Regional Blood Flow Alterations Following Pediatric Concussion: A PedCARE^{+MRI} Substudy

by

Rachel Kardish

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Carleton University, Ottawa, Ontario

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Rachel Kardish

Abstract

Background: This study examined whether cerebral blood flow (CBF) differed between children with concussion and orthopedic injury (OI) controls at 72 hours and 4 weeks post-injury. It also examined whether psychological resilience and acute CBF improved prediction of 2- and 4-week concussion symptoms beyond the existing 5P score prediction tool.

Methods: Concussed and OI participants, aged 10-18 years, were enrolled from CHEO's Emergency Department. Arterial spin labelling was used to measure CBF at 72 hours and 4 weeks post-injury. Symptoms were assessed using the Health and Behaviour Inventory at 2 and 4 weeks. Self-reported psychological resilience was measured with the Connor-Davidson Resilience Scale. Crude and adjusted mixed model analyses were conducted to assess absolute CBF (aCBF) and normalized aCBF in both groups over time. Multiple regression analyses assessed whether the 5P score, regional CBF, and resilience combined predicted 2- and 4-week symptoms for the concussion group.

Results: A total of 70 participants with concussion (M_{age}=13.05±2.02, 47% female) and 29 with OI (M_{age}=12.59±1.97, 41% female) were included. For aCBF, a significant group*time interaction was found in the left anterior cingulate/medial frontal cortex (L_ACC_MFC) and right middle frontal gyrus (R_MFG). In the L_ACC_MFC, the concussion group showed increased CBF compared to OIs both time points (p<.001). In the R_MFG, CBF was increased compared to OIs at 4 weeks (p<.001), but not 72 hours. In both regions, CBF increased over time in the concussion group (p≤.001), but did not differ between time points for OIs. Concussed participants also had increased CBF in the left angular gyrus (L_angular) that did not differ between time points. For normalized aCBF, the concussion group displayed significantly

increased CBF in the L_ACC_MFC, R_MFG, and L_angular, and significantly decreased CBF in the right superior temporal gyrus (R_STG), right fusiform gyrus (R_fusiform), and bilateral lingual gyri. The multiple regression model revealed that the 5P score, L_ACC_MFC or R_MFG CBF, and resilience combined did not significantly predict 2- or 4-week symptoms for the concussion group.

Conclusion: Though clinical significance remains unclear, these results are an important contribution to the pediatric concussion literature, as they indicate clear CBF alterations in pediatric concussion with some regional CBF varying in time. These results are important for understanding persistent neurobiological deficits after concussion.

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List of Abbreviations

5P	Predicting and Preventing Post-Concussion Problems in Pediatrics
aCBF	Absolute cerebral blood flow
ADHD	Attention-Deficit/Hyperactivity Disorder
ASL	Arterial spin labeling
ATP	Adenosine triphosphate
AUC	Area under the curve
BIC	Brain imaging centre
CBF	Cerebral blood flow
CD-RISC	Connor-Davidson Resilience Scale
CHEO	Children's Hospital of Eastern Ontario
CT	Computerized tomography
ED	Emergency department
FA	Flip angle
FD	Framewise displacement
FOV	Field of view
FWE	Family-wise error
HBI	Health and Behaviour Inventory
L_ACC_MFC	Left anterior cingulate cortex/medial frontal cortex
L_Angular	Left angular gyrus
L_MFG	Left middle frontal gyrus
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NVU	Neurovascular unit
OI	Orthopedic injury
PCSI	Post-Concussion Symptom Inventory
PedCARE	Pediatric Concussion Assessment of Rest and Exertion
PERC	Pediatric Emergency Research Canada
PET	Positron emission tomography
PPCS	Persistent post-concussion symptoms
R_fusiform	Right fusiform gyrus
R_MFG	Right middle frontal gyrus
R_STG	Right superior temporal gyrus
R_SMG	Right supramarginal gyrus
RA	Research assistant
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
ROI	Region of interest
SNR	Signal-to-noise ratio

SPM12	Statistical Parametric Mapping 12
SPSS	Statistical Package for the Social Sciences
TBI	Traumatic brain injury
TE	Echo time
TR	Repetition time

List of Tables

Table 1. 5P Score Criteria and Points Allotment *12*
Table 2. Summary of Assessments *15*
Table 3. Participant Demographics *21*
Table 4. Whole Brain Absolute Perfusion Analysis *24*
Table 5. Whole Brain Normalized Absolute Perfusion Analysis *30*
Table 6. Mean Values for the Variables Included in the Multiple Regression Analyses *37*

List of Figures

Figure 1. Enrolment, attrition, and final sample breakdown for concussed participants *19*
Figure 2. Enrolment, attrition, and final sample breakdown for orthopedic injury participants *20*
Figure 4. Mean global grey matter perfusion. *23*
Figure 5. Whole brain absolute perfusion results *25*
Figure 6. Mean absolute perfusion *27*
Figure 7. Mean crude absolute perfusion *29*
Figure 8. Whole brain normalized absolute perfusion. *31*
Figure 9. Mean normalized absolute perfusion. *34*
Figure 10. Mean crude normalized absolute perfusion *36*

Table of Contents

Abstract ..... *ii*

Acknowledgements ..... *iv*

List of Abbreviations ..... *v*

List of Tables ..... *vii*

List of Figures ..... *viii*

Introduction *1*

Impact of concussion: Persistent post-concussive symptoms. **2**

Predicting post-concussive symptoms. **3**

Potential predictors of persistent symptoms: Cerebral blood flow. **4**

Potential predictors of persistent symptoms: Psychological resilience **7**

Study objectives and hypotheses **9**

Methods *10*

Study design and setting **10**

Inclusion and exclusion criteria **11**

Measures **12**

5P score. 12

MRI acquisition. 13

Psychological resilience. 13

Post-concussion symptoms. 14

Procedure **14**

Data Analysis **16**

Preprocessing 16

Statistical analyses. 17

Results *18*

Participant Characteristics **18**

Analysis 1: Changes in CBF by group and by time point **22**

Mean global grey matter perfusion 22

Absolute perfusion 24

Normalized absolute perfusion: adjusting for mean global grey matter perfusion 30

Analysis 2: 5P score, resilience, and CBF predicting 2- and 4-week concussion symptoms **36**

Exploratory analyses: acute CBF predicting 4-week symptoms by group **38**

Moderating effect of group on perfusion and HBI scores 38

Discussion *39*

Changes in CBF by group and by time point **41**

Mean global grey matter perfusion 41

Regional perfusion 41
5P score, resilience, and CBF predicting 2- and 4-week concussion symptoms.....44
Exploratory analyses: acute CBF predicting 4-week symptoms by group 45
***Strengths*.....48**
***Limitations*.....49**
***Future Directions*.....49**
***References*.....52**

Introduction

Concussion is a form of mild traumatic brain injury caused by a direct or indirect blow to the head, leading to transient disturbances to brain function (McCrory et al., 2013). In Ontario, more than 35,000 cases of pediatric concussion are reported in physician offices and emergency departments (EDs) each year (Zemek et al., 2017). Common mechanisms of injury include motor vehicle accidents, falls, sport, being struck by an object, and assault (Haarbauer-Krupa et al., 2018).

Disturbances following concussion include disruptions to ionic flux, cerebral blood flow, and neurotransmission (Giza & Hovda, 2014). Concussion results in a wide range of symptoms that fall into 4 categories: somatic, cognitive, emotional/behavioural, and sleep-related symptoms (Pardini et al., 2004). Generally, symptoms subside without the need for intervention (Graham et al., 2014; Shirley et al., 2018) and resolve within 7 to 10 days for adults (McKeon et al., 2013).

Children are more likely to sustain concussions than adults and are also prone to prolonged recovery due to ongoing brain development (McCrory et al., 2013). Recovery of symptoms usually occurs within 2 to 4 weeks in children (Ledoux et al., 2019), but a significant proportion experience persistent post-concussion symptoms (PPCS). Approximately 30% of children experience PPCS (Zemek et al., 2016), which can have serious short- and long-term consequences for school performance, mental health, and quality of life (Ewing-Cobbs et al., 2018; Novak et al., 2016; Yeates et al., 2012). It is important to explore ways to mitigate risk of PPCS, and therefore this thesis will investigate whether cerebral blood flow alterations and psychological resilience can improve PPCS prediction beyond an existing prediction tool.

Impact of concussion: Persistent post-concussive symptoms.

When a concussion occurs, the impact causes the brain to shift within the skull, leading to axonal damage and a subsequent "neurometabolic cascade" (Giza & Hovda, 2014). Initially, the impact produces shearing forces, which disrupts neuronal membranes and leads to axonal stretching. This damage is thought to cause ionic flux disruptions and an indiscriminate release of glutamate. In an effort to restore homeostasis, sodium-potassium pumps work in overdrive, which requires an increase in ATP production. This results in increased glucose metabolism, ultimately diminishing energy reserves. Additionally, excess calcium is sequestered to the mitochondria, hindering their ability to produce more ATP. There is a simultaneous increased demand for cellular energy paired with a decrease in cerebral flow, leading to impaired metabolism. Although yet to be confirmed, it is thought that these physiological changes correlate with clinical symptoms (Giza & Hovda, 2014).

Among children, pronounced symptom change following concussion tends to occur within a 2-week window and plateaus afterwards (Ledoux et al., 2019). A significant proportion of children, approximately 30%, experience symptoms lasting months post-injury (Zemek et al., 2016). PPCS in children are multidimensional, and are defined as somatic, cognitive, emotional/behavioural, and sleep-related symptoms lasting beyond 1-month post-injury (Zemek et al., 2016).

PPCS are thought to occur due to autonomic dysfunction following concussion. Both the parasympathetic and sympathetic divisions of the autonomic nervous system are affected (Blennow et al., 2012; Leddy et al., 2010), leading to common symptoms including dizziness, difficulty concentrating, and headache (Permenter et al., 2017). Persistence of symptoms is likely dependent on the interaction of numerous biopsychosocial factors (Wäljas et al., 2015), including

pre-injury physical and mental health conditions (Fordal et al., 2022; Gornall et al., 2019), poor coping skills (Cassetta et al., 2021), low resilience (Fordal et al., 2022; Skandsen et al., 2021), and personality characteristics (Garden et al., 2010; Skandsen et al., 2021).

PPCS may lead to significant functional impairment, interfering with academic performance (Holmes et al., 2020), sport participation (Cancelliere et al., 2014), and quality of life (Novak et al., 2016). Since PPCS can take a serious toll on a child's health and wellbeing, it is important to evaluate strategies to prevent or mitigate the potentially detrimental effects of PPCS. Moreover, since pronounced symptom reduction tends to occur within a 2-week window (Ledoux et al., 2019), early prediction of those most at risk can allow for early intervention.

Predicting post-concussive symptoms.

To better manage acute symptoms and prevent PPCS, it is necessary to develop tools to identify those most at risk. In 2013, the Pediatric Emergency Research Canada (PERC) concussion team conducted a study to derive and validate an easy-to-use PPCS prediction rule for clinicians called the 5P score (Zemek et al., 2013, 2016). A total of 3063 participants aged 5 to 17 years were recruited within 48 hours post-concussion from 9 pediatric EDs across Canada. Based on previous research and clinical experience, the research team selected 46 variables thought to be most associated with symptom persistence (Zemek et al., 2013). Univariate analysis assessed the strength of the relationship between each variable and PPCS, and those that were reliable and independently associated with PPCS were included in the final multivariable model. PPCS was defined as 3 or more new or worsening symptoms at 4 weeks compared to pre-injury, and the outcome variable was dichotomous: presence or absence of PPCS.

The derived rule included 9 variables most associated with prolonged recovery: age, sex, longest symptom duration from prior concussions, migraine history, answering questions slowly, abnormal tandem balance, headache, noise sensitivity, and fatigue.

Through comparison of the 5P score and unassisted physician prediction of PPCS, it was determined that the 5P score outperforms physician prediction, yet only has modest prediction ability (AUC = .68). Thus, the inclusion of other factors has the potential to improve prediction ability. Neither psychosocial factors nor imaging markers were assessed as part of the original 5P score derivation. Given the functional and structural features of concussion, and that the contribution of pre-injury conditions are better predictors of symptom persistence over time than injury factors (Barlow, 2016; McNally et al., 2013), neuroimaging markers and psychosocial factors may be important considerations in PPCS prediction models.

Potential predictors of persistent symptoms: Cerebral blood flow.

Concussion abnormalities are not visible with standard neuroimaging procedures, such as computerized tomography (CT) scans (McCrory et al., 2017). However, emerging evidence suggests that several advanced neuroimaging modalities that reveal microstructural and functional abnormalities may have prognostic utility for pediatric concussion, one of which is arterial spin labeling (ASL). ASL is a non-invasive functional magnetic resonance imaging (MRI) technique that measures cerebral blood flow (CBF) without the need for injection of contrast agents (Alsop et al., 2015), which makes it a useful tool for studies with children (Chappell et al., 2018). The terms cerebral perfusion and CBF are generally used interchangeably, and they refer to the quantitative measure of the delivery of nutrients and oxygen to tissue measured in units of ml/100g/minute (Petcharunpaisan, 2010). To obtain the

image, a blood-borne tracer is created in the neck through magnetic labeling, which involves inverting the hydrogen nuclei within water molecules using a radiofrequency pulse (Chappell et al., 2018). The image is acquired after a short delay, allowing for the labeled blood to reach the brain and accumulate in tissue (Wang & Licht, 2006). Multiple pairs of labeled and control images are acquired, and subtraction of these images results in a perfusion-weighted image. The perfusion-weighted images are averaged to obtain the final CBF map. Absolute CBF (aCBF), which refers to calibrated regional or global perfusion in units of ml/100g/minute (Chappell et al., 2018), can then be quantified.

The mechanisms contributing to altered blood flow following concussion are not well understood, however various potential mechanisms have been proposed. Cerebral blood flow is regulated by the autonomic nervous system, and concussion leads to a cascade of events resulting in dysregulation of this system (Giza & Hovda 2014). Neurovascular coupling refers to the tight link between local neural activity and CBF (Tan et al., 2014). Following concussion, "neurovascular uncoupling" occurs, in which CBF cannot keep up with increased metabolic demand, leading to a cerebral "energy crisis" (Giza & Hovda, 2014; Tan et al., 2014). This renders the brain susceptible to further damage and injury. Moreover, the neurovascular unit (NVU), which is a term used to describe the interactions between neuronal networks, glial cells, and blood vessels, may be impacted following concussion (Wang et al., 2019). The NVU contributes to normal neurovascular coupling, and therefore damage can lead to altered blood flow and persistent symptoms (Bartnik-Olson et al., 2014). Additionally, cerebral autoregulation, which is the brain's ability to maintain constant perfusion pressure in the face of systemic blood flow changes, is thought to be hindered following concussion (Len & Neary, 2011; Wright et al., 2018). Smooth muscle contributes to autoregulation by constricting or dilating in response to

pressure changes, but TBI can impair this system leading to cerebral hypoperfusion (Villalba et al., 2014). Cerebral vasoreactivity, which refers to the ability of blood vessels to constrict or dilate in response to changes in oxygen and carbon dioxide, is another mechanism thought to be impacted by concussion (Frantz et al., 2017; Purkayastha et al., 2019; Tan et al., 2014).

Although definitions of recovery stages differ between studies, generally, the acute stage refers to <72 hours post-injury, and subacute refers to >72 hours and <3 months (Wang et al., 2020). Alterations in CBF following concussion in both adult and pediatric samples are well documented, however there is considerable variability. In both the acute and subacute stages, both increased CBF and decreased CBF have been observed following concussion, likely due to differences in study design and sample characteristics, such as participant age, injury stage, and symptom status (Barlow et al., 2017; Churchill, Hutchison, Graham, et al., 2017; Maugans et al., 2012; Meier et al., 2015; Sours et al., 2015; Wang et al., 2020). Evaluation of the existing research also revealed many inconsistencies in regional perfusion differences post-concussion (Wang et al., 2020), thus warranting further investigation. Maugans et al. (2012) examined longitudinal CBF in children with sports-related concussion and found that CBF was decreased compared to controls in the acute stage but increased to within 10% of the control group's mean CBF at 4 weeks. Additionally, Barlow et al. (2017) found that at 40 days post-injury, symptomatic and asymptomatic children had increased and decreased perfusion, respectively, compared to healthy controls. Both of these studies are supported by Meier et al. (2015), who found that athletes with a sports-related concussion exhibited lower CBF acutely, which normalized in the subacute stage. It is important to note that this study had a sample of young adults rather than children. A more recent study by Li et al. (2020) examined acute blood flow changes in adults with concussion. They found regions of both increased and decreased CBF, but

increased CBF in the inferior temporal gyrus was negatively correlated with cognitive symptoms. Despite the variability, the general trend appears to be that CBF is reduced in the initial acute stages following concussion among adults and children, and normalizes over the course of recovery (Barlow et al., 2017; Churchill, Hutchison, Graham, et al., 2017; Maugans et al., 2012; Meier et al., 2015; Wang et al., 2016).

While there are demonstrated post-concussion alterations in CBF, most research has focused on symptom correlates at the same time point during which scans were obtained. However, a recent study by Barlow et al. (2021) demonstrated that mean global grey matter aCBF measured at 4 to 6 weeks post-injury predicted recovery at 8 to 10 weeks (AUC = .77) in a pediatric concussion sample. Barlow et al. (2017) previously found that children with PPCS at 1-month post-injury exhibited increased aCBF compared to those who had clinically recovered. Similarly in the 2021 study, CBF was higher in participants with poor recovery compared to good recovery at 4 to 6 weeks, and both declined over the following 4 to 6 weeks. However, there was a significantly steeper decline in aCBF in those with good recovery.

No studies to date have examined whether acute (<72 hour) CBF alterations can predict future symptoms in pediatric concussion. Therefore, investigating acute CBF as a predictor for PPCS in children is warranted.

Potential predictors of persistent symptoms: Psychological resilience.

Psychological resilience refers to the ability to positively adapt when faced with adversity (Connor & Davidson, 2003), such as illness or injury. It is a psychosocial, non-injury factor that is known to influence recovery in a number of conditions and injuries, including concussion. Losoi et al. (2015) examined resilience longitudinally post-concussion in an adult sample and

found that patients with moderate-to-high resilience at one-month reported less fatigue, insomnia, traumatic stress, and depressive symptoms, at one, six, and twelve months. Moreover, Durish et al. (2018, 2019) conducted two studies that examined psychological resilience as a predictor of symptoms in pediatric concussion. In the first study, low resilience predicted higher scores on the Post-Concussion Symptom Inventory, but more so for children who had previously sustained multiple concussions. Those that were more resilient reported lower fatigue and fewer emotional symptoms. In the second study of participants with poor recovery, resilience significantly predicted PPCS, and this was mediated by depressive and anxiety symptoms. More recently, Bunt et al. (2021) found that adolescents and young adults with sports-related concussion who reported themselves as less resilient within 10 days post-injury experienced greater symptom burden and delayed recovery at 3 months. Similarly, Fordal et al. (2022) found that low pre-injury resilience in adults with concussion was associated with persistent symptoms. Taken together, these studies provide a strong rationale to investigate resilience as a predictor of PPCS in pediatric concussion.

Rather than being a stable trait, resilience is a dynamic factor that is modifiable (Shrivastava & Desousa, 2016). Factors thought to promote resilience include social support (Netuveli et al., 2008), cognitive flexibility (Southwick et al., 2005), having a positive outlook (Southwick et al., 2005), an active coping style (Campbell-Sills et al., 2006), as well as higher levels of mindfulness (Mcgillivray & Pidgeon, 2015). Resilience may serve as a moderator between mental health and PPCS, given that resilience is strongly tied to pediatric mental health (Mesman et al., 2021), and poor pre- and post-injury mental health symptoms are known to predict poorer outcomes following concussion (Anderson et al., 2020; Gornall et al., 2021; Langer et al., 2021). Thus, resilience may be a good predictor of symptom burden following

concussion. Promoting resilience in children with low resilience initially post-concussion could therefore prevent or attenuate the long-term effects of PPCS.

Summary

Overall, although prediction ability of the 5P score is promising, it is not perfect (AUC = .68), warranting the consideration of additional factors. Since CBF alterations and psychological resilience have both previously been linked to symptom severity in pediatric concussion, they may have the potential to improve prediction of PPCS/symptom burden when considered in addition to the 5P score. Improving prediction of children most at risk can help clinicians initiate early intervention to prevent or mitigate consequences of PPCS, thereby improving health outcomes and quality of life. This can not only provide relief for patients and their families, but also for the Canadian healthcare system since resources can be directed to those most in need.

Study objectives and hypotheses

The objectives of this study are twofold:

1) To examine blood flow changes, both globally and regionally, in concussed children compared to orthopedic injury (OI) controls at 72 hours and 4 weeks post-injury, and
2) To examine whether the consideration of resilience and CBF alterations, in addition to the 5P clinical risk score, can improve prediction of symptoms at 2 and 4 weeks post-injury in children with concussion.

It is hypothesized that there will be decreased blood flow, both globally and regionally, in concussed participants compared to OI controls at 72 hours. It is expected that OI's CBF will

remain stable over time, and concussed participants' CBF will increase to resemble that of OI controls at 4 weeks. It is also hypothesized that lower resilience, decreased CBF, and a high 5P score combined will better predict symptoms in the concussion group at 2 and 4 weeks than a high 5P score on its own.

Methods

Study design and setting

This study is a planned secondary analysis of a randomized clinical trial (RCT) completed at CHEO from May 2018 to February 2020 called Pediatric Concussion Assessment of Rest and Exertion+MRI (PedCARE^{+MRI}), which was an adjunct study to Pediatric Concussion Assessment of Rest and Exertion (PedCARE) (Ledoux et al., 2019; Ledoux et al., 2022). The primary objective of the PedCARE^{+MRI} study was to investigate whether early resumption of physical activity at 72 hours post-concussion would lead to improved neurophysiological outcomes. Concussed participants were randomized to 2 groups: the physical activity group and the rest until asymptomatic group. OI controls were recruited as well, but not randomized to either group in order to serve as a normative sample. Children with OI were chosen as a control group, because this allows for control of injury-related characteristics that would not be present in a healthy sample (e.g., pain, post-traumatic stress, medical treatment) (Wilde et al., 2018). Although the parent study was an RCT, for this study the physical activity and rest until asymptomatic groups were combined, since it was previously found that the groups had similar patterns of physical activity (Ledoux et al., 2022). Recruitment took place through CHEO's Emergency Department. MRI scans were conducted at the Royal Ottawa Mental Health Centre's Brain Imaging Centre (BIC). Ethics approval was given by CHEO's Research Ethics Board.

Inclusion and exclusion criteria

Participants in the concussion group were included in the study if they were diagnosed with a concussion according to the Berlin consensus statement (McCrory et al., 2017), and concussion diagnosis was confirmed using physician judgement and an adapted version of the Centers for Disease Control and Prevention tiered framework (Peterson et al., 2021). At least one symptom from the "highest level of certainty" tier had to be present (e.g., dazed/confused/foggy, loss of consciousness, memory problems), or at least two from the "higher level of certainty" (e.g., nausea or vomiting, headache, vision changes, etc. immediately or within an hour post-injury). They also had to have been between the ages of 10 and 18 years, sustained a concussion within the previous 48 hours, and were fluent in English or French. Participants were excluded if they presented with a Glasgow Coma Scale score of <13; had any abnormal neuroimaging findings; required neurosurgery, intubation or intensive care; sustained multi-system injuries that required admission, operation or sedation; severe neurological condition preventing adequate communication; intoxication in the ED; no clear history of trauma as primary event; inability to resume physical activity; inability to obtain consent or assent; or if a legal guardian was not present. Participants were also excluded if they had any MRI contraindications (e.g., pacemakers, metal implants).

Participants in the OI group were included if they were between the ages of 10 and 18 years, had an injury that occurred within 48 hours of the ED visit, had an isolated upper extremity injury due to blunt force or trauma, and were proficient in English. Exclusion criteria were the same as for the concussion group, but the OI participants could not have sustained a concussion or traumatic brain injury within the previous year. They were also screened for concussion at the ED visit.

Measures

5P score. Calculation of the 5P score was based on the initial 5P study: factors were awarded either 0, 1, or 2 points based on strength of the association to PPCS (See Table 1). The factors known to be most associated with PPCS, which were age range from 13 to 18, female sex, and fatigue, were each awarded 2 points. In the original study, three cut-off points were selected to classify PPCS risk: 0 to 3 points for low risk, 4 to 8 points for medium risk, and 9 to 12 points for high risk. 5P variables were assessed in the ED and the score was calculated by summing responses, but only total scores were used in this study instead of risk group.

Table 1. *5P Score Criteria and Points Allotment*

Risk Factor	**Categories**	**Points**
Age	5-7 8-12 13-18	0 1 2
Sex	Male Female	0 2
Longest symptom duration from prior concussion(s)	No prior or <1 week 1+ week	0 1
Migraine history	No Yes	0 1
Answering questions slowly	No Yes	0 1
Tandem stance	0-3 errors 4+ or unable to do test	0 1
Headache	No Yes	0 1
Sensitivity to noise	No Yes	0 1

Fatigue	No	0
	Yes	2

MRI acquisition. Acquisition of the MRI scans took place at 72 ± 48 hours (Time 1) and at 4 weeks ± 5 days (Time 2) post-injury at the BIC. The 3-Tesla Siemens PET-MRI machine equipped with a 12-channel head coil was used. A 3D multi-inversion time pulsed ASL sequence with background suppression was used, and images were acquired along the anterior commissure-posterior commissure line with the prescription slab oriented at the base of the cerebellum. Images were acquired with the following parameters: Voxel size: 1.8 x 1.8 x 5.0 mm, slice thickness: 5mm, SNR: 1, repetition time (TR): 4600 msec, echo time (TE): 15.56 msec, bolus duration: 700 msec, 12 inversion times, field of view (FOV): 230 mm. The whole brain was covered and the entire ASL scan lasted approximately 5 minutes. T1-weighted structural images were also obtained with the following parameters: Voxel size: 0.9 x 0.9 x 1.0 mm, slice thickness: 5mm, SNR: 1, TI: 1160 msec, TE: 2.21;4.09;5.97;7.85 msec, TR: 2300 msec, flip angle (FA) = 8°, 192 transversal slices with FOV 230 × 230 mm, 256 × 256 pixel matrix, 0.9 × 0.9 mm in-plane resolution, with bandwidth = 650 Hertz per pixel for all 4 contrasts.

Psychological resilience. Psychological resilience was assessed at 72 hours post-injury using the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC) (Campbell-Sills & Stein, 2007; Connor & Davidson, 2003). The CD-RISC consists of 10 items rated on a 5-point self-report Likert scale ranging from 0 meaning “Not true at all”, to 4 meaning “True nearly all of the time”. Total scores were calculated by summing the responses (0-40), and higher scores reflected greater psychological resilience. The 10-item CD-RISC has been previously validated in studies of children with concussion (Laliberté Durish et al., 2018). Cronbach’s alpha = .89.

Post-concussion symptoms. Symptoms were assessed in the ED, at 2 weeks, and at 4 weeks post-injury using the Health and Behaviour Inventory (HBI) (Ayr et al., 2009). The HBI is 20-item self-report questionnaire rated on a 4-point Likert scale based on how often a symptom was experienced in the previous week, with 0 meaning "Never" and 3 meaning "Often". It also has a parent-rated retrospective component (rHBI), in which parents rate how often symptoms were experienced by their child pre-injury. The HBI is a validated and reliable assessment for children aged 8-15 (Ayr et al., 2009; Janusz et al., 2012). Total scores were calculated by summing the responses (0-60), and higher scores reflected greater symptom burden. The HBI also yields a cognitive and somatic symptom score (Hearps et al., 2017). Cronbach's alpha = .94.

Procedure

Children that presented to CHEO's ED with a concussion or an OI were approached by an ED volunteer to determine interest in participating in the PedCARE^{+MRI} study. A research assistant then screened the interested patients to determine eligibility. If deemed eligible, a written consent was completed by the child if they were capable of consenting by themselves. If the parent consented on their child's behalf, the child had to complete an assent form as well.

Once enrolled, the research assistant collected participant contact information, and then demographics and 5P variables were assessed and entered into the study's Research Electronic Data Capture (REDCap) (Harris et al., 2009, 2019) database. Concussed participants were randomized to either the physical activity group or the rest until asymptomatic group through REDCap. The physical activity group was instructed to resume noncontact aerobic activity at 72 hours post-injury, and the rest until asymptomatic group was instructed to resume physical activity only once symptoms subsided. OI participants were not randomized to either group in

order to serve as a normative sample, and they instead received care as usual. Follow-up questionnaires were sent to the participants at multiple time points (i.e. 72 hours, 1, 2 and 4 weeks) via email or phone during the 4-week study period (see Table 2 for a summary of assessments).

Table 2. *Summary of Assessments*

	Source/ reporter	Time to complete (mins)	ED (Visit)	72 hours	Day 1 -6	Day 7	Day 8-13	Day 14	Week 3	Week 4
ED visit										
5P variables	RA, MD	n/a	**X**							
Outcomes										
Neurobiological markers		60								
Cerebral perfusion (primary)	CC, OI	5		**X**						**X**
Post-concussive symptoms (secondary)										
Health and Behaviour Inventory and retrospective HBI	CC,P, OI	5-10	X					**X**		**X**
Psychological Assessments										
Connor-Davidson Resilience Scale	CC, OI	5		**X**						

Note: CC= Concussed Child, P=Parent/guardian, OI=Orthopedic Injury participants, RA=Research Assistant, MD=Treating ED Physician. **Bold** = used in this study. OI participants only completed assessments at 72 hours and 4 weeks.

Both concussion and OI participants were contacted to book the 2 MRI appointments on the day following their ED visit. They were sent parking information, a map of the location, and voucher instructions before their appointments. At the BIC, a signed consent form was presented to the MRI technician before the scan. The participants were instructed to remove their clothing

and all metal objects, and they were presented with a gown. During the ASL sequence, participants were instructed to close their eyes and rest their minds.

Data Analysis

MRI data analysis. The MRI data was assessed using FMRIB Software Library v6.0 (FSL) (Jenkinson et al., 2012), Statistical Parametric Mapping 12 (SPM12) software (Ashburner et al., 2021), and Matlab.

Motion assessment. Since head motion in the scanner can greatly affect the imaging results, motion was assessed through visual inspection of the structural images. ASL scans were co-registered with grey matter maps to account for motion, and both of these maps were normalized to the Montreal Neurological Institute (MNI) 152 standard space T1-weighted average structural template image. The structural image assessments were conducted based on a paper by Backhausen et al. (2016). Image sharpness, ringing, contrast to noise ratio of subcortical structures, and contrast to noise ratio of gray matter and white matter were all taken into consideration, and images were given a pass or fail rating. Any scans that failed were automatically excluded. Scans were also excluded if a radiologist determined that significant incidental findings were present (e.g., tumor).

Preprocessing

The ASL data was preprocessed using FSL (Jenkinson et al., 2012). Reorientation, cropping, bias-field correction, registration to standard space, brain extraction, tissue-type segmentation, and subcortical structure segmentation were all performed on the structural images using the *fsl_anat* (Jenkinson et al., 2012) command. Analysis of Functional Neuroimages (AFNI) *3dvolreg* (Oakes et al., 2005) command was used to assess motion in the ASL data

before and after motion correction. Additionally, framewise displacement (FD) (Power et al., 2012) calculations, involving the combination of six different head motion parameters, were conducted to yield a single scalar value for participant head motion. Motion correction was then performed using the *mcflirt* (Jenkinson et al., 2002) command. The decision to exclude participants based on motion took into account both motion correction using *mcflirt* (Jenkinson et al., 2002) and visual inspection of the structural images. Finally, the perfusion analysis was completed using *oxford_asl* (Chappell et al., 2018). This created calibrated perfusion images, which were used for further analysis.

Statistical analyses.

Statistical analyses were conducted using version 27 of IBM Statistical Package for the Social Sciences (SPSS) software for Mac OS. Demographic data for the participants were analyzed with descriptive statistics. Statistical significance was determined at $p < .05$ (two-tailed). Data cleaning was performed to ensure that all scores are within range, that multicollinearity between predictors was minimal, and that the assumptions of linearity, homogeneity of variance, normality, and independence of errors were met. Extreme scores were winsorized to ensure normality.

To assess CBF changes in the concussed and OI groups over time, the ASL data was analyzed using SPM12 and SPSS. First, a linear mixed model assessing mean global grey matter CBF adjusted for age, sex, and motion, for each group at each time point was conducted using SPSS. This analysis was also repeated without adjusting for age and sex (crude). Whole brain exploratory analyses were then conducted in SPM12 to determine regions of interest (ROI). For the absolute analysis, the calibrated perfusion images from the concussed group and OI group at Time 1 and Time 2 were compared using a full factorial model. Age, sex, and head motion (FD

value) were entered as covariates. To assess normalized absolute CBF, this model was repeated with the inclusion of global grey matter perfusion as a covariate. This was done to remove any naturally occurring variability in global grey matter perfusion, as it can differ greatly between individuals (Chappell et al., 2017). Independent anatomical masks were created for each significant ROI from the absolute and normalized absolute analyses, and values were extracted for further analysis in SPSS. Both adjusted and crude (not adjusted for age and sex) ROI analyses were conducted to assess the influence of the covariates on the results (Hyatt et al., 2020; Simmons et al., 2011).

Multiple regression models were conducted in SPSS to assess whether scores from the CD-RISC and CBF, combined with the 5P score, improved prediction of symptoms measured with the HBI. Only the concussed participants' data was used for this analysis, and motion was controlled for. Total HBI scores at both 2 and 4 weeks were entered as the outcome variables. Missing data was accounted for using pairwise deletion, and significance was determined by $p < 0.05$.

Results

Participant Characteristics

A total of 92 concussed participants and 46 OI participants were recruited in the CHEO ED from May 2018 to February 2020. Of these participants, 75 concussed and 30 OI participants completed MRI scans at both 72 hours and at 4 weeks. Following motion review, 5 concussed participants and 1 OI participant were excluded. See Figures 1 and 2 for enrolment breakdown.

In the final sample, 70 participants with concussion (M_{age}=13.05±2.02, 47% female) and 29 with OI (M_{age}=12.59±1.97, 41% female) were included. The predominant mechanism of injury for both groups was sport and recreational play. The most prevalent diagnoses for both

groups were anxiety, learning disability, and ADHD. Independent sample t-tests and Pearson's Chi-square tests revealed a significant difference between the concussion and OI groups for time from injury to MRI 1 (p = .001), but no significant group differences for any other demographic variable in the final sample. See Table 3 for participant demographics.

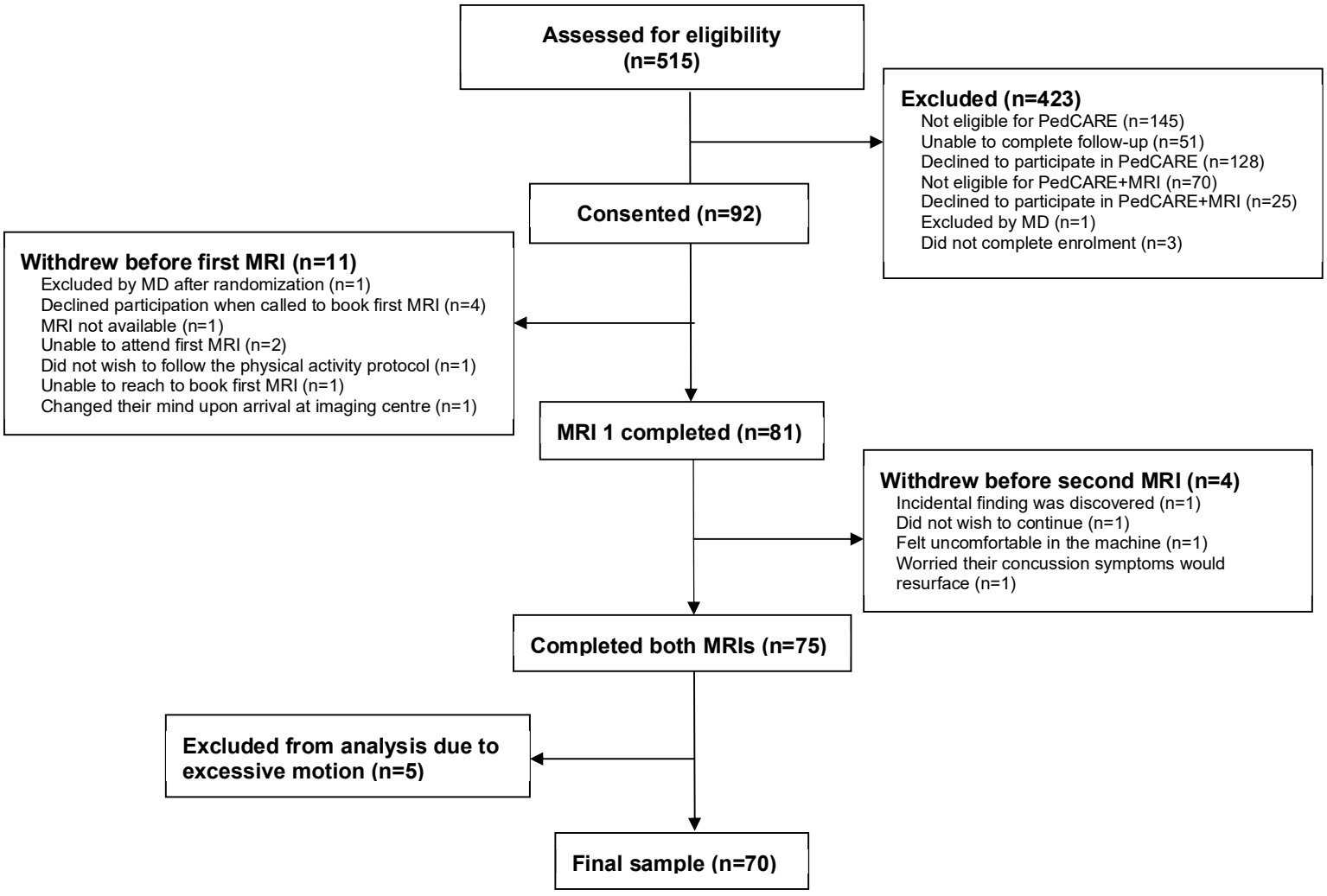


Figure 1. Enrolment, attrition, and final sample breakdown for concussed participants

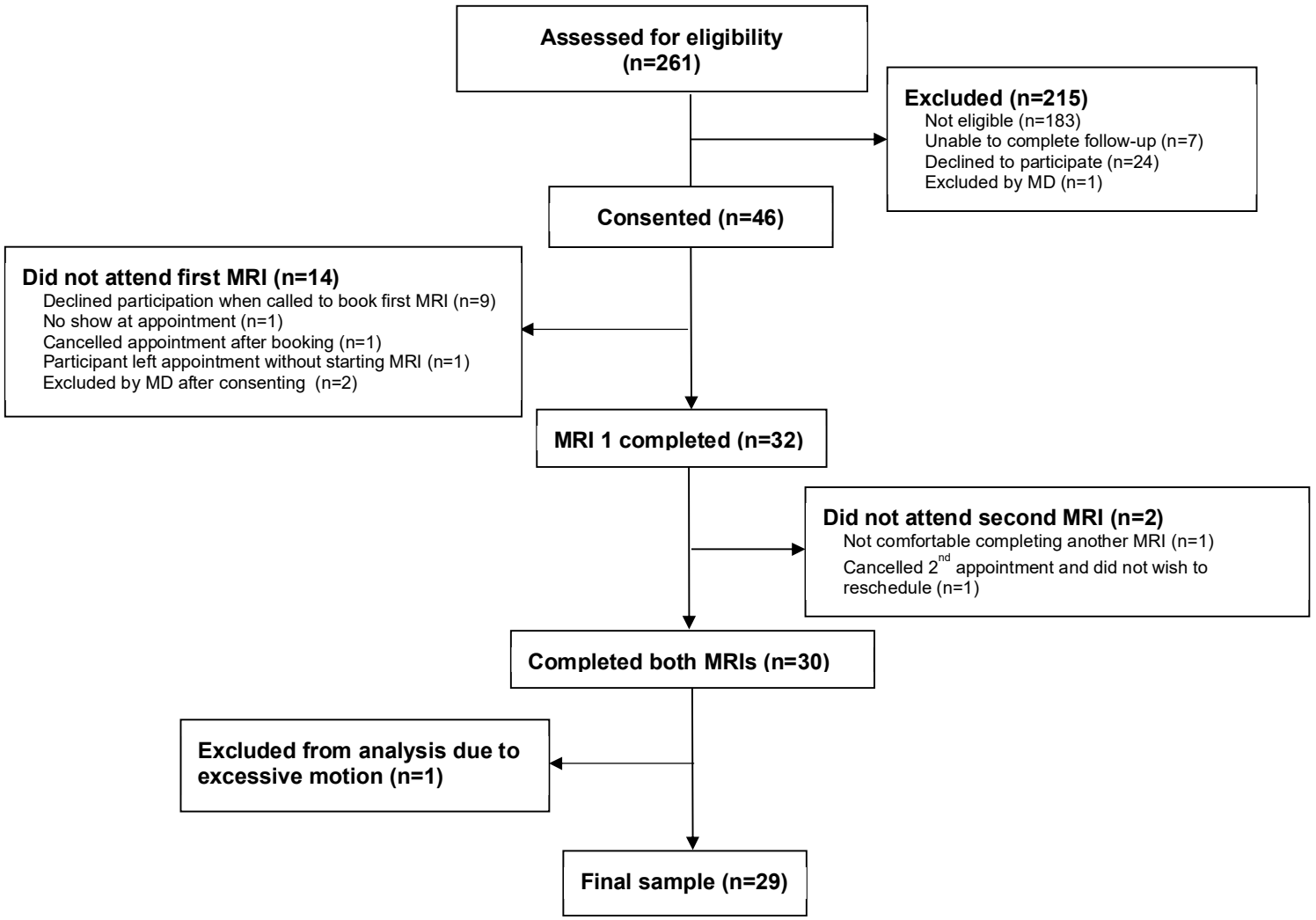


Figure 2. Enrolment, attrition, and final sample breakdown for orthopedic injury participants

Table 3. *Participant Demographics*

		Full Sample		*MRI Sample*		*Final Sample*	
		Concussed	*OI*	*Concussed*	*OI*	*Concussed*	*OI*
		N=92	*N=46*	*N=75*	*N=30*	*N=70*	*N=29*
Mean age ±SD (years)		13.05	12.84	13.06	12.64	13.05± 2.02	12.59±1.97
Sex	Female	41 (45%)	18 (39%)	36 (48%)	12 (40%)	33 (47%)	12 (41%)
	Male	51 (55%)	28 (61%)	39 (52%)	18 (60%)	37 (53%)	17 (59%)
Diagnoses	Learning disability	12 (13%)	4 (9%)	8 (11%)	2 (7%)	8 (11%)	2 (7%)
	ADHD	13 (14%)	7 (15%)	12 (16%)	4 (13%)	10 (14%)	4 (14%)
	Other developmental disorder	4 (4%)	1 (2%)	2 (3%)	1 (3%)	2 (3%)	1 (3%)
	Anxiety	15 (16%)	4 (9%)	13 (17%)	3 (10%)	12 (17%)	3 (10%)
	Depression	5 (5%)	2 (4%)	4 (5%)	1 (3%)	4 (6%)	1 (3%)
	Sleep disorder	2 (2%)	1 (2%)	2 (3%)	1 (3%)	2 (3%)	1 (3%)
	Other psychiatric disorder	0 (0%)	2 (4%)	0 (0%)	1 (3%)	0 (0%)	1 (3%)
	N/A	4 (4%)	1 (2%)	3 (4%)	1 (3%)	2 (3%)	0 (0%)
Mechanism of injury	Sport and recreational play	48 (52%)	28 (61%)	43 (57%)	20 (67%)	40 (57%)	19 (66%)
	Non-sport-related injury or fall	25 (27%)	10 (22%)	20 (27%)	4 (13%)	19 (27%)	4 (14%)

	Motor vehicle accident	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Assault	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Other	18 (20%)	8 (17%)	12 (16%)	6 (20%)	12 (17%)	6 (21%)
	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Median time (hours) from injury to ED presentation (IQR)		11.40	13.78	11.15	13.73	3.57 (1.69-19.33)	7.73 (2.87-21.12)
Median time (hours) from injury to MRI 1 (IQR)		-	-	74.75	108.50	75.13 (52.50-87.44)	117.00 (72.00-120.25)
Median time (days) from injury to MRI 2 (IQR)		-	-	30.14	30.38	30.24 (28.34-32.07)	30.70 (28.09-32.30)

Note. Full sample is comprised of all participants recruited in the ED. MRI sample is comprised of participants that completed both MRI scans. Final sample is comprised of participants that completed both MRI scans and were not excluded following motion review. SD = Standard Deviation, IQR = Interquartile Range.

Analysis 1: Changes in CBF by group and by time point

Mean global grey matter perfusion

Adjusted analysis

The linear mixed model, adjusted for sex, age, and motion, found no significant main effect of time or group, and no significant interaction between time and group. Although not significant, both the concussion and OI groups exhibited increased mean global grey matter perfusion at Time 2 compared to Time 1, and the concussed participants exhibited increased CBF at both time points. See Figure 4A.

Crude analysis

The crude linear mixed model, adjusted for only motion, found no significant main effect of time or group, and no significant interaction effect. Although not significant, the concussed group exhibited decreased perfusion compared to OI's at time 1, and increased perfusion at time 2. See Figure 4B.

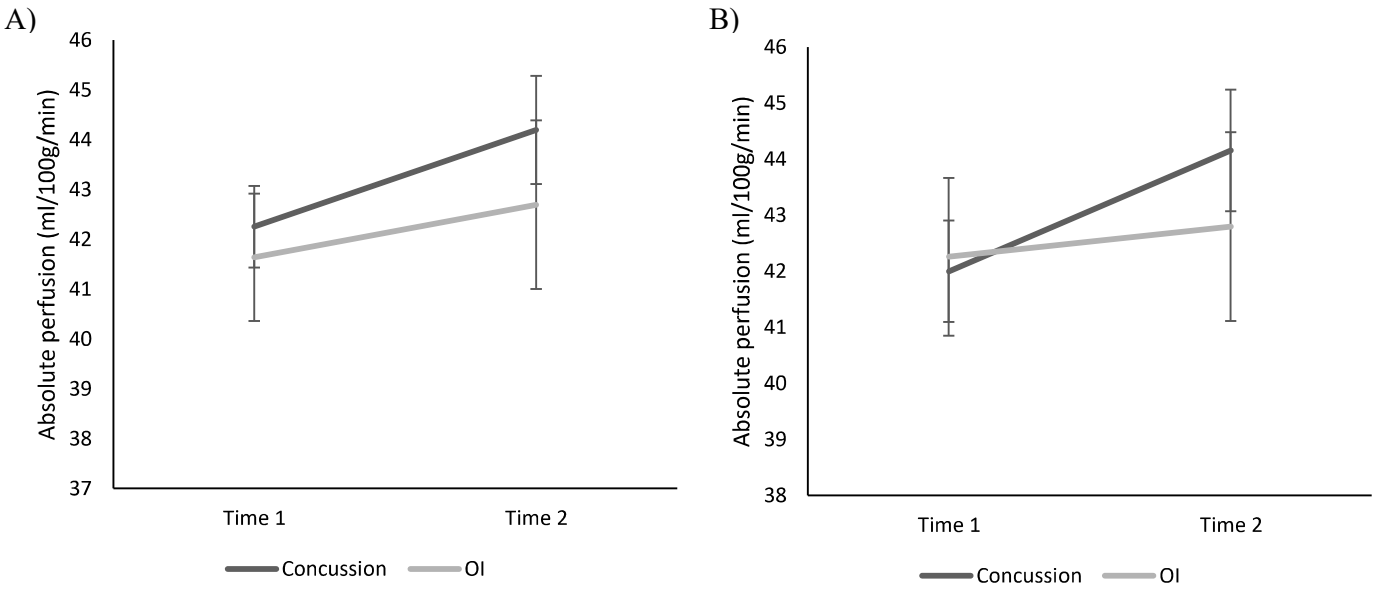


Figure 4. Mean global grey matter perfusion A) adjusted for age, sex, and motion, and B) crude (adjusted for only motion) in concussed and OI participants over time. Errors bars represent standard error.

Absolute perfusion

Whole brain analysis

The whole brain analyses, adjusted for age, sex and motion, revealed a significant main effect of group, but no significant time effect or interaction effect. Absolute CBF differed by group in the anterior cingulate cortex/medial frontal cortex (L_ACC_MFC) (cluster size 315, $p_{uncorr} < .001$), right middle frontal gyrus (R_MFG) (cluster size 135, $p_{uncorr} < .001$), and the left angular gyrus (L_angular) (cluster size 132, $p_{uncorr} < .001$). All significant clusters survived family-wise error correction ($p_{FWE} < .05$). See Table 4 for whole brain analysis results. Independent anatomical masks were created, and CBF values were extracted from each significant ROIs for further analysis in SPSS.

Table 4. *Whole Brain Absolute Perfusion Analysis*

	Hemisphere	Region	Peak MNI coordinates (x y z)[a]	Cluster size (voxels)[a]
Main effect of group	Left	Anterior cingulate/medial frontal cortex	-16 30 30	315
	Right	Middle frontal gyrus	34 6 44	135
	Left	Angular gyrus	-26 -54 34	132

[a]Cluster level analysis in SPM, $p_{uncorr} < .001$, $p_{FWE} < .05$

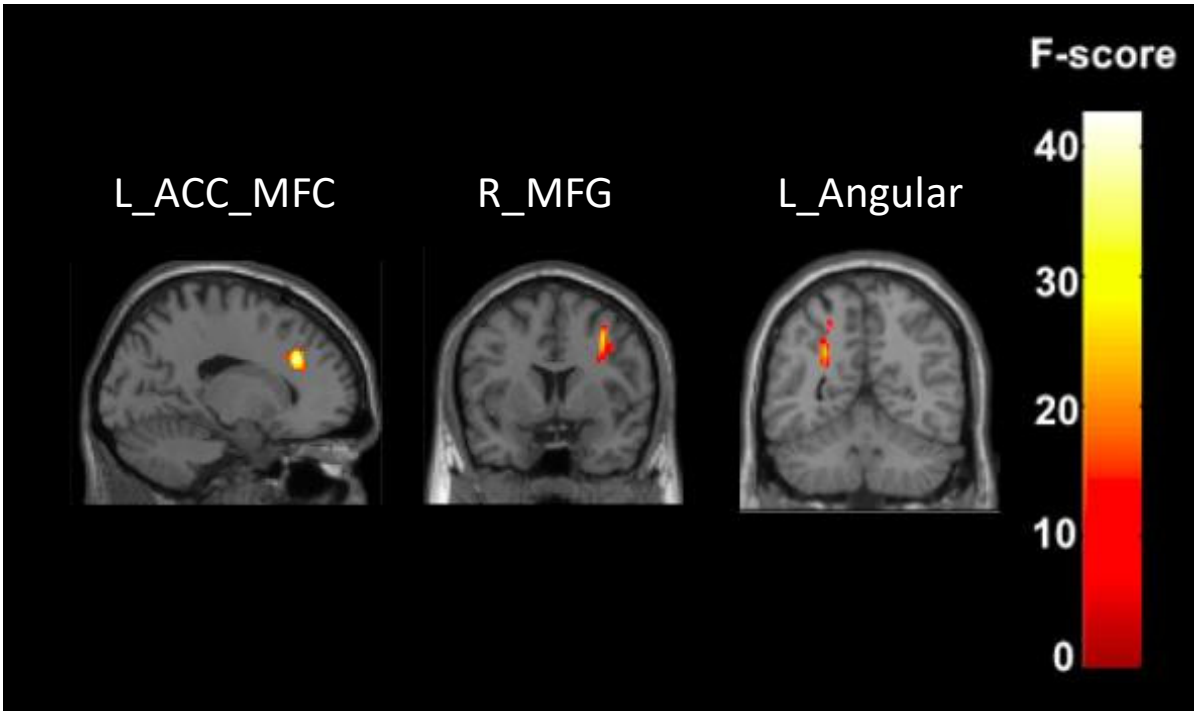


Figure 5. Whole brain absolute perfusion results in the left anterior cingulate/medial frontal cortex, right middle frontal gyrus, and left angular gyrus.

Adjusted ROI analysis

The linear mixed model for adjusted absolute perfusion confirmed the significant main effect of group in the L_ACC_MFC, $F(1,94) = 14.81$, $p < .001$, R_MFG, $F(1,95) = 9.08$, $p = .003$, and L_angular, $F(1,93) = 13.08$, $p < .001$. Each ROI's main effect of group survived after Bonferroni correction ($p < .017$). A significant interaction between group and time was also present in the L_ACC_MFC, $F(1,96) = 8.63$, $p = .004$, and R_MFG, $F(1,96) = 5.95$, $p = .017$, and both survived after Bonferroni correction. See Figure 6 for mean absolute perfusion values for each ROI.

Simple effects for the interaction in the L_ACC_MFC revealed that there was a significant difference in perfusion between OI and concussion groups at both time 1, $F(1,95) = 5.77$, $p = .018$, and time 2, $F(1,96) = 21.08$, $p < .001$. Perfusion in the concussion group was

significantly higher at time 2 compared to time 1, $F(1,96) = 11.96$, $p < .001$, but there was no significant difference over time for the OI group.

Simple effects for the interaction in the R_MFG revealed that there was a significant difference in perfusion between OI and concussion groups at time 2, $F(1,96) = 11.78$, $p < .001$, but this difference only approached significance at time 1, $F(1,95) = 3.80$, $p = .054$. Perfusion in the concussion group was significantly higher at time 2 compared to time 1, $F(1,96) = 11.46$, $p = .001$, but there was no significant difference over time for the OI group.

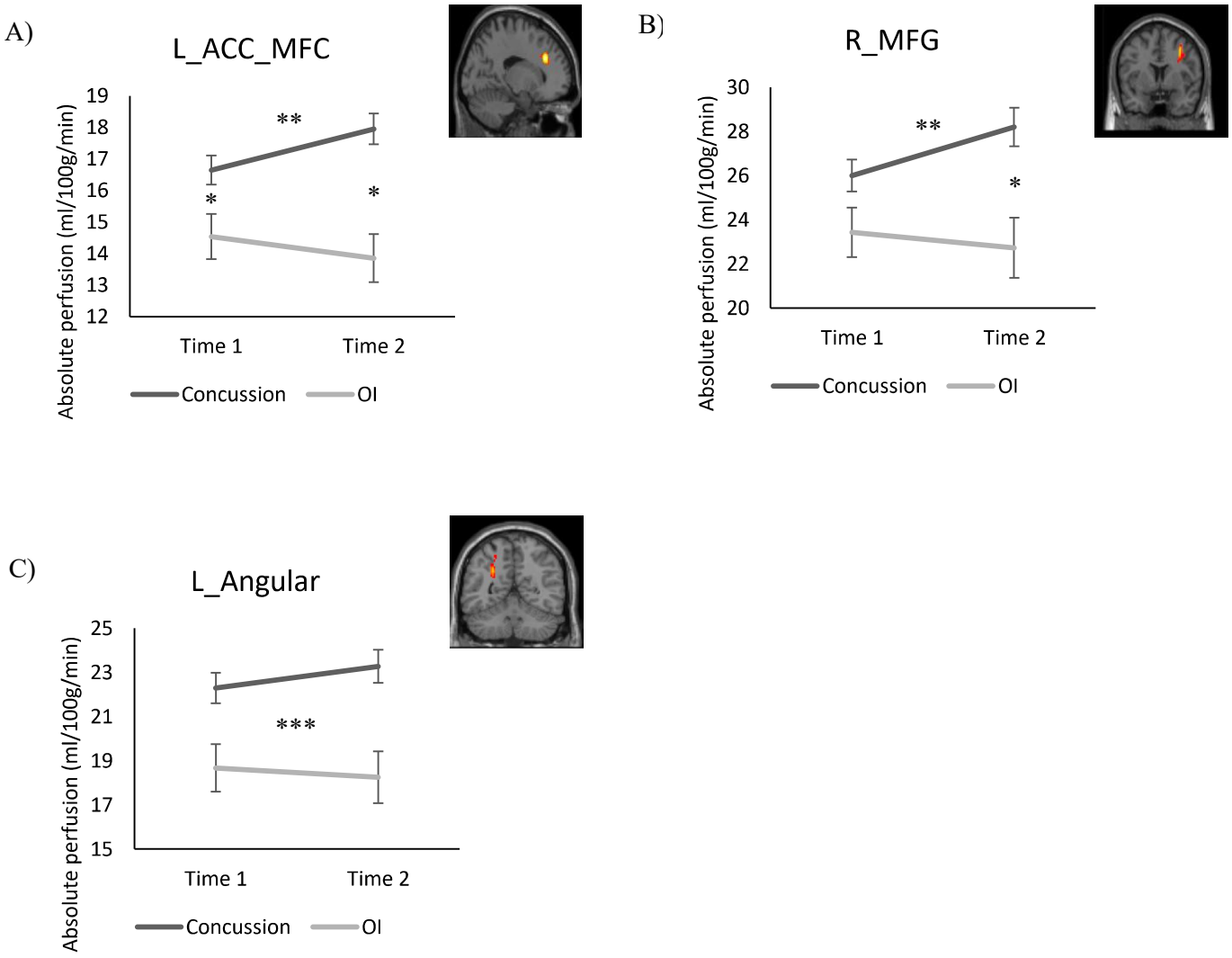


Figure 6. Mean absolute perfusion adjusted for age, sex, and motion in the A) left anterior cingulate/medial frontal cortex, B) right middle frontal gyrus, and C) left angular gyrus, in both concussion and OI groups over time. Error bars represent standard error. * = significant time difference between groups, ** = significant group difference over time, *** = significant difference between groups.

Crude ROI analysis

The linear mixed model for crude absolute perfusion (adjusted for motion only) confirmed the significant main effect of group in the L_ACC_MFC, $F(1,97) = 14.25$, $p < .001$, R_MFG, $F(1,97) = 8.47$, $p = .004$, and L_angular, $F(1,94) = 11.30$, $p = .001$. Each ROI's main effect of group survived after Bonferroni correction ($p < .017$). A significant interaction between group and time was also present in the L_ACC_MFC, $F(1,95) = 8.65$, $p = .004$, and R_MFG, $F(1,95)= 5.95$, $p = .017$, both of which survived Bonferroni correction. See Figure 7 for mean absolute perfusion values for each ROI.

Simple effects for the interaction in the L_ACC_MFC revealed that there was a significant difference in perfusion between OI and concussion groups at both time 1, $F(1,97) = 5.35$, $p = .023$, and time 2, $F(1,97) = 20.61$, $p < .001$. Perfusion in the concussion group was significantly higher at time 2 compared to time 1, $F(1,96) = 11.96$, $p < .001$, but there was no significant difference over time for the OI group.

Simple effects for the interaction in the R_MFG revealed that there was a significant difference in perfusion between OI and concussion groups only at time 2, $F(1,97) = 11.17$, $p = .001$. Perfusion in the concussion group was significantly higher at time 2 compared to time 1, $F(1,96) = 11.43$, $p = .001$, and there was no significant difference over time for the OI group.

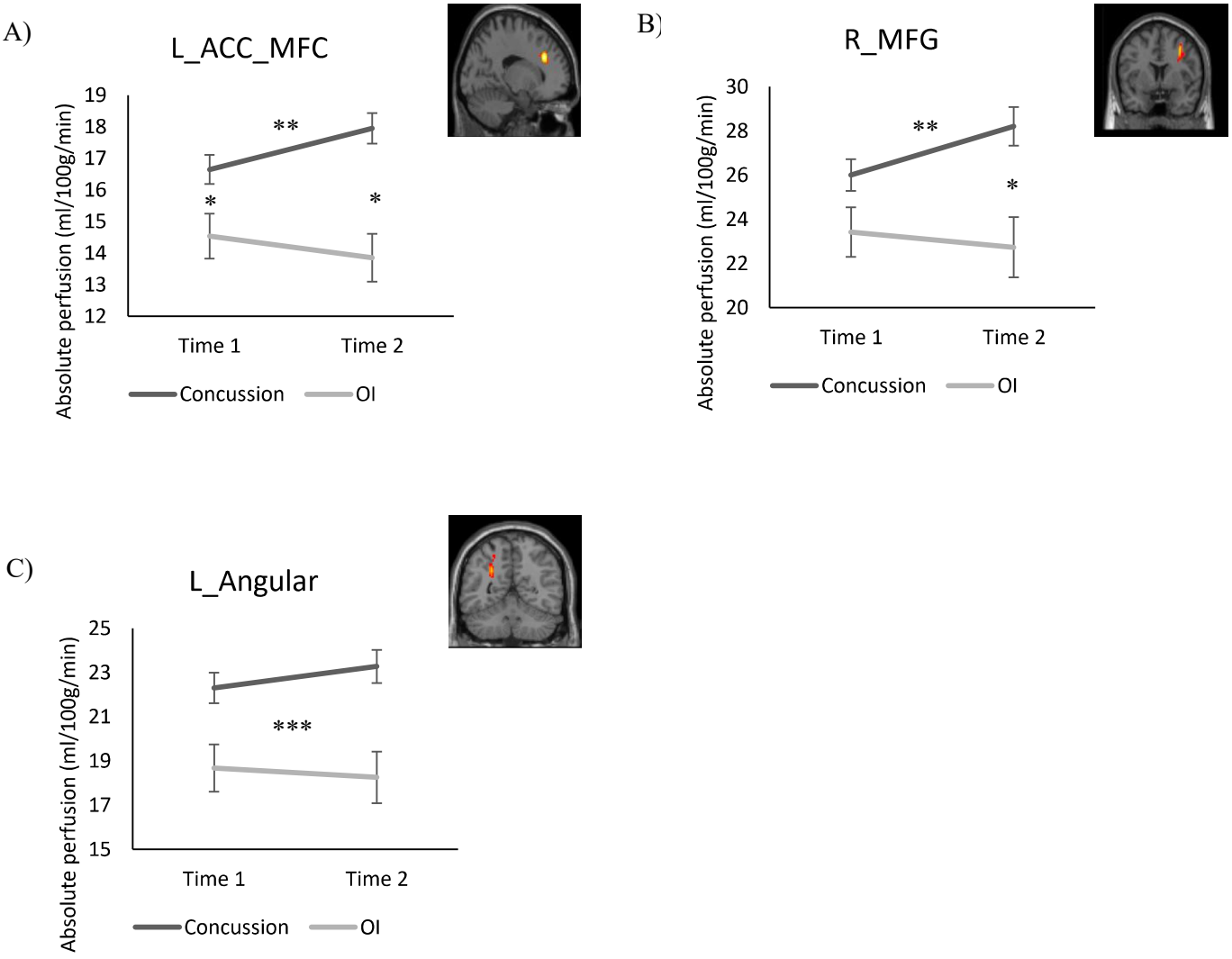


Figure 7. Mean crude absolute perfusion in the A) left anterior cingulate/medial frontal cortex, B) right middle frontal gyrus, and C) left angular gyrus, in both concussion and OI groups over time. Error bars represent standard error. * = significant time difference between groups, ** = significant group difference over time, *** = significant difference between groups.

Normalized absolute perfusion: adjusting for mean global grey matter perfusion

Whole brain analysis

The whole brain analysis, adjusted for age, sex, motion, and mean global grey matter perfusion revealed a significant main effect of group, but no significant time effect or interaction effect. Normalized absolute CBF differed by group in the L_ACC_MFC (cluster size 294, $p_{uncorr} < .001$), R_MFG (cluster size 143, $p_{uncorr} < .001$), left middle frontal gyrus (L_MFG) (cluster size 76, $p_{uncorr} = .001$), right superior temporal gyrus (R_STG) (cluster size 210, $p_{uncorr} < .001$), right fusiform gyrus (R_fusiform) (cluster size 115, $p_{uncorr} < .001$), L_angular (cluster size 113, $p_{uncorr} < .001$), right supramarginal gyrus (R_SMG) (cluster size 73, $p_{uncorr} = .001$), left lingual gyrus (cluster size 1874, $p_{uncorr} < .001$), and right lingual gyrus (cluster size 100, $p_{uncorr} < .001$). All significant clusters survived family-wise error correction ($p_{FWE} < .05$). See Table 5 for whole brain analysis results. Independent anatomical masks were created, and CBF values were extracted from each significant ROI for further analysis in SPSS. Due to the large size of the clusters, the left and right lingual gyrus were combined into one region (lingual) for ROI analyses.

Table 5. *Whole Brain Normalized Absolute Perfusion Analysis*

	Hemisphere	**Region**	**Peak MNI coordinates (x y z)[a]**	**Cluster size (voxels)[a]**
Main effect of group	Left	Anterior cingulate/medial frontal cortex	-16 30 30	294
	Right	Middle frontal gyrus	34 6 44	143
	Left	Middle frontal gyrus	-46 6 54	76

Right	Superior temporal gyrus	38 -32 10	210
Right	Fusiform gyrus	38 -38 -22	115
Left	Angular gyrus	-26 -54 34	113
Right	Supramarginal gyrus	38 -50 30	73
Left	Lingual gyrus	4 -68 -10	1874
Right	Lingual gyrus	8 -96 -12	100

[a]Cluster level analysis in SPM, $p_{uncorr} < .001$, $p_{FWE} < .05$

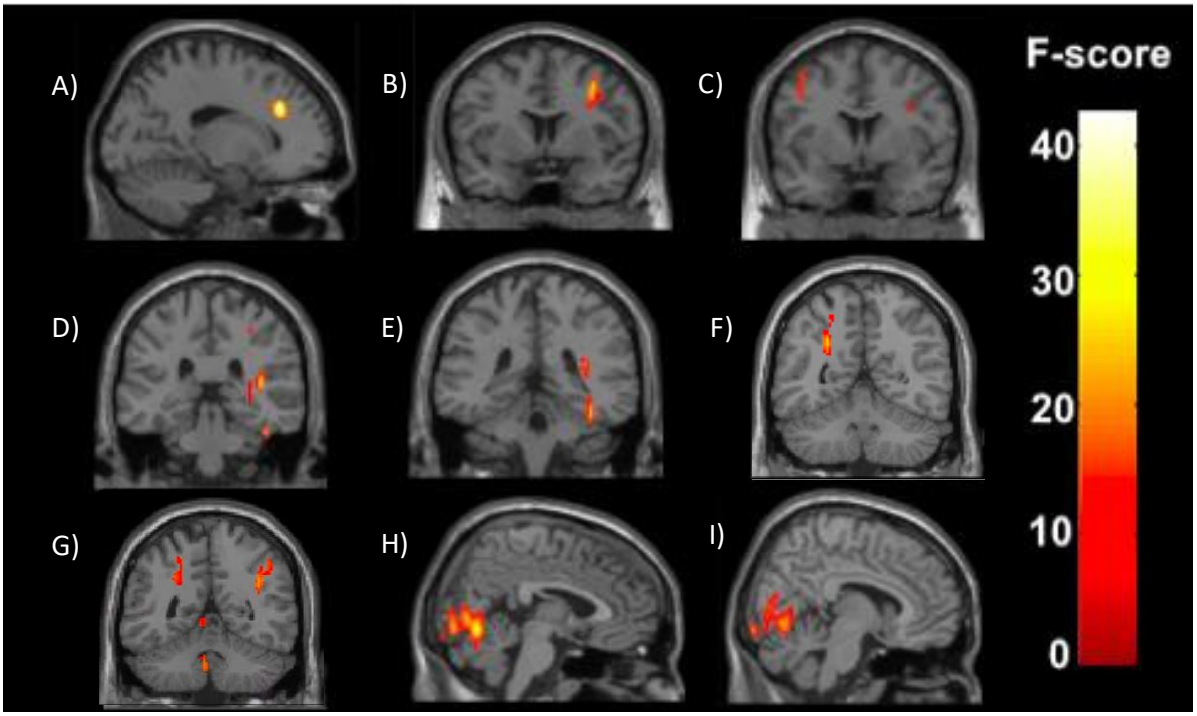
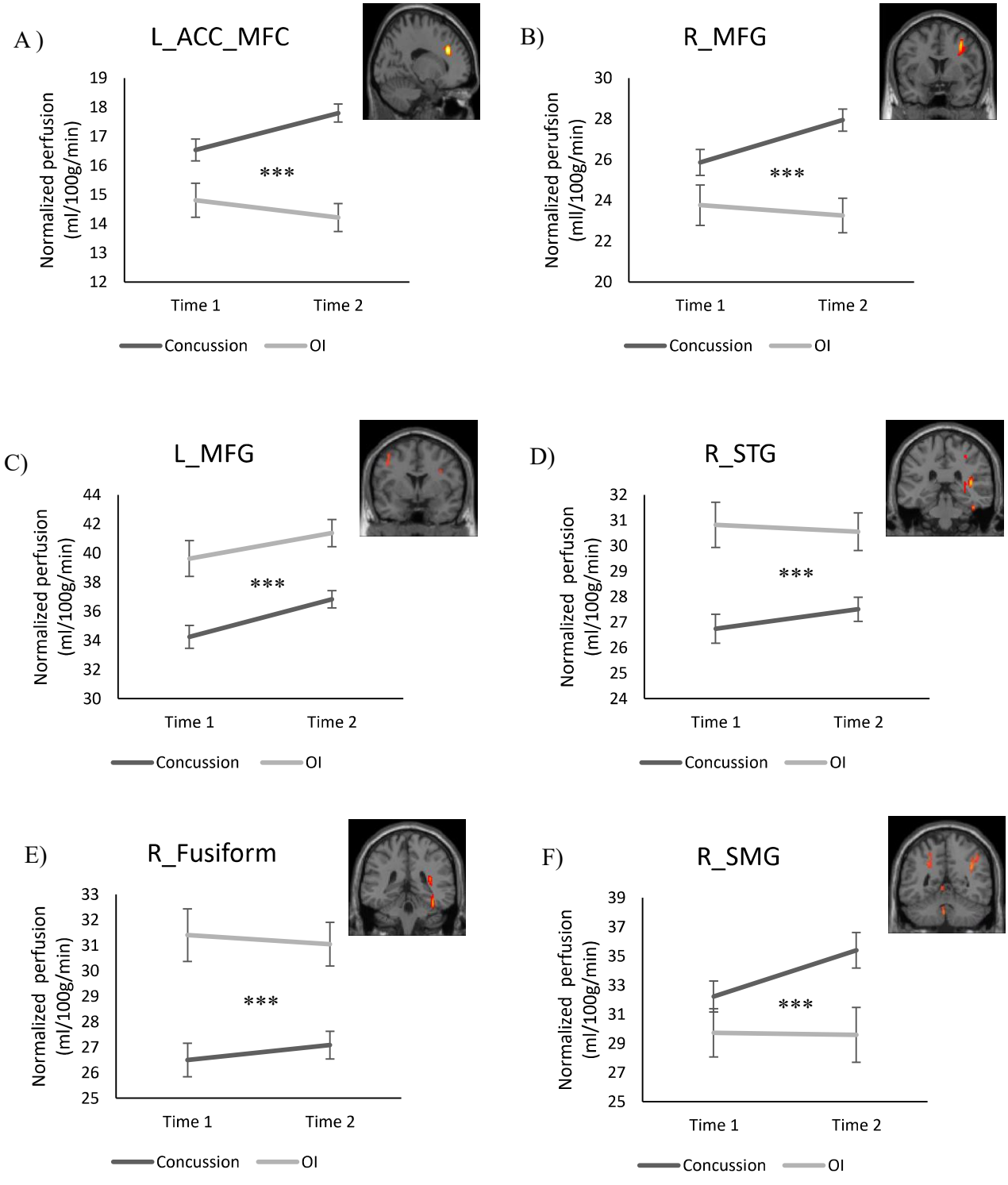


Figure 8. Whole brain normalized absolute perfusion in the A) left anterior cingulate/medial frontal cortex, B) right middle frontal gyrus, C) left middle frontal gyrus, D) right superior temporal gyrus, E) right fusiform gyrus, F) left angular gyrus, G) right supramarginal gyrus, H) left lingual gyrus, and I) right lingual gyrus.

Adjusted ROI analysis

The linear mixed model for adjusted normalized absolute perfusion confirmed the significant main effect of group in the L_ACC_MFC, $F(1,94) = 13.85$, $p < .001$, R_MFG, $F(1,95) = 7.89$, $p = .006$, L_MFG, $F(1,95) = 6.34$, $p = .014$, R_STG, $F(1,95) = 8.65$, $p = .004$, R_fusiform, $F(1,93) = 12.89$, $p < .001$, L_angular, $F(1,92) = 11.71$, $p < .001$, R_SMG, $F(1,95) = 5.95$, $p = .017$, and lingual $F(1,90) = 9.10$, $p = .003$. Each ROI's main effect of group survived after Bonferroni correction ($p < .0063$), except the L_MFG and R_SMG. The concussion group displayed significantly increased perfusion compared to OIs at both time points in the L_ACC_MFC, R_MFG, L_angular. The OI group displayed significantly increased perfusion at both time points in the R_STG, R_fusiform, and lingual. A significant interaction between group and time was also present in the L_ACC_MFC, R_MFG, and R_SMG, but none survived after Bonferroni correction. See Figure 9 for mean absolute perfusion values for each ROI.


A)
L_ACC_MFC
Normalized perfusion (ml/100g/min)
19
18
17
16
15
14
13
12
***
Time 1
Time 2
Concussion
OI
B)
R_MFG
Normalized perufsion (mll/100g/min)
30
28
26
24
22
20
***
Time 1
Time 2
Concussion
OI
C)
L_MFG
Normalized perfusion (ml/100g/min)
44
42
40
38
36
34
32
30
***
Time 1
Time 2
Concussion
OI
D)
R_STG
Normalized perfusion (ml/100g/min)
32
31
30
29
28
27
26
25
24
***
Time 1
Time 2
Concussion
OI
E)
R_Fusiform
Normalized perfusion (ml/100g/min)
33
32
31
30
29
28
27
26
25
***
Time 1
Time 2
Concussion
OI
F)
R_SMG
Normalized perfusion (ml/100g/min)
39
37
35
33
31
29
27
25
***
Time 1
Time 2
Concussion
OI

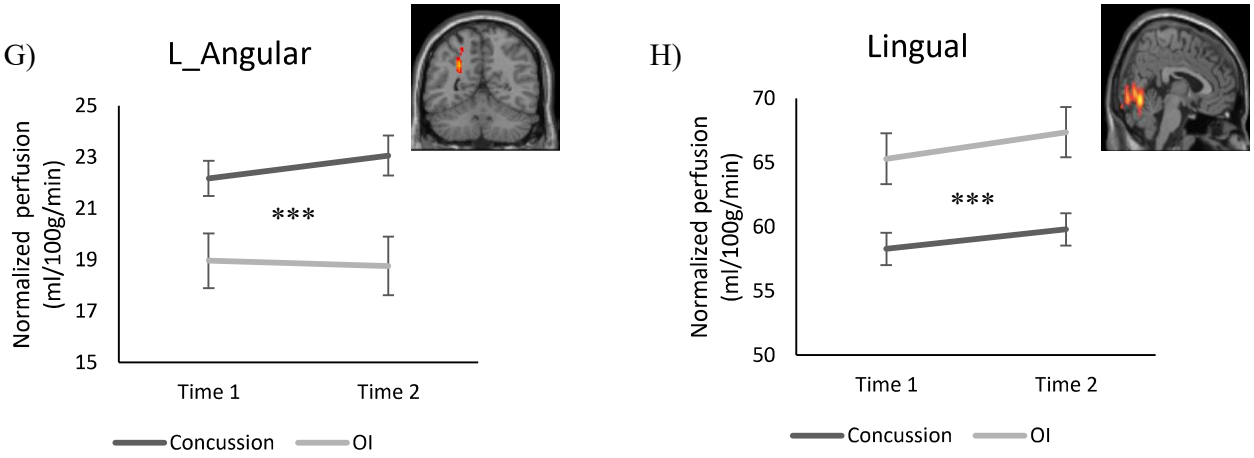
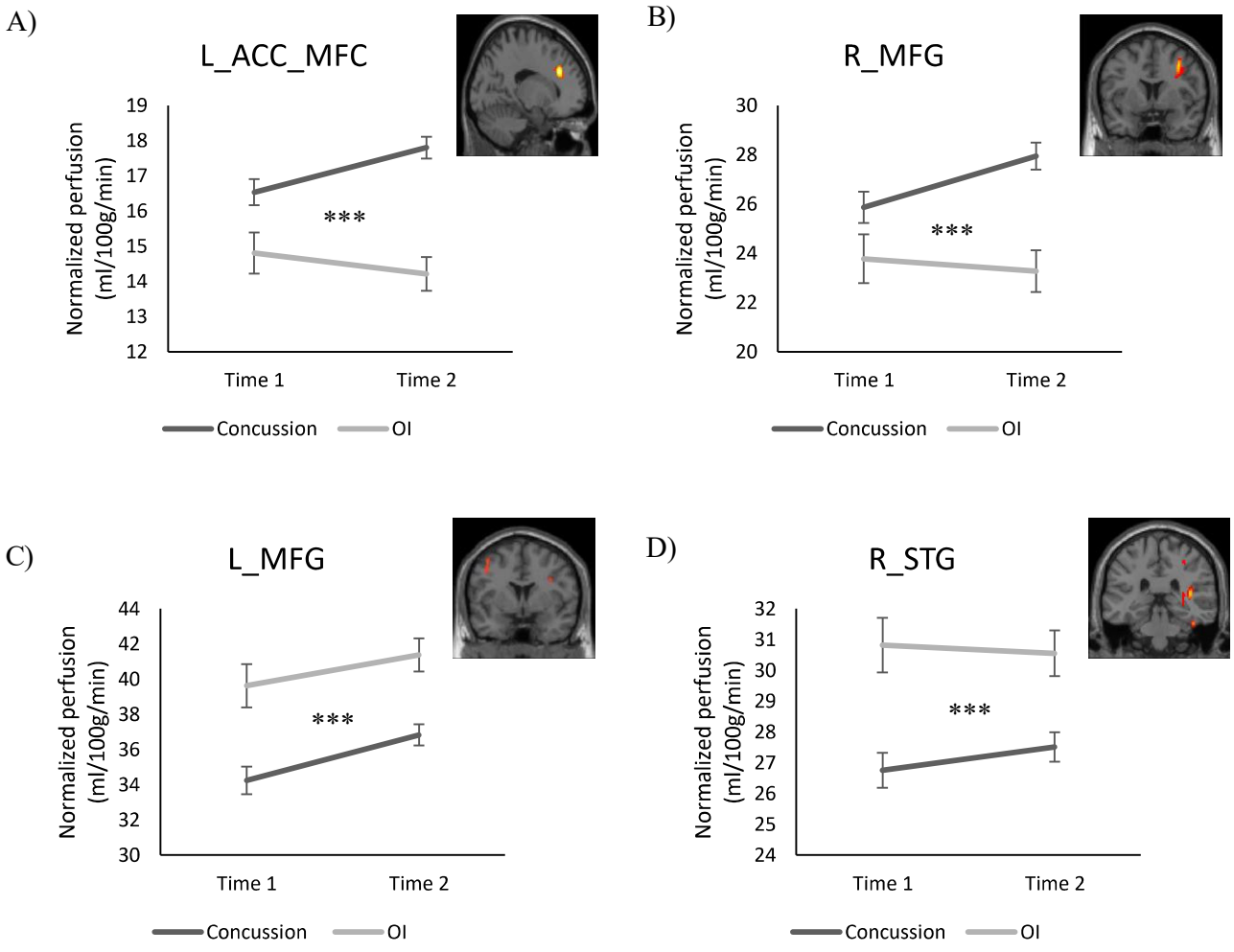


Figure 9. Mean normalized absolute perfusion adjusted for age, sex, motion, and mean global grey matter perfusion in the A) left anterior cingulate/medial frontal cortex, B) right middle frontal gyrus, C) left middle frontal gyrus, D) right superior temporal gyrus, E) right fusiform gyrus, F) right supramarginal gyrus, G) left angular gyrus, H) lingual gyri. Error bars represent standard error. *** = significant difference between groups.

Crude ROI analysis

The linear mixed model for crude normalized absolute perfusion (adjusted for motion and mean global grey matter perfusion only) confirmed the significant main effect of group in the L_ACC_MFC, $F(1,96) = 14.20$, $p < .001$, R_MFG, $F(1,96) = 8.05$, $p = .006$, L_MFG, $F(1,96) = 5.71$, $p = .019$, R_STG, $F(1,97) = 8.19$, $p = .005$, R_fusiform, $F(1,95) = 13.85$, $p < .001$, L_angular, $F(1,94) = 11.22$, $p = .001$, R_SMG, $F(1,96) = 5.46$, $p = .022$, and lingual gyrus, $F(1,93) = 9.65$, $p = .003$. Each ROI's main effect of group survived after Bonferroni correction ($p < .0063$), except the L_MFG and R_SMG. After Bonferroni correction, the concussion group

displayed significantly increased perfusion compared to OIs at both time points in the L_ACC_MFC, R_MFG, and L_angular, and the OI group displayed significantly increased perfusion at both time points in the R_STG, R_fusiform, and lingual. A significant interaction between group and time was also present in the L_ACC_MFC, R_MFG, and R_SMG, but none survived after Bonferroni correction. See Figure 10 for mean crude normalized absolute perfusion values for each ROI.



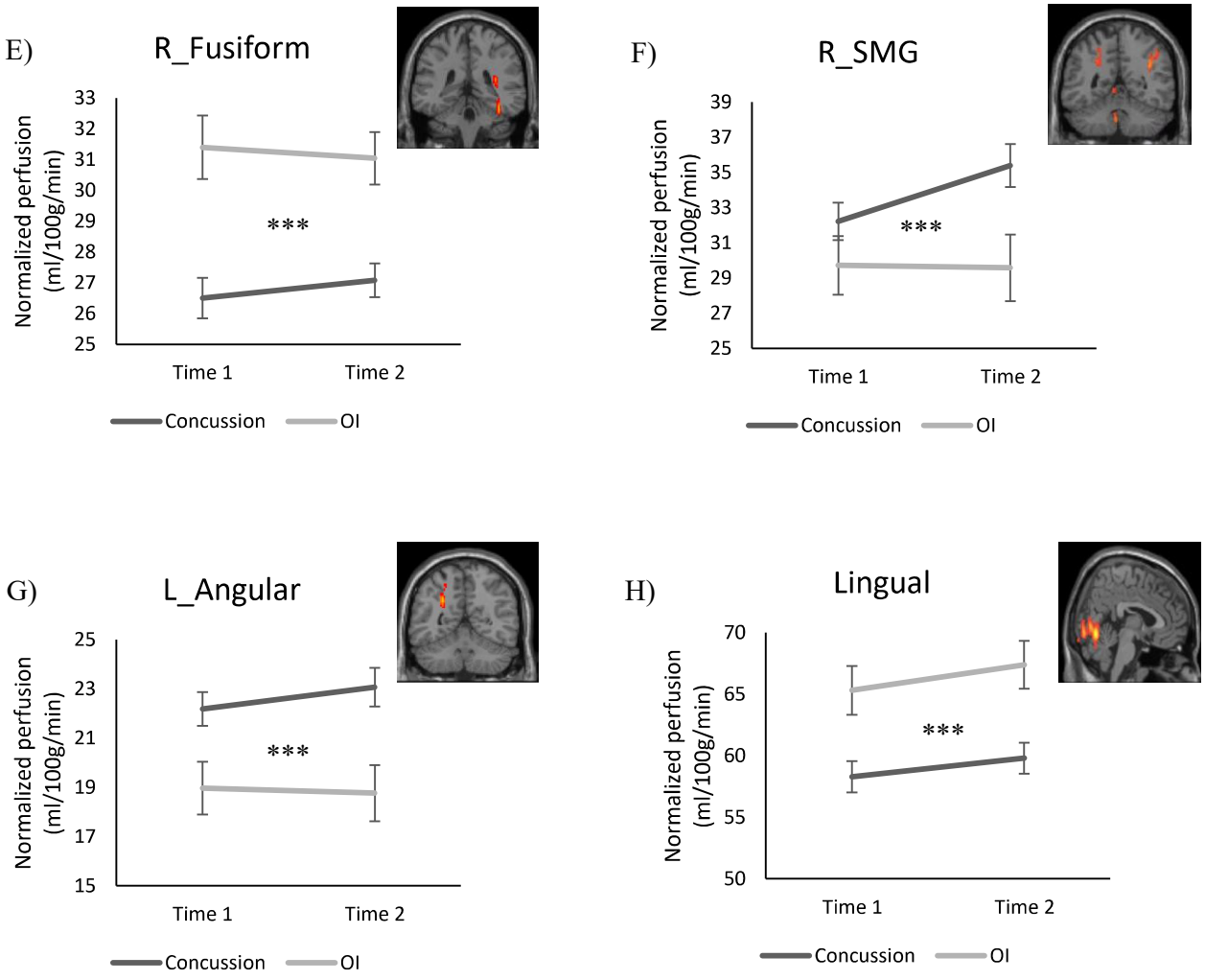


Figure 10. Mean crude normalized absolute perfusion in the A) left anterior cingulate/medial frontal cortex, B) right middle frontal gyrus, C) left middle frontal gyrus, D) right superior temporal gyrus, E) right fusiform gyrus, F) right supramarginal gyrus, G) left angular gyrus, H) lingual gyri. Error bars represent standard error. *** = significant difference between groups.

Analysis 2: 5P score, resilience, and CBF predicting 2- and 4-week concussion symptoms

Based on the results from analysis 1, mean global grey matter was excluded from further analyses since it did not differ between concussed and OI participants. Instead, absolute regional

perfusion in the L_ACC_MFC and R_MFG were used since they were determined to significantly differ between groups and over time. These regions also had significant interactions in the normalized absolute analyses, although they did not survive after Bonferroni correction.

The multiple regression model revealed that when controlling for motion, the 5P score, L_ACC_MFC perfusion, and resilience combined did not significantly predict 2-week (p = .12) or 4-week (p = .16) HBI scores for the concussion group. The 5P score (2 weeks: B = .55, p = .51, 4 weeks: B = .55, p = .51), L_ACC_MFC perfusion, (2 weeks: B = -.60, p = .29, 4 weeks: B = -.83, p = .12) and resilience (2 weeks: B = -.33, p = .11, 4 weeks: B = -.25, p = .18) also did not independently predict symptoms.

The same model, including R_MFG perfusion rather than L_ACC_MFC perfusion, also did not predict 2-week (p = .11) or 4-week (p = .23) scores. The 5P score (2 weeks: B = .60, p = .48, 4 weeks: B = 1.10, p = .16), R_MFG perfusion, (2 weeks: B = .25, p = .27, 4 weeks: B = .26, p = .23) and resilience (2 weeks: B = -.39, p = .07, 4 weeks: B = -.30, p = .12) also did not independently predict symptoms. See Table 6 for mean values of each variable for the concussion group.

Table 6. *Mean Values for the Variables Included in the Multiple Regression Analyses*

Variable	**Mean Value**
5P Score	6.63 ± 1.78 (medium risk)
CD_RISC	26.03 ± 7.18
L_ACC_MFC CBF	16.60 ± 3.92 ml/100g/min

R_MFG CBF	26.00 ± 6.23 ml/100g/min
2-week HBI	15.48 ± 11.20
4-week HBI	11.96 ± 10.76

Exploratory analyses: acute CBF predicting 4-week symptoms by group

Moderating effect of group on perfusion and HBI scores

Although perfusion, when combined with 5P score and resilience, were not predictive of symptoms for the concussion group, further exploratory analyses examined whether regional perfusion was predictive of symptoms, and whether this relationship was moderated by group (concussion versus OI). Only 4-week scores were used for this analysis since HBI scores were not collected for OI participants at 2 weeks. The mean 4-week HBI score was 12.45±10.17 for the OI group and 11.96±10.76 for the concussion group.

Moderation models, adjusted for age, sex, and motion (and mean global grey matter CBF for normalized aCBF), were conducted to examine the effect of group on the relationship between regional perfusion and symptoms. These were conducted using the PROCESS macro for SPSS (Hayes, 2013). Based on the first analysis, absolute perfusion in the L_ACC_MFC, R_MFG and L_angular, and normalized absolute perfusion in the L_ACC_MFC, R_MFG, L_angular, R_STG, R_fusiform, and lingual were all tested separately. None of these models yielded significant interactions, or significant main effects.

Discussion

The present study investigated changes in perfusion between concussed children and orthopedic injury controls from 72 hours to 4 weeks post-injury. Results from this analysis helped drive further analyses, which examined whether perfusion, when combined with psychological resilience and the 5P score, could improve prediction of concussion symptoms at 2 and 4 weeks post-injury. Additional exploratory analyses examined whether perfusion predicted symptoms at 4 weeks, and whether this differed between concussed participants and OI controls. It was hypothesized that perfusion would differ between groups and over time, such that the concussed group would exhibit decreased perfusion initially at 72 hours, and perfusion would increase to resemble that of OI controls by 4 weeks. It was also hypothesized that perfusion, the 5P score, and resilience combined would improve prediction of symptoms in the concussion group at 2 and 4 weeks.

The hypothesis concerning perfusion changes between groups over time was partially confirmed. There were no significant differences between groups or time points for mean global grey matter perfusion. However, regional CBF differed between groups and/or time points. For absolute regional perfusion analyses, there were significant group*time interactions in the L_ACC_MFC and R_MFG, and a significant group effect in the L_angular. In the L_ACC_MFC, the concussed group had significantly increased CBF at both time points compared to OI controls. For the R_MFG, the concussed group had significantly increased perfusion compared to OIs at 4 weeks only. The concussed participants' perfusion significantly increased over time in both the L_ACC_MFC and R_MFG. Further, in the L_angular, the concussed group had increased perfusion compared to OIs, but perfusion did not differ between time points for either group. For the normalized absolute regional perfusion analyses, some

regions showed increased perfusion compared to OI controls, and some showed decreased. After Bonferroni correction, the concussion group displayed significantly increased perfusion compared to OIs in the L_ACC_MFC, R_MFG, and L_angular, and significantly decreased perfusion in the R_STG, R_fusiform, and lingual. Neither group had statistically significant differences in perfusion between time points after Bonferroni correction. There were also group*time interactions for normalized absolute CBF in the L_ACC_MFC, R_MFG, and R_SMG, and main effects of group in the L_MFG and R_SMG. but these did not survive Bonferroni correction.

Finally, it was expected that the 5P score, psychological resilience, and acute CBF combined would improve prediction of symptoms at 2 and 4 weeks post-injury in the concussion group. This hypothesis was not confirmed, as the multiple regression models were not significant.

Since there were some significant regional alterations found in the first analysis, additional exploratory analyses were conducted to examine whether acute regional CBF could predict symptom burden, and whether this differed between OI and concussed groups. There was not a significant relationship between any region identified in the first analysis (aCBF in the L_ACC_MFC, R_MFG, L_angular, and normalized aCBF L_ACC_MFC, R_MFG, L_angular, R_STG, R_fusiform, lingual) and 4-week symptoms, and there was no moderating effect of group.

Changes in CBF by group and by time point

Mean global grey matter perfusion

While it was expected that mean global grey matter perfusion would differ between concussed and OI participants over time, there were no statistically significant differences in this sample. Although most previous research points to decreased mean global perfusion following concussion compared to controls, some studies have found no difference between groups, although they vary in terms of participant characteristics and image acquisition time (Churchill et al., 2019; M. J. Ellis et al., 2016; Militana et al., 2016; Möller et al., 2017; Mutch et al., 2018). Most previous studies that found acute decreased global perfusion in youth focused only on sport-related concussions, whereas our sample was recruited from the emergency department, with heterogeneity regarding mechanism of injury. It is possible that different mechanisms of injury (e.g., sport, falls, motor vehicle accidents) produce different patterns of altered CBF.

Recently, it was suggested that the CBF recovery process in mild to moderate TBI may occur regionally rather than globally (Quinn et al., 2020). Although mean global perfusion did not differ between groups or over time in this sample, there were some regional differences present. Similar to this study, three previous studies found regional perfusion abnormalities despite normal global perfusion values (Brooks et al., 2019; Churchill, Hutchison, Richards, et al., 2017; M. J. Ellis et al., 2016).

Regional perfusion

In our study, there were regions of both hypo- and hyperperfusion in concussed children compared to OI controls. Similarly, a study by Brooks et al. (2019) examining perfusion in children years after concussion (mean time since injury=2.7 years) found regions of both hypo

and hyperperfusion despite normal global CBF. Specifically, they found that youth with a history of concussion had increased perfusion in anterior/frontal regions years after concussion compared to OI controls. In adults with concussion, increased CBF in frontal regions compared to healthy controls has also been found in the acute and subacute stages (Doshi et al., 2015). Among children with sport-related concussion, increased CBF in the dorsal ACC was present at 2 weeks, and persisted at 6 weeks (Stephens et al., 2018). Our study corroborates these findings, as hyperperfusion was found in frontal regions, specifically the L_ACC_MFC and R_MFG. However, contrary to those studies, besides in the anterior regions our study also found hyperperfusion in the L_angular. Barlow et al. (2017) similarly found scattered regions (both anterior and posterior) of hyperperfusion in symptomatic children compared to asymptomatic children 4 to 6 weeks post-injury, including the L_angular. Although the time points of these studies all vary, it appears as though our results of hyperperfusion are in line with previous findings.

The same study by Brooks et al. (2019) also found hypoperfusion in posterior, inferior frontal and inferior temporal lobes. Regions included the bilateral lingual gyri, and left fusiform. In our study, both the lingual and right fusiform similarly exhibited hypoperfusion compared to OI controls. There was also hypoperfusion found in the R_STG in our study. Though we also found hyperperfusion in the R_SMG and hypoperfusion in the L_MFG, those regions did not survive Bonferroni correction, and might therefore be false positives. Overall, our study supports that the transition from the acute to subacute phase of a pediatric concussion is associated with scattered perfusion alterations. Specifically, there appears to be hyperperfusion in anterior regions of the brain and hypoperfusion in posterior/temporal regions.

The localization of hypo and hyperperfusion in this sample is interesting. It is possible that decreased CBF in certain regions leads to specific deficits, and hyperperfusion represents a compensation for deficits in regions with hypoperfusion (June et al., 2020; Li, Lu, Shang, Chen, Wang, Haidari, Chen, & Yin, 2020). Without multimodal imaging (e.g., measures of cerebral vasoreactivity and autoregulation), the mechanisms contributing to both increased and decreased perfusion are unclear. It is also worth noting that location of the injury may affect regional blood flow (Bigler et al., 2018; Churchill, Hutchison, Richards, et al., 2017; Eierud et al., 2014; McCrea et al., 2010), but this was not examined in the present study. It is possible that our sample experienced mainly coup-contre-coup injuries, which might explain why perfusion was affected in anterior and posterior regions. Multiple studies have also noted that the frontal and temporal lobes might be especially vulnerable to impact in concussion (Bigler et al., 2018; Churchill, Hutchison, Richards, et al., 2017; Eierud et al., 2014; McCrea et al., 2010). Since CBF in anterior/frontal regions was increased in our study, it is possible that this was an initial compensatory mechanism to restore homeostasis and meet increased metabolic demand (Doshi et al., 2015; Williams & Danan, 2016; Xu et al., 2021). Also, decreased posterior/temporal CBF in this sample could be due to damage to microvasculature (Len & Neary, 2011; Meier et al., 2015).

It is interesting that significant interactions were found in the L_ACC_MFC and R_MFG in the absolute analyses, meaning that CBF differed by group and by time point. These regions also had significant interactions in the normalized aCBF analyses, but did not survive Bonferroni correction. In both regions, absolute CBF increased from 72 hours to 4 weeks in children with concussion, but did not differ between time points for the OI group. Similar to Stephens et al. (2018) who found that dorsal ACC hyperperfusion persisted from 2 to 6 weeks post-injury, our

study also found that anterior hyperperfusion persisted over time. It is unclear as to why CBF continued to increase for concussed participants in these specific regions from 72 hours to 4 weeks, but Barlow et al. (2017) suggests that clinical recovery precedes recovery of CBF. It would be interesting to examine whether absolute CBF trajectories in these regions map onto clinical presentation and recovery.

5P score, resilience, and CBF predicting 2- and 4-week concussion symptoms

Our results demonstrated that CBF, psychological resilience, and the 5P score combined did not improve prediction of symptoms at 2 or 4 weeks in concussed children. Although unexpected, this potentially occurred due to the symptom scale used in our study, which was the HBI. Although the 5P score has previously been shown to predict symptoms measured with the HBI in a larger pediatric sample (Sader, 2021), the original 5P study used the post-concussion symptom inventory (PCSI), which reflects more domains. The HBI only comprises cognitive and somatic domains, and thus it is possible that our sample was experiencing more emotional and fatigue symptoms at 2 and 4 weeks that were not captured by the scale we used. Additionally, since psychological resilience is associated with pediatric mental health (Mesman et al., 2021), it may not have been predictive of cognitive or somatic symptoms measured with the HBI, since it is more likely predictive of emotional symptoms.

The sample size of this study is another potential reason as to why the 5P score and resilience were not predictive of symptoms. Since CBF was included in the analysis, this limited the number of participants that could be used, since they had to have underwent both MRI scans and passed motion review. The original 5P study also assessed presence/absence of PPCS as an outcome variable, but total symptom score was used in our study since the sample size was too

small to dichotomize the outcome. Since the concussion group, on average, was considered medium risk according to their 5P scores, it is also possible that most of our sample had clinically recovered by the 4-week time point. A larger sample size for both concussion and OI groups would likely provide a greater spectrum of risk scores, psychosocial factors, and recovery patterns.

The scale used to assess resilience may also explain why psychological resilience was not predictive of symptoms. While our study used the CD-RISC, it is possible that assessing other dimensions of resilience, such as protective factors (e.g., social support, optimism) may produce different results. It has also been suggested that resilience may not be an independent contributor to PPCS, and is rather mediated by anxiety and depressive symptoms (Durish et al., 2019). It would therefore be interesting to examine whether mental health diagnoses affect reporting of resilience and symptoms in pediatric concussion. It would also be of interest to compare multiple scales that assess different dimensions of resilience, rather than only the ability to bounce back.

Exploratory analyses: acute CBF predicting 4-week symptoms by group

Although regional CBF, when combined with resilience and the 5P score, was not predictive of symptoms, further exploratory analyses were conducted to determine whether any regions of interest identified in the first analysis was independently predictive of symptoms, and whether this differed between the concussion and OI groups. Regression analyses revealed there was no relationship between any ROI and 4-week symptoms, and no moderating effect of group. As few studies have examined whether CBF can predict symptoms, it is difficult to compare these results to other reports, however there are several potential reasons as to why these results may have come about. First, the OI group was reduced to 29 participants following motion

review, meaning that the sample size may not have been large enough to detect an effect in this group. Interestingly, the OI group also had a higher 4-week HBI score than the concussion group, but this may also be due to the small sample size.

Previous studies have found relationships between the ROIs identified in this study and concussion symptoms. One study found that increased CBF in the ACC was associated with self-reported fatigue in concussed adults in the chronic stage (Möller et al., 2017). On the contrary, another study found that lower ACC CBF was associated with increased fatigue and emotional symptoms in a mild-to-severe adult TBI population (Thomas et al., 2021). Although the direction of the relationship remains unclear, it is possible that the regions of interest in our study are more closely related to emotional and fatigue symptoms, which may not have been adequately captured by the HBI. However, one study found that increased left dorsal ACC perfusion predicted increased physical symptoms measured with the ImPACT post-concussion symptom scale in athletes at the subacute stage (Stephens et al., 2018). Additionally, Wang et al. (2019) found that CBF in the R_MFG was positively associated with memory symptoms, and negatively associated with impulse control. Both of these symptoms were also measured with the ImPACT test, which is comprised of a symptom scale and neurocognitive tests. Barlow et al. (2021) also found that generally, higher frontal relative CBF at 4 to 6 weeks predicted poorer recovery at 10 weeks. That study utilized the PCSI rather than the HBI, which also reflect more domains. These studies provide further support that a more extensive symptom scale, and looking at specific symptom subtypes, might help to elucidate how CBF alterations relate to symptom burden.

Our study results were most similar to those of Brooks et al. (2019), as ROIs were similar and patterns of CBF in the ROIs were similar. They examined the relationship between regional CBF years after concussion and demographics, pre-injury functioning, concussion history, time

since injury, and symptoms. They did not find any significant associations between CBF and those variables, similar to our findings. It is also possible that regions of increased blood flow were not associated with symptoms as this was compensatory (June 2020, Li 2020), and increases in CBF masked certain deficits. June et al. (2020) found increased CBF in temporal, frontal, and parietal regions that were previously shown to exhibit hypometabolism, and also relate to PPCS and cognitive symptoms. They postulated that increased CBF in those regions might serve to counteract the symptoms, as they found normal cognition among their sample. Li et al. (2020) also suggested that increased CBF found in the temporal lobe in the acute stage might be compensatory for cognitive deficits seen in mTBI. Once again, as the regions identified in this study were unrelated to symptom burden in this sample, it is unclear what the alterations in CBF may be compensating for. Further investigation should examine symptom correlates at the same time points during which scans are obtained to create a more clear picture of how CBF relates to symptoms.

Interestingly, Churchill et al. (2017) found that after separating concussed athletes into symptom subgroups, those experiencing predominantly somatic versus cognitive symptoms displayed different CBF patterns. Participants experiencing somatic symptoms displayed higher regional CBF, whereas those experiencing more cognitive symptoms showed reduced CBF. Churchill et al. (2017) suggest that the somatic group may exhibit increased CBF due to neuroinflammation, and that the cognitive group's symptoms might be due to lack of oxygen from reduced CBF. They also suggest that combining subgroups might obscure CBF abnormalities that are present. Perhaps separating concussed participants into distinct symptom subgroups would yield different results and shed light on how CBF alterations are related to specific symptom domains.

Strengths

There are a number of strengths to this research. To our knowledge, this is the first pediatric concussion study to acquire ASL images within 72 hours post-injury, and to examine longitudinal changes in CBF between concussion and OI groups from the acute to subacute stages. Most published studies have obtained scans at only one time point weeks-to-months post-injury, and were limited by having a small sample size. This study also had a relatively large sample size (*N*=99) for participants who underwent both MRI scans, which is greater than most published studies to-date. Additionally, we took a conservative approach to adjusting for multiple comparisons with the imaging data. All regions identified in the whole brain analyses survived family-wise error correction, and the final regions reported in the ROI analyses had to survive Bonferroni correction. These corrections all reduced the possibility of false positive findings in our study. Another strength of this study was the inclusion of orthopedic injury controls. Since the control group was also recruited from the emergency department, this allowed for control of injury-related characteristics that would not be present in a healthy control sample (e.g., pain, post-traumatic stress, medical treatment) (Wilde et al., 2018). The orthopedic injury control group also completed many of the same assessments as the concussion group, allowing us to ascertain whether certain outcomes are concussion-specific. Both the concussion and OI group were well-balanced with respect to age and sex, which are both important variables to consider in ASL studies (Wang et al., 2020). They were also well-balanced in terms of the other demographic variables, such as injury mechanisms and diagnoses. Finally, the concussion literature tends to focus on sports-related concussion and not consider other mechanisms of injury. Since recruitment took place in the emergency department, this allowed for the inclusion of children who were injured in a variety of ways, including sport.

Limitations

Despite many strengths of the present study, there are some limitations that need to be addressed. Since recruitment took place solely from the emergency department, this sample might represent children who present with more severe concussive injuries, which might therefore limit generalizability. Additionally, since there are currently no objective biomarkers to definitively diagnose concussion, we cannot be certain that the OI participants did not also have a concussion. However, the multiple screening tools used to detect concussion were thorough, and the diagnosis also relied on physician judgement. Moreover, only regions that differed between concussion and OI groups were considered as potential predictors of symptoms in the multiple regressions and exploratory analyses. Since we used Bonferroni correction for multiple comparisons, this created a stringent significance threshold, which could have produced false negative findings. It is possible that other regions not identified in the initial whole brain analysis are associated with symptoms. Finally, although sex and age were taken into account in this study, there are a number of other covariates that were not taken into account due to lack of power. Other potentially important covariates to consider include ethnicity and race (Holmes et al., 2016), socio-economic status (Harkins, 2020), and history of concussion (Churchill et al., 2019; M. Ellis et al., 2018). Although there is no consensus on which covariates are most important to include (besides age and sex), a larger sample size would have increased power and allowed for the inclusion of more prognostically important covariates.

Future Directions

There are a number of potential future directions for research of this nature:

1. Including scales that reflect more symptom domains is an important future direction. It would also be interesting to examine other markers of recovery besides subjective symptom reporting, such as balance, cognitive, and neuropsychological testing.
2. Adequately powered studies should take into account other prognostically important covariates, besides just age and sex.
3. Future studies could recruit healthy controls in addition to an orthopedic injury control group. This would allow for controlling of injury-related characteristics, as well as comparison to non-clinical, typically developing children (Wilde et al., 2018).
4. It would be interesting to compare CBF with measures of cerebral vasoreactivity and autoregulation, as this could help elucidate the mechanisms behind altered CBF following concussion.
5. Though resilience is strongly tied to mental health, future analyses could examine whether different mental health diagnoses contribute to persistent symptoms.
6. Future whole brain analyses should be conducted to assess whether any other regions not identified in this study are related to symptom burden following pediatric concussion. Our lab will be doing this analysis in the future, as well as looking at whether longitudinal changes in CBF relate to changes in symptom reporting, and whether this differs between concussion and OI groups. We will also be looking at total HBI symptom scores as well as cognitive and somatic sub-scores.

Conclusions

Regional differences in CBF between children with concussion and OI were found, but were unrelated to 4-week symptom burden in this sample. The combination of 5P score,

psychological resilience, and regional CBF also did not improve prediction of symptoms at 2 or 4 weeks post-injury. Nonetheless, these results are an important contribution to the pediatric concussion literature, as they indicate that longitudinal CBF alterations may be important for understanding persistent neurobiological deficits after concussion. The role of CBF as a biomarker for concussion recovery in children should not be ruled out based on these results, and more research is needed to determine how CBF alterations contribute to clinical presentation after pediatric concussion.

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