The HBI total scores were covaried due to previous findings demonstrating the significant association between symptoms and HRQoL after concussion (Novak et al., 2016). To prevent the reduction of power from the addition of categorical variables, we chose not to include handedness in the regression analyses and capped the number of covariates at 5. Although handedness contributes to FC (Raemaekers et al., 2018), there is increasing amounts of evidence supporting the influence of clinical and psychiatric diagnoses in concussion recovery outcomes (Brooks, Plourde, et al., 2019; Cairncross et al., 2021; Iverson et al., 2017) and network connectivity following concussion (Hilger & Fiebach, 2019; Plourde et al., 2020; van der Horn et al., 2017; van der Horn et al., 2016). In addition, since the regression sample consists of only concussion participants, we chose only the most relevant variables that could influence our target population. Age and sex remained in the analysis as well due to the participant age range falling within an important developmental period for FC changes (Sherman et al., 2014) and due to the documented effects of sex on concussion recovery patterns and FC (Ledoux et al., 2019; Shafi et al., 2020).

Additional crude linear regression and adjusted multivariate linear regression analyses were completed to assess the associations between the individual domains of the PedsQL (physical, emotional, social, and school) and FC within the main regions investigated above. The

covariates used for the adjusted regression analyses included age (Sherman et al., 2014), sex (Shafi et al., 2020), randomization group (experimental or rest group), a composite diagnostic score (based on self-reported diagnoses of a learning disability, ADHD (Hilger & Fiebach, 2019), anxiety (Iverson et al., 2017; van der Horn et al., 2016), depression (Iverson et al., 2017; van der Horn et al., 2017) and number of previous concussions (Plourde et al., 2020) and HBI total scores. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). An adjusted cluster threshold of $p < 0.0125$ with FWE correction was considered significant in order to correct for the number of times each model was used [4 subdomains were investigated so the cluster threshold of $p_{FWE} < 0.05$ (Stephens et al., 2018) was divided by 4]. An extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant.

Post-hoc Power Analysis. A post-hoc power analysis was conducted to assess the probability that a false-negative (or Type II) error did not occur in the regression analysis using the program G*Power version 3.1.9.6 (Faul et al., 2009). The alpha error probability and effect size were defined as 0.05 and 0.15, respectively.

Secondary Analysis of FC Within and Between the DMN, CEN and SN

The secondary analysis was completed using similar methods as the primary analysis with both crude and adjusted analyses conducted.

Between Group Differences in FC Within the CEN and SN. One-way ANCOVAs were conducted with the z-transformed FC maps to determine if differences exist within the CEN and SN (between internal hub regions). The adjusted ANCOVA analyses used the same covariates as defined for the primary ANCOVA analysis. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). A cluster threshold

of $p < 0.05$ with FWE correcting for multiple comparisons (Stephens et al., 2018) with an extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant. Visual brain maps indicating regions with differences were generated.

Between Group Differences in FC 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, respectively), and CEN-SN (the dlPFC and FIC, respectively). The adjusted ANCOVA analyses used the same covariates as defined for the primary ANCOVA analysis. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). A cluster threshold of $p < 0.05$ with FWE correcting for multiple comparisons (Stephens et al., 2018) with an extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant. Visual brain maps indicating regions with differences were generated.

Association Between HRQoL and FC Within the CEN and SN. The association between HRQoL and FC within the CEN and SN in the concussion group was explored with multivariate linear regressions in SPM. The regression analyses were conducted with the total PedsQL score at 4 weeks post-injury as the independent variable. FC within each network (CEN and SN) was used as the dependent variables. The adjusted regression analyses used the same covariates as defined for the primary regression analysis. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). A cluster threshold of $p < 0.05$ with FWE correcting for multiple comparisons (Stephens et al., 2018) with an extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant.

Similar to the primary analysis, additional regression analyses were completed (using the same covariates) to assess the associations between the individual domains of the PedsQL (physical, emotional, social and school) and FC within the main regions investigated. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). An adjusted cluster threshold of $p < 0.0125$ with FWE correction was considered significant in order to correct for the number of times each model was used [4 subdomains were investigated so the cluster threshold of $p_{FWE} < 0.05$ (Stephens et al., 2018) was divided by 4]. An extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant.

Association Between HRQoL and FC Between the DMN, CEN and SN. The association between HRQoL and FC between the DMN, CEN and SN in the concussion group was explored with multivariate linear regressions in SPM. The regression analyses were conducted with the total PedsQL score at 4 weeks post-injury as the independent variable. FC between each network's main hub region (DMN-CEN, DMN-SN, and CEN-SN) were used as the dependent variables. The adjusted regression analyses used the same covariates as defined for the primary regression analysis. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der Horn et al., 2016). A cluster threshold of $p < 0.05$ with FWE correcting for multiple comparisons (Stephens et al., 2018) with an extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant.

Similar to the primary analysis, additional regression analyses were completed (using the same covariates) to assess the associations between the individual domains of the PedsQL (physical, emotional, social and school) and FC between the main regions investigated. Significance was defined by a whole-brain voxel threshold of $p < 0.001$ (uncorrected) (van der

Horn et al., 2016). An adjusted cluster threshold of $p < 0.0125$ with FWE correction was considered significant in order to correct for the number of times each model was used [4 subdomains were investigated so the cluster threshold of $p_{FWE} < 0.05$ (Stephens et al., 2018) was divided by 4]. An extent threshold of 10 voxels (Lieberman & Cunningham, 2009) was considered significant.

Results

Participant Enrolment and Characteristics

A total of 92 concussion participants and 46 OI participants were enrolled in the study. Of these, 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 ANCOVA analyses. For the regression analyses, 2 additional participants were excluded due to missing HRQoL data at 4 weeks. A total of 53 concussion participants remained for the regression analyses. For a complete enrolment breakdown, see Appendix B.

Assessing the Importance of Physical Activity Levels in Concussion Subgroups

In order to determine the design of the study (i.e., whether to combine both randomized groups and whether PA should be included in the analyses as a covariate) adherence to assigned protocol (early return to PA or rest until symptom-free) was assessed within the MRI 2 subsample using the day 4 and day 7 criteria. Of the 55 concussion participants included in the analysis, a total of 48 had valid actical data (26 in the PA group and 22 in the rest group). Of these, 24 (50%) adhered to their assigned protocol (17 of the 26 in the PA group and 7 of the 22

in the rest group), meaning they had 10 hours a day of valid data for ≥ 4 days of the 2-week measurement period. Independent two-sample t-tests and Mann-Whitney U tests were performed in SPSS between the early return to PA and rest until asymptomatic group. All participants with valid actical data were included with the exception of 2 rest group participants with outlier PA data. The analyses revealed no significant differences at any activity level for the 14 days that the accelerometer was worn ($p < 0.05$; see Appendix C). Furthermore, preliminary investigation of FC within the DMN between both randomized groups indicates no significant differences. Therefore, for the purposes of this study, the 2 concussion groups were combined and PA was not added as an adjusted variable in our analyses.

Demographic and Clinical Characteristics

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 ($p > 0.05$).

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

Variable	Concussion Participants (N=55)	Orthopedic Injury (OI) Participants (N=27)	P Value ^a
Randomization group			
Group A (Rest Group)	25 (45.5%)	N/A	N/A
Group B (Experimental Group)	30 (54.5%)		
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

^a Continuous variables (age and time between injury and MRI) were analyzed with 2-sample t-tests.

Variables with non-normal distributions (number of previous concussions and composite diagnostic 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 $p < 0.05$.

Primary Functional Connectivity Analysis Within the DMN

Between Group Differences in FC Within the DMN

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 whole brain level threshold of $p_{\text{uncorr}} < 0.001$.

Association Between HRQoL and FC Within the DMN

When comparing the concussion and OI groups on clinical measure scores, no differences were found in symptoms (total HBI scores) or physical, emotional, social, school, or total quality of life (total and subdomain PedsQL scores) at 4 weeks ($p > 0.05$; see Table 2).

Table 2

Clinical Measure Results

Variable	Concussion Participants (n=53)	Orthopedic Injury (OI) Participants (n=27)	P Value ^a
Median HBI score at 4 weeks (IQR)	12.00 (4.00-19.00)	8 (3.00-18.00)	0.572
Median Total PedsQL score at 4 weeks (IQR)	86.96 (75.00-95.65)	89.13 (73.91-95.65)	0.416
Median Physical PedsQL score at 4 weeks (IQR)	93.75 (81.25-100.00)	93.75 (81.25-100.00)	0.795
Median Emotional PedsQL score at 4 weeks (IQR)	80.00 (70.00-95.00)	80.00 (70.00-100.00)	0.758
Median Social PedsQL score at 4 weeks (IQR)	100.00 (85.00-100.00)	90.00 (80.00-100.00)	0.192
Median School PedsQL score at 4 weeks (IQR)	85.00 (70.00-95.00)	85.00 (70.00-100.00)	0.781

^a Total PedsQL score was analyzed with a 2-sample t-test. Variables with non-normal distributions (total HBI score and sub-PedsQL scores) were analyzed with Mann-Whitney U tests. Significance was defined by $p < 0.05$.

The crude and adjusted regression analyses demonstrated no significant associations between total PedsQL score at 4 weeks post-injury and FC between the bilateral PCC and mPFC at whole brain level threshold of $p_{\text{uncorr}} < 0.001$. However, clusters within the bilateral mPFC that were functionally connected with the bilateral PCC were found to be significantly positively associated with age ($p_{\text{FWE}} < 0.05$). See Table 3 and Figure 2 for complete cluster results.

Additional crude and adjusted regression analyses assessing the associations between the individual domains of the PedsQL (physical, emotional, social, and school) and FC within the DMN revealed no significant findings at whole brain level threshold of $p_{\text{uncorr}} < 0.001$.

Table 3

DMN FC Associated with Age

Network	Seed Region	Significant Region	Cluster-size (voxels ^a)	Peak MNI coordinates			P Value
				x	y	z	
DMN	Left PCC	Left mPFC	24	-9	60	24	0.03
		Right mPFC	16	9	42	48	0.03
			20	6	48	3	0.027
			27	3	60	12	0.023
	Right PCC	Left mPFC	24	0	66	21	0.03
		Right mPFC	43	6	66	21	0.017

Note. Age, sex, randomization group, composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold.

A cluster threshold of $p_{\text{FWE}} < 0.05$ and extent threshold of 10 voxels was considered significant.

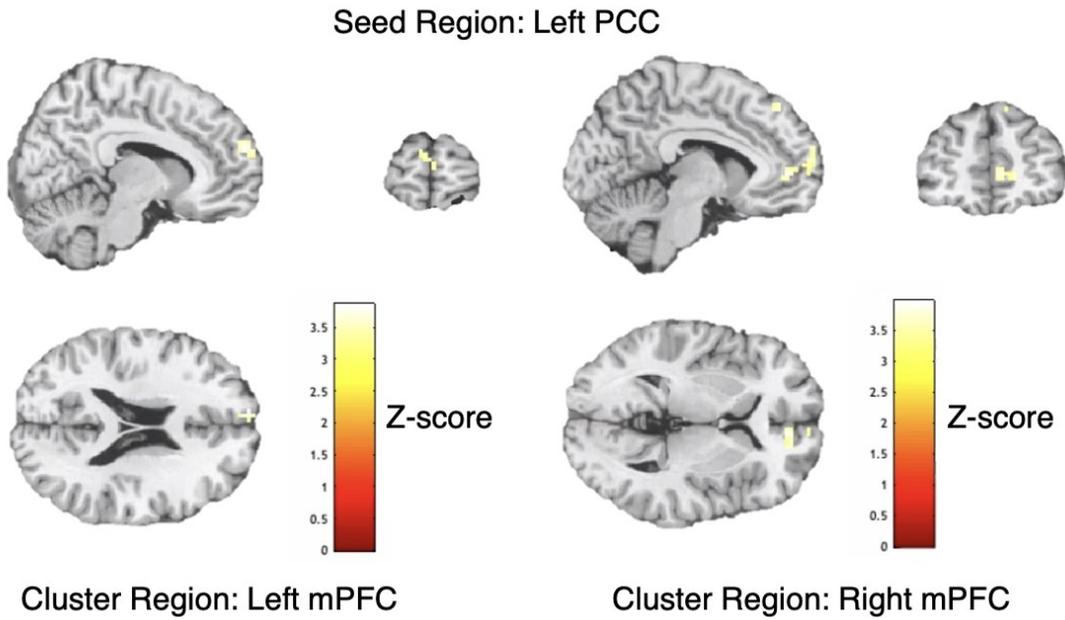
DMN=default mode network; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex

^a Voxel size = 3.6 mm x 3.6 mm x 3.6 mm

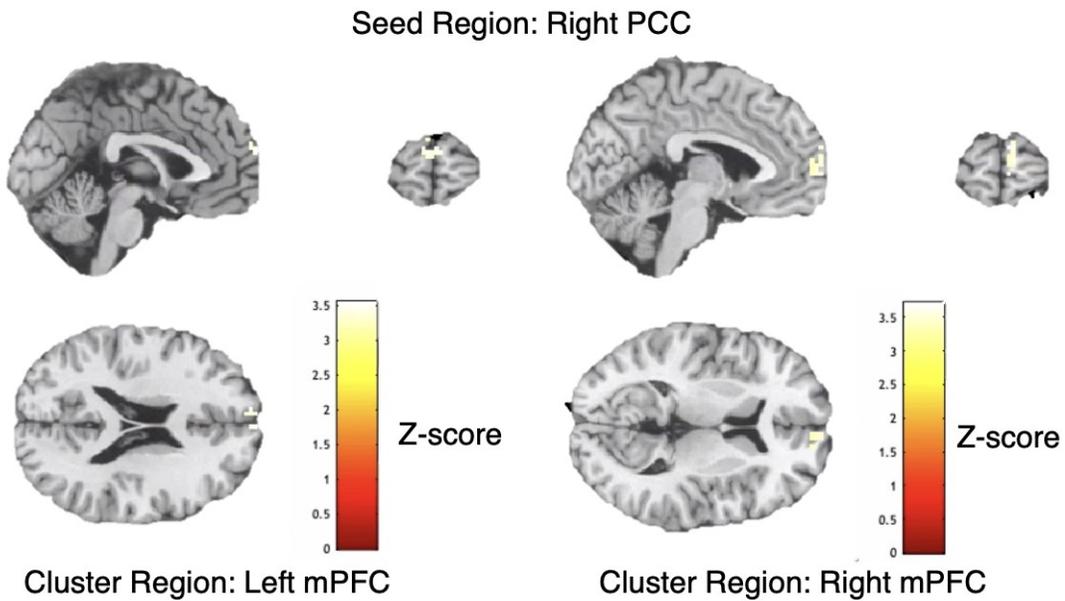
Figure 2

FC Within the DMN of the Concussion Group Positively Associated with Age

2a.



2b.



Note. Functionally connected clusters between the left PCC and bilateral mPFC (**2a**) and right PCC and bilateral mPFC (**2b**) were found to be significantly positively associated with age in the multivariate regression analyses completed with the concussion group (n=53). Age, sex, randomization group,

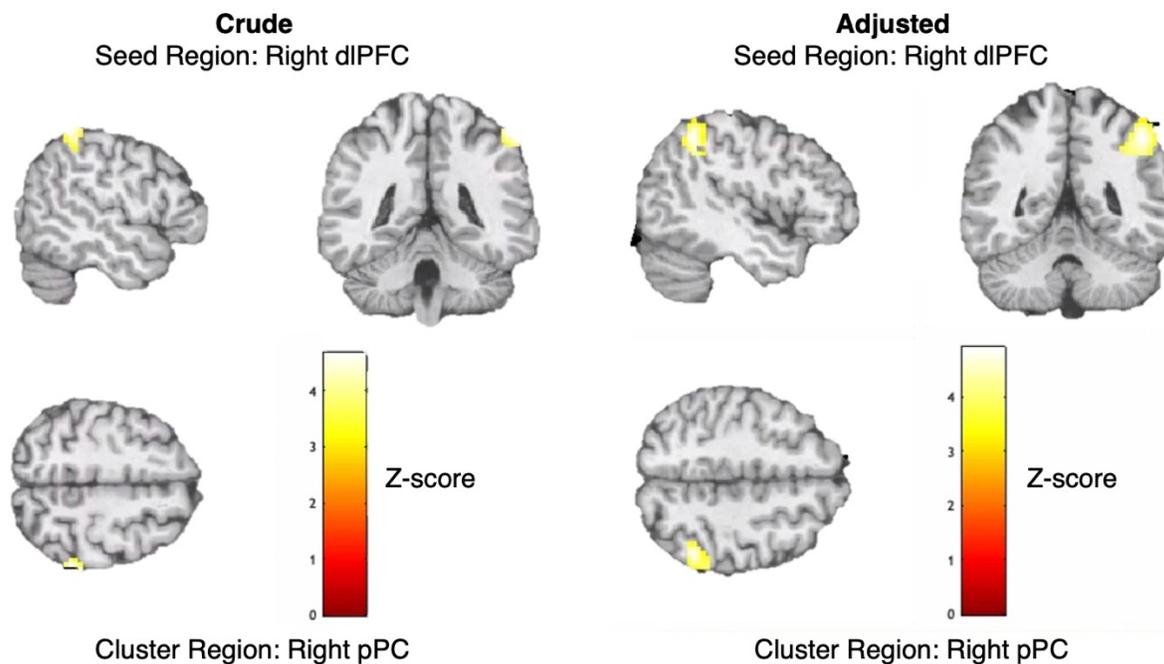
composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. DMN=default mode network; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex

Post-hoc Power Analysis. With the alpha error probability and effect size defined as 0.05 and 0.15, respectively, and with a sample size of 53 and 6 predictors, the power of the regression analysis was determined to be 0.788 (or a 79% probability that a Type II error did not occur in the analysis).

Secondary Analysis of FC Within and Between the DMN, CEN and SN

Between Group Differences in FC Within the CEN and SN

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 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 4 (CEN Network) and Figure 3 for complete ANCOVA cluster results.

Figure 3*Increased FC Within the CEN Identified in the Concussion Group*

Note. A cluster within the right pPC found to have significantly increased FC with the right dlPFC in the concussion group (n=55) compared to the OI group (n=27) in both the crude and adjusted ANCOVA analyses. 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 covaried. $P < 0.001$ (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

SN Within-Network Analyses. 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 (SN network) and Figure 4].

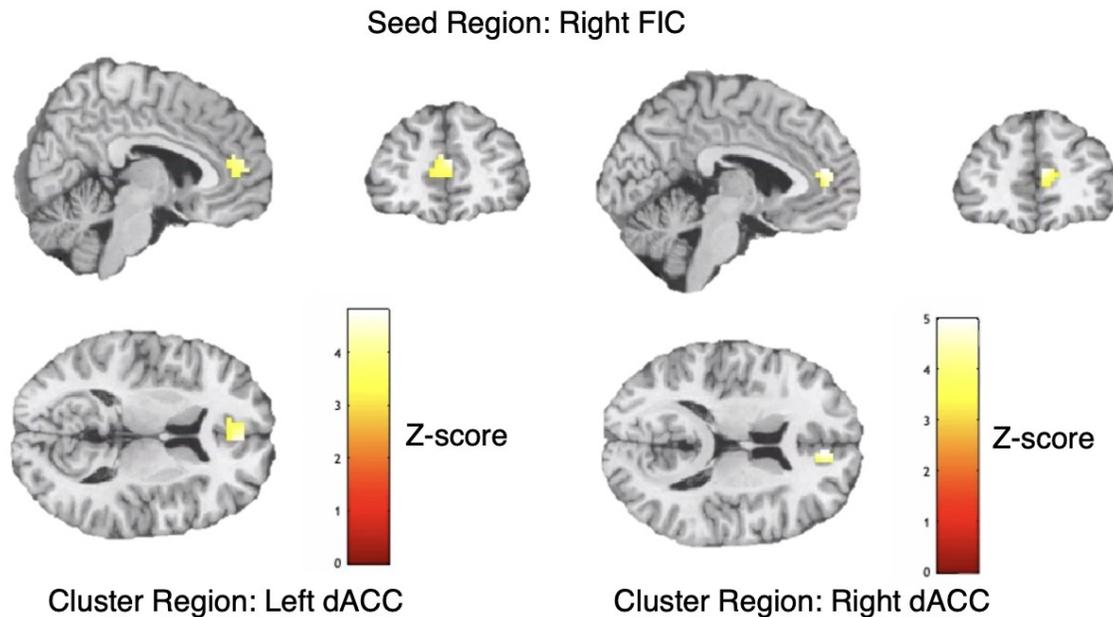
Table 4

Within-Network FC Differences in the Concussion Group Compared to the OI Group

Network	FC ↑ or ↓	Seed Region	Significant Region	Cluster- size (voxels ^a)	Peak MNI coordinates			P value
					x	y	z	
CEN	↑	Right dlPFC	Right pPC	145	45	-48	51	0.001
SN	↑	Right FIC	Left dACC	61	0	48	15	0.001
			Right dACC	41	3	45	15	0.002

Note. 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 covaried. $P < 0.001$ (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=frontoinsula cortex; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex; pPC=posterior parietal cortex; SN=salience network

^a Voxel size = 3.6 mm x 3.6 mm x 3.6 mm

Figure 4*Increased FC Within the SN Identified in the Concussion Group*

Note. Clusters within the bilateral dACC found to have significantly increased FC with the right FIC in the concussion group ($n=55$) compared to the OI group ($n=27$) in the ANCOVA analyses. 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 covaried. $P < 0.001$ (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=frontoinsula cortex; SN=salience network

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 but decreased FC in the concussion group compared to the OI group between the CEN-DMN. 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 Figure 5). 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 Figure 6). Finally, 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 Figure 7). Complete cluster results can be found in Table 5.

Table 5

Between-network FC Differences in the Concussion Group Compared to the OI Group

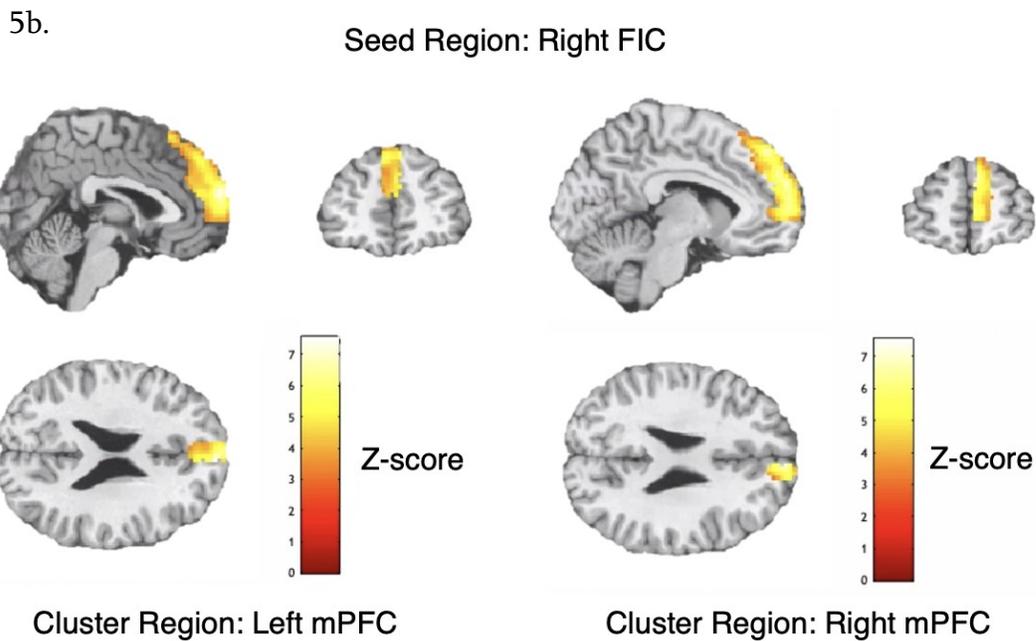
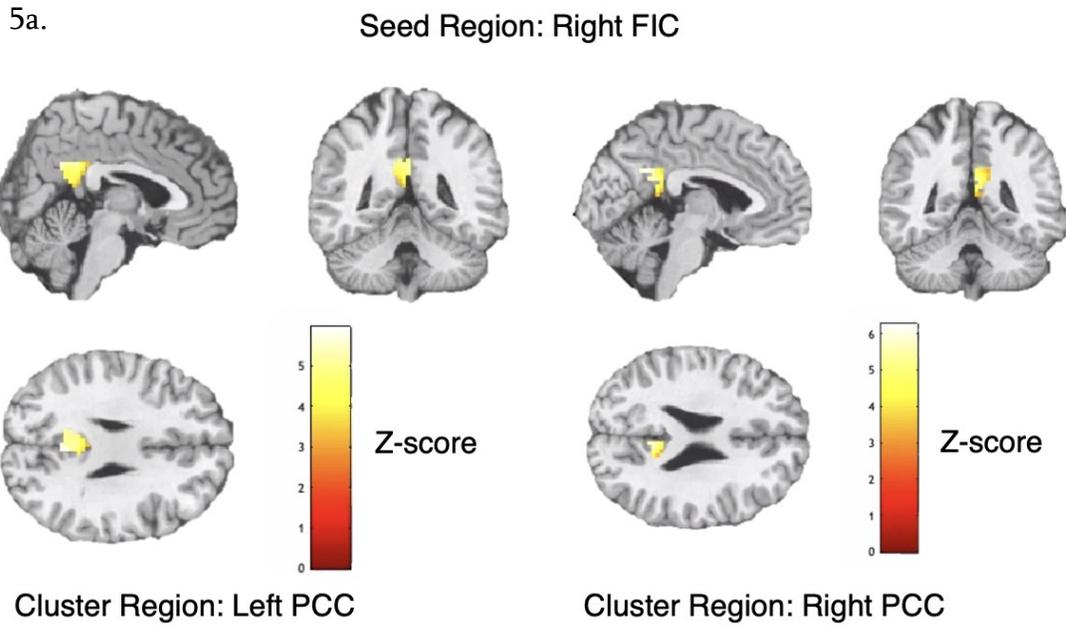
Network(s)	FC ↑ or ↓	Seed Region	Significant Region	Cluster- size (voxels ^a)	Peak MNI coordinates			P Value
					x	y	z	
SN-DMN	↑	Right FIC	Left PCC	84	0	-54	30	0.001
			Right PCC	56	3	-54	30	0.002
			Left mPFC	580	-3	63	18	0.000
			Right mPFC	490	3	60	24	0.000
SN-CEN	↑	Right FIC	Left dlPFC	81	-24	30	48	0.007
			Right dlPFC	107	39	18	51	0.004
CEN-DMN	↓	Right dlPFC	Left PCC	25	-6	-48	21	0.006

Note. 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 covaried. $P < 0.001$ (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=frontoinsula cortex; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex; pPC=posterior parietal cortex; SN=saliience network

^a Voxel size = 3.6 mm x 3.6 mm x 3.6 mm

Figure 5

Increased FC Between the SN and DMN Identified in the Concussion Group

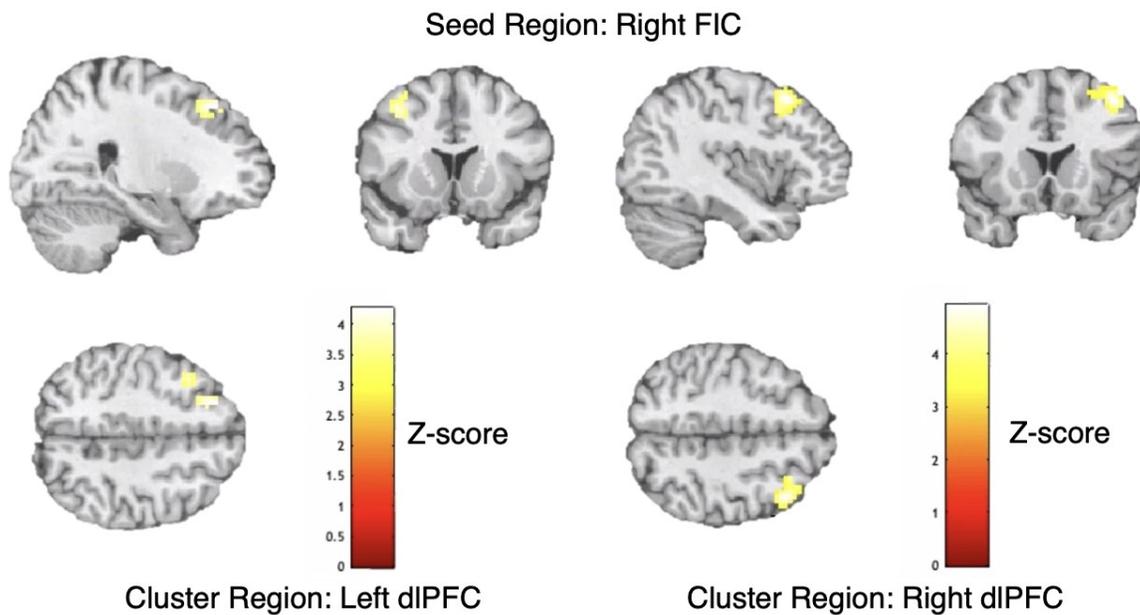


Note. ANCOVA analyses revealed clusters within the bilateral PCC (**5a**) and mPFC (**5b**) with significantly increased FC with the right FIC in the concussion group (n=55) compared to the OI group (n=27). Age, sex, handedness, randomization group, and composite diagnostic score (self-reported

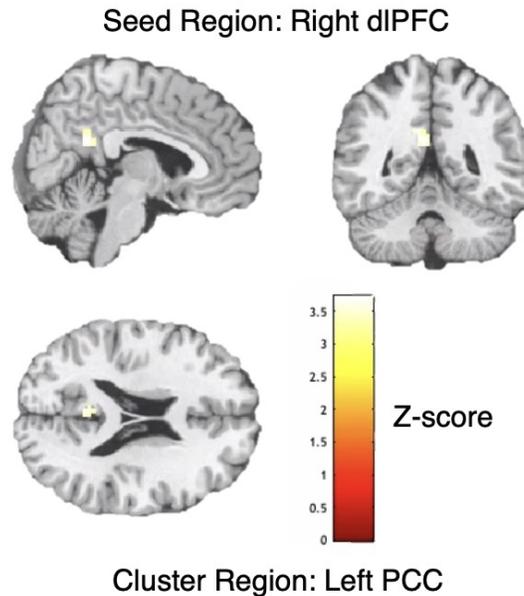
number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) were covaried. $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{FWE} < 0.05$ and extent threshold of 10 voxels was considered significant. DMN=default mode network; FIC=frontoinsula cortex; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex; SN=saliience network

Figure 6

Increased FC Between the SN and CEN Identified in the Concussion Group



Note. Clusters within the bilateral dlPFC found to have significantly increased FC with the right FIC in the concussion group (n=55) compared to the OI group (n=27) in the ANCOVA analyses. 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 covaried. $P < 0.001$ (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; FIC=frontoinsula cortex; SN=saliience network

Figure 7*Decreased FC Between the CEN and DMN Identified in the Concussion Group*

Note. ANCOVA analyses revealed a cluster within the left PCC with significantly decreased FC with the right dlPFC 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 covaried. $P < 0.001$ (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

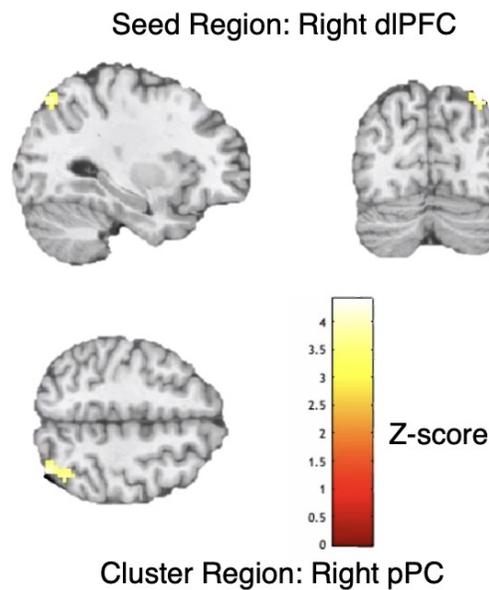
Association Between HRQoL and FC Within and Between the DMN, CEN and SN

Within-Network Analyses. The crude and adjusted analyses revealed no significant associations between total PedsQL score at 4 weeks post-injury and FC within the CEN and SN at whole brain level threshold of $p_{uncorr} < 0.001$. However, a cluster within the right pPC ($p_{FWE}=0.027$; 36 voxels) that was functionally connected with the right dlPFC was found to be positively associated with age (see Table 6 and Figure 8).

Additional crude and adjusted regression analyses assessing the associations between the individual domains of the PedsQL (physical, emotional, social, and school) and FC within the CEN and SN revealed no significant findings at whole brain level threshold of $p_{\text{uncorr}} < 0.001$.

Figure 8

FC Within the CEN of the Concussion Group Positively Associated with Age



Note. A cluster within the right pPC that was functionally connected with the right dlPFC was found to be significantly positively associated with age in the multivariate regression analyses completed with the concussion group ($n=53$). Age, sex, randomization group, composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{\text{FWE}} < 0.05$ and extent threshold of 10 voxels was considered significant. CEN=central executive network; dlPFC=dorsolateral prefrontal cortex; pPC=posterior parietal cortex

Between-Network Analyses. The crude and adjusted regression analyses revealed no significant associations between total PedsQL score at 4 weeks post-injury and FC between the

DMN-SN, DMN-CEN, and CEN-SN at whole brain level threshold of $p_{\text{uncorr}} < 0.001$. However, clusters in the left mPFC ($p_{\text{FWE}}=0.011$, 79 voxels; $p_{\text{FWE}}=0.037$, 16 voxels) and right mPFC ($p_{\text{FWE}}=0.033$; 13 voxels) of the DMN that were functionally connected with the right FIC of the SN were significantly positively associated with composite diagnostic score (see Figure 9). In addition, a cluster in the right PCC ($p_{\text{FWE}}=0.01$; 10 voxels) of the DMN that was functionally connected with the right dlPFC of the CEN was significantly positively associated with composite diagnostic score (see Figure 10). Finally, a cluster in the left mPFC of the DMN that was functionally connected with the right FIC of the SN was found to be significantly positively associated with being female (see Figure 11). See Table 6 for complete cluster results.

Table 6

FC Associated with Age, Sex and Composite Diagnostic Score

Network(s)	Associated Variable	Seed Region	Significant Region	Cluster-size (voxels ^a)	Peak MNI coordinates			P Value
					x	y	z	
CEN	Age	Right dlPFC	Right pPC	36	33	-75	54	0.027
DMN-CEN	Composite	Right dlPFC	Right PCC	10	9	-48	30	0.01
SN-DMN	Composite	Right FIC	Left mPFC	79	0	45	39	0.011
				16	-3	48	24	0.037
			Right mPFC	13	3	51	36	0.033
SN-DMN	Female	Right FIC	Left mPFC	16	-3	54	30	0.037

Note. Age, sex, randomization group, composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold.

A cluster threshold of $p_{\text{FWE}} < 0.05$ and extent threshold of 10 voxels was considered significant.

CEN=central executive network; dlPFC=dorsolateral prefrontal cortex; DMN=default mode network;

FIC=frontoinsula cortex; mPFC=medial prefrontal cortex; PCC=posterior cingulate cortex;

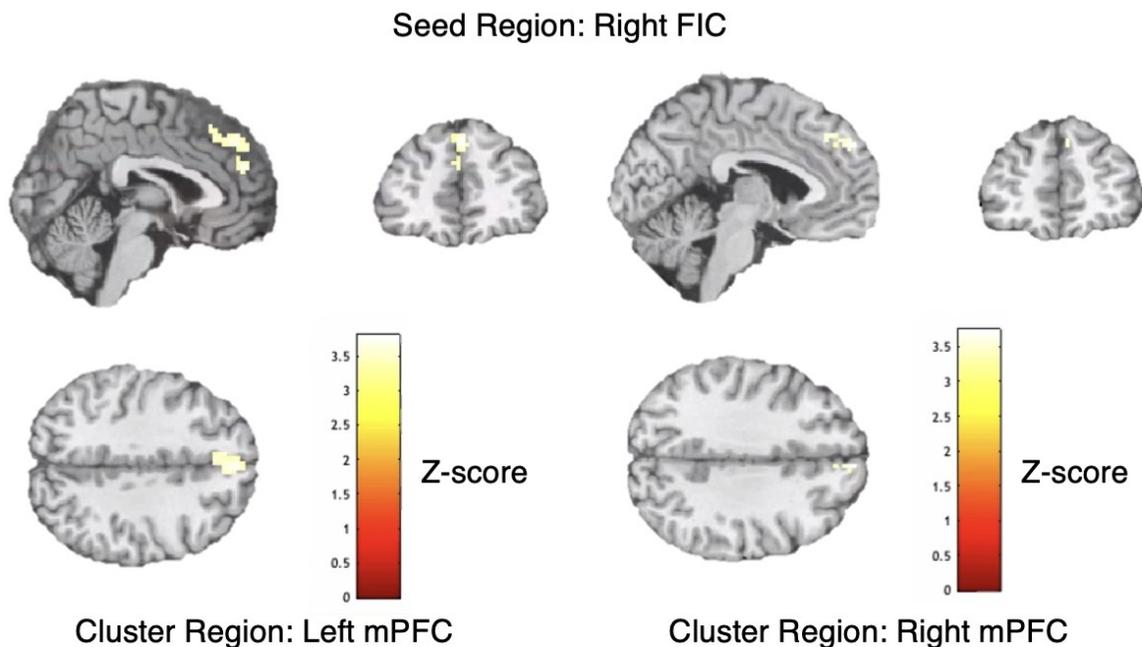
pPC=posterior parietal cortex; SN=salience network

^a Voxel size = 3.6 mm x 3.6 mm x 3.6 mm

Additional crude and adjusted regression analyses assessing the associations between the individual domains of the PedsQL (physical, emotional, social, and school) and FC between the DMN-SN, DMN-CEN, and CEN-SN, revealed no significant findings at whole brain level threshold of $p_{\text{uncorr}} < 0.001$.

Figure 9

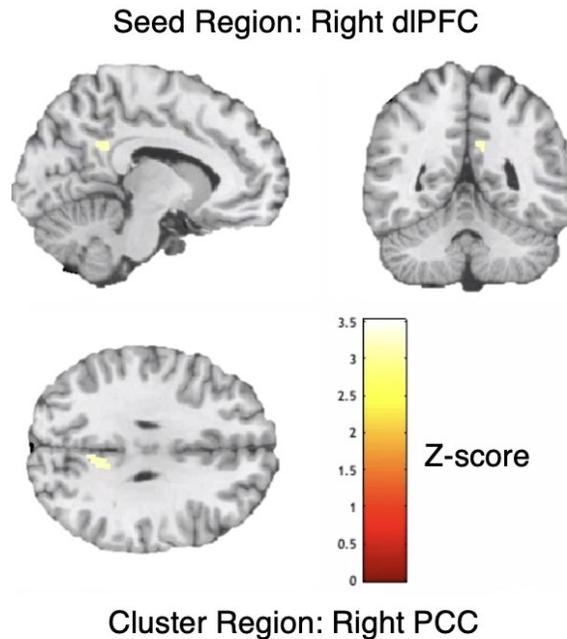
FC Between the SN and DMN of the Concussion Group Positively Associated with Composite Diagnostic Score



Note. Clusters within the bilateral mPFC that were functionally connected with the right FIC were found to be significantly positively associated with composite diagnostic score in the multivariate regression analyses completed with the concussion group ($n=53$). Age, sex, randomization group, composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (uncorrected) was used as the whole-brain voxel threshold. A cluster threshold of $p_{\text{FWE}} < 0.05$ and extent threshold of 10 voxels was considered significant. DMN=default mode network; FIC=frontoinsular cortex; mPFC=medial prefrontal cortex; SN=salience network

Figure 10

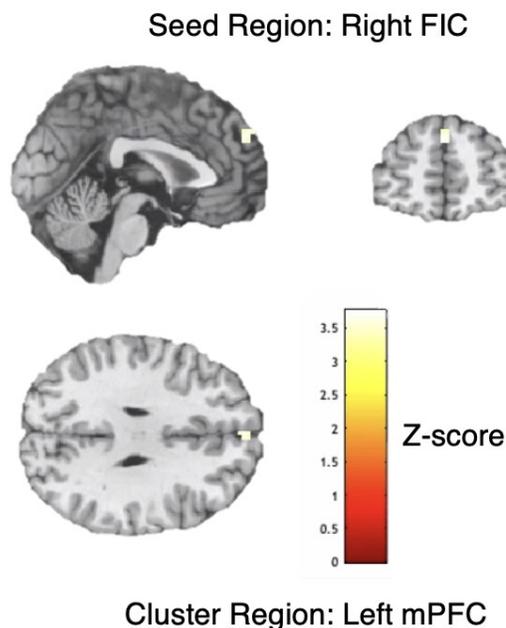
FC Between the CEN and DMN of the Concussion Group Positively Associated with Composite Diagnostic Score



Note. A cluster within the right PCC that was functionally connected with the right dlPFC was found to be significantly positively associated with composite diagnostic score in the multivariate regression analyses completed with the concussion group ($n=53$). Age, sex, randomization group, composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (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

Figure 11

FC Between the SN and DMN of the Concussion Group Positively Associated with Sex (Female)



Note. A cluster within the left mPFC that was functionally connected with the right FIC was found to be significantly positively associated with being female in the multivariate regression analyses completed with the concussion group (n=53). Age, sex, randomization group, composite diagnostic score (self-reported number of previous concussions and diagnoses of a learning disability, ADHD, anxiety, and depression) and total HBI score were covaried (where applicable). $P < 0.001$ (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. DMN=default mode network; FIC=fronto-insular cortex; mPFC=medial prefrontal cortex; SN=salience network

Discussion

Summary of Findings

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. Associations of FC

within and between the DMN, CEN and SN and HRQoL were also investigated in concussed youth at 4 weeks post-injury. It was hypothesized that increased within-network connectivity of the DMN and SN, as well as increased connectivity between the DMN and CEN, would be present in the concussion group and would be associated with reduced HRQoL.

Contrary to what was hypothesized, no significant differences in within-network DMN FC were found between the concussion and OI group in both the crude and adjusted analysis. However, increased within-network FC of the CEN and SN were present in the concussion group. Both the crude and adjusted analysis of the CEN revealed a cluster in the right pPC with increased FC to the right dlPFC in the concussion group and the cluster size increased when the covariates were added. As hypothesized, the adjusted SN analysis found increased FC in the concussion group between clusters in the bilateral dACC and the right FIC. In summary, when compared to the OI group, the concussion group had increased connectivity within the CEN and SN but not in the DMN.

Increased FC was also found in the between-network analysis of concussion and OI participants. Adjusted analyses found significantly increased connectivity in the concussion group between clusters in the bilateral PCC and mPFC of the DMN and the right FIC of the SN. Increased connectivity in the concussion group was also found between clusters in the bilateral dlPFC of the CEN and the right FIC of the SN. When comparing connectivity between the DMN and CEN, however, the concussion group had significantly decreased FC compared to the OI group between a cluster in the left PCC and the right dlPFC as opposed to what was hypothesized. In summary, increased connectivity between the DMN-SN, CEN-SN and decreased connectivity between the DMN-CEN was found in the concussion group when compared to the OI group.

When investigating HRQoL, both crude and adjusted analyses revealed no significant associations between total PedsQL score, or scores on any of the 4 individual PedsQL domains (physical, emotional, social, and school), and FC within and between the DMN, CEN and SN at 4 weeks post-injury. However, an intraconnected cluster within the right hemisphere of the CEN (in the right pPC, functionally connected with the right dlPFC) was found to be positively associated with age. In addition, clusters within the DMN (in the bilateral mPFC) that were functionally connected with the SN (the right FIC), and a cluster in the right PCC of the DMN that was functionally connected with the CEN (the right dlPFC), were positively associated with composite diagnostic score—a score consisting of previous diagnoses of learning disability, ADHD, anxiety, depression, and number of previous concussions. Finally, a cluster in the left mPFC of the DMN that was functionally connected with the right FIC of the SN was found to be significantly positively associated with being female. In summary, HRQoL was not associated with FC within and between these networks in pediatric concussion.

Novel Findings in Connectivity 1 Month after 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 we 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., 2016), between-network connectivity of the DMN and SN, as well as the CEN and SN, has not previously been investigated in a pediatric sample. We found significantly increased connectivity between the SN and DMN, and SN and CEN, in the

concussion group compared to the OI group, and the SN-DMN hyperconnectivity was positively associated with composite diagnostic score and being female.

Interpretation of Results

Increased SN Connectivity in Concussion: Within and Between Networks

Increased SN intraconnectivity has 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). In studies on healthy young adults outside of concussion, increased SN connectivity has been positively correlated with measurements of anxiety (Seeley et al., 2007). Contrastingly, FC between the bilateral FIC and dACC of the SN was 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 as further research is needed to investigate the associations of this intra-connectivity with cognitive symptomatology post-concussion.

The right FIC was also found to have increased connectivity between the bilateral dlPFC, PCC and mPFC. 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 more than 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. Our finding of a positive association between composite diagnostic score and DMN-SN connectivity at 4 weeks post-injury further supports this mechanism since it has been demonstrated that adolescents with pre-existing diagnoses of executive function difficulties and mental illness have worse concussion recovery outcomes (Cairncross et al., 2021). In addition, adolescent females have been shown to have

worse recovery outcomes than younger children and adolescent males of the same age (Ledoux et al., 2019) and a positive association between DMN-SN connectivity and being female was found in our sample. It is also possible these differences in connectivity were present pre-injury due to the pre-existing characteristics, however, the concussion and OI groups did not significantly differ in clinical history and important prognostic variables were covaried 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., 2016). 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.

Differential CEN Connectivity in Concussion: Within and Between Networks

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., 2016). 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).

Similar to the findings by Sullivan et al. (2018), we found reduced connectivity between the DMN and CEN. However, this finding of hypoconnectivity (between the right dlPFC and left PCC) 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., 2016). 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 recovery of the participants at that timepoint. These differences in recovery 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). Additionally, the concussed group DMN-CEN connectivity was positively associated with composite diagnostic score (which includes diagnostic history of anxiety and depression). Since 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), this finding supports the theory that recovery length may impact connectivity as less DMN interference with the CEN is associated with fewer pre-existing conditions.

No Differences in Within-Network DMN Connectivity 1 Month after Concussion

Our finding of no differences in within-network DMN connectivity was partially supported by prior research. In pediatric concussion groups compared to healthy controls, studies have shown no differences in within-network DMN FC (Iyer et al., 2019), as well as increased posterior DMN and decreased anterior DMN FC (Borich et al., 2015) at 1 month post-injury. In the late chronic phase (30-40 months post-injury on average), the findings of increased posterior DMN FC (Orr et al., 2016) and reduced anterior DMN FC (Orr et al., 2016; Plourde et al., 2020) were further supported. 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. In adults 4 weeks post-mTBI, no significant differences were found in DMN FC compared to healthy controls (van der Horn et al., 2016). 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, especially with increased compensation from SN activity. Further analyses comparing the time 1 scans (i.e., within 72 hours) to the 4-

week scans may shed more light on the recovery timeline of the DMN following a pediatric concussion.

Potential Influence of Differential Duration of Recovery

Based on our findings and supporting research, the differential duration of recovery of our concussed sample may be preventing us from identifying group differences in comparison to the OI group. When comparing the preinjury HBI scores (recorded retrospectively in the ED) to the HBI scores at 4 weeks, 69.8% of the concussion group were considered recovered (i.e., had no symptoms at 4 weeks relative to preinjury scores). When dividing into randomization groups, 75% of the rest until asymptomatic group and 66% of the early PA group had recovered. This 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. Concussion studies have found connectivity differences between asymptomatic concussion participants and healthy controls using rs-fMRI (Johnson et al., 2012; Newsome et al., 2016; Orr et al., 2016) and have noted differences in CBF using arterial spin labelling (Barlow et al., 2017; Brooks et al., 2019; Hamer et al., 2020). Further, 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.

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, 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) (Stephens et al., 2018). 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., 2018). Further investigation of CBF recovery patterns of our sample may strengthen our FC findings.

No Associations Found Between FC and HRQoL 1 Month after Concussion

We found no associations between HRQoL in any domain and connectivity of the networks in question. In addition, no significant difference in reported HRQoL was found between the concussion and OI groups. Our findings of no difference in self-reported HRQoL were similar to other mTBI studies in adolescents and adults 1 month post-injury (Losoi et al., 2016; McLeod et al., 2019). The study conducted in concussed adolescents concluded that the impact of HRQoL was minimal in participants who recovered within the first week post-injury (McLeod et al., 2019), suggesting that if associations did exist with connectivity, it would be more apparent in the acute stages of injury (within the first 1-2 weeks). It is possible that a portion of the 70% of participants who did recover by 1 month in our sample may have recovered in the first week, suggesting that analyses comparing those who recovered and those

still symptomatic may give a clearer picture of the influence of HRQoL. In addition, a systematic review noted that only a small percentage (~11%) of patients who suffered a pediatric concussion had consistent decreases in HRQoL 3 and 12 months post-injury and these decreases were associated with persisting symptoms (Fineblit et al., 2016). It has also been demonstrated that youth with worse HRQoL in the acute stage (< 7 days post-injury) were more likely to develop symptoms lasting longer than 1 month (Russell et al., 2017). Since HRQoL was assessed in the acute injury stage of our sample population, assessing its predictive abilities of network connectivity differences at 4 weeks may be beneficial.

Despite our findings of no associations between connectivity and HRQoL, associations have been found in youth with other diagnoses. QoL was negatively correlated with FC between the anterior DMN and the dACC of the SN in 18-year old participants suffering from subthreshold depression who underwent cognitive behavioural therapy (Yokoyama et al., 2018). In children with epilepsy, whole-brain connectivity (measured with an overall clustering coefficient) was negatively correlated with QoL (Nawani et al., 2019) and a negative correlation was found between QoL and the complexity of DMN connectivity in young adults with Down syndrome (Carbó-Carreté et al., 2020). These studies point to the possibility that increased FC may contribute to worse outcomes in multiple conditions. It is also possible that HRQoL does not contribute to connectivity patterns in pediatric concussion. Due to the associations between FC of the DMN-SN and the DMN-CEN and composite diagnostic score, it could be that symptoms of depression, anxiety, ADHD, or learning disabilities that are aggravated by a concussion may be contributing to network connectivity differences seen in the concussion group. Future analyses should explore the associations between these symptoms and network connectivity following a concussion.

Potential Influence of Image Processing Methodology

Image processing methodology could have influenced the ANCOVA and regression results. Rather than taking a more conservative approach to motion correction by scrubbing volumes that exceeded the FD Power criteria for motion (Power et al., 2014), we instead chose to identify those volumes and covary their FD values to preserve statistical power within the analyses. In addition, independent component analysis (ICA) and seed-based analysis are 2 widely used methods implemented for measuring FC. ICA works in a top-down fashion, identifying functional networks within the study sample that can then be analysed and compared (Joel et al., 2011). Seed-based analysis derives the temporal correlation between voxels within regions chosen by the researcher based on past literature (Joel et al., 2011). Since both analyses produce similar results (Joel et al., 2011) and specific brain network dysregulations have been previously identified within the concussion literature, seed-based analyses were conducted with our study sample.

Strengths

This study has numerous strengths. First, the timing of the MRI scans (72 hours and 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.

Limitations

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 & Fransson, 2011). 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. Based on other concussion studies in the literature, 8 mm was used (Iyer et al., 2019; Sridharan et al., 2008).

Insufficient power may have also posed an issue. The power analysis of the regression analysis revealed 79% power, not quite reaching the preferred 80% power to reduce the possibility of type II errors. Therefore, it is possible that connectivity findings were missed due to the insufficient sample size. In addition to power, 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 & 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).

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.

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, age and pubertal status have significant effects on network connectivity and recovery. Additional grouping of smaller age ranges may help identify age-specific results.

Finally, preliminary findings in the CBF data suggest group differences in the concussion sample between those assigned to rest versus PA despite showing no significant differences in PA activity levels. Splitting these groups may help to identify group differences that may also influence network FC.

Future Directions

A number of potential future analyses have been identified from our findings. First, our finding of SN-DMN hyperconnectivity was also found in a study by Liu et al. (2020) with adults. They found that the increased SN-DMN connectivity was correlated with a measurement of executive functioning from the NIH Cognitive Toolbox (Akshoomoff et al., 2014). NIH Cognitive Toolbox data was also collected from our concussed and OI participants at 72 hours and 4 weeks postinjury. Investigating the association between executive functioning and SN-DMN connectivity in our sample may shed light on whether the hyperconnectivity is compensatory or maladaptive 1 month following injury in the pediatric population.

Second, due to the finding that composite diagnostic scores were associated with DMN-CEN and DMN-SN connectivity, and the many findings in the literature linking connectivity between these regions to symptomology, assessing the associations between individual components of the composite score (e.g., diagnosis of depression, anxiety, or ADHD) and connectivity may be beneficial. This could shed light on the most prevalent symptoms or diagnoses associated with recovery and aberrant connectivity of those particular networks.

Third, it is suggested by the concussion literature that the stage of recovery may influence network connectivity. Since our sample was not fully recovered by 4 weeks, future analyses that divide participants by those still symptomatic versus those who are asymptomatic would be beneficial in order to further define brain network states in recovery following pediatric concussion.

Fourth, due to the associations between perfusion and network connectivity, comparing brain network connectivity to the regional perfusion data of the same study participants (collected at the same time points as the resting-state data) may further pinpoint brain network dysregulation post-concussion.

Fifth, future analyses should investigate the predictive value of acute HRQoL for network connectivity differences at 4 weeks post-injury since HRQoL (when measured in the acute stage) has been demonstrated to predict recovery outcomes in the chronic stage and is typically normalized by 1 month post-injury.

Finally, considering there were no differences in HBI or HRQoL measures between the concussion and OI groups, including a comparative sample of uninjured participants may provide more insight to further differentiate brain network changes following a concussion versus a non-head injury.

Conclusion

To our knowledge, this is the first study to investigate FC between all 3 networks in a resting-state and its associations with quality of life following a pediatric concussion. Although no associations were found between health-related quality of life and functional connectivity, our findings suggest patterns of network compensations 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, however in doing so, may contribute to cognitive fatigue over time. Decreased connectivity between the CEN and DMN may be associated with improved recovery outcomes due to the positive association between increased connectivity and pre-existing conditions shown to prolong recovery. Future analyses are needed to assess these network connectivity characteristics based on recovery status and their associations with specific pre-existing diagnoses and cognition.

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Appendix A

Clinical Measures

Appendix A1

The Pediatric Quality of Life Inventory (PedsQL™) is protected by a copyright agreement that does not permit its inclusion in this thesis.

Appendix A2

Health and Behavior Inventory

Directions: Below is a list of problems you may or may not have. For each problem, please rate yourself using the scale below based on how you have felt in the last week.

0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often

1. I have trouble paying attention
2. I get distracted easily
3. I have a hard time concentrating
4. I have problems remembering what people tell me
5. I have problems following directions
6. I daydream too much
7. I get confused
8. I forget things
9. I have problems finishing things
10. I have trouble figuring things out
11. It's hard for me to learn new things
12. I have headaches
13. I feel dizzy

- 14. I feel like the room is spinning
- 15. I feel like I'm going to faint
- 16. Things are blurry when I look at them
- 17. I see double
- 18. I feel sick to my stomach
- 19. I get tired a lot
- 20. I get tired easily

Appendix A3

Diagnostic History

Developmental History:

Prior diagnosis of learning disabilities? Yes No

Prior diagnosis of Attention-deficit / Hyperactivity Disorder? Yes No

Prior diagnosis of other developmental disorder? Yes No

If yes, please specify: _____

Psychiatric History:

Prior diagnosis of Anxiety? Yes No

Prior diagnosis of Depression? Yes No

Prior diagnosis of a sleep disorder? Yes No

Prior diagnosis of other psychiatric disorder? Yes No

If yes, please specify: _____

Appendix B

Enrolment Breakdown of the Concussion and OI Groups

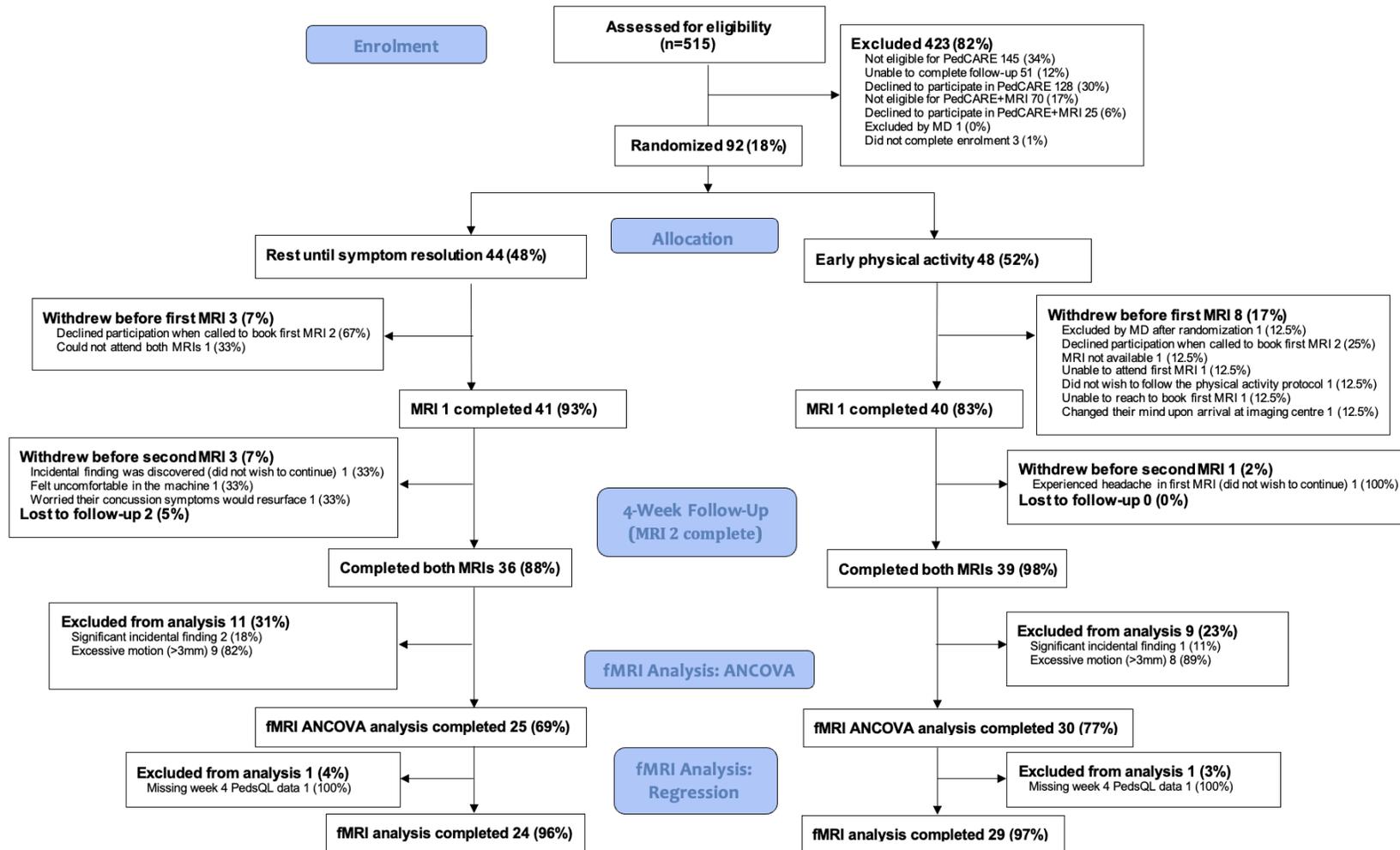


Figure B1. Enrolment, adherence and final sample breakdown of the randomized concussion participants

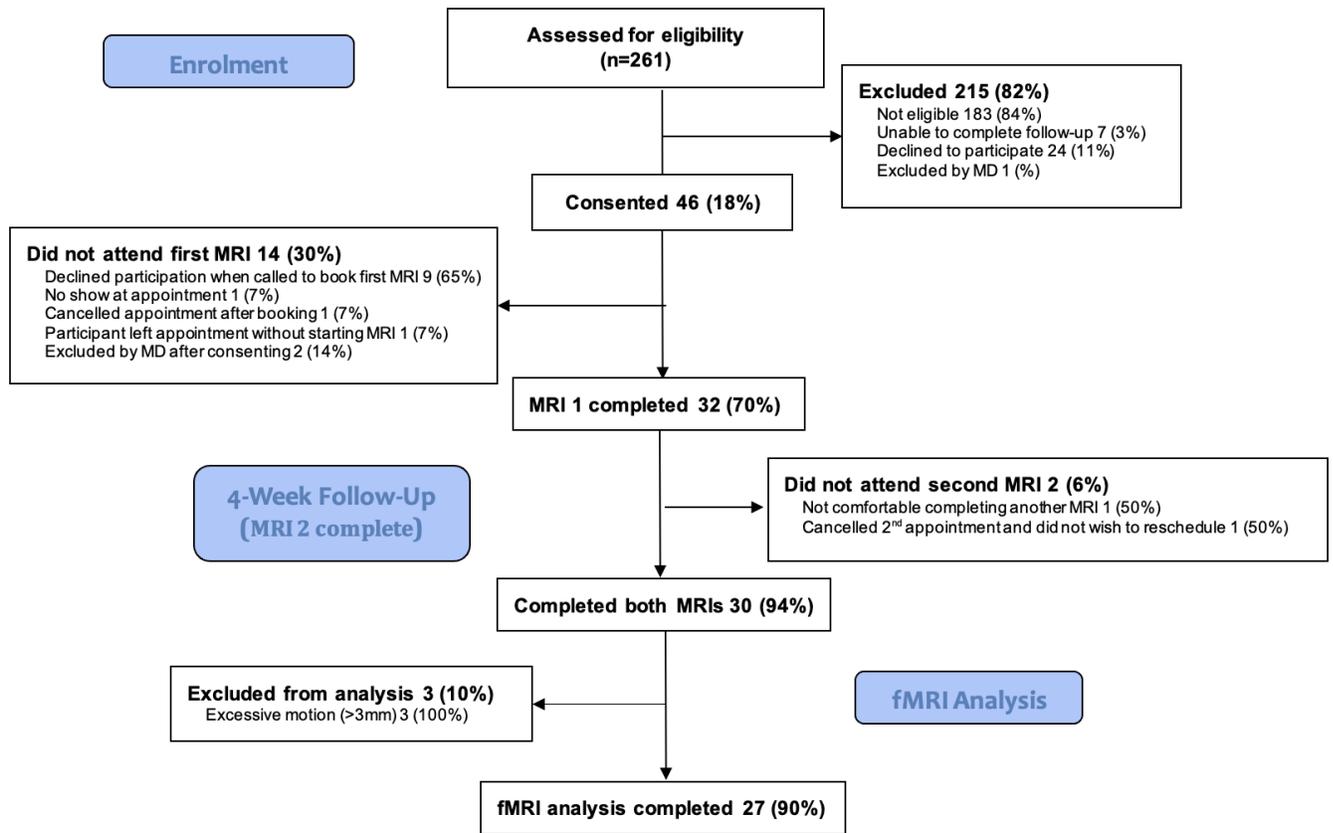


Figure B2. Enrolment, adherence and final sample breakdown of the Orthopedic Injury (OI) participants

Appendix C

Average Daily PA Levels of the PA Group (Group B) and Rest until Asymptomatic Group

(Group A) Concussion Participants Over 14 Days (measured in minutes)

Physical Activity Intensity	Group A (n=20)	Group B (n=26)	P Value ^a
Median light-intensity physical activity (LPA) (IQR)	190.23 (149.71-228.44)	182.66 (134.00-217.02)	0.788
LPA days 1-3 (IQR)	155.67 (134.00-206.00)	153.33 (123.00-201.00)	0.733
LPA days 4-7 (IQR)	182.25 (158.75-234.67)	191.75 (143.25-221.00)	0.689
LPA days 8-13 (IQR)	208.90 (163.83-228.17)	197.53 (153.50-242.67)	0.182
Median moderate-intensity physical activity (MPA) (IQR)	24.86 (8.12-40.73)	24.94 (12.56-36.00)	0.929
MPA days 1-3 (IQR)	7.00 (2.00-19.00)	8.33 (1.33-18.50)	0.948
MPA days 4-7 (IQR)	29.00 (6.67-53.50)	22.50 (13.00-41.50)	0.661
MPA days 8-13 (IQR)	43.75 (17.33-63.67)	35.90 (25.40-51.83)	0.403
Median vigorous-intensity physical activity (VPA) (IQR)	0.12 (0.00-0.77)	0.17 (0.00-0.50)	0.844
VPA days 1-3 (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.376
VPA days 4-7 (IQR)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.082
VPA days 8-13 (IQR)	0.40 (0.00-1.00)	0.00 (0.00-0.60)	0.459
Median moderate- to vigorous-intensity physical activity (MVPA) (IQR)	25.15 (8.12-41.83)	25.03 (14.00-37.78)	0.929
MVPA days 1-3 (IQR)	7.00 (2.00-19.00)	8.33 (1.33-19.00)	0.958
MVPA days 4-7 (IQR)	29.50 (6.67-54.50)	22.50 (13.00-41.75)	0.652
MVPA days 8-13 (IQR)	44.75 (17.33-64.33)	37.20 (25.40-52.67)	0.431

^a All variables of LPA were analyzed with independent sample t-tests. All other variables had non-normal distributions, therefore, were analyzed with Mann-Whitney U tests. Significance was defined by $p < 0.05$.