EXERCISE, NEUROIMAGING, AND PEDIATRIC CONCUSSION

FROM PHYSICAL ACTIVITY TO BRAIN ACTIVITY: AN EXERCISE SCIENCE AND FUNCTIONAL NEUROIMAGING STUDY OF PEDIATRIC CONCUSSION

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LAY ABSTRACT

Until a few years ago, the advice children received after a concussion (or mild brain injury) was to rest until they no longer had symptoms. But the way concussions are being treated is changing. Scientists have found that exercising soon after a concussion can lessen symptoms. It is no longer thought that *rest-is-best*. Instead, it is now believed that *exercise-is-medicine*. But there are still important questions about the role of exercise after a concussion that have not been answered. The four studies in this thesis had the goal of answering some of those questions. In the first study, we found that while exercise improves symptoms after a concussion, we know less about how it impacts the brain and our ability to think. From the second study, we learned that a concussion impacts the brains of boys and girls in different ways, and that girls may have longer lasting brain changes after a concussion than boys. Our third study showed that after a concussion, girls take part in less physical activity than boys throughout the day. The fourth study suggests that there may be a link between brain activity and physical activity in children with a concussion. This thesis adds to our knowledge of the role of exercise in concussion. It also raises some important questions that should be answered by new studies in the near future.

ABSTRACT

Concussion management is changing. Recent years have marked a sea change, with the former *rest-is-best* approach being supplanted by an *exercise-is-medicine* mindset. Despite this, important questions remain unanswered in the pediatric exercise-concussion literature. The overarching aim of this thesis was to examine the effects of *exercise* on outcomes beyond concussion symptoms, and build our understanding of the relationship between pediatric concussion and *physical activity*.

Four studies were performed to this end. First, per a systematic review, we found that randomized trials on the effects of exercise on neuroimaging and cognitive outcomes remain limited. Studies suggest that exercise may improve brain structure and function post-concussion, while data with respect to cognitive outcome were mixed. Second, we provided the first evidence that the functional neuropathology of pediatric concussion differs by sex at 1 month post-injury, with females demonstrating impairment not observed in males. Namely, only females with concussion showed patterns of both hyper-connectivity (between the lateral pre-frontal cortex & inferior frontal gyrus, lateral pre-frontal cortex & lateral occipital cortex, and the posterior cingulate cortex & cerebellum; all p-corrected <0.05) and hypo-connectivity (between the anterior cingulate cortex & precuneus, anterior cingulate cortex & cingulate gyrus, and posterior cingulate cortex & paracingulate gyrus; all p-corrected <0.05). Third, we provided the first accelerometer-based characterization of physical activity and sedentary time in children with concussion in comparison to 1:1 matched healthy controls. Relative to healthy controls, children with concussion were more sedentary, with a mean difference [MD] of 38.3 minutes/day (95% confidence interval [CI] 11.2 to 65.4, $p<0.01$), and they also performed less light (MD -19.5 minutes/day, CI -5.3 to -33.7, $p<0.01$), moderate (MD -9.8 minutes/day, CI -5.7 to -13.8, $p<0.001$) and vigorous physical activity (MD -12.0, CI -6.9 to -17.2, $p<0.001$); greater physical activity deficits were observed in females with concussion. Fourth, per the first study to employ both accelerometry and functional neuroimaging in pediatric concussion, we found that intra-network connectivity of the default mode network was associated with subsequent accelerometer-measured light ($F_{(2, 11)} = 7.053$, $p = 0.011$, $R_a^2 = 0.562$; $\beta = 0.469$), moderate ($F_{(2, 11)} = 6.159$, $p = 0.016$, $R_a^2 = 0.528$; $\beta = 0.725$), and vigorous ($F_{(2, 11)} = 10.855$, $p = 0.002$, $R_a^2 = 0.664$; $\beta = 0.792$) physical activity. This study provides the insight into a potential link between brain activity and physical activity in pediatric concussion. The next wave of exercise and physical activity research in concussion needs to move beyond symptom studies, employ sex-specific analyses, understand the impact of exercise on brain function, and consider interventions that increase habitual physical activity. Doing so is necessary for exercise to become medicine for concussion patients.

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By happenstance, I decided to train for my first marathon the year I would defend my PhD. I would cross the finish lines of these two races within months of one another. Both, the latter more so, were collaborative efforts for which I owe much thanks to many people.

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I stepped into a lab with little knowledge in exercise science. Thank you to all my (far more experienced) lab mates for sharing your research with me and taking an interest in mine. It was my goal to learn from all those around me when I joined CHEMP. I hope this thesis shows that I did.

When asked what I do, most of my friends shrug and say "he does brain stuff". I hope after this thesis, I will earn a second shrug as you say "he does exercise stuff, too". Thank you for not-quite-understanding-but-supporting.

To my family. I don't know if I am as supportive of your goals as you are of mine–it seems hard to be with all that you do. Mom and dad, you would give your all for the smallest gain of mine. I write this now as a reminder to myself to thank you more often for being who you are and for building me up the way you have. Shanna, you have more faith in me than I do, which has gotten me through stretches of doubt and difficulty. You are the *sine qua non* to anything and everything that I accomplish.

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LIST OF ABBREVIATIONS

ABIDE-II	Autism Brain Imaging Data Exchange II
aCompCorr	Anatomical component-based noise correction procedure
AD	Axial diffusivity
ANS	Autonomic nervous system
APOE-ε4	Apolipoprotein E allele 4
ART	Artifact detection tool
ATP	Adenosine triphosphate
BCBT	Buffalo Concussion Bike Test
BCTT	Buffalo Concussion Treadmill Test
BDNF	Brain derived neurotrophic factor
BOLD	Blood-oxygen-level-dependent
BPM	Beats per minute
CBF	Cerebral blood flow
CNS	Central nervous system
CO2	Carbon dioxide
CVR	Cerebrovascular reactivity
DBP	Diastolic blood pressure
deoxyHb	Deoxygenated hemoglobin
DMN	Default mode network
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
EEG	Electroencephalogram
FA	Fractional anisotropy
fALFF	Fractional amplitude of low frequency fluctuations
FITT	Frequency, Intensity, Time, Type
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FPN	Fronto-parietal network
FWE	Family-wise error
GE	General Electric
GLM	General linear model
HR	Heart rate
HRR	Heart rate reserve
HRV	Heart rate variability
Hz	Hertz
ImPACT	Immediate Post-Concussion Assessment and Cognitive Test

IRC	Imaging Research Centre
LPA	Light physical activity
MD	Mean diffusivity
MD	Mean difference
MET	Metabolic equivalent
mmHg	Millimetre of mercury
MNI	Montreal Neurological Institute
MPA	Moderate activity
MPFC	Medial pre-frontal cortex
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
mTBI	Mild traumatic brain injury
MVPA	Moderate-to-vigorous physical activity
NIRS	Near infrared spectroscopy
NAA	N-acetylasparate
NMDA	N-methyl-D-aspartate
oxyHb	Oxygenated hemoglobin
PaCO2	Partial pressure of arterial carbon dioxide
PCC	Posterior cingulate cortex
PCS	Post-concussion syndrome
PCSS	Post-concussion symptom scale
PedsQL	Pediatric Quality of Life Inventory™
P_{ETCO2}	End-tidal partial pressure of carbon dioxide
PICO	Population, Intervention, Comparison, Outcome
PNC	Philadelphia Neurodevelopmental Cohort
PNS	Parasympathetic nervous system
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	Randomized controlled trial
RD	Radial diffusivity
ReHo	Regional homogeneity
ROI	Region of interest
RPE	Rating of Perceived Exertion
rs-fMRI	Resting state functional magnetic resonance imaging
SA	Salience network
SBP	Systolic blood pressure
SCAT	Sport concussion assessment tool
SD	Standard deviation

SMD	Standard mean difference
SMN	Sensorimotor network
SNS	Sympathetic nervous system
SPM	Statistical parametric mapping
SRC	Sport-related concussion
TBI	Traumatic brain injury
TFCE	Threshold free cluster enhancement
VAN	Ventral attention network
$\dot{V}CO_2$	Volume of carbon dioxide produced
$\dot{V}E$	Minute ventilation
VE	Pulmonary ventilation
$\dot{V}O_2$	Volume of oxygen consumed
VPA	Vigorous activity

DECLARATION OF ACADEMIC ACHEIVEMENT

This “sandwich” thesis includes a general introduction (Chapter 1) and a general discussion (Chapter 6), with four standalone, first-authored research manuscripts in between (Chapter 2, Chapter 3, Chapter 4, and Chapter 5). At the time of submission, of the research manuscripts, Chapter 2 has been published in *Brain Injury* and is reproduced herein with permission from the publisher. Chapter 3 has been submitted to *JAMA Network Open* as of July 6th, 2021. Chapter 4 is under review at *BJSM* (#bjsports-2021-104666). Finally, Chapter 5 has been submitted to *BJSM* as of July 6th, 2021.

The contributions of all authors on multi-authored publications are outlined below, manuscript-by-manuscript:

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CHAPTER 1

General introduction

Understanding pediatric concussion

Definition

Traumatic brain injury (TBI) is defined by an alteration in brain function caused by linear and/or rotational external biomechanical forces (Menon et al., 2010). TBI is broadly classified as either mild, moderate, or severe based on the extent and duration of trauma-induced alterations in consciousness (Malec et al., 2007; Savitsky et al., 2016).

Concussions are a *sub-type* of mild TBI (mTBI) that typically do not result in structural brain damage (McCrory et al., 2013). Per the fifth and most recent international consensus statement on concussion in sport issued in 2016 (McCrory et al., 2017b) and a more recent consensus statement developed for team physicians by six professional medical associations (Herring et al., 2021), concussions are defined as brain injuries that:

i. are induced by external forces.

ii. can be caused by either direct head impacts or impulsive forces transmitted to the head following impact elsewhere to the body.

iii. do not necessitate a loss of consciousness.

iv. induce symptoms that typically resolve spontaneously.

v. result in symptoms that are not explainable by co-morbidities (e.g., psychological disorders), secondary injuries (to, for example, the cervical spine or vestibular system), or medications and/or intoxicants.

vi. are acutely associated with *functional brain chan*ges rather than a *structural neuropathology*.

This definition was established in a sports context, and it is not pediatric-specific. However, it was selected as the reference definition for this thesis given that it is supported by an extensive literature review and two expert panels. Further, this definition remains applicable to pediatric populations (the population germane to this thesis) as the injury definition is based on the mechanism of impact and the *type* of neuropathology associated with the injury, and not the clinical presentation of the injury itself (which can differ between children and adults, as discussed below).

Pediatric concussion considerations

Although pediatric and adult concussion share many core pathological and symptomalogical features, there are important considerations to make when studying the concussed pediatric brain.

First, the nervous system is continually developing throughout childhood and adolescence (Blakemore, 2012; Giedd et al., 1999; Giedd et al., 2010; Huang et al., 2015; Johnston, 2003; Satterthwaite et al., 2014). This neuroplasticity allows neural networks, tissues, and structures to undergo critical development and maturation. For example, neurotransmitter systems reorganize and influence behaviour during neurodevelopment (Colver et al., 2013), the volume of signal conducting white matter increases steadily from ages 6 to 20 helping integrate neural circuits (Lenroot et al., 2007), and maturation of important brain regions begets parallel cognitive development (Erus et al., 2015). This critical period of neuroplasticity sets the trajectory for healthy brain and cognitive neurodevelopment, yet it also creates a window in which children and adolescents are vulnerable to developmentally disruptive stressors, including concussion (Andersen, 2003; Fuhrmann et al., 2015; Konrad et al., 2013). Brain injuries sustained in early childhood can lead to aberrant patterns of cortical organization in adolescence (Wilde et al., 2020).

Second, there are biomechanical differences in how pediatric and adult concussion are experienced. Differences in muscle strength (particularly in relation to neck musculature) influence how force transfers to the brain upon impact (Carmichael et al., 2019; Collins et al., 2014; Duma et al., 2014; Gutierrez et al., 2014; Kirkwood et al., 2006; Rowson et al., 2012). A given force may not result in the same concussive injury in children and adults. Such biomechanical differences may contribute to variable neuropathology and clinical presentation of pediatric and adult concussion.

The line between pediatric and adult concussion is perhaps best drawn by a systematic review of 134 studies. Pediatric concussion was found to be distinct from adult concussion with respect to its symptom profile, expected recovery time, and predictors of recovery. The available evidence led the authors of the review to conclude that: age-specific guidelines are required for concussion management, age-appropriate symptom rating scales should be used to better understand symptomatology in pediatric concussion, and recovery times of children with concussion should be expected to be longer than those in adults (Davis et al., 2017a).

Collectively, these data highlight that pediatric brain injuries are not brain injuries in “little adults” (Giza et al., 2007). Dedicated research into pediatric concussion is required to inform our understanding and management of brain injury in children.

Epidemiology

Concussions are among the most common pediatric injuries (Daneshvar et al., 2011a; Gardner et al., 2019; Halstead et al., 2010; Prien et al., 2018). While nationally sampled Canadian data are not available, American data suggest that up to 3.8 million sport-related brain injuries occur each year, of which up to 75% are mTBIs or concussion (Langlois et al., 2006). When extrapolated to a Canadian context, this equates to an annual incidence of more than 50,000 pediatric sport-related concussions (SRC) (*Statistics Canada: Population Estimates and Statistics*, 2017; *United States Census Buerau: Quick Facts*, 2016). With SRCs accounting for approximately half of all pediatric brain injuries (Yaramothu et al., 2019), the incidence of pediatric concussion in the general Canadian population can be estimated to be double that reported above.

Outside of a sports context, administrative data from Ontario (namely, physician billing records for all-cause concussion between 2008-2016) were used to determine concussion incidence within the province. With respect to pediatric populations, the authors reported that the incidence of concussion was highest for those aged 0-4 years at 3,600/100,000 children of that age group. The incidence was second highest for those aged 5-12 and 13-17, at approximately 1,500/100,000 for both age cohorts (Langer et al., 2020). Collectively, these data suggest a provincial pediatric concussion incidence of approximately 6,500/100,000 children, also equating to an overall annual caseload of approximately 100,000 cases within the province (*Statistics Canada: Population Estimates and Statistics*, 2017).

These incidence estimates, however, may be conservative, as concussion diagnosis is made challenging by the protracted presentation of symptoms and lack of diagnostic biomarkers that can preclude acute detection (Boutis et al., 2015; Makdissi et al., 2015; McCrory et al., 2017a). Further, athletes often underreport concussion symptoms (Meier et al., 2015; Williamson et al., 2006), leading to non-disclosed injuries in up to 20% of cases (Wallace et al., 2021). At the same time, the rates of concussion are increasing most rapidly in those aged 10-19 years (Zhang et al., 2016).

Taken together, the incidence of pediatric concussion is among the highest of all childhood injuries, potentially underestimated, yet increasing.

Diagnosis

Several diagnostic questionnaires have been developed to assess cognitive, behavioral, emotional, sleep-related, and/or balance/vestibular impairments following concussion (Guskiewicz et al., 2004; King et al., 1995; Lovell et al., 2006; McCrea et al., 1998; Piland et al., 2003; Roberts et al., 1997). These questionnaires are meant to be administrated in the acute stages of injury, often (as in the case of SRC) minutes after trauma. However, as the entry point into the healthcare system for most children with concussion is the emergency department (Thurman, 2016), these questionnaires are also often applied in such clinical settings. Among the most commonly used questionnaires are the Sport Concussion Assessment Tool (SCAT; recently revised and currently in its 5th version (Echemendia et al., 2017)) and its pediatric version (Child SCAT (Davis et al., 2017b)). Both versions of the SCAT involve an assessment of memory, consciousness, symptoms, cognition, balance, and the cervical spine. These questionnaires can be quickly administered by non-clinicians (including coaches and athletic trainers) to provide point-of-injury data. However, they have limited normative data, require further sensitivity analyses, and are recommended to be supplemented with a full physical, neurological, and vestibular assessment by a physician with experience in concussion (Davis et al., 2017c). The challenges of diagnosing a concussion are reiterated in a recent consensus statement developed for team physicians, which highlights that the non-specific nature of concussion symptoms and lack of a diagnostic neuroimaging or serum biomarker make this injury difficult to diagnose without a multi-faceted clinical assessment (Herring et al., 2021).

Clinical presentation

The present thesis does not focus on concussion symptoms, but instead the underlying functional neuropathology of the injury and other salient clinical features of concussion. Nonetheless, symptoms are an essential clinical consideration. As such, an overview of concussion symptoms is provided below.

While concussion symptomology is diverse, there are a number of common symptom sets: somatic (e.g., headache, dizziness), cognitive (e.g., difficulty concentrating, difficulty remembering, feeling ‘in a fog’), mood/emotional (e.g., anxiety, depression), and sleep-related (e.g., difficulty falling asleep) (Gagnon et al., 2017; Mittenberg et al., 2016). These symptoms may be measured using the Post Concussion Symptom Scale (PCSS), a widely used measure in both pediatric and adult populations (Alla et al., 2009; Echemendia et al., 2017; Lovell et al., 1998). The PCSS has high internal consistency (Crohnbach $\alpha = 0.87$), moderate-high test-retest reliability ($r = 0.65$) and high sensitivity and specificity (0.82 and 0.85, respectively).

Cognitive symptoms may outlast the somatic, per a cohort study involving 96 children (Teh et al., 2020), though research into individual symptom trajectories remains relatively limited in comparison to research on complete symptom recovery. Guidelines now suggest that resolution of *all* concussion symptoms is expected to occur within 4 weeks of injury in children (Herring et al., 2021; McCrory et al., 2017b). However, multiple research groups have reported that up to 30% of children may experience symptoms that persist beyond this timeframe (Eisenberg et al., 2014; Ledoux et al., 2019; Makdissi et al., 2017).

Insight into recovery curves by age group and sex was offered by a large, Canadian, multi-center study of over 3000 children. This study reported that in children aged 5-7, 75.6% of symptoms resolved within 2 weeks. The rate of symptom resolution was slightly higher (approximately 80%) for children aged 8-12 and 13-18 by 4 weeks post-injury, though a recovery plateau was observed from week 2 onwards. Further, adolescent girls were most likely to experience protracted recovery, with many still symptomatic at 12 weeks post-injury (Ledoux et al., 2019). These recovery curves map onto those reported in another large, prospective cohort study (n=822) of pediatric and adult SRC (Kara et al., 2020), and collectively support the notion of a “miserable minority”, or those who experience persisting symptoms following concussion (Rohling et al., 2012).

Furthermore, in a real-world context, a study of over 2000 children with concussion found that children with persistent symptoms had lower self-reported health-related quality of life (in the physical, emotional, social, and school sub-domains of the Pediatric Quality of Life Inventory [PedsQL] 4.0) at 4, 8, and 12 weeks post-injury in comparison to normative data on healthy children (Novak et al., 2016). Longer-term studies demonstrate that this relationship between persistent symptoms and health-related quality of life may persist up to 1 year post-injury (Chiang et al., 2016; DeMatteo et al., 2014; Fineblit et al., 2016; Novak et al., 2016; Theadom et al., 2016). In some cases, persistent symptoms may be associated with functional brain connectivity impairments (Iyer et al., 2019a), and concussion may alter long-term neurodevelopmental trajectories and lead to behavioural and emotional impairments (Daneshvar et al., 2011b). Overall, however, the relationship between concussion symptoms and the neuropathology of the injury requires further study, particularly in the pediatric population.

Pathophysiology

Metabolic dysfunction

The neurometabolic cascade following concussion has been thoroughly detailed in a seminal review (Giza et al., 2001), which has since been updated to reflect advances in our understanding of the basic science of concussion (Barkhoudarian et al., 2016). Much of the data included in said review were from animal studies, with limited corroborating data to date from clinical studies employing measures such as spectroscopy to examine post-concussion neurometabolic changes. Nonetheless, data on the neurometabolic cascade following concussion are reviewed here in brief, as they are important for understanding the core pathophysiology of the injury.

In concussion, the neurometabolic cascade that ensues following impact can be summarized as follows (Barkhoudarian et al., 2016):

1. Depolarization of axons impacted by trauma, leading to impact-induced, unregulated action potentials.
2. An indiscriminate release of neurotransmitters, including glutamate.
3. A potassium efflux triggered by the glutamate release, which increases extracellular levels of potassium beyond homeostatic levels.
4. Increased activity of sodium-potassium pumps (active transporters), activated to restore ionic imbalances (i.e., potassium efflux) to normal levels.
5. The increased activity of active transport pumps results in local hyperglycolysis, as an above-average amount of energy, or adenosine triphosphate (ATP), is required to fulfil the needs of the sodium-potassium pumps.
6. Lactate accumulation therefore occurs as a result of this period of hyperglycolysis.
7. Trauma-related cytoskeletal damage can lead to calcium influx (which can persist longer than other ionic imbalances), leading to local mitochondrial dysfunction as this impairs their oxidative capacity.
8. Mitochondrial dysfunction compromises ATP production (owing to the limitations on oxidative capacity, as above), and the hyperglycolysis which was initially observed is arrested leading to ‘metabolic depression’.

9. In some cases, calcium-dependent apoptotic mechanisms are triggered (via calpain proteases) by ionic imbalances (primarily related to calcium sequestration) which may lead to local neuronal death.

It is important to note that the first five events outlined above occur immediately following trauma. However, compromised ATP production can persist for the initial weeks post-injury (see **Figure 2**, from (Barkhoudarian et al., 2016)). There is some evidence that this metabolic imbalance (which can manifest as cerebral blood flow [CBF] impairments, given that the 'metabolic depression' observed post-injury reduces energy demands) is associated concussion symptoms. For example, the magnitude of CBF abnormalities post-injury in young adults has been associated with higher levels of self-reported symptoms (Churchill et al., 2017). In children, reduced CBF post-concussion was observed in the absence of structural or functional impairment (Maugans et al., 2012), and CBF velocity has been associated with PCS in pediatric populations (Clausen et al., 2016b). Additional research is required to more clearly establish the link between the neurometabolic cascade of concussion, concussion neuropathology, and injury-related symptoms.

Autonomic nervous system (ANS) dysfunction

The effects of TBI extend beyond the brain and more broadly to the central nervous system (CNS). Notably, the ANS is affected post-TBI, with its two constituent systems (the sympathetic nervous system [SNS] and parasympathetic nervous systems [PNS]) becoming increasingly uncoupled as a function of injury severity (Goldstein et al., 1998). This uncoupling has cardiovascular implications (which are relevant to current concussion management approaches, as discussed in subsequent sections), given that the cardiovascular system is innervated by both the SNS and PNS (Paton et al., 2005).

A recent systematic review of 36 concussion studies found that ANS abnormalities–measured as change in heart rate variability (HRV), arterial blood flow velocity, baroflex sensitivity, and electrocardiogram (ECG)–were reported in all but 3 articles (Pertab et al., 2018). However, despite this evidence-base, the review noted that the exact mechanism driving ANS abnormalities following concussion remains to be determined. Some evidence from animal (Sinha et al., 2017) and human studies (Adeboye et al., 2000; Callaway et al., 2019; Esterov et al., 2017) suggests that trauma-induced damage or dysfunction to the mid-brain and brainstem, regions involved in ANS regulation, are contributing factors to ANS abnormalities in concussion. The etiology of ANS impairment remains an important topic of study.

Regardless of its etiology, the impact of ANS dysfunction in concussion is broad. A narrative review identified that ANS dysfunction following mTBI can contribute to symptoms (potentially by driving changes in cerebral perfusion and CBF), and also neuroinflammation and oxidative stress that may have chronic consequences especially in multiple concussion (Purkayastha et al., 2019). A recent longitudinal case-control study (n=44) of children with concussion reported that recovery trajectories of ANS dysfunction are non-linear (within an initial decrease in HRV followed by a gradual rise) and variable (Paniccia et al., 2018). There is also some preliminary evidence that ANS dysfunction can lead to prolonged symptom resolution (Callaway et al., 2019; Middleton et al., 2010) and that it may persist even in asymptomatic patients (Abaji et al., 2016).

Two studies from one group examined SNS and PNS activity separately in concussion. Following face cooling (which engages the PNS via the trigeminal nerve), the root mean square of successive differences between R-R intervals (a proxy of HRV) was blunted in adolescents more than 1 year post-concussion in comparison to healthy controls. This suggests that the parasympathetic response to this stressor was reduced in adolescents with a concussion history (Haider et al., 2020). Another study from this group involved submerging the right hand of participants in ice water (i.e., the cold pressor test, designed to engage the SNS), and found that acutely concussed young adults (n=10) had smaller increases in HR relative to baseline and a more delayed increase in mean arterial pressure in comparison to healthy controls (n=10) (Johnson et al., 2020). These data indicate that the SNS response is also blunted in concussion.

In the context of exercise, pediatric brain injury studies show that there is reduced HRV following low-intensity (Biswas et al., 2000; Goldstein et al., 1996; Katz-Leurer et al., 2010) and steady state (Blake et al., 2016) exercise. In pediatric concussion specifically, no differences between acutely concussed and non-concussed athletes were reported at rest, although HRV differences were observed following low-to-moderate but not high-intensity exercise (Gall et al., 2004). Further, one study shows no differences in HRV between concussed and non-concussed youth athletes during an isometric hand grip test (La Fountaine et al., 2009). There is early evidence that strength is compromised in children with concussion, which may also be related to ANS dysfunction (Reed et al., 2016).

Further support that concussion can result in ANS dysfunction comes from studies examining blood pressure and the orthostatic response. In a study involving 12 concussed athletes and 11 non-concussed controls (with an average age of, respectively, 20.1 ± 0.9 and 21.7 ± 0.9), participants were assessed when breathing, standing, and performing the Valsalva breath-holding maneuver at four different time points (<48 hours of injury, 24 hours after the initial assessment, 1 week post-injury, and 2 weeks post-injury). The outcome measures, which served as proxies for cardioautonomic function, were heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP). At the first time point, the concussed group had significantly greater: (i) resting SBP, (ii) SBP responses to standing, (iii) 90% SBP normalization times, and (iv) resting HR. These effects, however, did not persist at the later time points (Dobson et al., 2017b). The abnormal blood pressure findings are similar to those reported by other groups (Kozlowski et al., 2013; Leddy et al., 2011). In line with this, during a supine-to-standing orthostatic test, children within 1 week of concussion self-reported dizziness and light headedness more frequently than controls, despite not meeting clinical criteria for orthostatic hypotension (Haider et al., 2021b). A second study from this group showed that middle cerebral artery velocity was increased only in those with concussion after 5 minutes of lower body partial pressure was applied (Worley et al., 2021). These data support the hypothesis that concussion can result in cardioautonomic dysfunction, and that measuring this dysfunction in the early stages of injury can serve as a marker of concussion recovery (Dobson et al., 2017a).

Collectively, the evidence-base suggests that ANS dysfunction is implicated with both acute and chronic complications of concussion, and that it is an underlying (and potentially longstanding) pathological feature of concussion that should be considered a target for intervention. As discussed in detail in subsequent sections of this thesis, part of the motivation for using exercise as an intervention for concussion management is its potential to regulate ANS dysfunction.

Functional neurological dysfunction and advanced neuroimaging

MRI as an outcome measure

Concussion is not typically associated with a structural neuropathology, and therefore on its own, standard clinical magnetic resonance imaging (MRI) is of limited utility for concussion diagnosis (Keightley et al., 2012). However, there is active research into the neuroimaging of concussion, which is motivated by a need to develop better and more objective single-subject diagnostic injury markers, monitor progression and recovery of non-structural concussion pathology, and assess how neuroimaging findings associate with clinical measures of the injury. Some advanced imaging modalities that are being actively studied are summarized in **Table 1**.

Table 1: Overview of common neuroimaging modalities used in pediatric brain injury.

Imaging technique	**Purpose**	**Clinical interpretation**
Functional MRI (fMRI)	Provides an estimation of neural activity by measuring blood oxygen. As metabolic demands increase in a region of interest (due to, for example, a cognitively demanding task), so too does blood flow and oxygen metabolism in said region; such alterations serve as a proxy for brain activity and are detected by fMRI. Moreover, fMRI can be used in a task-independent manner to understand resting functional brain activity	Patterns of neural activation during rest or while completing a cognitive task have been shown to vary between TBI patients and healthy individuals, thereby serving a potential diagnostic marker (Koerte et al., 2016). However, single-case fMRI diagnosis remains a challenge and research focus
Diffusion tensor imaging (DTI)	This MRI sequence detects changes in the diffusivity of water molecules, with increased diffusivity indicative of brain injury; restricted, predictable movement of water	As white matter tracts may be susceptible to damage following trauma (particularly trauma involving rotational forces which can cause shearing and diffuse axonal injury), DTI is an imaging

	molecules is suggestive of integral and healthy axonal membranes, filaments, and myelin sheaths. While structural damage post-concussion is typically not observable by means of a standard clinical MRI, advanced neuroimaging techniques (such as DTI) can provide insight into axonal injury	modality that has shown initial efficacy in group-wise diagnosis of milder brain injuries in children (Chu et al., 2010; Cubon et al., 2011; Henry et al., 2011; Mayer et al., 2010; Mayer et al., 2012; Stillo et al., 2021; Wilde et al., 2008). There is emerging evidence for the use of DTI at a single-subject diagnostic level (Stillo et al., 2021). Further, DTI findings have been associated with injury severity and cognitive outcome in children with TBI (Suskauer et al., 2009)
Magnetic resonance spectroscopy (MRS)	MRS is able to detect metabolite imbalances, which may also be relevant to the diagnosis of mTBI and concussion given the metabolic cascade that may ensue in the acute stages of these injuries (Hovda et al., 2014)	While there is not yet an MRS profile for TBI (Ashwal et al., 2014), studies suggest that reduced levels of N-acetylaspartate (NAA; found in high concentrations in neurons) may reflect neuronal damage, and may therefore serve as a marker of brain injury. In children, injury severity was shown to be correlated with MRS detected levels of NAA (Aaen et al., 2010; Ashwal et al., 2000; Ross et al., 1998; Signoretti et al., 2002)

Of these advanced neuroimaging methods, fMRI has been studied widely in concussion, as it is ideally suited for understanding the functional neuropathology of the injury. Results from resting-state and task-based fMRI studies are also easily interpretable and clinically applicable. In general, fMRI is a relatively young but increasingly studied technique in neurological populations (Bandettini, 2014).

fMRI relies on the blood-oxygen-level-dependent (BOLD) signal to assess the correlates of brain function. More specifically, neuronal activity triggers a hemodynamic response, or a change in regional blood flow and oxygenation in response to said activity (Huettel et al., 2004; Ogawa et al., 1998). When an increase in blood flow (and thus oxygenated hemoglobin; oxyHb) is directed towards activated neurons, the resultant venous output contains a higher concentration of deoxyhemoglobin (deoxyHb). Because deoxyHb is weakly paramagnetic, the local magnetic field (and thus T2* signal intensity) is distorted in a manner inversely proportional to the difference in concentration between deoxyHb and oxyHb. Therefore, the differences in the magnetic susceptibility between oxyHb and deoxyHb create the BOLD contrast, and provide a surrogate visualization of local functional neural activity (Huettel et al., 2004).

fMRI is a powerful tool that can provide whole brain volume functional activity mapping with spatial sensitivity on the order of millimetres and temporal sensitivity on the order of seconds. Further, it does not require any exogenous tracing agents or ionizing radiation, making it safe and feasible across multiple clinical populations.

Broadly, fMRI studies can be divided into two primary categories, namely those that are task-dependent (i.e., task-based fMRI) and those that are task-independent (i.e., resting state fMRI; rs-fMRI) (Mayer et al., 2015; Van Den Heuvel et al., 2010). Task-based fMRI involves providing the patient or research participant a stimulus (such as a cognitive or motor task, auditory cue, visual trigger) and then measuring the change in neuronal activity that subsequently occurs (Kundu et al., 2017). In rs-fMRI, resting neuronal activity is measured, providing a measure of brain function in the absence of external stimuli (Smitha et al., 2017). Among the most commonly studied resting state networks are the default mode network (DMN), salience network (SN), sensorimotor network (SMN), and frontal parietal network (FPN) (Johnson et al., 2014; Johnson et al., 2012; Militana et al., 2016; Puig et al., 2020; Zhu et al., 2015). It should be noted that while rs-fMRI implies that the brain is at “rest”, between 60-80% of the brain’s neural resources are utilized in the absence of a task; increases in neuronal metabolism onset by a task are often less than 5% (Smitha et al., 2017). Task-dependent and task-independent fMRI have broad applications, despite requiring different experimental set-ups and subsequent analyses.

rs-fMRI is ideally suited for understanding the effects of exercise on brain function in children with concussion as: 1) past studies have demonstrated that resting state functional activity shows differences between children with concussion and their healthy peers (Borich et al., 2015a; Chamard et al., 2018a; Schmidt et al., 2018); 2) it is task-independent and therefore does not require children to perform consistently (i.e., performance on a cognitive task may vary based on any cognitive impairment secondary to concussion, thereby introducing a potential confound with respect to task performance and thus neural activation), and 3) it is sensitive to the effects of exercise, and can be used to understand the immediate effects of exercise on the brain (Slobounov et al., 2011; Zhang et al., 2012).

Clinical fMRI studies in pediatric concussion

In pediatric concussion, the effects of concussion on functional brain activity have been consolidated through review. Chamard and Lichtenstein (2018) reviewed studies that used advanced neuroimaging techniques (including but not limited to fMRI) to study brain changes in pediatric concussion, and found that 11 assessed the impact of the injury using fMRI (Chamard et al., 2018b). Of these 11 studies, 3 studied the impact of concussion using rs-fMRI. One study found that changes in functional connectivity were region specific, with increased connectivity in the posterior cingulate gyrus and decreased connectivity in frontal and parietal regions in children with concussion compared to non-injured controls (Borich et al., 2015b). Two other studies (based on one independent sample) found that alterations in resting state functional activity varied across time (Abbas et al., 2015a; Abbas et al., 2015b). Consistently, studies published since the aforementioned review have demonstrated rs-fMRI disturbances in pediatric concussion (Iyer et al., 2019a; Iyer et al., 2019b; Manning et al., 2017; Meier et al., 2020; Plourde et al., 2020; Stephenson et al., 2020).

It is also important to characterize rs-fMRI changes across time to understand how the neuropathology of pediatric concussion evolves. In summarizing data along a time continuum, we find that the earliest time-point studied is the first week of injury, where in comparison to healthy controls, there is increased functional connectivity in the DMN and the ventral attention network (VAN) in children with concussion (Borich et al., 2015b; Murdaugh et al., 2018). A greater number of studies have examined resting state activity at approximately 1 month post-injury, or the time recovery from concussion is expected to occur (McCrory et al., 2017c). Most studies centered around this time-point show general patterns of hyper-connectivity (Borich et al., 2015b; Manning et al., 2017; Newsome et al., 2016), with only one demonstrating no groupwise differences (Murdaugh et al., 2018). Extending the observation window to 4 months post-injury and using rs-fMRI-based measures of regional homogeneity (ReHo) and fractional amplitude of low frequency fluctuations (fALFF) shows incomplete functional recovery in mTBI patients in comparison to controls, and the absence of a clear relationship between functional disturbance and symptomatology (Stephenson et al., 2020). DMN dysfunction has also been observed in children with a history of multiple concussions (Plourde et al., 2020) and those with high exposure to collision sports (and thus repeat sub-concussive impacts (Abbas et al., 2015b)), with no linear association established with concussion symptoms. Reduced connectivity between two seed regions of the DMN has also been associated with lower grey matter volume and sleep disturbance in children with

PCS (Iyer et al., 2019b). Interestingly, a second paper from this group involving the same participant cohorts showed that intra-network resting state functional connectivity of 7 networks did not differ between children with PCS and their healthy peers. However, intra-network connectivity was associated with PCS symptoms in the concussion cohort (Iyer et al., 2019a).

The only study to examine the effects of an exercise intervention using fMRI was conducted in adults who were between 2-6 months post-injury. In this study (n=12), patients who completed an exercise intervention were similar to a healthy control group with respect to functional activation during a cognitive task, while those allocated to a placebo stretching group had reduced functional activity following the intervention (Leddy et al., 2013a). Further research is required in this area to understand the effects of exercise not only on symptoms, but also on the functional neuropathology of concussion.

The review by Chamard and Lichtenstein (2018) introduced above also found that 8 studies examined the effects of concussion in children on functional activity using task-based fMRI. Consolidating the evidence across these studies is more challenging, given the heterogeneity in tasks administered and thus the neural resources recruited; a cognitive task recruits different neural resources than a motor task, and further still, a mnemonic memory task activates different areas of the brain than a task involving arithmetic. Nonetheless, collectively, the studies demonstrated that concussion results in alterations in task-based functional activity in comparison to controls (Schmidt et al., 2018), which is similar to what is observed in adults (Chamard et al., 2018a; Dettwiler et al., 2014; Hutchison et al., 2014).

Limitations of fMRI studies in pediatric concussion

The findings above are informative and provide insight into rs-fMRI disturbance following pediatric concussion. However, a key limitation of the current rs-fMRI evidence-base is the lack of sex-specific data. Many of the aforementioned studies had samples comprised only of males (Abbas et al., 2015b; Manning et al., 2017; Murdaugh et al., 2018), and a few reported no data on sex (Dona et al., 2017; Kaushal et al., 2019). Other studies had a minority representation of females in their samples (Borich et al., 2015b; Newsome et al., 2016). Even studies that approached an even number of males and females in their samples did not stratify or report findings by sex (Iyer et al., 2019a; Iyer et al., 2019b; Plourde et al., 2020; Stephenson et al., 2020). Therefore, sex-specific data on rs-fMRI activity in children with concussion remain absent to date.

This represents a critical knowledge gap. In concussion, brain injury, and neuroscience more broadly, sex has been recognized as an overlooked biological variable, despite its relevance to multiple clinically salient outcomes (Beery et al., 2011; Cahill, 2006; Mamlouk et al., 2020). In concussion, symptoms are a primary and widely studied outcome, and there is research demonstrating that symptoms vary by sex in pediatric brain injury (Ledoux et al., 2019; Levin et al., 2021). Two recent systematic reviews speak further to symptom differences by sex in pediatric concussion, while identifying other clinical measures on which females show greater impairment than males (Koerte et al., 2020; Merritt et al., 2019).

Whether such sex effects extend to the functional neuropathology of concussion remains unknown. A critical research need is to understand how the functional neuropathology of pediatric concussion, as measured using rs-fMRI, differs by sex.

Treatment strategies

Paradigm shift

Recent years have marked the beginning of a paradigm shift in concussion management. The traditional "*rest-is-best*" approach has been challenged, with prolonged rest now being avoided alongside growing recognition that "*exercise-is-medicine"* for concussion (Leddy et al., 2018b; McCrory et al., 2017b). Data that supported this shift in thinking are detailed below.

Traditional strategies – Rest is best

The longstanding approach towards managing pediatric and adult concussion was to rest until symptom-free (Silverberg et al., 2013b). Such clinical decision-making was largely motivated by animal research, which demonstrated acute metabolic dysfunction coupled with increased energy demands and ionic imbalance in the days following induced brain injury (see Barkhoudarian et al. (Barkhoudarian et al., 2016) for a detailed review). This disruption of neurological homeostasis was considered to be exacerbated by physical activity (Broglio et al., 2015), a notion corroborated by a small evidence-base (Giza et al., 2005; Griesbach et al., 2004; Majerske et al., 2008). Further motivation for the *rest-is-best* approach was driven by an interest in reducing the risk of a secondary concussion (by limiting exposure to potential injury environments) prior to recovery from the first, as a second traumatic insult experienced during a period of neurological imbalance can have lasting consequences (Broglio et al., 2015). As such, secondary injury avoidance–or worsening of the initial injury–was prioritized over proactive recovery.

Emerging strategies – Exercise as medicine

Contrary to the former *status quo*, it has now been suggested that extended rest may be deleterious following concussion, in that it may *prolong* or *worsen* symptoms (Buckley et al., 2016; DiFazio et al., 2016; Silverberg et al., 2013a). Moreover, the known benefits of physical activity on common concussion comorbidities (e.g., anxiety and depression (Mandolesi et al., 2018)) speaks to its importance in brain injury rehabilitation. Further, there is considerable animal and human literature that shows that physical activity begets neuroplasticity, which can lead to beneficial neural, synaptic, and functional adaptations in the healthy and injured brain (Cotman et al., 2002; Curlik et al., 2013; Kempermann et al., 2010).

Exercise is also safe and feasible following concussion, with pediatric patients tolerating sub-maximal aerobic exercise without adverse event

(Cordingley et al., 2016), delaying recovery (Leddy et al., 2018a), or worsening acute symptoms (Howell et al., 2020). Further, any exercise-related symptom spikes resolve naturally and return to pre-exercise levels within a day (Haider et al., 2021a; Rutschmann et al., 2020), suggesting that exercise-onset symptom exacerbation, if present, is temporary. Together, these data suggest a potential *role* of exercise in the management and rehabilitation of concussion.

The paradigm shift in concussion management may have also in part been driven by the lack of effective pharmaceutical treatment. Pharmaceutical research in brain injury, while focused on adults and more severe brain injury, has largely been unsuccessful (Gross et al., 2010; Hawryluk et al., 2016). Phase III progesterone trials in TBI have failed to show effect (Skolnick et al., 2014; Stein, 2016), as have studies of erythropoietin (Robertson et al., 2014), atomoxetine (Ripley et al., 2014), and other pharmaceutical agents. In over 30 late-phase clinical trials, therapeutic agents identified in pre-clinical research have failed to yield effect when advanced to clinical study (Hawryluk et al., 2016). The lack of the ability to manage brain injury through pharmacotherapy may be a factor that encouraged the exploration of alternative, non-pharmaceutical treatment strategies, such as sub-maximal aerobic exercise.

Rest, exercise, and concussion symptoms

Exercise tests in concussion

In concussion, most exercise protocols have first used a sub-maximal aerobic test to understand patient tolerance to exercise during the acute stages (i.e., first week) of injury. These tests are also used to identify and prescribe the patient-specific symptom-limited exercise intensity at which participants begin their exercise interventions. The most common and widely studied of these tests is the Buffalo Concussion Treadmill Test (BCTT), which is a modified version of the Balke protocol (Leddy et al., 2016a); an analogous bike protocol has also been created by the developers of the BCTT which may be more suitable for patients with balance or lower extremity impairments (Haider et al., 2019a). During the BCTT, patients are asked to walk at a fixed-speed on a treadmill (at 3.2 or 3.6 miles/hour, depending on height and thus stride length) whose gradient is increased by 1%/minute for 15 minutes. Only after 15 minutes is the speed increased by 0.4 miles/hour/minute until the test is terminated. Unless patients can exercise to ≥90% of age-predicted HR with a low rating of perceived exertion (RPE) and no signs of distress, the primary stopping criterion of the BCTT and BCBT is symptom exacerbation. Once the test is terminated, the HR at the time the test is stopped is noted, and patients are then advised to begin their exercise protocol at 80% of the symptom-limited HR achieved during the BCTT. Exercise intensity can be increased every 1-2 weeks based on new findings from a secondary BCTT or increased tolerability to aerobic stimuli. In pediatric populations, HR at symptom exacerbation is significantly higher in females than males (141.5 ± 25 bpm vs. 134.7 ± 23 bpm), although the change in heart rate from rest to BCTT termination is equivalent between sexes (Chizuk et al., 2021).

The BCTT has good reliability for assessing maximum HR (with an intra-class correlation coefficient of 0.79 (Leddy et al., 2011)) and has moderate sensitivity and specificity for predicting prolonged recovery (Haider et al., 2019b). Early research on the cardiorespiratory response to the BCTT is mixed. Some studies have reported no differences between concussed adolescents and controls with respect to resting HR, resting DBP and SBP, or change in oxygen consumption ($\Delta\dot{V}O_2$), carbon dioxide production ($\Delta\dot{V}CO_2$), or minute ventilation ($\Delta\dot{V}E$) from rest to after 5 minutes of performing the BCTT (Morissette et al., 2020). Others show elevated end-tidal CO_2 in PCS patients compared to controls during physical activity (Siedlecki et al., 2018). Further research in this area is required.

Effects of rest and exercise on concussion symptoms

Studies have examined the impact of both rest and physical activity on concussion symptoms to understand the potential therapeutic role of exercise in this population. One of the few randomized trials (n = 99) on the topic allocated children and young adults (aged 11-22 years) to either 1-2 days of strict rest followed by a graduated return-to-activity program, or 5 days of strict rest and then resumption of usual care. Between-group comparisons demonstrated that a longer period of post-injury rest resulted in greater symptom endorsement throughout the first 10 days of injury (187.9 vs. 131.9 total 10 day symptom score in the concussion and control group, respectively) and protracted recovery (Thomas et al., 2015a).

Further, a large Canadian, multi-centre study of over 3000 children with concussion studied the impact of early (i.e., within 7 days of injury) self-reported physical activity on concussion symptoms. Per a sub-set of 2413 of these children, multiple analyses (i.e., unadjusted, 1:1 propensity score matching, and inverse probability of treatment weighting) showed that participating in physical activity within 1 week of injury was associated with a reduced risk of developing persistent symptoms (absolute risk difference of 18.9%, 11.4%, and 9.7% for each of the analyses above, respectively) at 4 weeks post-injury in comparison to children who were acutely inactive. Further, in patients who were symptomatic at day-7 post-injury, participation in light, moderate, and full-contact activity was associated with reduced risk of persistent symptoms in comparison to their inactive peers (Grool et al., 2016).

A recent randomized trial (n=103) examined recovery times in adolescents allocated to a sub-maximal aerobic exercise program or a placebo stretching group (Leddy et al., 2019). Those in the aerobic exercise arm recovered in a median of 13 days (IQR, 10-18.5), which was significantly lower than the median recovery time of 17 days (IQR, 13-23) for those in the stretching program. Another large, retrospective analysis of 178 children with concussion found that those who participated in self-reported MVPA at the time they presented to clinic recovered, on average, 21 days sooner than children who participated in no activity or light physical activity (LPA) (Coslick et al., 2020). Contrary to this evidence, one study (using accelerometry rather than self-reported physical activity) found that participation in MVPA acutely is associated with delayed recovery in youth ice hockey players (Lishchynsky et al., 2019).

Many other prospective cohort studies of sub-maximal aerobic exercise (typically performed for 20 minutes, 5-6 days/week on a treadmill or stationary bicycle) following concussion consistently demonstrate the benefits of exercise on symptom burden (Chrisman et al., 2017; Clausen et al., 2016a; Del Rossi et al., 2020; Dematteo et al., 2015; Gagnon et al., 2009; Gagnon et al., 2016; Howell et al., 2016; Kurowski et al., 2017; Leddy et al., 2013b; Majerske et al., 2008; Popovich et al., 2018; Thomas et al., 2015b). The most recent meta-analysis of exercise intervention studies in concussion reported that exercise had a large effect (*Hedge's g* = 1.71) on symptoms (Carter et al., 2021). Other recent meta-analyses have reported that exercise-related improvements on PCSS scores were observed for multiple sub-groups of patients, including adolescents (Lal et al., 2018). Yet another recent meta-analysis of exercise effects in concussion focused on RCTs and identified 7 eligible trials (6 of which were pediatric-specific, with the other focused on collegiate athletes) involving on 326 patients. This meta-analysis reported that the standard mean difference (SMD) between those participating in sub-maximal exercise compared to controls with respect to concussion symptoms was -0.44 (95% CI, -0.68, -0.19), and a similar

SMD was observed when exercise was started acutely (SMD = -0.43, 95% CI -0.71, -0.15) (Langevin et al., 2020). This suggests that early exercise is safe and efficacious.

In sum, exercise has therapeutic potential in concussion. While the evidence base is growing and becoming more compelling, more research is required to determine how to optimize the timing, type, intensity and frequency of exercise interventions for concussion (McIntyre et al., 2020).

The physiological effects of exercise on concussion symptoms

Impairments to cerebrovascular reactivity (CVR) and CO_2 sensitivity–markers of the ability to autoregulate CBF during rest and exercise in response to vasoactive stimuli (Mutch et al., 2016a)–are observed even after mild trauma (Gardner et al., 2015). In concussion as in the healthy state, the most relevant of such stimuli is the partial pressure of arterial CO_2 (Pa_{CO2}) (Querido et al., 2007). CBF is highly sensitive to changes in Pa_{CO2}; a 1 mmHg increase in $PaCO_2$ can correspond to a 15% increase in CBF (Ellis et al., 2016; Len et al., 2011). In concussion and PCS, MRI CO_2 stress testing (wherein delivery of CO_2/O_2/N_2 gas solutions creates a transient state of hypercapnia, permitting whole-brain CVR mapping) reveals resting CVR impairments. These impairments reflect the inability to autoregulate resting CBF in response to vasoactive stimuli or changing metabolic demands (Ellis et al., 2016; Mutch et al., 2014; Mutch et al., 2016a; Mutch et al., 2016b; Rangel-Castilla et al., 2008). While CVR and CO_2 sensitivity are analogous measures, CVR assesses cerebral vasculature changes in response to CO_2, while CO_2 sensitivity is a gross physiological measure of the ability to process CO_2.

The hypercapnic environment referenced above is akin to that created by aerobic exercise in concussion and PCS. In the healthy state, CBF is directly proportional to Pa_{CO2}. At a given level of CO_2 production, Pa_{CO2} is inversely proportional to pulmonary ventilation (V_E). Normally, Pa_{CO2} increases during exercise until the ventilatory threshold, or the point at which excess lactic acid accumulates and triggers hyperventilation; this increases V_E and decreases Pa_{CO2} and thus CBF (Ogoh et al., 2009; Querido et al., 2007). While there is inter-individual variation in CO_2 sensitivity (i.e., the point at which V_E rises), in brain injury a relative *hypoventilation* is observed, wherein CO_2 sensitivity (and thus V_E) are lowered. This increases Pa_{CO2} and CBF out-of-proportion with exercise intensity (Clausen et al., 2016a; Leddy et al., 2016b) (**Figure 1**).

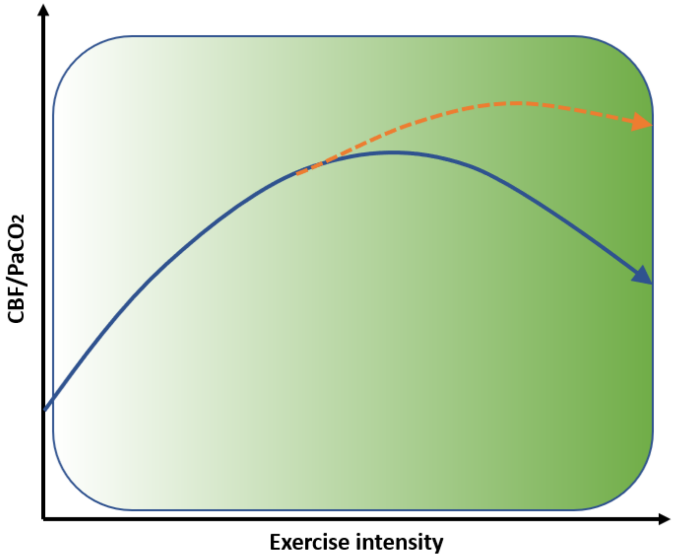

Figure 1: CBF response to exercise (blue = healthy; orange = concussion) at increasing intensity, represented by deeper shades of green.

Collectively, these studies and others have established CBF abnormalities as a pathological feature of concussion (Barlow et al., 2017; Len et al., 2011; Rangel-Castilla et al., 2008; Tan et al., 2014; Wang et al., 2016). Importantly, CBF has been associated with concussion symptoms at rest and during exercise (Churchill et al., 2017; Clausen et al., 2016a; Leddy et al., 2016b; Leddy et al., 2013a; Marsden et al., 2015), suggesting that abnormalities in CBF have clinical impact.

Exercise induced conditioning–wherein the brain adapts to gradual increases in Pa_{CO2} during an exercise program–is hypothesized to normalize CO_2 sensitivity and thus CBF (Clausen et al., 2016a). On the other hand, it has been suggested that deconditioning (which may occur as a result of prolonged rest) can lead to compromised cerebrovascular (and thus CBF) control (Gardner et al., 2015; Hassett et al., 2016; Mossberg et al., 2007), and may be a factor contributing to prolonged symptoms in those advised to avoid activity. Further, exercise may result in the forced engagement of cerebral autoregulation mechanisms (Tan et al., 2014), which can lead to restoration of the CBF-regulating ANS. This body of literature suggests that exercise, by restoring CBF abnormalities, can improve concussion symptoms.

Limitations of current studies

A key limitation of the evidence base on the effects of exercise (or rest) on concussion symptoms is the lack of an objective measure of physical activity and/or sedentary time. Although a recent study has demonstrated that children and adolescents can recall their pre-injury *symptom ratings* reliably (Teel et al., 2019), no analogous data are available on the ability of children with concussion to recall their levels of physical activity prior to injury. Studies that use valid and objective measures of physical activity, such as accelerometry, would make valuable contributions to the pediatric concussion literature, especially as accelerometry has been shown to be valid in children and adolescents with brain injury (Baque et al., 2016).

A primer on accelerometry

Accelerometers provide an objective measure of habitual physical activity and are now broadly applied to profile the activity and inactivity of pediatric and adult healthy and clinical populations (Elmesmari et al., 2018; Elmesmari et al., 2017; Liang et al., 2020). In addition to offering more detailed and quantifiable insight into patterns of physical activity and sedentary time, accelerometers also address the recall limitations associated with self-report surveys. Recent studies show that self-report measures, in comparison to accelerometers, result in an under-estimation of sedentary time and an over-estimation of physical activity in both children and adults (Colley et al., 2019; Garriguet et al., 2014; Prince et al., 2020).

The increased use and popularity of accelerometers (in both scientific circles for research purposes as well as in consumer products for daily activity tracking) has led to a number of devices on the market. The technology used in these devices can differ, and the algorithms used to quantify activity (or steps in consumer devices) based on the raw data collected can be proprietary. Research-grade accelerometers collect high-resolution data that can be readily manipulated to understand movement patterns. Consumer devices provide high-level activity metrics and typically do not offer users access to raw data. However, some consumer accelerometers are comparable to research grade devices with respect to step counts (Chu et al., 2017; Imboden et al., 2018), though the between-device variance can differ across different walking speeds

(Gusmer et al., 2014; Jones et al., 2018). Research-grade accelerometers therefore remain important for scientific study.

Studies subsequently presented in this thesis measured physical activity and sedentary time data using the ActiGraph GT3x (ActiGraph, Pensacola, FL). This accelerometer measures accelerations at a high-resolution (up to 1 Hz) across three-axes per parallel plate capacitance-based measurements of movement. At a high-level, micro-electromechanical system lithography is used to create a fixed plate conductor and a conducting plate that moves in response to external accelerations (i.e., physical activity or motion). In an undisturbed state the differential capacitance, or the ratio of the amount of electric charge stored on each conductor to the voltage between them, is known. External accelerations cause the non-fixed conducting plate to move, which changes the magnitude of stored voltage between the plates in an acceleration-dependent manner. The magnitude of this change is quantified as an activity count, which is then used to compute the intensity of the physical activity that triggered the acceleration. The ActiGraph GT3x computes movements and thus activity counts in three-axes (vertical, antero-posterior, and medio-lateral). User-defined or published cut-points can then be used to quantify sedentary time, LPA, MPA, and VPA based on activity counts. The selection of which cut-points are best suited are largely dependent on the population under study (Hulett et al.).

Accelerometer studies in concussion

Accelerometer studies in concussion (pediatric or adult) remain limited. One study of male youth ice hocky players (n=30) categorized participants per a median split defined at 148.5 minutes of accelerometer-measured MPVA in the first three-days of injury as being in either “low” or “high” activity groups. The authors reported that those in the latter group had delayed concussion recovery, suggesting that intensive forms of activity in the initial days post-injury may lead to prolonged symptoms (Lishchynsky et al., 2019). Another group examined the association between ActiGraph-measured steps within the first week of injury and concussion symptoms in 83 youth. The number of steps performed on days 1-3, 4-5, and 6-7 post-injury were correlated with symptom scores at the same time-points; increased activity between days 1-3 post-injury was also negatively associated with activity on days 4-5 post-injury (Yang et al., 2020). Another pilot study found that the maximum intensity of accelerometer-measured physical activity increased from days 0-6 post-injury, and that these activity metrics were associated with poorer vestibular and oculomotor outcome (Sufrinko et al., 2018). Research involving commercial accelerometers (i.e., the FitBit Charge) similarly show that physical activity is decreased in the initial days post-injury, with a subsequent return to normal levels (Huber et al., 2019). In pediatric concussion sleep has also been measured using the ActiGraph, with one study finding that accelerometer-measured sleep-efficiency was below the threshold for “normal” sleep (Berger et al., 2017) and another that poorer sleep efficiency was associated with greater next-day symptoms (Trbovich et al., 2021).

No studies, however, have used accelerometers to compare levels of accelerometer-measured activity and inactivity in children (or adults) with concussion in comparison to healthy controls. This knowledge gap is large, as it leaves our understanding of how concussion impacts a critical aspect of daily functioning, namely habitual *physical activity*, incomplete.

The next wave of concussion research

Moving beyond symptoms

The majority of studies on exercise in concussion have primarily studied self-reported symptoms. Observational cohort studies have consistently demonstrated that exercise improves concussion symptoms in both children and adults, and there are a few randomized exercise trials reporting similar findings (Carter et al., 2021; Lal et al., 2017; Langevin et al., 2020). Data from other exercise trials related to other outcomes germane to brain injury (including cognition and neuroimaging) need to be consolidated through review. This will help establish the state of the science and inform the next wave of non-symptom exercise and physical activity intervention research in concussion.

Understanding rs-fMRI sex differences in pediatric concussion

A growing evidence-base suggests that concussion is experienced differently by males and females with respect to (for example) symptoms, quality of life, and mental health outcomes (Koerte et al., 2020; Merritt et al., 2019). Despite this, we do not yet know how the functional neuropathology of concussion differs by sex. As exercise and physical activity intervention research moves to studying outcomes beyond symptoms, it is critical to know how aerobic activity impacts the concussed pediatric brain, and whether males and females experience the same functional neurological benefits of exercise. The first step in doing so is to understand what, if any, sex differences there are with respect to rs-fMRI in pediatric concussion.

Measuring physical activity objectively

Despite the accumulation of evidence that physical activity post-concussion improves outcome and the concussion guidelines that support this notion (Herring et al., 2021; McCrory et al., 2017c), habitual *physical activity* in concussion has not been measured and compared to healthy controls using accelerometry. Therefore, we do not yet know (per objective measures of physical activity) how physically active and sedentary children are following concussion. We need to be able to quantify the post-concussion physical activity deficit (if present) to understand if interventions need to target, for example, increased sedentariness to best improve outcome.

Exploring the link between physical activity and brain activity

The increase in rs-fMRI research in recent years had improved our understanding of how functional connectivity disturbances in concussion relate to multiple outcomes in concussion. However, we do not yet know how the functional neuropathology of concussion relates to participation in habitual physical activity. Given the increasingly recognized importance of resuming physical activity post-concussion soon after injury (Carter et al., 2021), it is important to learn whether the functional neuropathology of concussion is associated with post-injury physical activity. This will improve our understanding of the impacts of concussion on an important aspect of daily living (i.e., habitual physical activity and sedentary time) and can help target future intervention efforts.

Objectives and hypotheses

General objective

Overall, the objective of this thesis is to push towards the next wave of exercise research in concussion. This requires expanding our understanding of the effects of exercise on non-symptom outcomes. It also requires shedding light on how the known functional neuropathology of concussion differs by sex, to inform management and treatment accordingly. Using accelerometry to understand habitual *physical activity* in concussion is also required to usher the next wave of exercise and/or physical activity interventions in concussion.

The intention of this thesis is to build on the exercise-concussion research already performed, and open new avenues of inquiry based on the findings presented herein.

Specific objectives

The specific objectives of this thesis were to:

1. Systematically review the literature to understand the effect of exercise on outcomes other than symptoms (namely, cognition and neuroimaging) using only data from randomized studies (Chapter 2).
2. Provide the first insights into sex differences in rs-fMRI activity in pediatric concussion (Chapter 3).
3. Offer the first characterization and quantification of accelerometer-measured physical activity and sedentary time in children with concussion in comparison to matched healthy peers (Chapter 4).
4. Explore the association between functional brain activity and habitual physical activity in children with concussion (Chapter 5).

Specific hypotheses

The specific hypothesis of this thesis were that:

1. Randomized trials examining the effects of exercise on non-symptom outcomes in concussion would be limited, but would nonetheless demonstrate a positive effect on cognition and imaging-based measures (Chapter 2).
2. Consistent with the larger evidence-base on the disproportionate impact of concussion on females, there would be greater rs-fMRI disturbance in females at 1 month post-injury than in males (Chapter 3).

3. Children with concussion would be more sedentary and less physically active than their healthy peers within the first month of concussion (`Chapter 4`).

4. Increased functional disturbance would be associated with reduced participation in habitual physical activity and increased sedentary time in children with concussion (`Chapter 5`).

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CHAPTER 2

Cognitive and neural effects of exercise following traumatic brain injury: A systematic review of randomized and controlled clinical trials

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ABSTRACT

Objective: Sub-maximal aerobic exercise can alleviate brain injury-related symptom burden. There is substantial data from animal studies and a growing clinical evidence base to suggest that exercise may also improve cognitive and neural outcomes following brain injury. We performed this systematic review to consolidate evidence from randomized and clinical controlled trials on the effects of exercise on cognitive and neuroimaging outcomes following brain injury in humans. **Design:** Systematic review. **Data sources:** MEDLINE, EMBASE, PsychINFO, CINAHL, SPORTDiscus, and Cochrane Central Database.

Eligibility criteria for screening studies: Randomized or clinical controlled trials examining the effects of exercise on cognitive and/or neuroimaging outcomes in traumatic brain injury. No restriction was placed on age (or other demographic variables) or severity of injury. **Results:** Six studies (with an average sample of 42 participants) met eligibility criteria. Three studies used neuroimaging and reported exercise-related improvements as measured by either functional or diffusion-based imaging. The remainder of the trials that employed cognitive outcomes reported largely null findings.

Summary/Conclusion: This review demonstrates that exercise shows promise (primarily with respect to neuroimaging outcomes) as a brain injury intervention. While the field is young and heterogeneity between studies precludes meta-analysis, this review raises important questions that need be addressed by future trials.

KEYWORDS: Brain injury; concussion; exercise medicine; sport medicine; neuroplasticity, neuroimaging.

INTRODUCTION

The scope and impact of traumatic brain injury (TBI) is extensive. Internationally, its annual incidence has reached 295/100,000 (Nguyen et al., 2016), and the World Health Organization predicts that TBI will become the third leading cause of death and disability worldwide by the year 2020 (Lancet, 2012). Although the clinical manifestation of TBI is diverse, even milder brain injuries (such as concussion) are associated with a broad symptom set, which includes cognitive impairment that may persist for more than 3-months in nearly half of patients (McInnes et al., 2017). Further, in more severe injuries, atrophy and impairment of neural tissues, structures, and networks is observed (Bigler, 2013; Johnson et al., 2013), and neurodegeneration may be observed after repeat concussive and sub-concussive impacts (Baugh et al., 2012). The targets of TBI interventions should, therefore, not only be the symptoms associated with brain injury, but also the potentially chronic neuropathology underlying these impairments.

Current treatment options for TBI, however, are limited. While some interventions (e.g., working memory or attention training, cognitive behavioural therapy, mindfulness meditation) have demonstrated moderate efficacy in managing specific cognitive (and psychosocial) symptoms (Bédard et al., 2014; Cicerone et al., 2011; Fann et al., 2015; Radomski et al., 2016), other trials have failed to demonstrate efficacy, particularly in more severe brain injury (Hawryluk et al., 2016). Most notably, acute stage pharmaceutical trials of agents such as progesterone have failed to effect neurological and functional outcomes (see Stein (Stein, 2015) for an overview). This represents just one of more than 30 therapeutic agents identified in pre-clinical studies that did not improve clinical outcomes when advanced to late-stage clinical trial (Hawryluk et al., 2016), which currently precludes a pharmacological approach to TBI treatment.

There are, however, non-pharmacological treatment options for TBI that demonstrate promise. Specifically, aerobic exercise interventions (defined as those which tax the cardiovascular and pulmonary systems to meet temporarily elevated oxygen demands (Malina et al., 2004)) have rehabilitative potential, as not only can they alleviate brain injury-related symptom burden (particularly in concussion) (Lal et al., 2017), but according to animal studies, they can also promote cognitive and neural recovery by facilitating adaptive molecular and cellular neuroplastic changes (Archer et al., 2012; Cotman et al., 2002; Van Praag, 2008). More specifically, studies involving both healthy and brain injured animals have demonstrated that physical activity can improve cognitive ability such as spatial navigation (a surrogate for learning and memory performance in animals) (Griesbach et al., 2009), while conferring a series of neural benefits including increased proliferation and survival of newborn neurons in the hippocampus (a structure integral to memory) (Van Praag et al., 2000), upregulation of critical neural growth factors (Griesbach et al., 2004), and elevated synaptogenesis and angiogenesis (Clemenson et al., 2015).

Importantly, recent studies show that the benefits of exercise on the injured brain also extend to humans. In concussion, exercise has a positive effect on symptom burden; most notably, a recent meta-analysis of 14 studies found that compared to a non-active control condition, exercise significantly decreased symptom scores on the 132-item Post Concussion Symptom Scale (PCSS; mean difference, -13.06; 95% CI, -16.57 to -9.55; $I^2 = 44\%$) (Lal et al., 2017). Comparatively, there are fewer studies examining the effects of exercise on cognitive and neural outcomes in clinical brain injury. Preliminarily, these studies do suggest that exercise can improve cognition following brain injury in both adolescents and adults (Imhoff et al., 2016; Lal et al., 2017; Manikas et al., 2017), and lead to adaptive neural changes (Leddy et al., 2013; Polak et al., 2015).

Although the literature on the effects of exercise following TBI in humans has been consolidated through review as it relates to *symptom resolution* (Lal et al., 2017), systematic reviews on the *cognitive* and *neural* effects of exercise in humans have not been performed. Current reviews on the topic that have been performed are either not systematic, not based on comprehensive searches of multiple health sciences databases, or do not limit their study samples to traumatic brain injury (and instead keep the area of study broader by including patients with stroke and other acquired brain injuries) (Morris et al., 2016; Vanderbeken et al., 2017). Further, a review on the cognitive and neural effects of post-TBI exercise examining only clinical trials (rather than, for example, cohort studies or case-series) has not been performed, despite the need for such review to better understand and establish the state of the science, generate new research questions, and best inform future exercise-based trials in brain injury. This systematic review was performed to consolidate evidence from randomized and clinical controlled trials on the effects of exercise on cognitive and neural outcomes following traumatic brain injury.

MATERIALS AND METHODS

This review was registered with the international prospective register of systematic reviews PROSPERO network (registration number CRD42017058157) on February 26th, 2017. Our review was reported as per reporting guidance provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Shamseer et al., 2015).

Search strategy

A comprehensive search strategy was developed in consultation with a health sciences librarian, and adapted for each of the following health sciences databases (grey literature was not included): MEDLINE, EMBASE, PsychINFO, CINAHL, SPORTDiscus, and Cochrane Central Database. Further, it reflected the PICO (Population, Intervention, Comparison, Outcome) strategy for evidence searches (Santos et al., 2007): our focus Population, Intervention, Comparison, and Outcomes were brain injury, exercise, non-active controls, and cognition and/or neuroimaging, respectively.

Searches were initially run in February, 2017 and were re-run in December, 2018 prior to publication to ensure results were current. The search strategy involved three sets of terms, namely, those related to: 1) traumatic brain injury and/or concussion, 2) exercise and/or physical activity, and 3) randomized and/or clinical controlled trials. Exercise type (e.g., aerobic, anaerobic) was not specified in the search strategy, as it may have limited the breadth of the search.

Further, the outcome measures (i.e., those specific to cognitive outcomes and neuroimaging) were not included in the search strategy (as per the advice of the consulting librarian) in order to ensure the search was not overly restrictive. Instead, outcomes were screened for during the title/abstract and full-text stages. A sample search strategy can be found in Appendix 1.

Screening procedure

Searches for each database were conducted independently, with an optimized database-specific strategy; therefore, six searches were run in total. The results of the six searches were exported into EndNote Reference Management Software and duplicates were removed using a series of filters. The final, de-duplicated library was then imported into Covidence (an online systematic review screening platform) for title and abstract screening.

Titles and abstracts of articles were reviewed by two authors in Covidence, and screened against pre-defined inclusion criteria. More specifically, the inclusion criteria were: 1) randomized or clinical controlled trial design; 2) traumatic brain injury population; 3) evaluation of an aerobic exercise intervention; 4) primary and/or secondary outcomes assessing cognitive and/or neural changes. Exclusion criteria were: 1) non-peer reviewed publication; 2) review and guideline article; 3) inappropriate study design; 4) inappropriate population; and 5) lack of appropriate outcome measures. No exclusion criteria were enforced surrounding date or language of publication. Titles and/or abstracts over which there was initial disagreement were jointly re-evaluated against the *a priori* inclusion and exclusion criteria until a consensus on inclusion was reached by the two reviewers. Although not required, the two reviewers decided at study onset to advance any articles over which consensus was not reached to a third reviewer.

The same two reviewers then conducted full-text screening independently, also in Covidence, resolving conflicts as above. Reference lists of articles included in the review were then examined to identify any additional articles that may have been relevant to the review; these articles were then screened in full for inclusion. Articles that cited the studies included in our review were also screened in full for inclusion, as well as the 'Published ahead of print' section of leading journals in the field.

Data extraction

Data were extracted using standardized forms developed by the research team. Variable fields on this form included study design (e.g., number of participants, trial arms, randomization processes), intervention characteristics (frequency, intensity, time, and type of exercise), participant demographics (age, sex, injury severity, time post-injury), and study findings (baseline measures as well as exercise-related changes to cognition or neural outcomes). The form was populated by each reviewer, and then data were compared to ensure consistency of extraction.

Quality assessment

The two reviewers used the widely used Cochrane Risk of Bias Tool (Higgins et al., 2011) (in Review Manager v5.3) to identify risk of bias in study design. This tool assesses seven biases, related to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome measures, incomplete outcome data, selective reporting, and other biases (which may include biases such as observer variability, or measurement error). As with the screening process, risk of bias evaluations were independently performed by each reviewer and discussion was then held to resolve any inconsistencies.

RESULTS

The number of articles reviewed and excluded at each stage is overviewed in Figure 1. Due to the limited number of articles, heterogeneity between study samples, and diversity of outcome measures used, a meta-analysis was not conducted; the papers were instead analyzed narratively.

Study characteristics (e.g., design, participant demographics) are summarized in Table 1. Participants ranged from adolescents to middle-aged adults, and samples were heterogenous with respect to time-post injury and injury severity. Mechanism of injury was not reported in studies examining cognitive outcomes, but in those employing neuroimaging, most injuries were sport-related, with the remainder primarily caused by falls and being struck by/against an object (Table 1). Table 2 provides an overview of the exercise interventions employed in each study, categorized by fitness, intensity, type, and time (i.e., the F.I.T.T. principle (Medicine, 2013)).

Risk of bias within and across studies is summarized in Figures 2a and 2b. In general, there was high or unclear risk of bias with respect to random sequence allocation and allocation concealment. Risk of bias was low for outcome reporting, as all studies reported on all outcomes and addressed loss to follow-up.

Neuroimaging outcomes

Three of the six included studies examined neuroimaging outcomes (Leddy et al., 2013; Polak et al., 2015; Yuan et al., 2017). While heterogeneity between study samples and designs limits the ability to draw generalized conclusions, it should be noted that pre- post-intervention improvements on a diversity of neuroimaging outcomes (as discussed below) were observed across studies.

Leddy et al. (Leddy et al., 2013) studied eight individuals with post-concussion syndrome who were selectively yet equally allocated to either an exercise intervention (see Table 2) or a stretching control group (and were advised not to exceed 40-50% of maximum age-predicted heart rate); additionally, four age-, sex-, and activity status-matched healthy controls were included in the study. Participants in both the exercise and stretching arms of the trial conducted their respective activities at home or in a community gym. Participants were assessed using functional magnetic resonance imaging (fMRI) while completing a modified version of a commonly used neuropsychological math task, involving basic arithmetic (namely, the addition or subtraction of three numbers); during the 5-minute trial of 72-questions, participants were asked to answer whether the solution to the arithmetic problems they were presented was greater or less than five. Participants administered to the exercise intervention were assessed on this task at baseline, and again once they were able to exercise to age-predicted maximum heart-rate without symptom exacerbation, after a span of approximately 12-weeks; participants in the stretching group and the healthy controls were also assessed roughly along these timelines. It is important to note the sex disparity between groups (Table 2) and that those administered to the stretching group were, on average, nearly 6-months post-injury, while patients in the exercise group were approximately 2-months post-injury at the time of their first neuroimaging assessment.

At baseline, no significant differences in functional activation between those administered to the exercise group or stretching group were detected; moreover, at this time, there were no differences in activation between healthy controls and either the exercise group or stretching group. However, when pooling data across all patients with post-concussion syndrome, the healthy controls showed relatively increased task-based activation in certain brain regions, namely the cerebellum, posterior cingulate gyrus, and lingual gyrus at baseline. At follow-up, there were no significant differences in activation between those in the exercise group and healthy controls, while reduced activity in the cerebellum, cingulate gyrus, and thalamus (with no regions showing increased activity) were observed in those allocated to the stretching group relative to healthy controls. In comparing the two PCS groups, a trend towards a significant difference was reported with respect to functional activation within a small cluster (7 voxels) in the cingulate gyrus, with the exercise group showing greater activity than the stretching group at follow-up. These findings suggest that aerobic exercise may restore functional brain activity following concussion in select brain regions.

In a later study by this group, Polak et al. (Polak et al., 2015) used diffusion tensor imaging (DTI) to assess exercise-related brain changes in individuals with post-concussion syndrome. DTI is an imaging modality sensitive to water diffusion, and quantifies white matter microstructure (and thus diffusivity of water and neuronal health) with metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) (Le Bihan et al., 2001). Polak et al. (Polak et al., 2015) reported on DTI data on eight participants, and while methodology was shared with the former trial, a larger sample of 15 healthy controls was used.

At baseline, no white matter abnormalities were reported when those with concussion (in either arm) were compared to healthy controls. However, using a voxel-wise methodology, reduced FA (an indication of compromised white matter microstructure) in voxels proximal to the genu and corpus callosum, was observed in patients relative to healthy controls at baseline and at follow-up, although the number of voxels within the area of difference was smaller at the later time-point. Further, at baseline but not follow-up, increased MD and RD (also indicative of compromised white matter microstructure) were observed. When using a region of interest approach, corroborating evidence was generated; decreased mean FA and increased MD and RD in the genu of the corpus callosum were significant at baseline but less pronounced at follow-up when comparing participants with post-concussion syndrome to healthy controls. Longitudinally, no significant changes in any of these DTI metrics were observed between the exercise and healthy control groups, stretching and healthy control groups, and exercise and stretching groups. Further, a ‘pothole’ analysis, wherein clusters of white matter voxels that had a ± 3 standard deviation difference in FA relative to the mean value of these clusters in the healthy control group were set as the unit of analysis, demonstrated that the number of ‘potholes’ in concussed individuals was significantly greater than those in healthy controls at both baseline and follow-up.

The most recent study to examine the neural effects of exercise following concussion was conducted by Yuan et al. (Yuan et al., 2017). In this study, structural connectivity was assessed in adolescents (n = 22) with persistent symptoms related to mild TBI (mTBI) versus age- and sex-matched historical healthy controls (n = 20) using DTI tractography. This study performed structural connectivity analysis using graph theory, and first required the construction of neural networks using an existing architecture(Bassett et al., 2011), which was comprised of 90 cortical and sub-cortical gray matter regions and the white matter tracts connecting them. Graph theory analysis was then used to measure regional and global connectivity. Those with mTBI were randomly allocated to either an exercise intervention (see Table 2) or a stretching program; due to attrition, imaging was performed on 17 participants pre- and post-intervention, with 8 and 9 participants in the exercise and stretching groups assessed at both times, respectively. This study also included measures of symptom burden, which are reported on more extensively in a previous trial by this group (Kurowski et al., 2017).

At baseline, adolescents with mTBI, relative to the historical controls, had significantly reduced global efficiency and higher normalized clustering coefficient, normalized characteristic path length, and small-worldness, all of which are graph theory measures of network connectivity, and are indirectly indicative of compromised white matter microstructure. Further, no baseline differences were observed between those in the exercise and stretching groups. Longitudinally, significant increases in global efficiency and significant decreases in normalized characteristic path length were observed in the exercise group (these findings, indicative of recovery, were correlated with changes in symptom reporting), but not the stretching group. Between-group comparisons (i.e., exercise vs. stretching) did not reveal any significant differences in structural connectivity.

In sum, these trials suggest that following traumatic brain injury in humans, exercise may have positive effects on neuroimaging outcomes (and in particular, functional and diffusion-based metrics).

Cognitive outcomes

Of the six included studies, three (Lee et al., 2014; Maerlender et al., 2015; McMillan et al., 2002) examined cognitive-related outcomes post-exercise intervention. Unlike the studies which employed neuroimaging outcome measures, in general, intervention effects were not observed in studies that assessed cognitive outcomes, as detailed below.

In the earliest and largest trial (n = 130) to examine the effects of exercise on cognitive outcomes following TBI (McMillan et al., 2002), participants were allocated to either an exercise intervention (n = 38), an attentional control program (n = 44), or a non-active control group (n = 48). Cognitive testing was conducted at baseline, following the intervention, and at long-term follow-up. The tests which comprised the cognitive battery included the Test of Everyday Attention (Robertson et al., 1994), Adult Memory and Information Processing Battery (Coughlan et al., 1985), Paced Auditory Serial Addition Test (Lezak, 2004), Trail Making Test (Lezak, 2004), Sunderland Memory Questionnaire (Sunderland et al., 1984), Cognitive Failures Questionnaire (Broadbent et al., 1982); measures of anxiety, general health, and post-concussion symptoms were also used, but are not discussed in the present review. No significant between-group differences were observed at baseline across any of the cognitive outcome measures, except the Cognitive Failures Questionnaire (a self-report measure of memory, perception, and motor function); both treatment arms self-reported more cognitive failures than the control group. Similarly, no between-group differences reached significance during the subsequent testing sessions, aside from the Cognitive Failures Questionnaire at long-term follow-up.

In a waitlist cross-over trial (n = 21) by Lee et al. (Lee et al., 2014), the effects of exercise on cognitive outcomes in adults with chronic TBI of all severities (Table 1) were evaluated. More specifically, participants completed a 60-minute exercise intervention (Table 2) twice-weekly for 8-weeks in an out-patient medical centre. Neuropsychological testing was initially conducted at baseline, then at cross-over, and again after the group which was initially waitlisted completed the intervention. (It should be noted that this study also included mood and psychological outcomes, but they are not discussed here given the scope of the review.) The tests that comprised the neuropsychological assessment were the Stroop Colour and Word Test (Golden, 1978), Digit Spans Forwards and Backwards (Wechsler, 2008), and Trail Making Test Parts A & B (Reitan et al., 1986), which served as measures of, processing speed, immediate attention and working memory, and mental flexibility and attention, respectively. It is important to note, however, that only 12 participants completed all assessments and that the exercise intervention employed in this study involved more than cardiorespiratory training; 5-10 minutes of the hour-long intervention involved self-affirmation exercises, and the 10-minute cool-down period also involved meditation. At baseline, there were no significant differences on cognitive measures between those who were initially waitlisted and those initially administered to the intervention. Further, when comparing pre- post-intervention cognitive changes between the two intervention arms, no significant differences were observed on any cognitive measures. However, when collapsing the two groups and assessing pre- post-intervention cognitive changes for the entire group, a significant effect was found with respect to the Word Trial of the Stroop Task; no other cognitive improvements were reported.

In a randomized trial by Maerlender et al. (Maerlender et al., 2015), concussed collegiate athletes were administered to either “standard concussion recovery recommendations” (n = 15) or were prescribed daily, moderate physical activity (n = 13). Athletes were initially assessed using the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) in the acute stages of injury (median = 2 days), once available for evaluation by an athletic trainer; other non-cognitive and non-neural outcome measures were employed but are not reported on here. The exercise intervention involved 20-minutes of cycling on a stationary ergometer, with ratings of perceived exertion (as per the Borg Ratings of Perceived Exertion scale) and symptom exacerbation assessed at the end of the exercise session. Participants then met with the trainer daily to monitor their medical status and activity, and to assess recovery; athletes were considered to have recovered if their assessment test scores, balance, and symptoms returned to baseline. Maerlender et al. (Maerlender et al., 2015) reported the median time to recovery for the exercise and control group was 15 and 13 days, respectively. Within-group pre- post-intervention changes in ImPACT scores for verbal memory, visual memory, visual motor speed, and reaction were reported; increases were observed with respect to visual motor speed–with declines observed in the other domains–although these changes did not reach significance. Between-group comparisons were not reported.

Collectively, to date, trials on the effect of exercise on cognitive outcomes following traumatic brain injury have reported largely null findings.

DISCUSSION

To date, clinical exercise trials in TBI have provided limited but largely consistent evidence on the positive effects of exercise on neuroimaging outcomes (as assessed using fMRI or DTI) (Leddy et al., 2013; Polak et al., 2015; Yuan et al., 2017), and predominantly null findings with respect to cognition (Lee et al., 2014; Maerlender et al., 2015; McMillan et al., 2002). Current literature on exercise, TBI, and cognitive and neuroimaging outcomes, while not yet conclusive, is able to inform the design of future trials and generate additional research questions which can continue to develop the field. Heterogeneity between studies (with respect to, for example, structure of exercise intervention, participant age, injury severity, mechanism of injury, and outcome measure selection and sensitivity/specificity) in addition to the limited total participant pool and quality of evidence (see Figures 2a and 2b) are caveats to the questions and hypotheses discussed below.

Therapeutic window

A fundamental and unanswered question is whether the therapeutic window of exercise varies by outcome. The trials included in this review did not incorporate both cognitive and neuroimaging outcome measures, thereby precluding a single sample evaluation of whether recovery of these two outcomes occurs in parallel. Animal literature suggests that physical activity increases the number of cells in the hippocampi, yet the survival of these cells is dependent on subsequent sustained exposure to sufficiently challenging cognitive stimuli (Curlik et al., 2013). Other animal studies show that exercise results in rapid increases in neural vasculature (within 72 hours) (Van der Borght et al., 2009), which begets the generation of new neurons; cessation of exercise results in a similarly rapid return to baseline levels of capillary density, which may be coupled with the loss of newly generated neurons, unless exercise is accompanied by cognitive enrichment (Thomas et al., 2012). Thus, neural changes may be exercise-dependent and therefore detectable following an exercise-only intervention, while cognitive changes (dependent on the survival integration of new neurons) may be primed by exercise, but not realized until there is appropriate cognitive exposure. Future studies are encouraged to include multiple treatment arms (e.g., physical activity, cognitive exercises, and a combination thereof) to assess their relative contribution to TBI recovery.

Furthermore, the relation between exercise and cognitive recovery may be mediated by time post-injury. Recent evidence from Manikas et al. (Manikas et al., 2017) indicates that processing speed in children and adolescents with concussion is time-sensitive, with, surprisingly, slower post-exercise processing speed observed in children when assessed on the 10th day after injury than when the same children were assessed earlier on the 2nd day post-injury. This study, in addition to those included in our review, further queries how the effects of exercise on cognition are mediated by time post-injury (and also timing of the exercise intervention), and whether changes in cognition observed earlier in recovery are *bona fide* indicators of cognitive recovery, or if they instead represent a period of transience. Such a period may correspond to the metabolic imbalance observed following brain injury (Brooks et al., 2014). Together, these results suggest that the potential effect of exercise interventions may be mediated by time post-injury, a question that can best be answered with trials employing multiple arms with exercise interventions administered at different times post-injury. Further, future exercise trials should include repeated cognitive assessments as well as neuroimaging outcomes to better understand the relationship between exercise, cognition, and plasticity in TBI.

Rest versus exercise debate

Until recently, the status quo has been to rest and refrain from activity following sport-related brain injury until symptom resolution; current studies and guidelines have challenged this precedent (McCrory et al., 2017; Schneider et al., 2017). While the studies included in this review did not all center on the acute stages of injury (where return-to-play considerations predominate), the results suggest that exercise, if not beneficial, may not be deleterious. Studies have shown that symptom spikes following concussion are typically not associated with prior activity (Silverberg et al., 2016), and that exercise can mitigate symptom burden (Lal et al., 2017). Further, a large, multi-center prospective cohort study (n = 2413) found that activity within 7-days of concussion in children and adolescents was associated with a reduced risk of developing persistent post-concussive symptoms 4-weeks post-injury (Grool et al., 2016). Thomas et al.

(2015) in a randomized trial found that children administered to strict rest for 5 days rather than 1-2 days of rest and subsequent graduated return-to-activity took longer to reach symptom resolution and reported more post-concussion symptoms within the first 10-days of injury (Thomas et al., 2015). It should be noted that the effects of exercise duration, intensity, time, and type following brain injury remain to be studied; however, a recent review suggests that given the current evidence base, exercise prescription should include low-intensity aerobic exercise in order to ensure tolerability and reduce the risk of symptom exacerbation (Worts et al., 2019). Collectively, the findings from this review (on the cognitive and neural effects of exercise) along with those from published meta-analyses (speaking to the positive effect of exercise on symptom burden (Lal et al., 2017)) suggest that exercise may have a role in the management of brain injury. Future research should focus on determining the timing and type of exercise that is required to best improve patient outcome.

Global mechanisms of neural repair

The studies included in this review used different neuroimaging outcome measures, which detected exercise-related effects to varying degrees (Leddy et al., 2013; Polak et al., 2015; Yuan et al., 2017). While each study was limited in its sample size (which may reduce reproducibility of results), the current evidence-base nonetheless suggests that the neural effects of exercise on the injured brain can be observed using multiple imaging modalities. Further, it suggests that exercise has an influence on multiple neural substrates (e.g., white matter microstructure, structural connectivity). This also suggests that there may be a common underlying mechanism driving such changes, rather than a series of multiple, independent mechanistic effects.

It has been purported (albeit in the healthy state) that angiogenesis or changes in cerebral blood volume secondary to exercise may be responsible for the suite of exercise-induced neural changes (Thomas et al., 2012). Studies have demonstrated that in mTBI, patients with persistent symptoms and no structural brain abnormalities have regional hypoperfusion (relative to healthy controls) in several brain areas, including the frontal, pre-frontal, and temporal cortices, as well as sub-cortical structures (Bonne et al., 2003). (See Len et al. (Len et al., 2011) for a review on the persisting nature of cerebral blood flow (CBF) reductions following brain injury, as well as how trauma can impact cerebral autoregulation, reactivity, and oxygenation.) Moreover, longitudinal studies have shown that normalization of CBF in athletes with concussion is associated with recovery (Meier et al., 2015), while other prospective studies have related gray matter cerebrovascular reactivity with symptom burden in adults with mTBI (da Costa et al., 2016). Given the association between CBF and TBI-related impairments, and that exercise (as per a recent and methodologically rigorous study using oxygen-15-labelled H_20 and positron emission tomography (Hiura et al., 2014)) increases regional CBF in the early and late stages of exercise in healthy male adolescents, future studies should examine the effects of exercise interventions in TBI on CBF. Further, assessing the association between CBF with other markers of TBI recovery (such as heart rate variability, which has previously and preliminarily been correlated with regional CBF (Richard Jennings et al., 2015)) can offer evidence that changes in readily measured heart rate variability serve as proxy for neural recovery *via* CBF normalization.

Future experimental considerations and limitations

Many studies included in this review controlled for demographic variables such as age during analysis. There are, however, other variables that have a known influence on exercise-induced plasticity and require similar statistical control. In particular, future trials should statistically control for more than conventional demographic variables of age, sex, educational status, and time post-injury; measures of stress and depressive status (which can attenuate neuroplasticity (Fuchs et al., 2004; Fumagalli et al., 2007; Pittenger et al., 2008)) may also require statistical control. Moreover, as most of the injuries in our sample occurred during sport participation and, presumably, participants injured during sport were active prior to injury, intervention-related effects may have been influenced by pre-injury activity levels; animal studies show that pre-injury exercise exposure can be protective against trauma, as well as a facilitator of recovery (Gomez-Pinilla et al., 2008; Griesbach, 2011). In addition, while most studies involved individual exercise, the effects of social interaction as well as level of cognitive stimulation should be measured and controlled, given that such environmental enrichment has positive effects on neuroplasticity in brain injury (Werner et al., 2015) (and thus may be a potential confounder with respect to exercise-related brain changes). Further, some studies included a non-active control and others a stretching group (Table 1); whether the effects of these control arms on cognitive and neural outcomes is comparable is unknown, as is the suitability of a stretching program as a true control condition. The implementation of such additional considerations and control variables in future randomized trials can yield more rigorous and conclusive analyses and assessment of intervention effects. Ultimately, a greater number of studies and trials (that account for factors such as those detailed above) are required to improve the current evidence-base.

CONCLUSIONS

Evidence on the neural and cognitive effects of exercise following brain injury based on randomized or clinical controlled trials remains limited, but offers promising new directions and considerations for future research. Consistent with basic science findings, exercise may have a positive effect on neuroimaging outcomes (as assessed using functional of diffusion-based imaging) following brain injury in humans, although a similar effect on cognition was not observed. Inclusion of both neuroimaging and cognitive outcomes in a single study can help determine whether exercise-induced neural recovery (for which there is preliminary evidence) manifests as cognitive change. Other questions, such as whether exercise impacts neural and cognitive outcomes equally and determining when the effects of exercise are greatest, can lead to the development of more tailored interventions. Ongoing research on the topic is encouraged to understand whether the therapeutic potential of exercise can be realized in brain injury.

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DECLARATION OF INTEREST

The authors have no conflicts of interest to declare.

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TABLES

	Study					
	Leddy et al. (2012)[a]	**Polak et al. (2015)[a]**	**Yuan et al. (2017)**	**McMillan et al. (2002)**	**Lee et al. (2014)**	**Maerlender et al. (2015)**
Design	Clinical controlled trial	Clinical controlled trial	Randomized controlled trial	Randomized controlled trial	Wait list clinical controlled trial	Randomized controlled trial
Sample	Total: 12 Exercise, PCS: 4 Stretching, PCS: 4 Healthy control: 4	Total: 23 Exercise, PCS: 4 Stretching, PCS: 4 Healthy control: 15	Total: 37 Exercise, TBI: 8 Stretching, TBI: 9 Healthy control: 20	Total: 130 Exercise, TBI: 38 Attention training, TBI: 44 Non-intervention control, TBI: 48	Total: 21 Exercise (immediate), TBI: 9 Exercise (waitlist), TBI: 12	Total: 28 Exercise, TBI: 13 Standard care, TBI: 15

Primary outcome	Task-dependent fMRI	DTI	DTI tractography (to assess structural connectivity)	Test of Everyday Attention, Adult Memory and Information Processing Battery, Paced Auditory Serial Addition Test, Trail Making Test, Sunderland Memory Questionnaire, Cognitive	Stroop Colour and Word Test, Digit Spans Forwards and Backwards, and Trail Making Test Parts A & B	ImPACT

				Failures Questionnaire		
Mean age at baseline, years	Exercise, PCS: 24 Stretching, PCS: 21 Healthy control: 21 ***N.b.*** Standard deviations were not reported	Exercise, PCS: 25.2 ± 5.7 Stretching, PCS: 22.8 ± 6.2 Healthy control: 26.2 ± 1.7	Exercise, TBI: 15.04 ± 1.35 Exercise, Stretching: 15.48 ± 2.08 Healthy control: 16.28 ± 1.38	Exercise, TBI: 31.4 ± 13.0 Attention training, TBI: 34.6 ± 11.4 Non-intervention control, TBI: 36.2 ± 13.4	Exercise (immediate), TBI: 48.22 ± 18.19 Exercise (waitlist), TBI: 44.50 ± 12.97	Collegiate athletes; mean age not reported
Time post-injury	Exercise, PCS: 65.25 days Stretching, PCS: 170.75 days	*First evaluation* Exercise, PCS: 37.2 ± 6.5 days	Exercise, TBI: 56.98 ± 24.24 days	Between 3- to 12-months post-injury. ***N.b.*** Means per	Exercise (immediate), TBI: 88.11 ± 83.56 months	Median of 2 days

		Stretching, PCS: 154.5 ± 124.0 days *At baseline MRI* Exercise, PCS: 66.0 ± 6.6 days Stretching, PCS: 170.8 ± 118.8 days	Stretching, TBI: 56.06 ± 25.04 days	group were unavailable	Exercise (waitlist), TBI: 27.30 ± 22.01	
Sex, % male	Exercise, PCS: 25% Stretching, PCS: 75% Healthy control: 0%	Exercise, PCS: 25% Stretching, PCS: 75%	Exercise, TBI: 50% Stretching, TBI: 66.67%	Exercise, TBI: 79% Attention training, TBI: 80%	Exercise (immediate), TBI: 44%	Exercise, TBI: 20% Standard care, TBI: 38%

		Healthy control: 47%		Non-intervention control, TBI: 75%	Exercise (waitlist), TBI: 42%	
Mechanism of injury	-	TBI exercise, 50.0% sports, 50.0% falls TBI stretching; 50.0% sports, 25.0% falls, 25.0% struck by object	-	TBI exercise, 50.0% sport-related TBI stretching, 77.8% sport-related		
Injury severity	Concussion (diagnosed with PCS as per the ICD 10)		Excluded if GCS below 13	Exercise, TBI: Median GCS 10	All severities; breakdown by	Concussion

			Attention training, TBI: Median GCS 9 Non-intervention control, TBI: Median GCS 9	severity not provided	
Country in which study was conducted	United States	United States	United Kingdom	United States	United States

Table 1: Study design and participant demographics. ^{a}Studies were collapsed, as needed, as participants were derived from the same pool. **Abbreviations:** fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging;

ImPACT, Immediate Post-Concussion Assessment and Cognitive Test; PCS, Post-concussion syndrome; ICD, International Classification of Disease; GCS, Glasgow Coma Scale.

	Study					
	Leddy et al. (2012)[a]	**Polak et al. (2015)[a]**	**Yuan et al. (2017)**	**McMillan et al. (2002)**	**Lee et al. (2014)**	**Maerlender et al. (2015)**
Frequency	6 days per week, for approximately 12 weeks		5-to-6 days per week, until recovery to baseline	5 sessions, over 4 weeks	2 days per week, for 8 weeks	Daily, until recovery to baseline
Intensity	80% of symptom-limited exercise threshold		80% of symptom-limited exercise threshold	-	-	Mild-to-moderate intensity, as per the Borg Rating of Perceived Exertion Scale
Time	20 minutes per day		Duration equivalent to	45 minutes per session	60 minutes per day	20 minutes per day

		that which resulted in symptom exacerbation at baseline testing			
Type	Aerobic exercise (e.g., treadmill or stationary bicycle)	Aerobic exercise (on a stationary bicycle)	-	Aerobic exercise, in addition to self-affirmation and meditation exercises	Aerobic exercise (on a stationary bicycle)

Table 2: Characteristics of the exercise interventions employed in each study, categorized by the F.I.T.T. principle.

[a]Intervention was common between studies.

FIGURES

Figure 1:

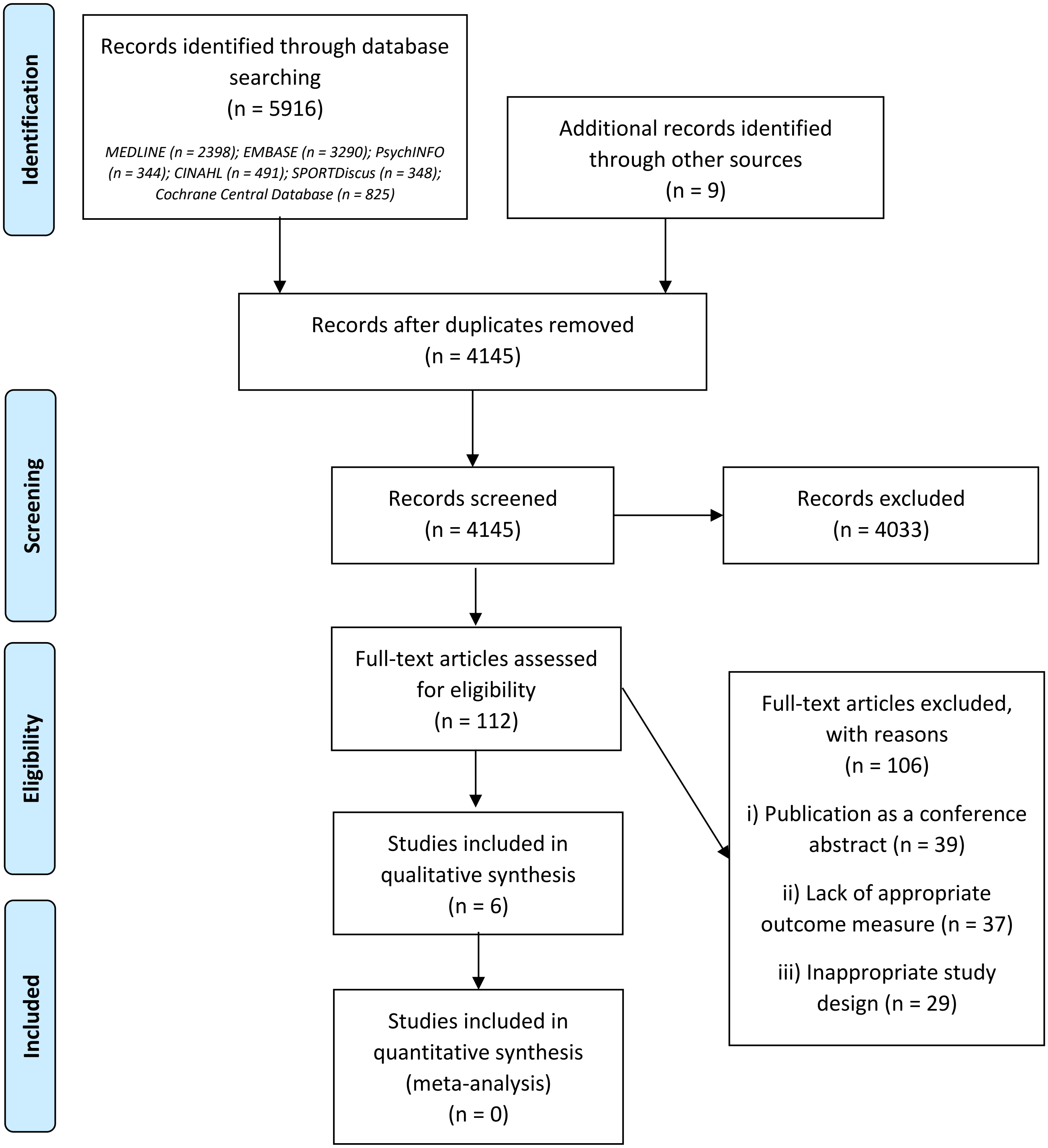
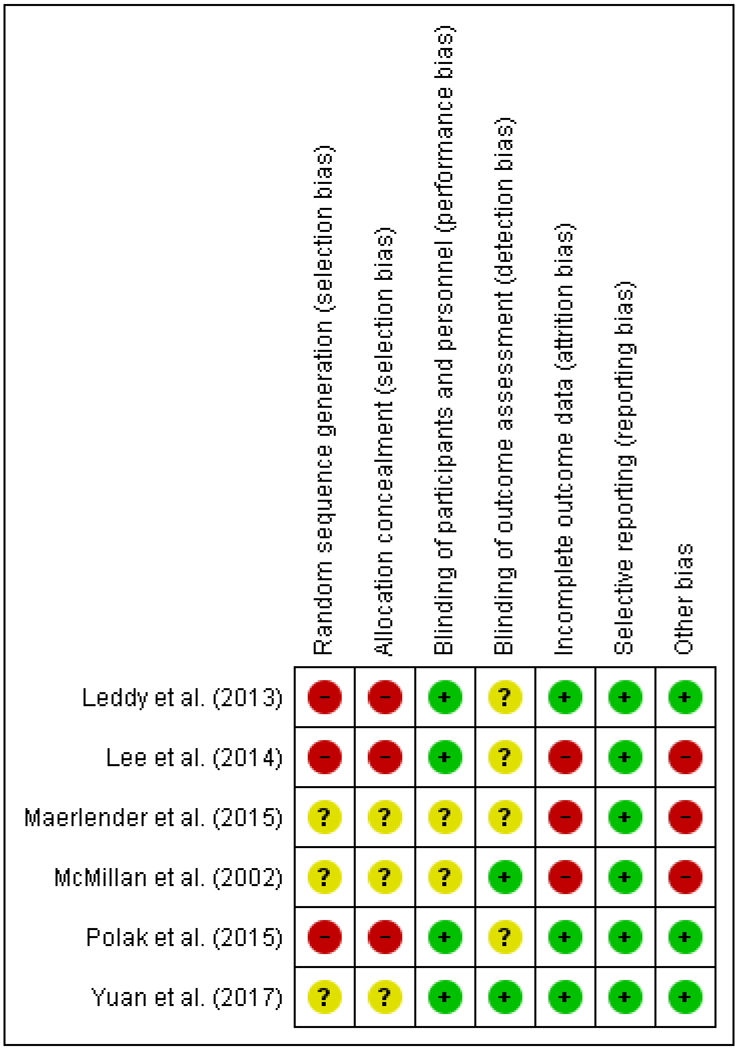


Figure 2a:



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Leddy et al. (2013)	−	−	+	?	+	+	+
Lee et al. (2014)	−	−	+	?	−	+	−
Maerlender et al. (2015)	?	?	?	?	−	+	−
McMillan et al. (2002)	?	?	?	+	−	+	−
Polak et al. (2015)	−	−	+	?	+	+	+
Yuan et al. (2017)	?	?	+	+	+	+	+

Legend: Red, green, and yellow denote high, low, and unclear risk of bias, respectively.

Figure 2b:

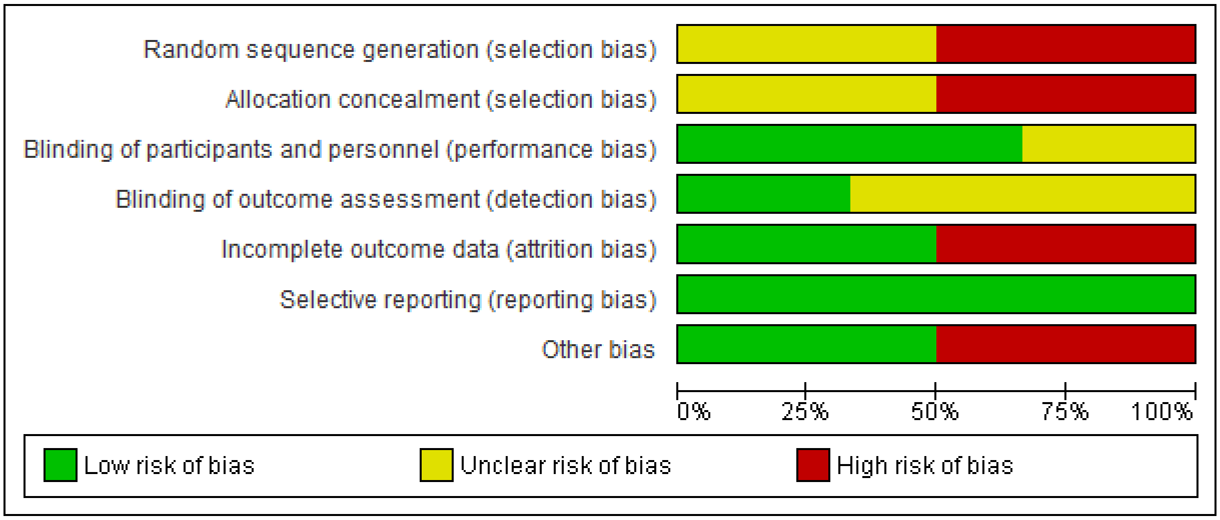

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

FIGURE CAPTIONS

Figure 1: PRISMA flow diagram representing the identification, screening, eligibility, and inclusion of studies in this review.

Figure 2a: Risk of bias for included studies, as assessed using the Cochrane Risk of Bias Tool.

Figure 2b: Risk of bias summarized across all studies, as assessed using the Cochrane Risk of Bias Tool.

CHAPTER 3

Sex-specific differences in resting-state functional brain activity in pediatric concussion

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ABSTRACT

Importance: Pediatric concussion has a rising incidence and can lead to long-term symptoms in nearly 30% of children. Resting state functional magnetic resonance imaging (rs-fMRI) disturbances are a common pathological feature of concussion, though no studies have examined sex differences with respect to this outcome. Despite known sex differences in how pediatric concussion presents, females have remained understudied in rs-fMRI studies, precluding a sex-specific understanding of the functional neuropathology of pediatric concussion.

Objective: To provide the first insights into sex-specific rs-fMRI differences in pediatric concussion.

Design, setting, and participants: Secondary data analysis of rs-fMRI data collected on children with concussion recruited from in a pediatric hospital setting, with control data accessed from the open-source ABIDE-II database. In total, 27 children with concussion (14 females) approximately one-month post-injury and 1:1 age- and sex-matched healthy controls comprised our sample.

Exposure: Patients received a physician diagnosis of concussion. ABIDE-II healthy controls were typically developing.

Main outcomes & measures: Seed-based (which permitted an examination of whole-brain connectivity, fitting with the exploratory nature of the present study) and region of interest (ROI) analyses were used to examine sex-based rs-fMRI differences. Threshold-free cluster enhancement (TFCE) and a family-wise error (FWE) corrected p-values were used to identify significantly different clusters.

Results: In comparing females with concussion to healthy females, seed-based analyses (in order of largest effect) showed hypo-connectivity between the anterior cingulate cortex of the salience network and the precuneus (TFCE=1173.6, p=FWE=0.002) and cingulate gyrus (TFCE=1039.7, p-FWE=0.008), and the posterior cingulate cortex (PCC) of the default mode network and the paracingulate gyrus (TFCE=870.1, p-FWE=0.015) and sub-callosal cortex (TFCE=795.4, p-FWE=0.037); hyper-connectivity was observed between the lateral pre-frontal cortex and inferior frontal gyrus (TFCE=1215.4, p-FWE=0.002) and lateral occipital cortex (TFCE=854.9, p-FWE=0.020) and between the PCC and cerebellum (TFCE=791.0, p-FWE=0.038). ROI analyses showed primarily patterns of hyper-connectivity in females. No differences were observed between males with concussion and healthy males on seed-based or ROI analyses.

Conclusions and relevance: There are alterations in rs-fMRI in females with concussion at one-month post-injury that are not present in males, which provides further evidence that recovery timelines in pediatric concussion may differ by sex.

INTRODUCTION

Concussion is a mild form of traumatic brain injury (TBI) that results in altered neurological function after biomechanical impact[1]. In pediatric populations, concussion is of particular concern given that it is one of the most common injuries among children and adolescents[2-4] and has a rapidly rising incidence in those aged 10-19[5,6]. While the injury is transient for the majority of pediatric patients, between 14-29% experience persistent concussion symptoms[7-9] (PCS; previously referred to as post-concussion syndrome, marked by symptoms which last in excess of four weeks[1]). PCS can include somatic, cognitive, emotional, and sleep-related features that negatively impact academic outcomes[10] and health-related quality of life[11,12].

Brain function in pediatric concussion has been studied to understand the nature and extent of its impairment post-injury, as well as its potential etiological role with respect to concussion symptoms. Studies have measured brain function using resting-state functional magnetic resonance imaging (rs-fMRI), which maps regions of brain activity (by proxy of the blood-oxygen-level-dependent, or BOLD, response) and the relative associations between them in a task-independent manner. Pediatric rs-fMRI studies have shown increased functional connectivity in comparison to healthy controls in widely-studied brain networks within the first week of injury[13-15]. At one-month post-injury (the expected time of recovery[1]), results of rs-fMRI studies are mixed[13,14,16-18]. With respect to studies of children diagnosed with PCS, one study found that within-network functional connectivity across seven validated brain networks did not differ between children with PCS (n=110) vs. healthy peers (n=20), although select PCS symptoms, sleep impairment, and poorer cognition were associated with connectivity in the concussed cohort[19,20].

A notable limitation common to many pediatric concussion rs-fMRI studies are the imbalanced samples with respect to sex. Some studies involved male only cohorts[14,16,21], whereas others had less than 25% female representation in their samples[13,17]; in some cases, data on sex were not reported[18,22]. Only a few studies had samples that approached balance (40-45% female) with respect to sex distribution[15,19,20,23], though these studies did not stratify their results by sex, instead providing group-level data comparing mixed-sex cohorts of children with concussion to their healthy peers. The most direct data on sex-specific rs-fMRI differences come from a recent study involving adults with PCS[24]. The lack of a sex-specific understanding of rs-fMRI differences in pediatric concussion is a considerable knowledge gap, given that sex, as a biological variable, has been recognized as an understudied yet important consideration in neuroscience[25-27]. Further, a growing body of research demonstrates that concussion presents differently in boys vs. girls[28,29]. For example, a recent cohort study (n=986) found that female adolescents with concussion endorse more symptoms on the 22-item and widely used SCAT5[30] than concussed males, and are more likely to have a higher total symptom score[31]. Two large-scale, multi-center cohort studies have shown that females have a protracted recovery in comparison to males[28,29], which align with other clinical data on disparate sex effects in concussion summarized in two recent systematic reviews[32,33]. Therefore, we studied sex-specific rs-fMRI differences in pediatric concussion to address an important knowledge gap, and advance our understanding of how the functional neuropathology of concussion differs between males and females.

METHODS

Design

The present study is a secondary analysis of data collected as part of two cohort studies (sharing recruitment methods, inclusion/exclusion criteria, and imaging parameters, as detailed below) on pediatric concussion. Control data were obtained from an open-source pediatric neuroimaging database (detailed below). This study was approved by the Hamilton Integrated Research Ethics Board (https://hireb.ca).

Participants

Children (aged 9-17) experiencing concussion symptoms were recruited by the clinical study team from sites at or affiliated with McMaster University, including the McMaster Children’s Hospital and associated rehabilitation and sports medicine clinics, as well as through direct referral from community physicians. Children diagnosed with a concussion, and their families, were recruited for an intake assessment. Neuroimaging data were then collected as soon after recruitment as scheduling permitted. For the present and larger studies, exclusion criteria included: i) more severe forms of head injury that required surgery, resuscitation, or admission to the critical care unit, ii) complex injuries involving multiple organ systems, and iii) diagnosed neurological disorder or developmental delay.

Imaging data on healthy children were acquired from the multi-site, internationally compiled, open-source Autism Brain Imaging Data Exchange II (ABIDE-II) database[34]. The ABIDE-II database is comprised of over one-thousand anonymized brains (including 557 healthy controls) collected from 19 sites, primarily in North America and continental Europe, yielding nearly 75 publications to date. Both anatomical and functional scans from the ABIDE-II database were pulled to serve as 1:1 age- and sex-matched typically developing controls for our participants with concussion.

MRI procedures data acquisition

All children with concussion were scanned at a single site (Imaging Research Centre [IRC] at St. Joseph's Hospital) using a 3-Tesla GE Discovery MR750 MRI scanner and a 32-channel phased array head receiver coil. Upon entering the IRC, participants (as well as their parents and/or guardians if aged 16 years or younger) were led through an intake questionnaire by the MRI technologist, which informed participants about what to expect during the MRI and to ensure that there were no contraindications to MRI. The MRI technologist situated the participant in the MRI, using foam cushioning to minimize discomfort and motion during the scan, and earplugs were provided. The MRI technologist remained in verbal contact with the participant via intercom throughout the scan.

With respect to MRI data collection, first, a 3-plane localizer with calibration sequences was acquired. Anatomical images were then collected using a 3D inversion recovery-prepped fast SPGR T1-weighted sequence (TR/TE=11.36/4.25ms, flip angle=12°, 512x256 matrix interpolated to 512x512, 22cm axial FOV, 1mm thick). Resting state fMRI involved BOLD imaging (gradient echo EPI, TR/TE=2000/35ms, flip angle=90°, 64x64 matrix, 180 time points, 3mm thick, 22 cm FOV), wherein participants were asked to remain awake, keep their eyes open, and not to think of anything in particular. A B_0 map was acquired for resting state scans, using the same geometric prescription and a B_0 mapping tool available on the GE scanner which provides a parametric map of field homogeneity in Hz. In regards to the scanning sequence, the rs-fMRI data were acquired within 10-minutes of entering the MRI, as to avoid motion onset by restlessness later in scans as we have observed in this population. Additional data were collected (including DTI[35] and task-based fMRI data[36]) as part of the imaging battery, but are not relevant to the present study.

With respect to control data from the ABIDE-II database, only scans with a minimum of 180 time-points were used as age- and sex- matched controls. B_0 data were not available for healthy controls.

MRI pre-processing and analyses

Pre-processing of imaging data was performed in CONN 19c[37] (which draws on some the functionality of SPM12[38]), run on MATLAB R2020a. For concussion data only, given that B_0 maps were not available for controls, unwarping of functional data was performed outside of CONN using the *epiunwarp* script[39]. Unwarped images were then inputted into the pre-processing pipeline which involved the following steps: 1) Functional realignment, wherein all scans were co-registered to the first image acquired[40]. 2) Slice-timing correction to correct for the inherent sequential process of image acquisition, wherein the functional data is time-shifted and resampled (per sinc-interpolation) to match the time in the mid-point of each TR[41]. 3) Functional data outlier detection using SPM's Artifact Detection Tool (ART)[38], wherein outliers are detected based on subject motion (>0.9mm framewise displacement) and relative BOLD signal fluctuations (scans ≥5 standard deviations identified as potential outliers). 4) Direct segmentation and normalization/registration of functional data to MNI space (1mm and 2mm isotropic voxels for anatomical and functional data, respectively), based on posterior tissue probability maps. And 5) spatial smoothing of functional data with a Gaussian kernel of full-width at half-maximum of 6mm. All data were inspected visually after pre-processing, as well as by running CONN's quality assurance checks.

Next, de-noising procedures were performed in CONN. First, ordinary least squares regression was used to project out noise components (associated with cerebral white matter and cerebrospinal regions[42], outlier scans[43], and subject motion[44]) using CONN's anatomical component-based noise correction procedure (aCompCorr). Subsequently, temporal filtering was performed, filtering out frequencies below 0.008Hz and above 0.01Hz. Data were again inspected visually and per the quality assurance metrics offered by CONN.

Seed-based connectivity and ROI-to-ROI based connectivity measures were then computed for each individual subject; groupwise comparisons (comparing all children with concussion to all control participants, healthy girls to girls with concussion, and healthy boys to boys with concussion) were then performed. Seed regions from four, large-scale, validated and clinically-salient (in pediatric concussion and otherwise) resting-state brain networks were used[45-48]. These included the DMN (seeded at the posterior cingulate cortex [1, -61, 38]), salience network (SN, seeded at the anterior cingulate cortex [0, 22, 35]), fronto-parietal network (FPN, seeded at the lateral pre-frontal cortices), and sensorimotor network (SMN, seeded superiorly at the pre-central gyrus [0, -31, 67]). Given that this study is the first to look at sex differences in rs-fMRI in pediatric concussion, seed-based analyses were employed to explore the relation between these seeds and all other voxels of the brain; an accompanying ROI-to-ROI analysis was also performed (which examines the associations between 164 regions defined by the Harvard-Oxford atlas).

Cluster-level inferences were made per Threshold Free Cluster Enhancement (TFCE)[49], which avoids the use of an *a priori* cluster-forming height threshold. More specifically, TFCE scores are weighted based cluster extend (or how broad the cluster is, spatially speaking) and the cluster-height (without examining only at the “peaks” of clusters that survive the threshold that is otherwise arbitrarily set). For each groupwise contrast (as specified above) permutation tests (involving 10,000 permutations) were used to derive a null distribution that the observed effects were then compared to, and a TFCE score associated with family-wise error (FWE) corrected p-value for each cluster was obtained. TFCE has the advantage of being associated with a lower false-positive rate than traditional cluster-size tests based on random field theory[50].

Between-group contrasts (i.e., all healthy vs. all concussed, healthy males vs. males with concussion, healthy females vs. females with concussion) were set up in CONN 19c as independent samples t-tests. For each contrast and for each seed-region, significantly different clusters were identified using TFCE. The effect sizes associated with each significant cluster were computed, along with a t-score to statistically compare effect size differences at the cluster level between groups.

RESULTS

Demographic and injury data of the 27 children with concussion and 27 controls are summarized in **Table 1**. Age did not significantly differ between males and females in either cohort, and males and females with concussion had similar PCSS scores (47.8 vs. 41.6, p=0.511) at time of imaging per an independent samples t-test. Patients with concussion were, on average, approximately one-month post-injury (28.8 ± 14.5 days) at time of imaging, and had no history of anxiety, depression, sleep disorder, or psychiatric diagnosis.

[insert Table 1 here]

Concussion vs. control group comparison

In the concussion cohort, there was significantly reduced functional connectivity (all p-FWE <0.05, with corresponding TFCE scores in **Figure 1**) between the seed-region of the: i) DMN and the superior frontal gyrus (bilaterally), paracingulate gyrus (right), and sub-callosal cortex; ii) SMN and superior frontal gyrus (left), lateral occipital cortex (left), and cuneal cortex (left); iii) SA and precuneous cortex, cingulate gyrus (left) and hippocampus (left), and intra-calcarine cortex (left). Further, there was increased functional connectivity between the seed-region of the FPN and the inferior frontal gyrus (left) and lateral occipital cortex (left); there was also increased functional connectivity observed between the DMN seed and cerebellum (left). These data are depicted in **Figures 1** and **eFigure1**.

[insert Figure 1 here]

At the ROI-to-ROI level, there was a broad pattern of increased functional connectivity between multiple brain regions bilaterally, and fewer instances of decreased connectivity between pairs of ROIs. The pairs of ROIs with significantly reduced connectivity included: the lateral parietal node (left) and supramarginal gyrus (left), superior frontal gyrus (left) and thalamus (right), inferior frontal gyrus (right) and thalamus (left) (see **Figure 2**).

[insert Figure 2 here]

Healthy males vs. males with concussion

Per both seed-based and ROI-to-ROI level analyses, there were no significant groupwise differences observed between healthy males and males with concussion.

Healthy females vs. females with concussion

In females, with respect to the DMN, there was increased connectivity between the DMN seed and parts of the cuneal cortex (right), and reduced connectivity between said seed and primarily the insular cortex (left), frontal oribital cortex (left), and temporal pole (left). The seed region of the SA was associated with reduced functional activity with the thalamus (left) and parahippocampal region (left). Further, the seed region of the FPN was associated with increased functional connectivity with the lateral occipital cortex (left) and frontal pole (left), and reduced connectivity with the paracingulate gyrus (bilaterally) and superior frontal gyrus (bilaterally); see **Figures 3** and **eFigure2**.

[insert Figure 3 here]

In females, groupwise ROI-to-ROI analyses showed that there was increased connectivity between ROIs in the cuneal cortex and cerebellum, as well as between the cingulate gyrus and cerebellar regions. There was also reduced connectivity between the parahippocampal gyrus (posterior division, right) and both the medial pre-frontal cortex and frontal medial cortex in girls with concussion compared to healthy girls (**Figure 4**).

DISCUSSION

Our study is the first to report that in pediatric concussion, there are rs-fMRI disturbances observed in females that are not present in the males. To date, the majority of studies on rs-fMRI in pediatric concussion have either not studied females or had a small female representation (<25%) in their samples. Our findings, therefore, provide the first insight into functional disturbances in pediatric concussion by sex.

In pediatric concussion, studies have attempted to link rs-fMRI disturbance to symptoms but have not found a clear relationship[14,18,23]. This may in part be attributable to symptom and rs-fMRI data not being disaggregated by sex in prior studies that have studied both of these measures. Our results show that following concussion, at approximately one-month post-injury, there are alterations in rs-fMRI activity in females (in comparison to their healthy peers) that are not observed in males. Symptom studies align with this, reporting sex differences with respect to symptoms in pediatric concussion[28,29,31-33]. With a large evidence-base suggesting that symptom presentation differs in pediatric concussion by sex, and with the current study demonstrating sex-based rs-fMRI differences in children with concussion, there is reason to hypothesize that this variable symptom presentation has an underlying functional sex-specific neuropathology. Past studies that did not find a clear relationship between concussion symptoms and functional brain pathology may not have observed such an effect because their analyses were not stratified by sex, which (as shown in the present study) provides insights that mixed-sex analyses do not. Future studies should collect data on symptoms and rs-fMRI and stratify analyses by sex to better understand the relationship between these variables.

Data on the risk of secondary concussion by sex are limited, with the majority of studies to date focusing on predominantly male samples[51]. Our study, however, shows that in females, concussion can impact regions of the brain including the insular cortex, cuneal cortex, and thalamus, which are involved in processing of sensory and/or visual information as well as motor control[52]. These findings may suggest that females, particularly in a sport-related context, may be at elevated risk of secondary injury (owing to potential sensory and/or motor impairments). While data on whether brain function remains impaired at medical clearance to return to activity are mixed[53,54], our findings (wherein imaging was performed, on average, at the time when clinical recovery from concussion is expected to occur) suggest that functional brain impairments persist in females but not males. This suggests that resolution of functional pathologies in sensory and motor areas of the brain may be sex-dependent, and that return-to-sport guidelines stand to be informed by sex-specific data.

A recent review on sex differences in concussion (pediatric and adult) identified that injury may lead to alterations in the hypothalamic-pituitary-ovarian axis, and subsequent hormonal fluctuations that may be responsible for the more severe symptoms in females[55]. rs-fMRI studies in other endocrinological populations demonstrate that alterations in functional brain activity are associated with abnormal hormonal responses[56-59]. With our study pointing to rs-fMRI disturbances in females with concussion that are not present in males, these functional brain changes may mediate or be related to a variable hormonal response that has an ultimate impact on the female concussion symptomology. Research that directly examines the relationship between brain activity, hormonal fluctuations, and symptomatology is required to build on this possibility.

Large-scale studies (such as the Philadelphia Neurodevelopmental Cohort [PNC], which included nearly 1600 imaging assessments on those aged 8 to 21 years[60,61]) have shown that rs-fMRI patterns vary by sex throughout neurodevelopment. Other studies have also demonstrated sex differences with respect to functional brain activity (and brain morphology, more broadly), and that these differences relate to variable neurodevelopment of networks such as the DMN[62]. In our analyses, we compared concussed males and females to their respective age- and sex-matched control groups, thereby avoiding the potential confounding neurodevelopmental effects that may arise when comparing males to females directly.

LIMITATIONS AND FUTURE DIRECTIONS

Future studies should include longitudinal assessments to determine if sex differences in rs-fMRI activity in pediatric concussion vary from acute to the chronic stages of injury. This line of research, combined with existing evidence on pediatric symptom trajectories post-concussion, would help in understanding whether there is a functional neuropathology driving the symptom response longitudinally in children who have delayed recoveries. These studies should also perform rs-fMRI assessments in children who are asymptomatic, given that the broader literature has shown that neurophysiological disturbances can outlast symptoms[63]; understanding whether functional neuropathology outlasts clinical recovery can improve our understanding of the vulnerability of the brain to secondary injuries in a sex-specific manner.

CONCLUSIONS

This is the first study to report on sex-specific rs-fMRI differences in pediatric concussion. At one-month post-injury, we report on differences in females with concussion (in comparison to their healthy peers) that are not apparent in males. This research further speaks to the need for more sex-specific analyses in concussion research.

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FIGURE LEGENDS

Figure 1. rs-fMRI differences between children with concussion and their healthy peers (mixed-sex cohorts). Clusters (x, y, z) denote standard MNI coordinates at the center of cluster mass, and size represents number of voxels. Only statistics for clusters that survived a p-FWE <0.05 per TFCE are displayed.

eFigure 1. For each significant cluster (per TFCE), the effect size associated with that cluster, by group, is depicted below. An associated independent samples t-test (with 52 degrees of freedom) compares the effect sizes at each cluster between groups. Blue and red bars indicate effect sizes for the concussion and control cohorts, respectively.

Figure 2. (A) Significantly increased (warm colours) and decreased (cool colours) ROI-to-ROI connectivity in children with concussion in comparison to controls (mixed-sex sample). (B) Depiction of the ROI-to-ROI changes summarized in panel A on a 3D glass brain to more clearly depict altered patterns of connectivity in an anatomically relevant space.

Figure 3. rs-fMRI differences between females with concussion and healthy age-matched females. Clusters (x, y, z) denote standard MNI coordinates at the center of cluster mass, and size represents number of voxels. Only statistics for clusters that survived a p-FWE <0.05 per TFCE are displayed.

eFigure 2. For each significant cluster (per TFCE), the effect size associated with that cluster by group (healthy females vs. females with concussion) is depicted below. An associated independent samples t-test (with 25 degrees of freedom) compares the effect sizes at each cluster between groups. Blue and red bars indicate effect sizes for the concussion and control cohorts, respectively.

Figure 4. (A) Significantly increased (warm colours) and decreased (cool colours) ROI-to-ROI connectivity in females with concussion in comparison to healthy female controls. (B) Depiction of the ROI-to-ROI changes summarized in panel A on a 3D glass brain to more clearly depict altered patterns of connectivity in an anatomically relevant space.

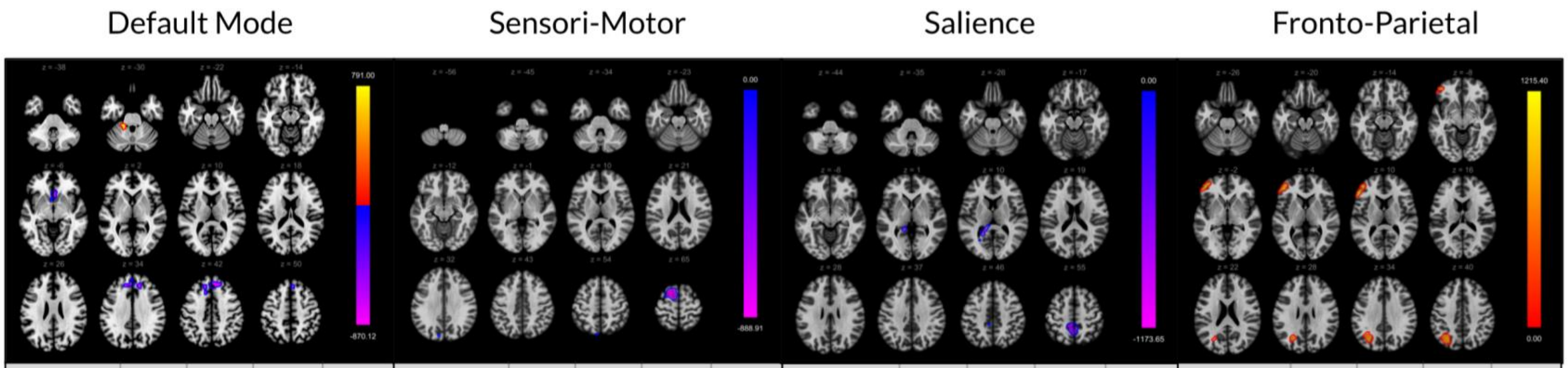
TABLES

Table 1. Demographic and injury-related variables.

	Concussion (n=27)	***Healthy (n=27)***
Age	11.2 (6.2)	11.0 (6.1)
% female	55.6%	55.6%
Time-post injury	28.8 (14.5)	-
Previous concussion	0, n= 17 (62.9%) 1, n= 8 (29.6%) 2, n = 2 (7.4%)	-
Mechanism of injury	70.3% sport 22.2% non-sport related falls 7.4% motor vehicle collision	-

FIGURES

Figure 1



Default Mode					Sensori-Motor					Salience					Fronto-Parietal				
Cluster (x,y,z)	Size	Peaks	TFCE	p-FWE	Cluster (x,y,z)	Size	Peaks	TFCE	p-FWE	Cluster (x,y,z)	Size	Peaks	TFCE	p-FWE	Cluster (x,y,z)	Size	Peaks	TFCE	p-FWE
Paracingulate gyrus +14 +34 +32	580	19	870.12	0.015	Superior frontal gyrus -18 +04 +66	418	5	888.91	0.024	Precuneous cortex -04 -40 +50	451	5	1173.6	0.002	Inferior frontal gyrus -58 +30 +06	532	11	1215.4	0.002
Sub-callosal cortex +02 +20 -10	227	5	795.45	0.037	Lateral occipital cortex -10 -82 +52	25	3	783.93	0.043	Cingluate gyrus posterior -14 -42 +02	215	3	1039.7	0.008	Lateral occipital cortex -30 -70 +22	598	1	845.9	0.02
Cerebellar region -22 -36 -36	82	1	791.00	0.038	Cuneal cortex -10 -84 +32	53	1	766.40	0.047	Intracalcarine cortex -28 -60 +04	38	3	756.11	0.046	-	-	-	-	-

Figure 2

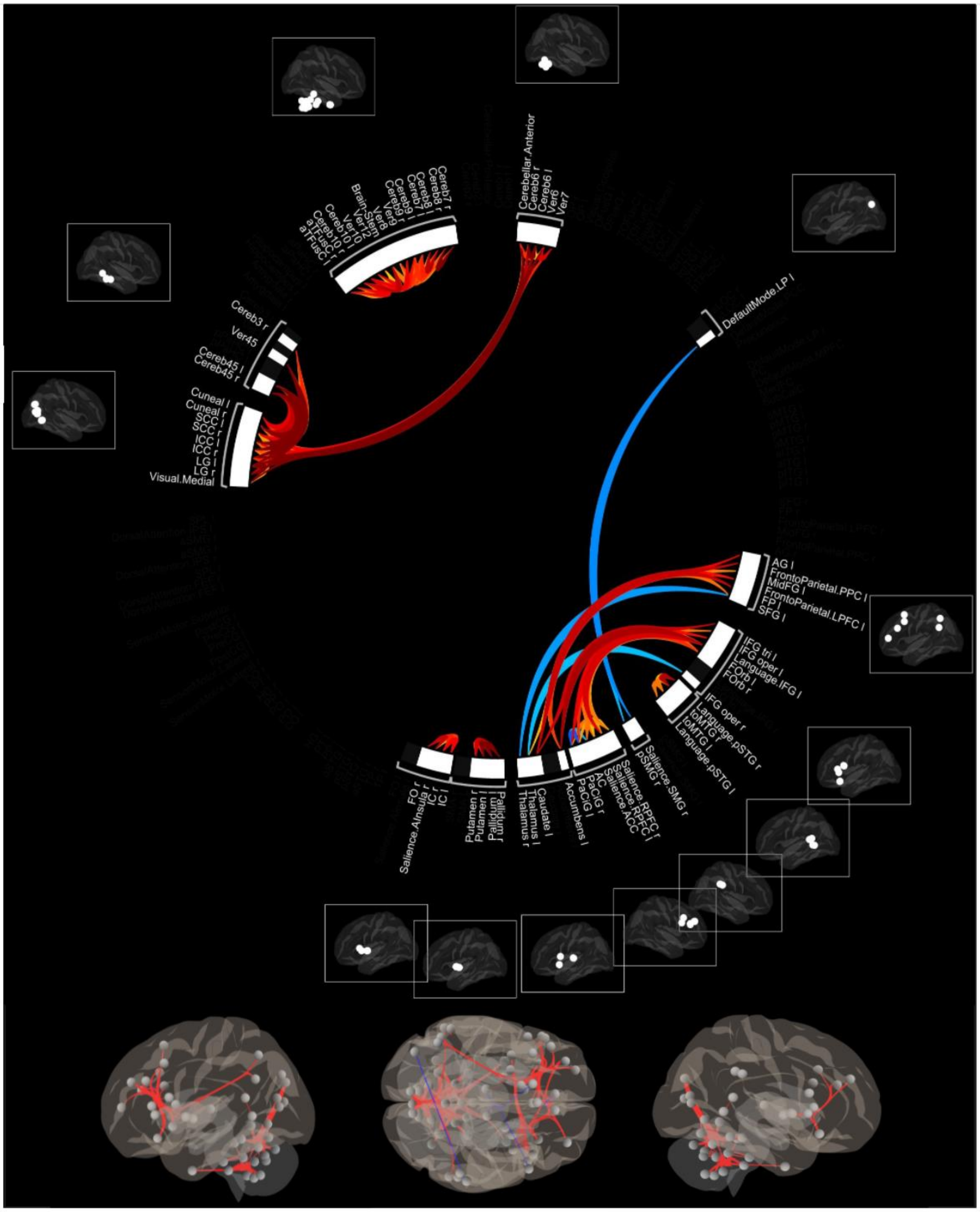
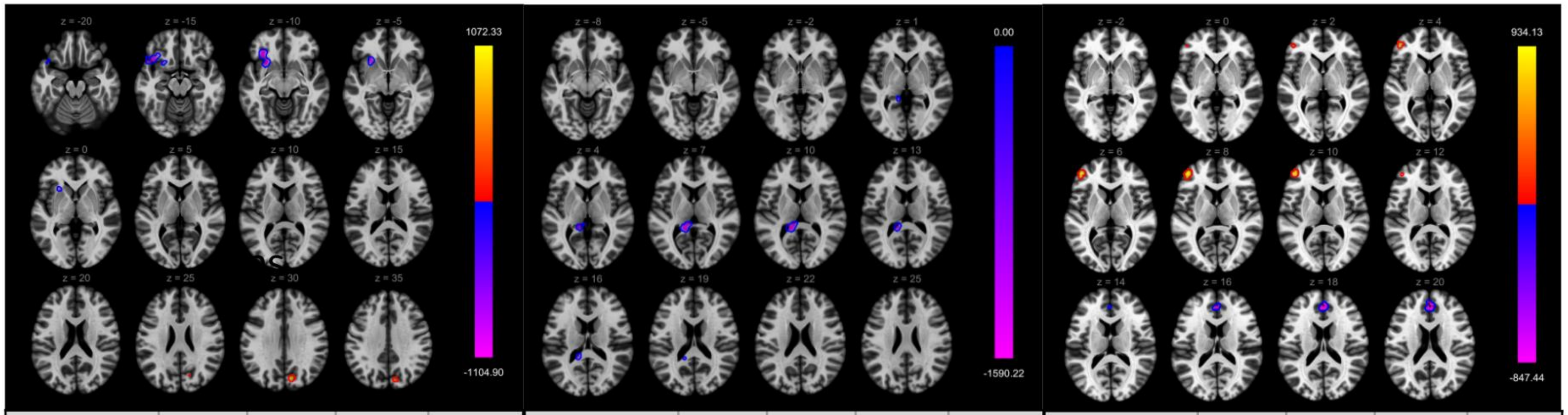
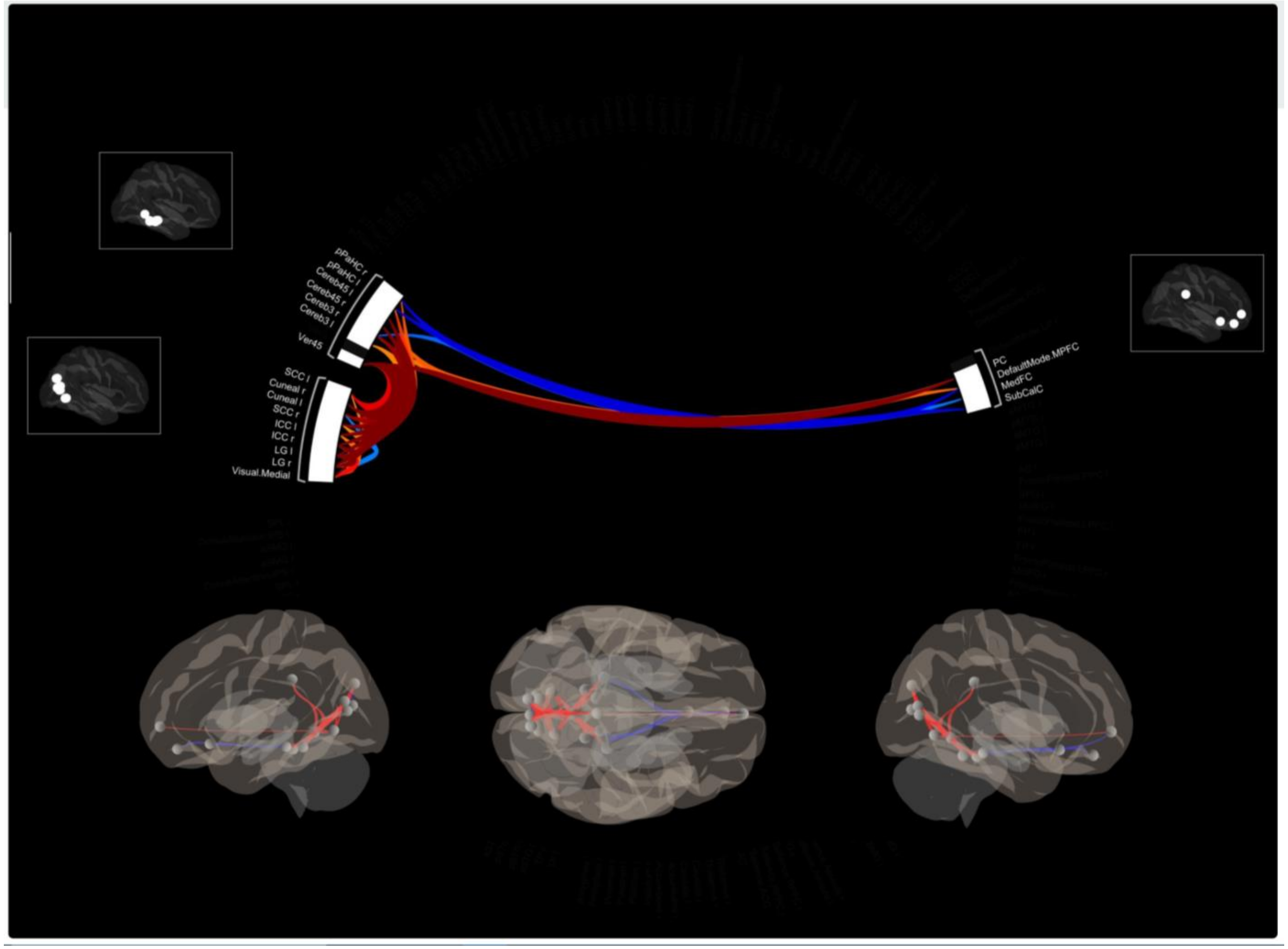

Cerebellar.Anterior
Cereb6 r
Cereb6 l
Ver6
Ver7
Cereb7 r
Cereb8 r
Cereb8 l
Cereb7 l
Cereb9 l
Cereb9 r
Ver9
Ver8
Brain-Stem
Ver12
Ver10
Cereb10 l
Cereb10 r
aTFusC r
aTFusC l
Cereb3 r
Ver45
Cereb45 l
Cereb45 r
Cuneal l
Cuneal r
SCC l
SCC r
ICC l
ICC r
LG l
LG r
Visual.Medial
DefaultMode.LP l
AG l
FrontoParietal.PPC l
MidFG l
FrontoParietal.LPFC l
FP l
SFG l
IFG tri l
IFG oper l
Language.IFG l
FOrb l
FOrb r
IFG oper r
Language.pSTG r
toMTG r
toMTG l
Language.pSTG l
Salience.SMG r
pSMG r
Salience.RPFC r
Salience.RPFC l
Salience.ACC
AC
PaCiG r
PaCiG l
Accumbens l
Caudate l
Thalamus l
Thalamus r
Putamen r
Putamen l
Pallidum l
Pallidum r
FO r
Salience.AInsula r
IC r
IC l

Figure 3



Default Mode					Salience					Fronto-Parietal				
Cluster (x,y,z)	**Size**	**Peaks**	**TFCE**	**p-FWE**	**Cluster (x,y,z)**	**Size**	**Peaks**	**TFCE**	**p-FWE**	**Cluster (x,y,z)**	**Size**	**Peaks**	**TFCE**	**p-FWE**
Insular cortex -26 +18 -06	364	11	1104.9	0.018	Thalamus -12 -42 +02	221	1	1590.2	0.000	Lateral occipital cortex -30 -66 +34	113	1	934.13	0.021
Cuneal cortex +14 -72 +24	76	1	1072.3	0.020	-	-	-	-	-	Frontal pole -46 +44 +00	107	1	872.05	0.036
-	-	-	-	-	-	-	-	-	-	Paracingulate gyrus --02 +42 +14	186	1	847.44	0.042

Figure 4


pPaHC r
pPaHC l
Cereb45 l
Cereb45 r
Cereb3 r
Cereb3 l
Ver45
SCC l
Cuneal r
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SCC r
ICC l
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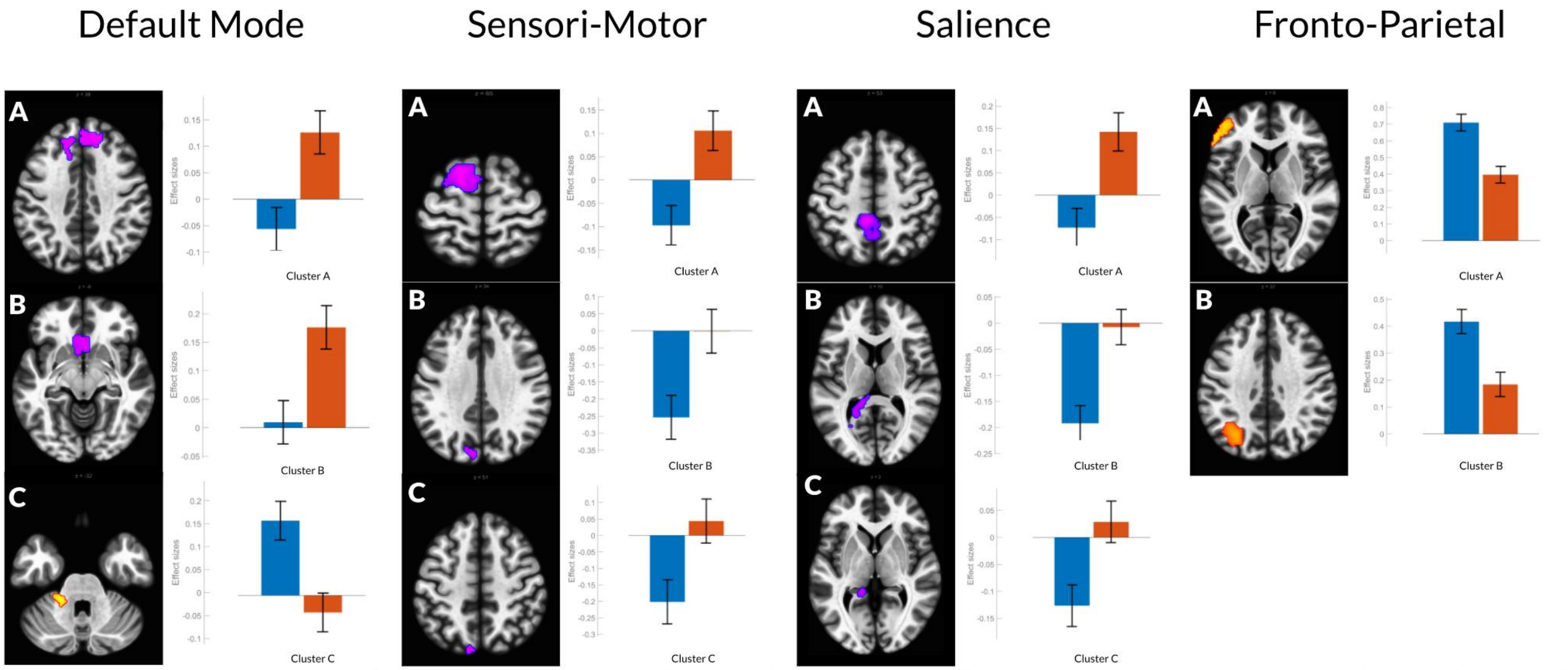
LG l
LG r
Visual.Medial
PC
DefaultMode.MPFC
MedFC
SubCalC

eFigure 1



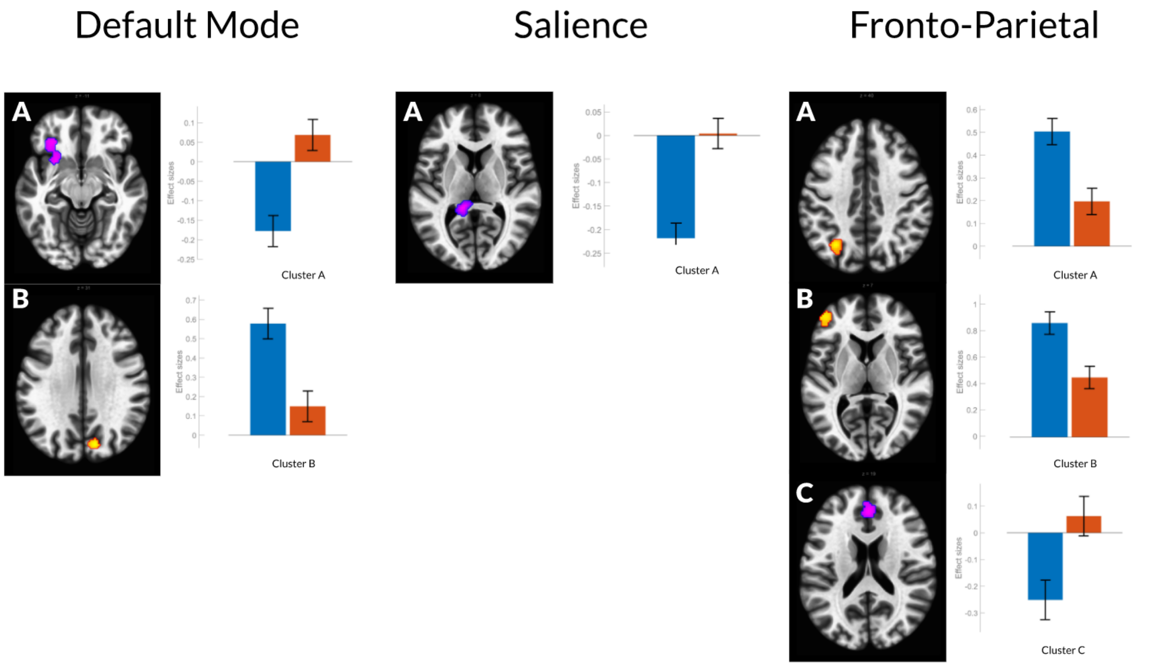
Cluster (x,y,z)	t-stat	p-FDR
Cluster A +14 +34 +32	-5.29	< 0.0001
Cluster B +02 +20 -10	-5.17	< 0.0001
Cluster C -22 -36 -36	5.61	< 0.0001

Cluster (x,y,z)	t-stat	p-FDR
Cluster A -18 +04 +66	-5.67	< 0.0001
Cluster B -10 -82 +52	-4.66	< 0.0001
Cluster C -10 -84 +32	-4.34	< 0.0001

Cluster (x,y,z)	t-stat	p-FDR
Cluster A -04 -40 +50	-5.92	< 0.0001
Cluster B -14 -42 +02	-6.43	< 0.0001
Cluster C -28 -60 +04	-4.77	< 0.0001

Cluster (x,y,z)	t-stat	p-FDR
Cluster A -58 +30 +06	7.34	< 0.0001
Cluster B -30 -70 +22	6.13	< 0.0001

eFigure 2



Cluster (x,y,z)	t-stat	p-FDR
Cluster A -26 +18 -06	-7.43	< 0.0001
Cluster B +14 -72 +24	6.51	< 0.0001

Cluster (x,y,z)	t-stat	p-FDR
Cluster A -12 --42 +02	-8.31	< 0.0001

Cluster (x,y,z)	t-stat	p-FDR
Cluster A -30 -66 +34	6.40	< 0.0001
Cluster B -46 +44 +0	5.83	< 0.0001
Cluster C -02 +42 +14	-5.09	< 0.0001

CHAPTER 4

Accelerometer-measured habitual physical activity and sedentary time in pediatric concussion: A controlled cohort study

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ABSTRACT

Objectives: To characterize and quantify differences in accelerometer-measured physical activity and sedentary time between children with concussion (within the first month of injury) and 1:1 matched healthy controls.

Methods: Secondary analysis of accelerometer data collected on 60 children with concussion and 60 healthy controls matched for age, sex, and season of accelerometer wear. Daily and hourly sedentary time, light physical activity (LPA), moderate physical activity (MPA), and vigorous physical activity (VPA) were compared between groups per independent samples t-tests.

Results: Children with concussion (12.74 ± 2.85 years, 31 females) were significantly more sedentary than controls (12.43 ± 2.71 years, 31 females; mean difference [MD], 38.3 minutes/day, $p=0.006$), and spent less time performing LPA (MD, -19.5 minutes/day, $p=0.008$), MPA (MD, -9.8 minutes/day, $p<0.001$), and VPA(MD, -12.0 minutes/day, $p<0.001$); hour-by-hour analyses showed that these differences were observed from 8:00AM to 9:00PM. Sex-specific analyses identified that girls with concussion were less active and more sedentary than both boys with concussion (MD, 50.8 minutes/day; $p=0.010$) and healthy girls (MD, 51.1 minutes/day; $p<0.010$). Days post-injury significantly predicted MPA ($\beta=0.071$, $p=0.032$) and VPA ($\beta=0.095$, $p=0.004$), but not LPA or sedentariness in children with concussion.

Conclusion: Clinical management should continue to advise against prolonged rest following pediatric concussion, given the activity debt observed within the

first-month of injury. Currently, clinical management of concussion is shifting towards prescribing a single bout of daily sub-maximal aerobic exercise. Interventions aimed at reducing overall sedentary time and increasing habitual physical activity in pediatric concussion also warrant study.

INTRODUCTION

Concussions are brain injuries that are caused by biomechanical impact and result in functional neurological disturbance[1]. These injuries are particularly common in pediatric populations where the incidence of concussion is rising[2-5]. While the majority of pediatric concussion cases resolve within an expected four-week window[1], nearly 30% may result in long-term symptoms[6-8]. Delayed recovery can lead to poor academic outcomes[9], health-related quality of life[10-12], and mental health[13].

Accordingly, research into an effective treatment for concussion has become a priority. Sub-maximal aerobic exercise has recently emerged as a leading candidate for the treatment of concussion symptoms[14-16]. The rapidly accumulating evidence on the benefits of exercise in concussion has been summarized by multiple meta-analyses[17-19], the most recent of which examined 23 studies (N=2547), finding that sub-maximal aerobic exercise has a large, positive effect (*Hedges' g*=1.71) on concussion recovery[17]. A paradigm shift in concussion management is occurring, wherein sub-maximal aerobic exercise is supplanting prolonged rest as a management strategy in both pediatric and adult concussion[15,20,21].

However, levels of habitual physical activity and sedentary time in children with concussion have not been studied, and we do not yet know whether these levels differ from their typically developing peers or whether they vary by sex (as do many other clinical features of concussion[22,23]). In a field where the deleterious impacts of prolonged rest on recovery are being increasingly recognized[19,24,25], a lack of knowledge of baseline physical activity and sedentary time after pediatric concussion represents a critical knowledge gap. Not only are we unaware of whether there is a potentially symptom prolonging physical activity deficit that needs to be overcome in pediatric concussion, but we also do not know of the impact of concussion on a critical aspect of daily functioning, namely participation in routine activity. In a cohort of adults with concussion (n=180), per a self-recall questionnaire, 85% identified as meeting physical activity guidelines pre-injury, compared to 28% post-concussion[26]. Similar data are not available on children. Such data, however, create opportunity to examine whether current exercise interventions aimed at providing a once-a-day aerobic stimulus are adequate[14-16], or if interventions that increase levels of habitual physical activity and reduce overall sedentariness throughout the day are warranted.

Habitual physical activity can be objectively quantified using accelerometers[27,28], which permit high temporal resolution quantification of movement by measuring multi-axis accelerations. Accelerometers have been used in many pediatric neurological and chronic disease populations to compare the activity of these children to their typically developing peers[29-31], providing insights about the intensity, time, and frequency of physical activity that recall surveys cannot capture. In concussion, accelerometry has been used to begin to understand the relationship between concussion symptoms and activity[32-34], although no controlled studies have quantified levels of sedentary time and habitual physical activity.

This study was performed to characterize accelerometer-measured physical activity patterns of children with concussion in comparison to their healthy peers. Learning more about habitual physical activity and sedentary time within the first month after concussion can aid in clinical management and informing the next wave of exercise intervention research.

METHODS

This study was approved by the Hamilton Integrated Research Ethics Board (www.hireb.ca).

Design

This study is a secondary analysis of accelerometer data collected as part of a prospective cohort study (led by the senior authors) aimed at developing protocols for safe resumption of activity following pediatric concussion.

Participants

Children (aged 6-17) presenting acutely to the emergency department at McMaster Children's Hospital, or to affiliated community physicians and sports medicine clinics, who received a diagnosis of concussion were referred to the research team. Informed consent from parents and assent/consent (as appropriate) from teenagers was obtained. Exclusion criteria were more severe brain injury or complex injuries involving multiple organ systems, and clinically diagnosed neurological or developmental disorder.

Participants with a concussion were matched 1:1 to healthy controls. The healthy controls were children who participated in prior studies in our lab, either as participants in longitudinal physical activity studies of healthy children or as controls of children from clinical populations. Patients with concussion were matched to healthy controls on three criteria, namely chronological age, sex, and season/month the accelerometer was worn. Matching for season/month (within

60 days) was important given known accelerometer-measured seasonal variation in both sedentary and active time in children[35].

Procedures

At initial intake, participants were provided with a waist-worn accelerometer to measure habitual physical activity. More specifically, the accelerometer used was the ActiGraph GT3x (Pensacola, FL, USA), a tri-axial axes accelerometer that is small, light-weight and unobtrusive during daily wear. This unit has also been shown to measure physical activity in acquired brain injury with high reproducibility[36]. The accelerometer was set to record movement at 30 Hertz. Participants were instructed to wear the accelerometer on their right hip during waking hours, except when engaged in water-based activities. Participants with concussion were asked to wear the device throughout their recovery, up to a maximum of 6 months; the current study focuses on the first 4 weeks, or the expected timeframe for recovery. Healthy controls were asked to wear the device for 7 to 9 consecutive days. Further, participants were given a logbook and instructed to note every time the device was taken off and re-worn.

All accelerometer data were downloaded in 3-second epochs and processed in ActiLife Software (ActiGraph; Pensacola, FL, USA). A semi-automated data cleaning procedure was used to detect any periods ≥5 minutes of zeros. Each of these bouts were inspected and only non-wear periods identified using the participant logbooks were excluded from subsequent data processing.

Days with missing logbook entries were also excluded from the analysis. The manually cleaned data were then scored to determine activity by intensity, using the validated Evenson cut points[37]. These cut points were scaled to 3-sec epoch data, and included time spent in sedentary time (0-25 counts/15s), light physical activity (LPA; 26-573 counts/15s), moderate physical activity (MPA; 574-1002 counts/15s), and vigorous physical activity (VPA; 1003+ counts/15s).

A sedentary bout analysis was also performed to quantify the length of individual sedentary bouts and the time between them. Sedentary bouts were defined as at least 1 epoch (3-sec) in length with an activity count ≤100 counts per minute, with a drop time of no more than 2-epochs. This meant that within any given sedentary bout, up to 6-sec of non-sedentary time was ignored (i.e., dropped), which would be akin to a positioning adjustment or reaching for a remote control or phone.

Data analysis

Data were imported into SPSS Version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY). Minimum wear time criteria were ≥ 600 minutes of for ≥ 4 days[38]. For hour-by-hour analyses, we included only hours with ≥ 50 minutes of wear time to ensure that the data were representative of the activities performed in the hour. Once the final sample of participants with valid wear data was acquired, daily average and hour-by-hour average activity and sedentary time was computed at the single-subject and group levels. Normality was assessed using Shapiro-Wilk tests, and independent sample t-tests were then used to compare accelerometer data by group, at both the daily and hourly levels. More specifically, sedentary time, LPA, MPA, and VPA were compared between groups, with Bonferroni corrections to adjust for family-wise multiple comparisons. Further, we examined the association between sedentary time and activity levels with days post-injury. General linear models (GLMs) were developed (to understand activity as a function of time post-injury) with sedentariness and activity levels as outcomes, and days post-injury and age as predictors; distribution of residuals was subsequently tested.

RESULTS

Overview

Our sample was comprised of 60 children with concussion and 60 healthy controls. Children with concussion wore their accelerometers for significantly longer overall; however, wear time per day was not significantly different between groups. These data along with demographics and the number of days and hours dropped from the analysis for not meeting wear time requirements, per group, are reported in **Table 1**.

[insert Table 1 here]

Groupwise activity and inactivity differences

Sedentary time was higher in children with concussion in comparison to healthy controls (mean difference [MD], 38.3 minutes/day; p=0.006). Accordingly, LPA (MD, -19.5 minutes/day; p=0.008), MPA (MD, -9.8 minutes/day; p<0.001), and VPA (MA, -12.0 minutes/day; p<0.001) were significantly lower in children with concussion relative to controls (**Table 2**). Girls with concussion were significantly more sedentary than boys with concussion (MD, 50.8 minutes/day; p=0.010) and less active with respect to LPA (MD, -25.0 minutes/day; p=0.010) and MPA (MD, -8.7 minutes/day; p=0.004). There were no differences between healthy boys and girls. However, girls with concussion were significantly more sedentary and less active, across all intensities, than healthy girls (**Table 3**).

[insert Table 2 here]

[insert Table 3 here]

Hourly analyses showed that from 8:00 AM to 9:00 PM, children with concussion were consistently more sedentary and less active than their healthy peers (**Figure 1**). Data from the earlier hours (i.e., before 8:00 AM) were not including in the analysis owing to limited availability of valid accelerometer data during this time. The effect sizes for the differences in hour-by-hour accelerometer-measured sedentary time and activity between children with concussion and healthy controls are presented in **Figure 1**.

[insert Figure 1]

Sedentary bout analysis

Our sedentary bout analysis revealed that healthy children had significantly more short sedentary bouts/hour (<1 minute) than children with concussion. However, children with concussion engaged in a significantly greater number of 5-to-10-minute sedentary bouts/hour than healthy controls (**Tables 4** and **5**).

[insert Table 4]

[insert Table 5]

Activity and inactivity as a function of days post-injury

GLMs predicting activity levels as a function of days post-injury and age were only significant for models (unstandardized betas reported) with MPA ($\beta_{Days\ Post}$=0.177, $t_{2,842}$=2.432, p=0.015) and VPA ($\beta_{Days\ Post}$=0.265, $t_{2,842}$=3.227, p=0.001) as the outcomes (**Supplement 1**). Therefore, as time post-injury increased, there were modest increases in minutes of daily MPA and VPA, but not sedentary time or LPA.

DISCUSSION

This is the first study to characterize habitual physical activity and sedentary time using accelerometry in children with concussion in comparison to healthy controls. We report that children with concussion are significantly more sedentary and less active (with respect to LPA, MPA, and VPA) than matched healthy controls; this is observed throughout the day, from 8:00AM to 9:00PM. Sex-specific analyses showed that girls with concussion are less active (across all intensities studied) and more sedentary than boys with concussion as well as healthy girls. Increased days post-injury significantly predicted higher levels of MPA and VPA–but not sedentary time or LPA–in children with concussion, which may be expected as a natural part of concussion recovery.

Prolonged inactivity in concussion

We identified a mean difference of 38.3 minutes/day (95% CI, 11.2, 65.4) of increased sedentary time in children with concussion compared to their healthy peers, which amounts to nearly 4.5 hours a week. This difference is even greater when comparing girls with concussion to healthy girls, where the mean difference in sedentary time is 51.1 minutes/day, or approximately 6 hours over a week. Concussion guidelines now suggest that prolonged rest should be avoided after the first 24-48 hours of injury[1], and a recent randomized trial[25], large-scale cohort study[24], and systematic review[19] support this notion. However, what constitutes prolonged rest (or sedentariness) is not yet well-defined, as indicated in the most recent sport concussion guidelines[1]. Our data do not establish a definition of prolonged rest post-concussion, but they do quantify the magnitude of the physical activity observed within the first month of injury. Instead of (or in addition to) prescribing a designed 20-minute period of aerobic activity as is current best practice[14-16], advising patients to interrupt their sitting may be advantageous, especially given the known benefits of such actions on multiple health outcomes in healthy and other clinical populations[39-41]. The optimal amount of sedentary time and physical activity following concussion, and whether a single bout of activity has greater benefits than interrupted sitting, requires further study. It is also important to note that sedentary time is not the inverse of physical activity, with each having different physiological effects[42]. The contribution of each to concussion outcome needs further study.

Engaging key stakeholders in the exercise discussion

With the accumulation of data on the benefits of exercise in concussion, the traditional “rest is best” approach is being overturned, with an “exercise is medicine” mindset becoming more commonplace. However, a knowledge translation gap still exists, wherein primary care providers have not yet adopted this new approach to concussion management; more than 80% of concussion patients are still advised to rest for more than 2-days, despite contrary evidence from recent guidelines and reviews[1,17,20]. A recent study aimed at providing primary care providers with guidelines for de-implementing prolonged rest found that the intervention improved knowledge about avoiding prolonged rest post-concussion, and increased clinician adherence to guideline recommendations from 25% to nearly 90%[43]. Further, per research on military service members with concussion, primary care providers relaying information to patients about the consequences of prolonged rest led to patients more promptly resuming physical activity and self-reporting lower levels of symptoms sooner[44]. Future research should not only continue to build on the evidence, but also ensure that key findings are translated to relevant knowledge users.

Towards F.I.T.T. informed exercise interventions in concussion

The bulk of exercise research in concussion has been on sub-maximal aerobic exercise[45]. Studying the impact of low-to-moderate intensity aerobic activity was motivated by the desire to engage patients in a safe, symptom-limited amount of activity that had a high likelihood of being well-tolerated. The optimal exercise frequency, intensity, time, and type (F.I.T.T.) of exercise in concussion has not been directly studied, though such study is necessary to maximize clinical benefit and increase exercise adherence in clinical populations[46]. Recently, however, research has started to provide insight into F.I.T.T principles for exercise prescription in concussion. Accelerometer studies show that engaging in MVPA following concussion can lead to longer recovery times[32], which supports the continued use of low-to-moderate intensity graded sub-maximal aerobic exercise programs at this time[15]. Further, in adolescents, participating in low-intensity aerobic exercise for less than 100 minutes/week was associated with greater symptom burden at one-month post-injury, while exercising more than 160 minutes/week resulted in symptom resolution when assessed at the same timepoint[47]. These data, in addition to the current findings that quantify the physical activity debt observed in pediatric concussion, are helpful for building towards an understanding of the optimal frequency and time of exercise interventions in concussion. Our data (**Supplement 1**) also show that the effect sizes for the difference in sedentary time between children with concussion and healthy controls is greatest from 8:00 AM to 1:00 PM, and then again from 8:00 PM to 9:00 PM. Given that sedentariness is observed throughout the day, but particularly so during school-going hours, there may be opportunity to incorporate physical activity programs as part of return-to-learn programs.

Accelerometery in concussion-exercise research

Despite the recognized importance of physical activity on concussion symptoms, accelerometer research in pediatric concussion has been limited. To date, studies have used accelerometry to assess the relationship between physical activity with subsequent outcome in non-controlled cohort studies. More specifically, one study showed that the number of accelerometer-measured steps from days 1-3, 4-5, and 6-7 post-injury were significantly correlated with symptom scores at each of these intervals, and the increased activity (i.e., number of steps) from days 1-3 post-injury predicted lower activity on days 4-5 post-injury[33]. A second study by this group reported that there was no association between physical *and* cognitive activity and time to concussion recovery[34]. Another group studied male youth hockey players wearing accelerometers in the early stages of injury and found that those in the “high” activity group (based on a median split, performing more than 148.5 minutes of MVPA/day) took significantly longer to recover than those in the “low” activity group[32]. Our study, in comparing accelerometer-measured sedentariness and activity between cohorts of concussed and healthy children, shows that there are considerable differences in sedentary time and physical activity within the first-month of injury. Future research should continue to use accelerometers over self-recall questionnaires to build on these insights. Importantly, self-report measures of physical activity have been shown to under-estimate sedentary time and over-estimate activity in comparison to device-measured physical activity behaviours in both children[48,49] and adults[49,50]. Moreover, adopting accelerometry broadly in concussion research creates opportunities for data sharing and big data analysis, recognized as an important aspect in the next wave of neuroscience research[51,52].

LIMITATIONS AND FUTURE DIRECTIONS

Our study is limited by the absence of symptom data that preclude exploration of the association between accelerometer-measured physical activity and clinical outcome. Participants in our study also wore the accelerometer over their right hip; whether there are differences in measured activity based on location of wear remains unknown. Further, for our sedentary bout analysis, we used a 6-second drop-time as this length of time was estimated to not be physiologically-relevant yet akin to slight movement such as repositioning or reaching for a device. Drop time criterion can be better established by future research.

Additional research is required to understand the threshold of total volume or number of bouts of sedentary time beyond which concussion recovery is compromised. Alternate accelerometer-based physical activity metrics, including indices of movement variability, can also provide more insight into how activity patterns differ in children with concussion in comparison to their healthy peers. Cohort studies and longitudinal research examining how acute clinical features of the injury associate with subsequent physical activity are needed for identifying children at high risk of sedentariness post-concussion.

CONCLUSIONS

This is the first study to profile accelerometer-measured physical activity and sedentariness following pediatric concussion, finding that in the first-month of injury children with concussion are more sedentary (MD, 38.3 minutes/day) and less active (across all intensities studied) than their healthy peers. We also report that as time post-injury increases, levels of MPA and VPA increase in children with concussion, which may be consistent with natural recovery. Future exercise-concussion research should examine the impact of interventions that reduce sedentary time, and in general engage key stakeholders (including primary care providers) to improve knowledge translation and the adoption of exercise in clinical practice.

STATEMENTS

Competing interests: The authors have no competing interests to declare.

Contributorship: BW Timmons, MD Noseworthy, and C DeMatteo were involved in conceptualizing, planning, and securing funding for the parent study. C DeMatteo maintained study oversight over the parent study. J Obeid provided oversight over accelerometer data collection and analyses. B Sharma defined the research question for this secondary data analysis, cleaned and analyzed all accelerometer data, and prepared the first draft of the manuscript.

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Ethical approval information: The study was approved by the Hamilton Integrated Research Ethics Board (www.hireb.ca) # 14-376.

Data sharing agreement: Data are available upon request.

Patient involvement: Given that this study is a secondary data analysis, patient and public involvement was not part of this analysis. For the parent study, however, patients and the public: were involved with research at the time of recruitment; did not inform the research question or outcome measures; were not involved in study design; were actively recruited as community-based research participants; were informed of the time requirements of the study; and were active in the knowledge translation plan.

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TABLES

Table 1. Demographic and wear time data for the study.

	Concussion (n=60)	Control (n=60)	p-value
Age Years	12.74 ± 2.85	12.43 ± 2.71	0.542
Sex M:F	29:31	29:31	-
Wear time Overall, days	15.84 ± 5.79	7.28 ± 1.39	<0.001
Wear time/day Minutes/day	794.93 ± 59.37	797.90 ± 53.67	0.775
Weekday:Weekend Ratio	2.95 : 1.00	2.82 : 1.00	0.759
Days dropped n (%)	121 (12.5%)	54 (12.3%)	0.962
Hours dropped n (%)	1190 (14.5%)	909 (15.2%)	0.317

Statistical comparisons between cohorts were made using independent samples t-tests as data were normally distributed.

Table 2. Group-wise sedentariness and activity levels.

		Concussion, mean ± SD (n=60)	**Control, mean ± SD** (n=60)	**Mean difference, 95% CI**	**t-stat** (118 df)	**p-value**
Minutes/day	Sedentary	618.8 ± 77.2	580.5 ± 72.7	38.3 (11.2, 65.4)	2.800	0.006*
	LPA	130.2 ± 42.9	149.7 ± 35.2	-19.5 (-5.3, -33.7)	-2.717	0.008*
	MPA	27.2 ± 10.6	37.0 ± 11.7	-9.8 (-5.7, -13.8)	-4.799	<0.001*
	VPA	18.7 ± 12.6	30.7 ± 15.7	-12.0 (-6.9, -17.2)	-4.362	<0.001*

*denotes significant findings at Bonferroni-corrected p-value of α/4 (0.0125).

Table 3. Sex-based differences in sedentariness and activity between groups.

		Children with Concussion			**Healthy Controls**		
		Boys (n=29)	Girls (n=31)	t-stat p-value	Boys (n=29)	Girls (n=31)	t-stat p-value
Minutes/day	Sedentary[a]	592.5 ± 60.2	643.3 ± 83.9	-2.677 0.010*	567.0 ± 68.2	592.2 ± 75.5	-1.347 0.183
	LPA[a]	143.1 ± 36.7	118.1 ± 45.3	2.335 0.012*	150.8 ± 25.8	148.7 ± 42.2	0.226 0.822
	MPA[a]	32.2 ± 9.7	23.5 ± 10.1	3.024 0.004*	38.5 ± 12.0	35.7 ± 11.5	0.920 0.361
	VPA[a]	22.3 ± 10.6	15.3 ± 13.5	2.367 0.011*	34.3 ± 16.3	27.6 ± 14.7	1.672 0.100

*denotes significant findings at Bonferroni-corrected p-value of α/4 (0.0125). [a] Significantly different from healthy girls ($p<0.0125$).

Table 4. Group-wise sedentary bout analysis.

		Concussion, mean ± SD (n=60)	**Control, mean ± SD** (n=60)	**Mean difference, 95% CI**	**t-stat** (118 df)	**p-value**
Sedentary bouts/hour	<1 minute	31.02 ± 11.9	37.17 ± 12.5	-6.15 (-1.7, -10.6)	-2.762	0.003*
	1- to 5-minutes	9.65 ± 1.8	9.76 ± 1.6	-0.11 (-0.50, 0.71)	-0.359	0.720
	5- to 10-minutes	1.24 ± 0.3	1.12 ± 0.3	0.13 (0.01, 0.24)	2.492	0.007*
	10- to 20-minutes	0.45 ± 0.2	0.38 ± 0.2	0.07 (-0.01, 0.15)	1.910	0.059
	20- to 30-minutes	0.08 ± 0.06	0.06 ± 0.06	0.02 (-0.01, 0.03)	1.326	0.187
	30- to 60-minutes	0.04 ± 0.04	0.03 ± 0.04	0.01 (-0.01, 0.03)	1.598	0.113
Breaks between bouts	<1 minute	40.8 ± 12.2	46.2 ± 12.2	-5.4 (-0.9, -9.8)	2.420	0.017
	1- to 5-minutes	1.6 ± 0.7	2.1 ± 0.9	-0.6 (-0.3, -0.9)	3.959	0.000*
	5- to 10-minutes	0.05 ± 0.05	0.09 ± 0.07	-0.04 (-0.02, -0.06)	3.476	0.001*
	10- to 20-minutes	0.01 ± 0.01	0.03 ± 0.03	-0.02 (-0.00, -0.02)	3.246	0.002*
	20- to 30-minutes	0.01 ± 0.01	0.01 ± 0.01	0.00 (0.00, 0.01)	0.07	0.946
	30- to 60-minutes	0.01 ± 0.01	0.01 ± 0.01	0.00 (0.00, 0.01)	1.357	0.177

*denotes significant findings at Bonferroni-corrected p-value of α/6 (0.008).

Table 5. Sedentary bout analysis, by sex and group.

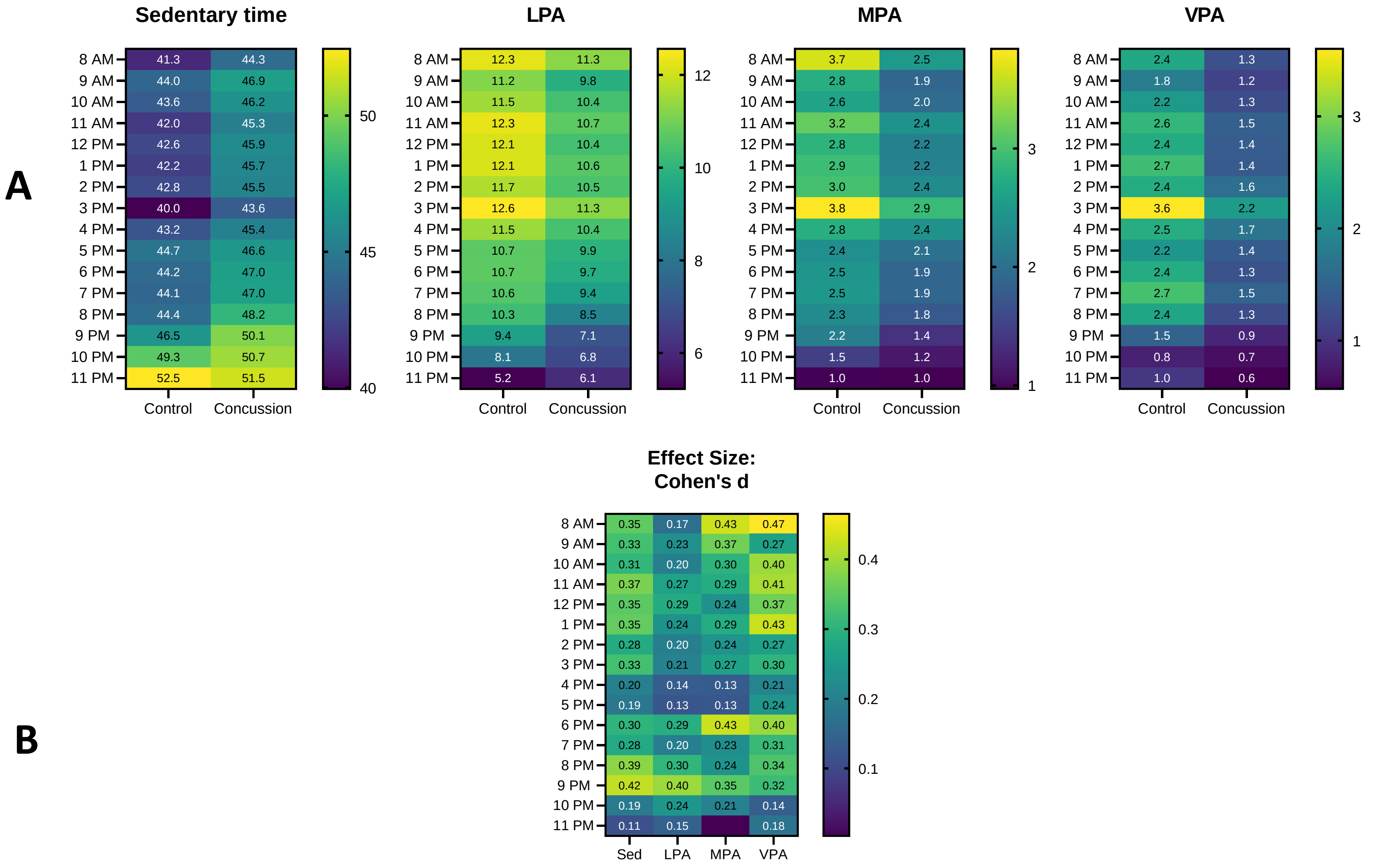
		Children with Concussion			**Healthy Controls**		
		Boys (n=29)	Girls (n=31)	t-stat p-value	Boys (n=29)	Girls (n=31)	t-stat p-value
Sedentary bouts/hour	<1 minute[a]	33.84 ± 10.0	28.38 ± 13.0	1.815 0.075	35.42 ± 11.3	38.69 ± 13.5	-1.012 0.316
	1- to 5-minutes	10.37 ± 1.5	8.98 ± 1.9	3.210 0.002*	9.66 ± 1.9	9.85 ± 1.2	-0.483 0.631
	5- to 10-minutes	1.23 ± 0.3	1.26 ± 0.3	-0.384 0.702	1.14 ± 0.3	1.10 0.4	0.550 0.585
	10- to 20-minutes	0.41 ± 0.2	0.49 ± 0.2	-1.460 0.150	0.39 ± 0.2	0.37 ± 0.2	0.479 0.634
	20- to 30-minutes	0.06 ± 0.05	0.09 ± 0.06	-2.240 0.029	0.07 ± 0.06	0.06 ± 0.05	0.708 0.489
	30- to 60-minutes	0.03 ± 0.04	0.05 ± 0.04	-2.023 0.048	0.03 ± 0.01	0.02 ± 0.01	0.327 0.745

*denotes significant findings at Bonferroni-corrected p-value of α/6 (0.008). [a] Significantly different (p<0.008) from healthy girls.

FIGURE LEGENDS

Figure 1. *Panel A.* Hour-by-hour sedentariness and activity (from 8:00 AM to 12:00 AM) in children with concussion in comparison to healthy controls. The numbers within the cells represent the average number of minutes of sedentariness or activity per hour (all differences significant *except* the hours of 10PM and 11PM). The bars represent minutes/hour. *Panel B.* The effect sizes (*Cohen's d*) associated with the comparisons presented in Figure 1. Lighter cell colours represent larger effect sizes. (LPA = light physical activity; MPA = moderate physical activity; VPA = vigorous physical activity; ns = non-significant).

FIGURES - Figure 1



Sedentary time

	Control	Concussion
8 AM	41.3	44.3
9 AM	44.0	46.9
10 AM	43.6	46.2
11 AM	42.0	45.3
12 PM	42.6	45.9
1 PM	42.2	45.7
2 PM	42.8	45.5
3 PM	40.0	43.6
4 PM	43.2	45.4
5 PM	44.7	46.6
6 PM	44.2	47.0
7 PM	44.1	47.0
8 PM	44.4	48.2
9 PM	46.5	50.1
10 PM	49.3	50.7
11 PM	52.5	51.5

LPA

	Control	Concussion
8 AM	12.3	11.3
9 AM	11.2	9.8
10 AM	11.5	10.4
11 AM	12.3	10.7
12 PM	12.1	10.4
1 PM	12.1	10.6
2 PM	11.7	10.5
3 PM	12.6	11.3
4 PM	11.5	10.4
5 PM	10.7	9.9
6 PM	10.7	9.7
7 PM	10.6	9.4
8 PM	10.3	8.5
9 PM	9.4	7.1
10 PM	8.1	6.8
11 PM	5.2	6.1

MPA

	Control	Concussion
8 AM	3.7	2.5
9 AM	2.8	1.9
10 AM	2.6	2.0
11 AM	3.2	2.4
12 PM	2.8	2.2
1 PM	2.9	2.2
2 PM	3.0	2.4
3 PM	3.8	2.9
4 PM	2.8	2.4
5 PM	2.4	2.1
6 PM	2.5	1.9
7 PM	2.5	1.9
8 PM	2.3	1.8
9 PM	2.2	1.4
10 PM	1.5	1.2
11 PM	1.0	1.0

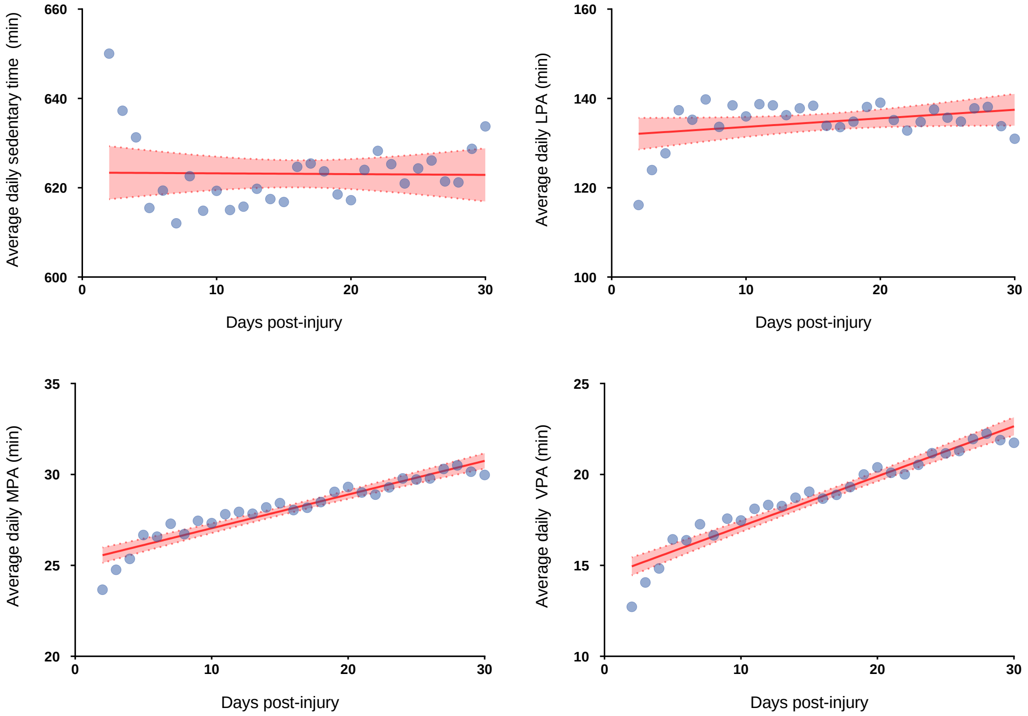
VPA

	Control	Concussion
8 AM	2.4	1.3
9 AM	1.8	1.2
10 AM	2.2	1.3
11 AM	2.6	1.5
12 PM	2.4	1.4
1 PM	2.7	1.4
2 PM	2.4	1.6
3 PM	3.6	2.2
4 PM	2.5	1.7
5 PM	2.2	1.4
6 PM	2.4	1.3
7 PM	2.7	1.5
8 PM	2.4	1.3
9 PM	1.5	0.9
10 PM	0.8	0.7
11 PM	1.0	0.6

Effect Size: Cohen's d

	Sed	LPA	MPA	VPA
8 AM	0.35	0.17	0.43	0.47
9 AM	0.33	0.23	0.37	0.27
10 AM	0.31	0.20	0.30	0.40
11 AM	0.37	0.27	0.29	0.41
12 PM	0.35	0.29	0.24	0.37
1 PM	0.35	0.24	0.29	0.43
2 PM	0.28	0.20	0.24	0.27
3 PM	0.33	0.21	0.27	0.30
4 PM	0.20	0.14	0.13	0.21
5 PM	0.19	0.13	0.13	0.24
6 PM	0.30	0.29	0.43	0.40
7 PM	0.28	0.20	0.23	0.31
8 PM	0.39	0.30	0.24	0.34
9 PM	0.42	0.40	0.35	0.32
10 PM	0.19	0.24	0.21	0.14
11 PM	0.11	0.15		0.18

SUPPLEMENT



Supplement 1. Predicted % activity levels plotted as a function of days post-injury. Only models specific to MPA and VPA were significant (LPA = light physical activity; MPA = moderate physical activity; VPA = vigorous physical activity).

CHAPTER 5

Exploring the relationship between resting state intra-network connectivity and accelerometer-measured physical activity in pediatric concussion: A cohort study

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ABSTRACT

Objectives: To explore the association between resting state functional connectivity and accelerometer-measured physical activity in pediatric concussion.

Methods: Fourteen children with concussion (aged 14.54 ± 2.39 years, 8 female) were included in this secondary data-analysis. Participants had neuroimaging at 15.3 ± 6.7 days post-injury and subsequently a mean of 11.1 ± 5.0 days of accelerometer data. Intra-network connectivity of the default mode network (DMN), sensorimotor network (SMN), salience network (SN), and fronto-parietal network (FPN) was computed.

Results: Per general linear models, only intra-network connectivity of the DMN was associated with habitual physical activity levels. More specifically, increased intra-network connectivity of the DMN was significantly associated with higher levels of subsequent accelerometer-measured light physical activity ($F_{(2, 11)} = 7.053$, $p = 0.011$, $R_a^2 = 0.562$; $\beta = 0.469$), moderate physical activity ($F_{(2, 11)} = 6.159$, $p = 0.016$, $R_a^2 = 0.528$; $\beta = 0.725$), and vigorous physical activity ($F_{(2, 11)} = 10.855$, $p = 0.002$, $R_a^2 = 0.664$; $\beta = 0.792$). Intra-network connectivity of the DMN did not significantly predict sedentary time. Likewise, the SMN, SA, and FPN were not significantly associated with either sedentary time or physical activity.

Conclusion: These findings suggest that there is a positive association between the intra-network connectivity of the DMN and device-measured physical activity

in children with concussion. Given that DMN impairment can be commonplace following concussion, this may be associated with lower levels of habitual physical activity, which can preclude children from experiencing the symptom-improving benefits of sub-maximal physical activity.

INTRODUCTION

Concussions are mild traumatic brain injuries that result in functional neurological disturbance in the absence of gross structural damage (McCrory et al., 2017). While on the mild end of the brain injury spectrum, concussions can nonetheless result in enduring symptoms that negatively impact multiple aspects of daily living (Voormolen et al., 2019). In children, a population in which rates of concussion are increasing rapidly (Fridman et al., 2018; Meehan III et al., 2010; Veliz et al., 2021), nearly 30% experience symptoms that persist beyond the expected recovery window of four weeks (Barlow, 2016; Barlow et al., 2010; McCrory et al., 2017). These symptoms can lead to quality-of-life deficits that can last for months (Fineblit et al., 2016; Novak et al., 2016; Plourde et al., 2018; Russell et al., 2017).

A growing body of research has used resting-state functional magnetic resonance imaging (rs-fMRI). In this study, rs-fMRI was used to provide insight into areas of the brain that are synchronously active at rest in the absence of any particular cognitive stimuli) to explore the functional neuropathology of concussion. While the brain regions and/or networks studied, time of imaging, and rs-fMRI analysis methods themselves have varied across studies, studies consistently show that there are rs-fMRI disturbances in children with concussion in comparison to their healthy peers (Abbas et al., 2015; Borich et al., 2015; Dona et al., 2017; Iyer et al., 2019a; Iyer et al., 2019b; Kaushal et al., 2019; Manning et al., 2017; Meier et al., 2020; Murdaugh et al., 2018; Newsome et al., 2016;

Plourde et al., 2020; Stephenson et al., 2020). Collectively, these studies have shown patterns of both hyper- and hypo-connectivity within the initial weeks of injury (Rausa et al., 2020), abnormal rs-fMRI activity in children with protracted symptoms (Iyer et al., 2019a), and a persistence of functional impairment in asymptomatic children who have been medically cleared to return-to-sport (Newsome et al., 2016).

With rs-fMRI disturbances in pediatric concussion now better characterized, studies have aimed at understanding the relationship between functional connectivity and other relevant and widely studied clinical outcomes including symptoms, sleep, cognition, mood (Gornall et al., 2021; Iyer et al., 2019a; Iyer et al., 2019b; Kaushal et al., 2019). However, the associations between resting state brain activity and other salient features of pediatric concussion are still understudied. In particular, the impact of rs-fMRI activity on habitual physical activity in pediatric concussion remains unexplored. Within the current landscape of concussion research and clinical management, wherein the importance of exercise has been increasingly recognized and established in recent years (Carter et al., 2021; Langevin et al., 2020), this represents a considerable knowledge gap. There is now a shift away from prolonged rest (Grool et al., 2016; Thomas et al., 2015), which was the former *status quo* in concussion management (Leddy et al., 2018). Conversely, sub-maximal aerobic exercise studies in concussion–and meta-analyses of them–suggest that engaging in physical activity within two-weeks of injury improves symptoms

(Carter et al., 2021; Lal et al., 2017; Langevin et al., 2020). Therefore, there is now considerable evidence that exercise, and conversely prolonged rest, have an impact on concussion recovery. What is not known is how the widely established rs-fMRI disturbances observed in pediatric concussion relate to sedentary time or physical activity levels post-injury.

With the recent wave of research on exercise in pediatric concussion, understanding the relationship between functional brain impairment and physical activity has become as germane as understanding the relationship between rs-fMRI and symptomatology or other clinical features. Therefore, in this study, we examined the relationship between intra-network rs-fMRI activity (within four widely researched and validated resting state networks) and accelerometer-measured habitual physical activity and sedentary time up to one-month post-injury in children with concussion. It was hypothesized that reduced intra-network rs-fMRI activity (a measure of functional neuropathology) is associated with increased sedentary time and reduced physical activity levels.

METHODS

The Hamilton Integrated Research Ethics Board approved this study.

Design

The data reported here were initially collected as part of the *Back-to-Play* study, a larger cohort study (led by the senior authors) with the goal of informing return-to-activity guidelines for children with concussion. This report is a secondary data analysis of accelerometer and rs-fMRI data collected as part of the larger cohort. The present sample is comprised only of participants from the parent study with both neuroimaging data and subsequently collected accelerometer data (up to 1-month post-injury).

Participants

Participants in the parent study were recruited at McMaster Children's Hospital and/or its affiliated rehabilitation and sports medicine clinics. Patients who were diagnosed with concussion by a member of our clinical team were informed about the *Back to Play* study. Those interested in participating were referred to our research team for more information about its objectives, risks, and potential benefits. After this initial discussion, those intent on participating were consented (or assented, along with parental consent, if aged under 16 years) recruited. An intake assessment was then scheduled by the research team as soon after the initial clinical consultation as possible. Exclusion criteria for the larger study included more severe injuries or those requiring more complex care.

For the present study, patients were required to have neuroimaging and then subsequently at least 5 days of valid accelerometer wear.

Data collection procedures

Neuroimaging

All neuroimaging data were collected using a 3-Tesla GE Discovery 750 MRI scanner (with a 32-channel phased array receive coil) at the Imaging Research Centre (IRC) at St. Joseph's Healthcare, Hamilton. A screening questionnaire was performed by the IRC imaging technologist to ensure that the scan could be performed safely, and to inform patients and their families about the MRI procedure. The technologist then positioned the patient in the MRI, immobilizing their head with foam pads to minimize motion and to improve patient comfort.

The neuroimaging battery began with a 3-plane localizer with calibration sequences. Anatomical images were then collected, per a 3D IR-prepped fast SPGR T1-weighted sequence (TR/TE=11/36/4.25ms, flip angle=12°, interpolated 512x512 matrix, 22 cm FOV). Immediately prior to the resting state scan, a fieldmap was acquired (to correct for magnetic field inhomogeneities) using the same geometry as the functional scan (as follows). Resting state functional data were collected using axial 2D acquisition, gradient echo EPI, TR/TE=2000/35ms, flip angle=90°, 64x64 matrix, 300 time points (10min), 22 cm FOV). During the resting state scan, patients were asked to remain awake with their eyes open, and not think of “anything in particular”.

Accelerometry

Patients were given a compact and light-weight waist-worn tri-axial accelerometer at their intake assessment to wear until self-reported symptom resolution, at which point the accelerometer was mailed back to the study team and acceleration data were downloaded. The accelerometer used in the *Back-to-Play* study was the ActiGraph GT3x (Pensacola, FL), which has demonstrated high reproducibility in measuring physical activity in acquired brain injury (Baque et al., 2016). Per the parent study, movement was recorded continuously at 30-Hz and downloaded into 3-second epochs. Patients were also given a logbook, in which they noted when the device was put on and off in the morning and evening, respectively, as well as any other times the device was removed (when participating in water-based activities, for example). Patients were instructed by the research team at the intake assessment to wear the accelerometer on the right hip during all waking hours, except for water activities, and how to use the logbook.

Data processing and analyses

Neuroimaging

All MRI pre-processing and analyses were performed in CONN 19c (Whitfield-Gabrieli et al., 2012), which was run using SPM12 and MATLAB 2020a

(Mathworks, Natick, MA). The only exception in the pre-processing pipeline was that functional data were unwarped using the B_0 maps acquired immediately prior to the rs-fMRI scan outside of CONN 19c using *epiunwarp* (Davis et al., 2016), which draws on functionality in FSL (Jenkinson et al., 2012; Smith et al., 2004). The B_0-corrected maps were then uploaded into CONN 19c along with respective anatomical data for pre-processing.

The following steps were involved with pre-processing, and were guided by recommendations within CONN 19c and associated publications (Andersson et al., 2001; Henson et al., 1999). First, functional data were realigned and co-registered to a reference image (and adjusted to the movement-defined deformation field associated with the reference image). Second, slice-timing correction was performed to time-shift and resample the rs-fMRI data to coincide with the mid-point of each TR. Third, using SPM's Artifact Detection Tool (ART) (Ashburner et al., 2014), outlier scans in the functional data were flagged based on subject-motion exceeding a 0.9mm framewise displacement or BOLD signal fluctuations > 5 standard deviations from the mean signal. Fourth, functional data are normalized/registered to MNI space, based on posterior tissue probability maps. Fifth, spatial smoothing was performed, with a Gaussian kernel of full-width at half-maximum of 6mm. Subsequently, de-noising was performed in CONN 19c which involved two steps: 1) an anatomical component-based noise correction procedure (**aCompCorr**) to "regress out" noise components associated with cerebral white matter/cerebrospinal regions, outlier scans, subject motion (based on a 12-parameter affine transformation of the anatomical to functional data) (Behzadi et al., 2007; Friston et al., 1996; Power et al., 2014), and 2) temporal filtering, using a filter ranging from 0.008Hz and above 0.01Hz. After both pre-processing and de-noising, data were inspected visually and per the quality assurance metrics in CONN 19c.

Once data were ready for analysis, intra-network connectivity of four widely studied and validated brain networks was computed (Fornito et al., 2016; Power, 2020), namely the default mode network (DMN), sensorimotor network (SMN), salience network (SN) and fronto-parietal network (FPN) and habitual physical activity in children with concussion. Intra-network connectivity was selected as the measure of choice for this preliminary investigation as it is representative of a resting state network holistically, as has been shown in publications related to other neurological populations (Houck et al., 2017; Ke et al., 2018; Lang et al., 2020; Zhu et al., 2016).

Average within-network connectivity were computed using the Matlab command line script ***conn_withinbetweenROItest***, which extracted and exported single-subject intra-network correlation values which were Fisher Z-transformed to improve normality. Seed regions are listed in **Table 1**.

[insert Table 1 here]

Accelerometry

Data were downloaded from the ActiGraph GT3x devices using the accompanying software package, ActiLife Version 6 (Pensicola, FL). Triaxial accelerations collected at 30-Hz were downloaded into 3-sec sampling intervals or epochs, which were selected to reflect the median bout duration for high-intensity activities in children (Baquet et al., 2007). Once downloaded and converted into a 3-second epoch, wear-time validation was performed in ActiLife. First, a semi-automated procedure was performed to define a non-wear period of minimum length of 5-minutes. These periods were then inspected against the on- and off-times recorded in the patient logbooks, with non-wear periods excluded if they matched records from the patient log books. Days of accelerometer data without an associated log book entry were excluded. Data were then scored to determine activity intensity according to widely used Evenson cut-points (Evenson et al., 2008) which have the following activity count ranges: sedentary time (0-25 counts/15s), light physical activity (LPA; 26-573 counts/15s), moderate physical activity (MPA; 574-1002 counts/15s), and vigorous physical activity (VPA; 1003+ counts/15s).

Cleaned and scored data were then exported to SPSS Version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY). Only children with more than 4-wear days of data, with each day comprised of more than 600 minutes of wear time, were included in the analysis (Rich et al., 2013). Any accelerometer data beyond 30-days post-injury were excluded from the current analysis, given that the scope of the study.

Statistical analyses

Average daily sedentary time, as well as average daily LPA, MPA, and VPA were calculated for cleaned and validated accelerometer cases in SPSS. These summary data were then imported into CONN 19c, wherein the *Calculator* tool was used to build a general linear model (GLM) with intra-network connectivity and age as predictors of average daily activity (of the various intensities) or sedentary time. Therefore, for each network of interest, four models were built to examine the association between intra-network rs-fMRI connectivity and average time per day in: LPA, MPA, VPA, and sedentary. Given the sample size of our study, additional variables were not included in the model; age was selectively chosen given that connectivity of resting state networks has been shown to vary with age (Mak et al., 2017).

RESULTS

Overview

Fourteen children with concussion (aged 14.54 ± 2.39 years, 8 female) were imaged at 15.3 ± 6.7 days post-injury and had an average of 11.1 ± 5.0 days of accelerometer data (with ≥ 600 minutes of wear-time per day) thereafter. Average daily monitoring time, sedentary time, and time spent in activity is summarized in **Table 2**.

[insert Table 2 here]

The groupwise average intra-network connectivity values for each of the networks studied are presented in **Table 3** with associated standard deviations and ranges.

[insert Table 3 here]

Relating brain activity and physical activity

From the series of GLMs, the only significant models (and the only network-related beta-coefficients that were significant) pertained to models including the DMN. The intra-network connectivity of the SMN, SA, and FPN did not predict accelerometer-measured sedentary time, LPA, MPA, or VPA. **Figure 1** shows the model-predicted activity levels (along with 95% confidence intervals) by activity type against intra-network connectivity. The figures show that with respect to the DMN, increased intra-network connectivity is closely associated with increased levels of activity, in particular MPA and VPA. Intra-network connectivity of the DMN was not, however, associated with average daily sedentary time.

[insert Figure 1 here]

The DMN-specific models and their relevant parameters for all intensities of activity are summarized in **Table 4**. Both unstandardized beta coefficients (B) and standardized beta coefficients (β) are provided for interpretation. Overall, there was a trend for decreased DMN intra-network connectivity predicting more sedentary time, and conversely, increased intra-network connectivity of the DMN was significantly associated with increased LPA, MPA, and VPA. For significant models, the residuals were normally distributed.

DISCUSSION

This is the first study to examine the relationship between rs-fMRI impairment and subsequent activity levels in pediatric–or adult–concussion. We demonstrate that intra-network connectivity within the DMN–but not the SMN, SA, or FPN–is associated with accelerometer-measured LPA, MPA, and VPA within the first month of injury in pediatric concussion. Adding to the literature demonstrating associations between DMN impairment and concussion symptoms, depression, anxiety, and sleep-impairment (Iyer et al., 2019a; Iyer et al., 2019b), we show that intra-network connectivity within DMN may be implicated with habitual physical activity within the first month of injury in children.

The DMN and physical activity

Originally, the DMN was considered to be a “day dreaming network”, active in the absence of external stimuli as a type of neural baseline (Buckner et al., 2008). However, more recent research on the DMN has shown that it is also associated with higher-order cognitive processes and can be active during goal-oriented thoughts and tasks. More specifically, studies now show that the DMN can be engaged when individuals imagine or plan for the future (Konishi et al., 2015). Other studies suggest that the DMN is important in cognitive processes that result in immediate action or interfere with present behavioural goals (Smallwood et al., 2013). In adults, the DMN has also been linked to “internal mentation”, or introspective thoughts about constructs such as the future or personal intentions (Andrews-Hanna, 2012; Stawarczyk et al., 2019). Together, these findings would suggest that DMN impairments may have the capacity to influence planned behaviours, such as participation in physical activity, and that DMN impairments can alter how information about physical activity behaviours are perceived, processed, and planned. This would help explain our findings, wherein only the DMN was found to be associated with subsequent levels of physical activity. Further research is needed to build on this possibility.

Prior research shows that in young adults with concussion, in comparison to healthy controls, a sub-maximal aerobic fitness test resulted in functional disturbance of the DMN (Slobounov et al., 2011; Zhang et al., 2012). More specifically, said test reduced inter-network connectivity between seed regions of the DMN, namely the PCC and the lateral parietal ROI, PCC and the right lateral parietal ROI, and the PCC and MPFC (Zhang et al., 2012). Adding to this, our study suggests a bi-directional relationship, wherein intra-network impairment of the DMN may have an impact subsequent physical activity in children with concussion. Given that many studies have demonstrated DMN impairment in pediatric concussion (Dona et al., 2017; Iyer et al., 2019a; Iyer et al., 2019b; Kaushal et al., 2019; Manning et al., 2017; Meier et al., 2020; Newsome et al., 2016; Plourde et al., 2020), and our recent work demonstrates that children with concussion are less active than their healthy peers, the current findings suggest that widespread DMN impairment is associated with reduced levels of activity in children with concussion. Larger pediatric concussion cohorts are required to more definitively characterize the relationship between resting state brain activity and physical activity.

Exercise and concussion management

The status quo in concussion management is changing. The traditional “rest-is-best” approach is being supplanted by an “exercise is medicine” mindset (Leddy et al., 2018). However, the present study suggests that in pediatric concussion, DMN impairment (which is a common in concussion) has a moderate association with physical activity. This underscores the need for physicians to actively advise pediatric concussion patients to engage in safe, sub-maximal aerobic exercise after a short (24-48 hour) period of rest, as suggested by current guidelines (McCrory et al., 2017). Otherwise, patients with DMN impairment may not be physically active, and this precludes them from experiencing the benefits of light physical activity on concussion symptoms. Further, in the ultimate interest of promoting physical activity, interventions such mindfulness can be prescribed acutely given their positive impact on the functional connectivity of the DMN (Bauer et al., 2020; Berkovich-Ohana et al., 2012; Brewer et al., 2011; Doll et al., 2015; Wang et al., 2014). Mindfulness is not a contraindication to any other medications that may be prescribed after concussion, and it has other established benefits in brain injury, including improved self-efficacy (Azulay et al., 2013; Paniccia et al., 2019). Future research is needed in this area.

Generalizability

Our findings need to be studied in adults to understand if they generalize outside of a pediatric context, as several factors may make our findings pediatric-specific. For example, DMN functional connectivity is age-dependent, peaking in adulthood while being less coherent during childhood and senescence (Mak et al., 2017); physical activity also decreases with age (Guthold et al., 2018) This would suggest that the association between intra-network functional connectivity of the DMN and physical activity may be variable in children when compared to adults.. Further, cardiorespiratory fitness is also related to the functional integrity of multiple brain networks, including the DMN (Voss et al., 2016). While the present study did not control for cardiorespiratory fitness (though all participants had sport-related injuries and were physically active prior to injury), similar studies in adults should control for this metric given that it declines non-linearly and in an age-dependent rate in adults (Jackson et al., 2009), which may be confounding in adult samples with large age variance.

LIMITATIONS

This secondary data analysis is limited by the sample size. Larger studies examining the relationship between the DMN and post-concussion physical activity are warranted. We also cannot rule out the possibility that greater DMN impairment is associated with more severe symptoms that may, in turn, reduce participation in physical activity. This study design does not permit inference on causality. Further, this study did not exhaustively study all resting state networks and/or anatomical regions; future research should expand on the regions of interest. There are also other rs-fMRI and accelerometer analysis methods that can be used to characterize the relationship between brain activity and physical activity. The impact of physical activity on resting state networks in pediatric concussion also warrants study.

CONCLUSIONS

This exploratory study is the first to examine the association between intra-network connectivity and accelerometer-measured physical activity in pediatric concussion. We found that intra-network connectivity of the DMN–but not the SMN, SA, or FPN–was significantly associated with levels of LPA, MPA, and VPA performed within the first month after pediatric concussion. Given the increasing role of aerobic exercise in concussion management, and that the DMN is commonly perturbed following injury, children with concussion may be less likely to be physically active. Clinical management should continue to encourage participation in sub-maximal aerobic activity in the acute stages of injury.

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TABLES

Table 1: Seed regions used to calculate the intra-network connectivity of the four resting state networks of interest.

Network	Seeds MNI co-ordinates (x, y, z)
DMN	Medial pre-frontal cortex (1, 55, -3)
	Lateral parietal, left (-39, -77, 33)
	Lateral parietal, right (47, -67, 29)
	Posterior cingulate cortex (1, -61, 38)
SMN	Lateral seed, left (-55, -12, 29)
	Lateral seed, right (56, -10, 29)
	Superior seed (0, -31, 67)
SN	Anterior cingulate cortex (0, 22, 35)
	Anterior insula, left (-44, 13, 1)
	Anterior insula, right (47, 14, 0)
	Rostral pre-frontal cortex, left (-32, 45, 27)
	Rostral pre-frontal cortex, right (32, 46, 27)
	Supramarginal gyrus, left (-60, -39, 31)
	Supramarginal gyrus, right (62, -35, 32)
FPN	Lateral pre-frontal cortex, left (-43, 33, 28)
	Lateral pre-frontal cortex, right (41, 38, 30)
	Posterior cingulate cortex, left (-46, -58, 49)

	Posterior cingulate cortex, right (52, -52, 45)

Table 2: Average daily (in minutes/day) monitoring time and activity by intensity in our cohort. (LPA = light physical activity, MPA = moderate physical activity, VPA = vigorous physical activity).

	Mean	SD	Range
Monitoring time	798.3	68.0	686.8-914.5
Sedentary	631.0	75.9	504.2-733.2
LPA	116.1	33.9	68.9-172.2
MPA	28.6	11.3	13.4-48.6
VPA	22.7	16.9	3.3-57.8

Table 3: Average intra-network connectivity across the four networks of study (as Fisher Z-transformed correlation coefficients). (DMN = default mode network, SMN = sensorimotor network, SN = salience network, and FPN = fronto-parietal network).

	Mean	**SD**	**Range**
DMN	0.50	0.15	0.21-0.89
SMN	0.60	0.21	0.18-1.06
SA	0.48	0.11	0.23-0.70
FPC	0.58	0.16	0.34-0.81

Table 4: General linear model parameters for DMN-specific analyses. B=unstandardized beta coefficient; β=standardized beta coefficient. (LPA = light physical activity, MPA = moderate physical activity, VPA = vigorous physical activity).

Sedentary time					
Predictor	**B**	**95% CI for B**	**β**	**t**	**p**
DMN	-71.633	-311.907, 168.640	-0.146	-0.656	0.525
Age	20.998	5.601, 36.395	0.667	3.002	0.012
Model	$F_{(2, 11)} = 3.653$, $p = 0.061$, $R_a^2 = 0.458$				
LPA					
Predictor	**B**	**95% CI for B**	**β**	**t**	**p**
DMN	102.900	86.319, 289.261	0.469	2.346	0.039
Age	-8.486	-14.671, -2.301	-0.603	-3.020	0.012
Model	$F_{(2, 11)} = 7.053$, $p = 0.011$, $R_a^2 = 0.562$				
MPA					
Predictor	**B**	**95% CI for B**	**β**	**t**	**p**
DMN	52.908	19.627, 86.189	0.725	3.499	0.005
Age	-0.394	-2.527, 1.739	-0.084	-0.407	0.692
Model	$F_{(2, 11)} = 6.159$, $p = 0.016$, $R_a^2 = 0.528$				
VPA					
Predictor	**B**	**95% CI for B**	**β**	**t**	**p**
DMN	88.755	44.565, 128.945	0.792	4.526	0.001
Age	1.148	-1.555, 3.852	0.164	0.935	0.370
Model	$F_{(2, 11)} = 10.855$, $p = 0.002$, $R_a^2 = 0.664$				

FIGURES

Figure 1

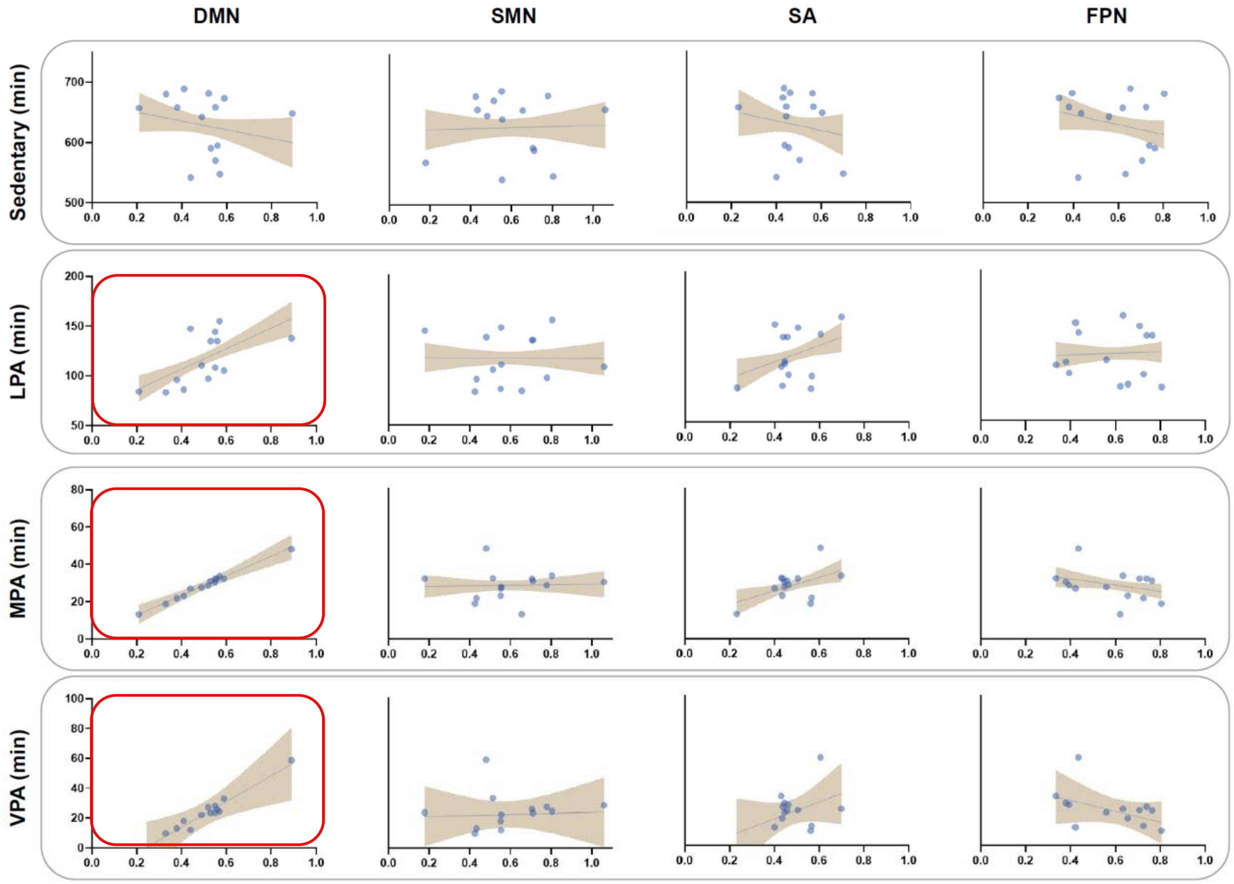

Figure 1: Model-predicted activity levels (in minutes/day) plotted against intra-network connectivity (Fisher Z-transformed correlation coefficients) and a linear fitted line. Only the models highlighted with a red box were significant. (LPA = light physical activity, MPA = moderate physical activity, VPA = vigorous physical activity).

CHAPTER 6

General discussion

Discussion overview

Exercise-concussion research has abounded in recent years, with its primary focus to date on understanding how sub-maximal aerobic activity can aid in the management of concussion symptoms. The field however remains at the headwaters, with data on the effects of exercise on concussion symptoms rapidly accumulating and gaining momentum in changing clinical practice. This thesis took aim at studying questions further downstream, or those that need to be asked once the initial and primary question of whether exercise can improve symptoms has been addressed.

More specifically, a goal of this thesis was to take the promise of exercise (as demonstrated in studies examining its effects on symptom burden) and begin to expand our understanding of its effects on non-symptom outcomes. In addition to this, studies were performed to further our knowledge of *physical activity*–not only exercise–in pediatric concussion. It is important to distinguish here that physical activity refers to any bodily movement that results in energy expenditure, while exercise is planned, structured, and intentioned physical activity (Caspersen et al., 1985). The field to date has focused on the effects of exercise while physical activity in pediatric concussion has been generally overlooked.

The existing body of exercise intervention research that is focused on symptoms is coined here as the *first wave* of exercise-concussion research. But because concussion is a multi-faceted injury with a complex neuropathology, the *second wave* of research in this field needs to be of a broader scope. For exercise to become standard clinical practice, we need to understand its impact on the neuropathology of concussion and other important clinical outcomes. We also need to understand more about habitual physical activity in concussion and use this data to inform and optimize exercise and/or physical activity interventions. Altogether, this can lead to personalized exercise and/or physical activity prescription that not only benefits symptoms, but also the neuropathology of concussion and other co-morbidities associated with the injury.

To this end, we systematically reviewed the literature to determine, per data from randomized studies, what the effects of exercise are on neuroimaging and cognitive outcomes in brain injury (see Chapter 2). We found that the number of randomized studies on the effects of exercise on the neuropathology of concussion were limited (n=6). With the knowledge that data on sex differences in the functional neuropathology of pediatric concussion are also limited, we performed a secondary data analysis (Chapter 3) of rs-fMRI data to build towards an understanding of the extent of functional impairment in boys and girls with concussion that stands to be improved by exercise. Further, while the *first wave* of exercise-concussion research focused on the effects of a single bout of daily exercise, what has been overlooked is the impact of concussion on levels of habitual physical activity and sedentary time. Chapter 4 used accelerometry to profile habitual activity and inactivity in children with concussion in comparison to healthy controls to build a foundational understanding of physical activity–and not just exercise–in pediatric concussion. Finally, we explored the association between physical activity and brain activity in pediatric concussion (Chapter 5) to determine if brain injury in children impacts a critical aspect of daily living, namely participation in habitual physical activity.

The studies included in this thesis are summarized below, chapter-by-chapter, followed by a more detailed discussion of their respective findings within the context of the current literature. Future directions for exercise and/or physical activity research in concussion are also discussed, with more general next steps outlined at the conclusion of this Chapter.

Expanding outcomes in exercise and physical activity concussion research

Chapter 2 was a systematic review of randomized trials on the effects exercise in pediatric and adult brain injury on outcomes other than symptoms, namely neuroimaging and cognition. Few eligible trials were identified (n=6), reinforcing that the focus of exercise-concussion research remains on symptoms. Nonetheless, the systematic review consolidated early evidence and concluded that the benefits of exercise interventions may extend to the structural (i.e., white matter) and functional neuropathologies of concussion. Data from randomized trials (n=3) on the effects of exercise on cognition following brain injury were mixed, with studies reporting both positive and null findings. As more exercise trials on non-symptom-related outcomes are performed as part of the *second wave* of research in the field, our understanding of the therapeutic potential of exercise will become more complete. The importance of studying outcomes beyond symptoms is underscored by a systematic review which reported that symptoms can resolve prior to other injury-related physiological and neurological impairments (Kamins et al., 2017).

Some outcomes that should be given additional consideration by future studies in the field are discussed below.

Neuroimaging

Functional neuroimaging

In addition to the findings from our systematic review discussed above, data from Chapter 3 of this thesis demonstrate that the functional neuropathology of concussion persists in girls–but not boys–at 1 month post-injury. These data suggest that exercise should take aim to not only improving concussion symptoms, but also the core neuropathology that may underlie them.

The question of whether exercise can improve functional brain activity impairments post-concussion becomes critically important when considering research that suggests that a single bout of aerobic exercise can exacerbate said impairment. In asymptomatic adults with concussion, an acute bout of aerobic exercise (akin to that currently being studied and prescribed) can lead to functional neurological disturbance. These data are reported in two studies from one group, and thus one cohort of 17 young adults with concussion and 1:1 age-and sex-matched controls. In these studies participants received rs-fMRI imaging at rest and then immediately after exercising to 70% of age-predicted HR maximum (per the YMCA bike stress test protocol); a third set of images were acquired while participants were recovering from aerobic activity. One study found that there were rs-fMRI differences between the concussed and healthy groups at rest that were exacerbated by exercise, including a further reduction in the inter-hemispheric connectivity of the hippocampi (Slobounov et al., 2011). The second study by this group showed that the YMCA stress test led to disruptions in the DMN in concussion patients that were not observed in controls. More specifically, there was reduced connectivity between the primary seed regions of the DMN, including the PCC and lateral parietal ROI (bilaterally) and PCC and MPFC (Zhang et al., 2012).

While Chapter 2 suggests that aerobic exercise may have beneficial effects on functional neurological disturbance in adults, the studies cited above suggest that exercise may acutely increase neurological vulnerability. Further research into this area is required given the lack of clarity on exercise effects on functional brain activity following concussion. Dedicated study into this topic is also required in pediatric populations, given the results of Chapter 3 showing pronounced rs-fMRI disturbance in girls with concussion at 1 month post-injury. With exercise becoming more commonly adopted as a management strategy in concussion, we need to disambiguate its effects on the functional neuropathology of the injury.

The response of the brain to exercise can also be assessed using non-MRI measures, such as near infrared spectroscopy (NIRS) and transcranial Doppler. Over MRI, these measures have the advantage of being less resource intensive and more easily administrable outside of a hospital setting or when exercising. In a cohort study of collegiate-aged male hockey players with concussion (n=7), NIRS measurements taken during exercise showed that there were no differences in pre-frontal cortex oxygenation during mild, moderate, and high-intensity exercise in comparison to 5 controls (Neary et al., 2020). Other studies employing NIRS have shown that there is reduced oxygenation of frontal cortices during balance tasks in symptomatic concussed athletes relative to asymptomatic athletes (Helmich et al., 2020). A transcranial Doppler study shows that following a mild brain injury in adolescents, there are multiple phases of cerebral hemodynamic recovery, suggesting that the brain may have different tolerances to exercise in a post-injury time-dependent manner (Thibeault et al., 2019). It is important to note, however, that NIRS and Doppler measurements were limited to the pre-frontal region, and do not assess whole brain neurophysiological response to exercise as can be done with rs-fMRI.

Our rs-fMRI data (Chapter 3) are driven by the BOLD response, which is related to changes in regional blood flow, but did not examine resting state brain activity response to exercise. Early and ongoing rs-fMRI research in our lab however does show that children with concussion (n=6) have a general pattern of reduced functional connectivity in comparison to matched healthy controls

(**Appendix B**). A primary goal of our ongoing research is to understand how the concussed pediatric brain responds to aerobic exercise to inform clinical decision-making. Our data also suggest that there are rs-fMRI differences between children <1 month post-injury and those who are more chronic (**Appendix C**). Future research should also examine the effects of exercise in acute and chronic pediatric concussion.

It will also be important to understand the functional brain response to different intensities of aerobic exercise. If more intensive activity triggers neurological vulnerability, then the findings from Chapter 4 of this thesis suggest that an alternate but related approach towards managing concussion may be encouraging more regular physical activity throughout the day. This may help efface the increased sedentary time observed in concussion by increasing activity and its associated benefits, while limiting the potentially neurologically provoking effects of more intensive bouts of activity.

White matter imaging

The findings from Chapter 2 also suggest that exercise may help increase white matter integrity following brain injury. In clinical research, white matter integrity is measured *in vivo* using DTI, which provides insight into whether movement of water is isotropic or anisotropic along white matter tracts. Injured white matter tracts are expected to have more isotopic, or non-linear, movement of water molecules, the extent of which can be quantified using DTI. In relation to the studies in this thesis, DTI data based on the same pool of participants that were studied in Chapter 3 suggest that concussion impairs white matter microstructure in children. These data, reported on in a separate publication (Stillo et al., 2021), in addition to the findings from our systematic review, suggest that white matter injury is a core neuropathological feature of concussion that stands to be improved by exercise or physical activity interventions. However, although our systematic review suggests that exercise may benefit white matter integrity in brain injury, data are still limited. We also do not understand whether exercise impacts white matter in a sex-specific manner.

In line with this, per the broader pediatric literature, sex-specific DTI data are limited. A systematic review identified 10 DTI studies in pediatric concussion, reporting that the injury consistently leads to microstructural damage of white matter (Chamard et al., 2018). However, in addition to overall sample size limitations, 4/10 studies included only males while the remaining 6/10 had <30% female representation, precluding sex-specific interpretation. Preliminary pooled pediatric DTI data from a recently developed concussion initiative (ENIGMA) found that fractional anisotropy is lower in younger brain injury patients as well as females (Dennis et al., 2018). These data are contradicted by those from a study where males were found to have more white matter damage post-injury (Wright et al., 2021), altogether highlighting the need for additional sex-specific analyses of DTI data.

This is particularly important given recent advances in our basic science understanding of axonal integrity. Recent, innovative research suggests that there may be sex-specific differences in axonal structure and the tolerance of male and female axons to trauma. Evidence for this comes from a study wherein parallel axonal tracts were developed *in vitro* using male and female rat and human neurons. Transmission electron microscopy was then used to quantify axon diameter, microtubule numbers, and microtubule density in each of the four samples (i.e., male rat, female rat, male human, female human). In all *in vitro* cultures, male axons had larger diameters and a greater number of microtubules. More specifically, male rat and human axons had 61% and 80% greater cross-sectional area than female axons, respectively. Similarly, male rat and human axons had 62% and 55% more microtubules than female axons, though microtubule density was significantly greater in males only for human cultures. The authors then used these data to create mathematical models aimed at understanding how these axons would respond to trauma, finding that under the same load or stretch forces, female axons were more likely to experience structural damage than male axons. Computational modelling suggested that this would lead to more structural damage and accumulation of calcium in female neural cells (Dollé et al., 2018). Altogether, this study suggests that there may be sex differences in axonal structure that may account for the variable neuropathology (see Chapter 3) and clinical presentation (see Chapter 4) of concussion in males and females.

Sex-specific DTI data are required in pediatric concussion to understand if the *in vitro* findings observed above translate into poorer axonal (and thus clinical) outcome in boys and girls with concussion. Further, additional research is required to understand whether the sex-specific rs-fMRI disturbance observed in children with concussion (Chapter 3) is related to the inherent sex differences in axonal integrity. A small number of studies show that functional and structural pathologies co-occur post-concussion (Churchill et al., 2017; Murdaugh et al., 2018) but data from these studies are not pediatric-specific nor conclusive. The rs-fMRI data presented in this thesis alongside DTI data on the same pool of patients published separately (Stillo et al., 2021) also suggest that functional and white matter neuropathologies are concurrent following pediatric concussion. The relation between these two pathologies still requires further research.

Cognition

Per Chapter 2, data on the effects of exercise on cognition in brain injury are mixed and inconclusive. This is largely due to heterogeneity in the outcome measures used, and variability among the parameters of exercise interventions studied (Sharma et al., 2020). As our systematic review identified only three eligible trials examining exercise effects on cognition, this precluded meta-analysis across cognitive outcome measures or even cognitive domains.

Other recent meta-analyses of non-randomized exercise studies in concussion have consolidated data on the effects of exercise on cognition using one outcome measure, namely the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) scale. This concussion-specific questionnaire has been widely studied, and has demonstrated validity (Alsalaheen et al., 2016) and normative data (Iverson et al., 2003). The aforementioned meta-analysis found that exercise had no effect on the multiple domains of the ImPACT that were studied, including verbal memory, visual memory, visual motor speed, reaction time, and impulse score (Lal et al., 2017). However, many of the studies included in the meta-analysis were from the same research group and thus cohort, which potentially biased the overall results.

Until there is a larger evidence-base to conclusively determine the effects of exercise in pediatric concussion (or lack thereof), exercise studies should be encouraged to continue to measure change on cognitive outcomes. In general and neurological populations, exercise has demonstrated cognitive benefits (Chang et al., 2012; de Souto Barreto et al., 2018; Ludyga et al., 2020), suggesting that there may be potential for exercise to also improve outcome in concussion. This is important in pediatric concussion given that a recent cohort study of nearly 2000 children showed that cognition is impaired following injury (Tanveer et al., 2017). Whether cognition is responsive to exercise and/or physical activity interventions in pediatric concussion remains to be determined by *second wave* studies in the field.

Additional outcomes for future consideration

As a consideration for future exercise and/or physical activity research in concussion, there are additional outcome measures that warrant study. Two important outcomes that were not directly studied in this thesis but may be responsive to exercise (and therefore important to examine as part of the *second wave* of research in the field) are balance and/or gait and mental health, as discussed below.

Balance and gait

A recent systematic review and meta-analysis of 22 studies reported that 2 weeks following concussion, balance and gait impairments persist in both children and adults (Wood et al., 2019). Other reviews (n=38) demonstrate that whether balance is measured using single-task paradigms (i.e., simple gait and/or balance measures) or dual-task paradigms (wherein participants are asked to complete a cognitive and motor task), impairments following concussion are common (Fino et al., 2018; Manaseer et al., 2020). Further, per 109 elite male rugby players, poorer dynamic balance was associated with a 3 times higher relative risk of sustaining a concussion during gameplay (Johnston et al., 2019).

However, what is less well understood is how exercise impacts balance in children with concussion. In healthy adults, exercise-induced fatigue compromises balance (Wilkins et al., 2004), gait (Schneiders et al., 2012) and postural control (Fox et al., 2008). Further, professional athletes committed significantly more errors on the balance component of the SCAT-3 after exercise in comparison to their pre-exercise baseline (Lee et al., 2017). Conversely, two small cohort studies demonstrated that exercise had little to no impact on balance in concussion (Billeck et al., 2020; Hunter, 2013). Data on the effects of exercise on balance are inconclusive, and pediatric data are limited.

Future exercise-concussion research should study the impact of exercise on balance. This has implications for return-to-play, as if balance is compromised by exercise (despite resolution of symptoms), children cleared to return-to-sport on the basis of symptoms may be resuming physical activity with greater secondary injury risk. In a sports context, research is required to understand the impact of gameplay-simulated activity on balance in children with concussion.

Mental health

Pediatric concussion is often co-morbid with anxiety and depression, and in more extreme cases, personality, behavioral, or internalizing disorders (Max, 2014). A retrospective chart review (n = 174) showed that 49.4% of pediatric concussion patients reported at least one emotional symptom on the PCSS following injury, with 11.5% meeting criteria for psychiatric disorders (Ellis et al., 2015). Moreover, in children, concussion results in a 3.3 fold greater risk of developing depression secondary to injury (Chrisman et al., 2014). A recent systematic review and meta-analysis (n=56,271) reported that in pediatric populations, there was a small-to-medium effect (*Hedge's g*=0.18-0.49) of concussion on developing subsequent mental health difficulties (Gornall et al., 2021).

Overall, the clinical impact of concussion extends beyond the primary symptomatology associated with the injury and to mental health outcomes. Exercise has demonstrated effect on mental health in healthy and clinical populations. Data on more than 1.2 million Americans shows that exercise lowers mental health burden by 11.8-22.3% (Chekroud et al., 2018), while other studies show that exercise has a large anti-depressive effect on those diagnosed with depression (Morres et al., 2019). *Second wave* studies need to expand their scope to examine the effects of exercise and physical activity on mental health, given the prevalence and burden of mental health complications following brain injury in children.

Sex-specific differences in resting state functional brain activity

The objective of Chapter 3 was to improve our understanding of the functional neuropathology of pediatric concussion. Per a controlled cohort study involving 27 symptomatic children and 1:1 age- and sex-matched controls (with 15 females per group), we found that there were rs-fMRI differences (including both hypo- and hyper-connectivity of multiple brain regions) in females that were not observed in males. These results suggest that the functional neuropathology of pediatric concussion differs by sex, with impairments in females–but not males–present at the expected time of recovery. This chapter did not directly add to the exercise-concussion literature, but it underscores that *second wave* studies that examine the impacts of exercise and/or physical activity on the functional neuropathology of concussion (which is a necessary next step for the field) should be guided by sex-based analyses.

Why functional neuropathology matters

Advancing our understanding of the functional neuropathology of pediatric concussion is important for a number of reasons, as detailed below.

First, the asymptomatic patient may not report symptoms and may therefore appear recovered, though an underlying neurological disturbance secondary to concussion may nonetheless persist (Churchill et al., 2019). Neurological impairment that persists in clinically asymptomatic patients may increase vulnerability to secondary injuries that can have compounding effects (Elbin et al., 2012; McCrea et al., 2020; Orr et al., 2016; Van Pelt et al., 2019). The added insight into rs-fMRI impairment in pediatric concussion offered by Chapter 3 creates new targets for intervention for *second wave* studies.

Second, studies detailed in prior sections show that in asymptomatic adults with concussion, exercise can exacerbate functional brain impairment (Slobounov et al., 2011; Zhang et al., 2012). These studies query whether children with concussion (even once symptom recovered) can experience similar neurological vulnerability post-exercise, and if so, how this impairment may manifest clinically or influence risk of secondary injury. In a sports context, if neurological vulnerability is onset by aerobic activity in asymptomatic athletes yet medical clearance to return to sport is based on symptom evaluation, it may be possible that symptom-free athletes are returning to sport despite ongoing and underlying functional neurological disturbance. Multiple injuries in short succession can lead to cumulative and longer-lasting effects, and in rare instances fatality (McLendon et al., 2016; Tator et al., 2019). Therefore, the *second wave* of exercise and physical activity research in concussion needs to better understand the impact of aerobic activity on rs-fMRI and other neurological measures to determine if sub-maximal exercise increases neurological vulnerability.

Third, the importance of studying sex effects in both pediatric and adult concussion have been increasingly recognized in recent years, consistent with the broader understanding that sex as a biological variable has been understudied in the neurosciences (Bale et al., 2017; Shansky et al., 2016). Accordingly, this thesis placed an emphasis on understanding the impact of sex on concussion outcome. The goal of doing so is to advance our basic understanding of how concussion presents in boys and girls, and in turn, to improve our ability to manage the functional neuropathology of concussion in a sex-specific manner.

Fourth, these findings can help explain the variable symptom response between boys and girls with concussion. In addition to females suffering a disproportionate number of injuries (Zemek et al., 2016), the burden of injury is also greater in females than it is in males. One large, multi-center, Canadian cohort study (n=3063) found that by 4 weeks post-injury, more than 90% of males experienced symptom recovery, in contrast to 80% of females (Ledoux et al., 2019). Others have reported that female sex predicts prolonged recovery (Fehr et al., 2019; Thomas et al., 2018) and that females report more symptoms and symptoms with a greater severity than males (Alsalaheen et al., 2021). These sex differences can translate to real-world impact. Desai and colleagues found that in their sample of children with concussion (n=175), in comparison to males, females took longer to return to: school without accommodations, non-contact physical activity, full-sport activity, and normal levels of neurocognitive and vestibular function. The rs-fMRI findings presented in `Chapter 3` are a possible explanation for the greater symptom burden observed in females with concussion.

Etiological explanations for sex differences in brain activity

The reasons behind the sex differences observed in pediatric concussion continue to be researched. However, there are some potential etiological explanations for the sex differences reported in `Chapter 3` of this thesis. It is hypothesized that biomechanical differences may lead to differential effects of a concussive impact in boys and girls, and that sex-specific neurodevelopmental differences may also partly explain our findings. The effects of hormones and genetics remains an active study of research, but there is emerging evidence that this too may influence concussion outcome. These hypotheses are elaborated below.

Biomechanics

From a biomechanical perspective, concussions (and more specifically the forces associated with the injury) are experienced differently by males and females. Sex differences in neck strength and girth influence the magnitude of linear and rotational force exerted on the head upon concussive and sub-concussive contact (Eckner et al., 2014; Streifer et al., 2019). Intervention research shows that increasing neck strength and anticipatory neck activation can reduce the risk of concussion in both males and females (Collins et al., 2014; Daly et al., 2021). Therefore, biological differences in neck strength and girth may influence the magnitude of the ultimate linear and rotational forces experienced upon impact, and thus the severity of impact and associated concussion risk. Findings from this thesis, such as sex-specific differences in rs-fMRI activity (see Chapter 3), may be a result of differential tolerance to external forces between males and females. Large cohort studies have reported sex differences in symptom recovery in adolescents but not younger pediatric patients (Ledoux et al., 2019). This supports the biomechanical hypothesis, as sex differences in symptom recovery would emerge only in older (i.e., post-pubertal) pediatric patients when there are presumably also sex differences in neck strength. The *second wave* of concussion and exercise and/or physical activity research will benefit from biomechanical research examining the associations between neck strength and real-world (i.e., helmet accelerometer-measured) or simulated head accelerations associated with varying external force in males and females. This will help determine the force threshold for a concussive impact. Such research to date has focused predominantly on males (Brennan et al., 2017), precluding sex-specific understanding.

Neurodevelopment

The largest study to examine neurodevelopment in children is the Philadelphia Neurodevelopmental Cohort (PNC), which included nearly 1500 children and young adults aged 8-21 years (Satterthwaite et al., 2014). In addition to studying brain volume changes throughout childhood and adolescence, rs-fMRI data were also collected on a subset (n=674) of these children. Data from this large cohort study suggest sex differences in rs-fMRI, with males demonstrating greater connectivity between "modules" (or key ROIs of known resting state networks), whereas females had greater within-nodule (or network) connectivity. Predictive models developed based on the PNC data were 71% accurate in predicting sex based on rs-fMRI phenotype, suggesting that there are sex-specific patterns of brain activity in children (Satterthwaite et al., 2015). These findings affirm that future research examining rs-fMRI activity should compare males and females with concussion to sex-matched controls (as in Chapter 3), as comparing males with concussion to females with concussion may be confounded by development differences. Whether such sex-specific developmental differences translate into windows of increased vulnerability to injury is not yet known but should be studied.

Hormones and genetics

The potential interplay between genetics and hormones, and whether this relates to sex-specific differences in concussion outcome, is being actively studied. Animal studies have attempted to separate the effects of sex (or X and Y chromosomes) and sex hormones on the brain and neurobehavioural traits. Some data suggest that the response of the brain to these two factors is dependent on the region studied, with some areas of the mouse brain under the influence of sex hormones and others under chromosomal influence (Corre et al., 2016). Similar studies have not been performed in the context of concussion. Other genetic factors, such as the presence of the apolipoprotein E allele 4 (APOE-ε4) have been associated with poorer recovery following brain injury in non-pediatric populations (Lawrence et al., 2015). Originally studied in the context of cholesterol research, APOE-ε4 has been associated with neuronal repair and regulation of neuroinflammatory processes, and thus has implications for brain injury recovery (Mahley et al., 2012). A meta-analysis and meta-regression on the effects of APOE-ε4 in children reported that the presence of this genetic factor is associated with a two-fold increased likelihood of poorer recovery following brain injury, though sex-effects were not observed (Kassam et al., 2016). Overall, while genetics are not a modifiable prognosticator of recovery in brain injury, further research can be done to better understand which genetic predispositions create vulnerability to poorer concussion outcome by sex.

The physical activity deficit in pediatric concussion

Chapter 4 quantified, for the first time, differences in accelerometer-physical activity and sedentary time in children with concussion (n=60) and matched healthy controls (n=60). Reduced LPA, MPA, and VPA and increased sedentary time were observed throughout the day (from 8:00 AM to 10:00 PM) in children with concussion when compared to healthy controls. Importantly, and building on the data from Chapter 3, these effects were more pronounced in females. This study quantifies the physical activity deficit in pediatric concussion and provides a foundational understanding of habitual activity and inactivity in this population. These data can inform *second wave* intervention research in concussion, which may take aim at reducing the increased sedentariness observed throughout the day to improve clinical outcome.

Towards physical activity guidelines for pediatric concussion

The data from Chapter 4 provide another foundation upon which interventions in concussion can be built. Instead of prescribing a single bout of aerobic activity (as is current practice (Leddy et al., 2018b)), these data query whether *physical activity* interventions aimed at increasing activity and decreasing sedentary time throughout the day are needed. Similar to how there are physical activity guidelines for Canadian youth aimed at improving general health and well-being (Tremblay et al., 2011), similar guidelines could be developed for pediatric concussion. This would require studies that first determine the optimal amounts of physical activity to be performed in order to, for example, reduce PCS risk, hasten symptom recovery, improve sleep, or help restore functional neurological disturbance. In relation to this, it has now been asked whether physical activity guidelines are required to improve outcomes (including those secondary to concussion) such as mental health (Teychenne et al., 2020). Given the magnitude of the physical activity deficit observed in concussion, the *second wave* of concussion research should also consider studying physical activity interventions in pediatric concussion.

Towards F.I.T.T. informed exercise in concussion

As research into the effects of physical activity interventions in pediatric concussion begins, exercise interventions will continue to be administered and researched given the considerable data to support their use for symptom management (see `Chapter 1`). It is important to remember, however, that the history of exercise prescription in concussion begins not from an exercise optimization perspective, but rather from a far more conservative approach that placed primary importance on ensuring exercise was not overly strenuous or symptom-exerting. The initial departure from the *rest-is-best* approach was a modest step.

There are now data to demonstrate the safety of standardized exercise tests in concussion (i.e., the BCTT and BCBT), and that these tests do not lead to significant clinical adverse effects or persisting symptom spikes (Leddy et al., 2018a). With this foundational work complete, the *second wave* of research can push to develop F.I.T.T. informed exercise interventions, or those optimized for frequency, intensity, time, and type of exercise. As the field moves towards personalized medicine, exercise protocol optimization will become a research priority. Some early considerations for developing F.I.T.T. informed exercise interventions are outlined below, along with questions that remain to be addressed.

Frequency

Research examining the optimal frequency of exercise for concussion patients is limited. Presently, an exercise frequency of 6-7 days per week is commonly prescribed (Leddy et al., 2018b). However, research specifically supporting the benefit of this frequency of exercise over others is unavailable. It is possible that this exercise frequency is now widely adopted given that early studies showed it was well-tolerated by patients and it was therefore safe to prescribe. Empirical study into exercise frequency in concussion is warranted to optimize exercise protocols. Neuroplastic factors that may aid with concussion recovery (primarily, and most well-studied, brain-derived neurotrophic factor; BDNF) may be responsive to exercise frequency (Worts et al., 2019). Chapter

4 of this thesis showed that there is increased sedentariness in children with concussion throughout the day, which queries whether a single bout of daily exercise (as currently prescribed) is the appropriate exercise frequency. More frequent but shorter activity, or interventions that interrupt sitting time, should be studied in concussion to understand their effects in comparison to usual care (i.e., no prescribed exercise) and a single bout of daily exercise (as current research advises). Such physical activity interventions have demonstrated positive effects in other neurological populations (English et al., 2018). Further, meta-analyses also show that the effects of exercise on BDNF are greatest in the initial 30-minutes after exercise (Szuhany et al., 2015). This raises the question of whether multiple bouts of daily exercise can lead to more persistently elevated levels of circulating BDNF, and whether this leads to a more adaptive neuroplastic response during concussion recovery. These are important research questions to be addressed by *second wave* exercise studies.

Intensity

Low-intensity exercise

Low-intensity exercise is defined as activity that achieves 30-40% of heart rate reserve [HRR], 57-63% of HR_{Max}, or is associated with an energy output of 1.6-3.9 metabolic equivalents (METs) (Worts et al., 2019). From a safety perspective, one reason this intensity of exercise is likely well-tolerated following concussion is that it does not increase CBF in either concussed or healthy individuals. This precludes the opportunity for symptom spikes secondary to CBF autoregulation dysfunction, which is a pathological feature of concussion (Fisher et al., 2008; Ide et al., 1999; Len et al., 2013; Len et al., 2011; Maugans et al., 2012; Meier et al., 2015).

Conversely, however, low-intensity exercise may not be of sufficient intensity to trigger adaptive physiological changes at the cellular level. More specifically, as stated above, BDNF has been implicated with adaptive neuroplasticity in multiple populations, including concussion (Dech et al., 2019). Part of the neurometabolic cascade of concussion (as detailed in Chapter 1) involves a dysregulation of synaptic plasticity, owing to an imbalance in neurotransmitter release, including glutamate. BDNF can mediate pre-synaptic glutamate release, which can help normalize the activity of its receptor (*N*-methyl-D-aspartate [NMDA]), which has a restorative effect on calcium imbalance and ultimately the neurometabolic dysfunction following concussion (Dech et al., 2019; Giza et al., 2014). Following brain trauma, however, BDNF is down-regulated (Dech et al., 2019). In healthy adults, low-intensity exercise may not be able to increase BDNF levels (McDonnell et al., 2013; Nofuji et al., 2012). This suggests that while low-intensity exercise is safe in concussion and has symptom-improving benefits, it may not help restore the neurometabolic disturbance at a cellular level. This raises important and interesting questions for the *second wave* of concussion research about how and when exercise intensity can be increased to optimize patient outcome and treat a potential cause of symptoms.

Moderate-intensity exercise

Moderate-intensity exercise achieves a HRR of 40-59%, 64-75% of HR_{Max}, or requires 4.0-5.9 METs of energy expenditure (Worts et al., 2019). Per the most recent and largest RCT of exercise in pediatric concussion (n=103), the average HR at symptom exacerbation on a baseline exercise test (namely, the BCTT) was 136.7 beats per minute (bpm); research from our lab converges with these data. Given that the average age of participants in said trial was 15.3 years, this would mean the age-predicted HR_{Max} of participants would be approximately 205 bpm. Therefore, children with concussion can exercise to approximately 66% of their age-predicted HR_{Max}. While this would, per the criteria above, qualify as moderate-intensity exercise, it is important to note that the BCTT is a graduated test, and this peak HR is only sustained for a short duration towards the end of the exercise test. Moreover, exercise that is prescribed following the BCTT is initially at an intensity equivalent to 80% of the symptom-limited HR, which equates to target HR of approximately 110 bpm, otherwise classified as low-intensity exercise.

Future moderate-intensity exercise research in concussion should consider the following. First, unlike data on low-intensity exercise which are consistent in that such exercise results in no significant elevation in CBF, the effects of moderate-intensity exercise on CBF are mixed (Worts et al., 2019). This queries whether moderate-intensity exercise may lead to the potentially symptom-provoking consequence of CBF elevation. On the other hand, forced engagement of cerebral autoregulatory mechanisms may help restore CBF velocity abnormalities (Clausen et al., 2016), though additional research is required to build on this possibility. Moderate-intensity exercise does have a stronger effect on upregulation of key neurotrophic factors such as BDNF, and data from healthy adults suggests that more intense exercise is implicated with a stronger neuroplastic response (Ploughman et al., 2015). Further, moderate-intensity exercise is also associated with improvements in depression and sleep-impairments, which are secondary and often persisting features of concussion (Kamrani et al., 2014; Miller et al., 2020; Paolucci et al., 2018; Stanton et al., 2014).

Future studies interested in examining the effects of moderate-intensity exercise should be aware of these issues and attempt to balance the upside of more intense exercise against the potential risk of CBF-related symptom exacerbation.

High-intensity exercise

High-intensity exercise (77-95% of HR_{Max} or 6.0-9.9 METs (Worts et al., 2019)) would be unadvisable in a population where cerebral autoregulation and ANS dysfunction is part of the core pathology of the injury. However, our data (presented as part of Chapter 4 in this thesis) suggest that levels of MPA and VPA increase naturally as a function of time post-injury. Therefore, without further intervention, the benefits of MPA and VPA may be realized by children with concussion once they are no longer in the early phase of injury recovery.

Time

Research on the ideal time of exercise following concussion in either children or adults is sparse. In one recent study, adolescents with concussion were allocated to an exercise program (n=17) or usual care (n=20). The exercise group was *advised* to exercise 5 days/week for 20 minutes/day at an intensity calibrated to the HR_{Max} achieved during an initial aerobic exercise test. However, because a primary objective of the study was assessing intervention feasibility, patients were allowed to exercise for more or less time than prescribed to understand tolerability of exercise and patient physical activity preferences. The authors reported that exercising for more than 160 minutes/week was the threshold able to distinguish between those with and without symptoms at 1 month post-injury (Howell et al., 2021), suggesting that this is the minimum weekly exercise volume required to achieve concussion recovery by 4 weeks post-injury. Another recent cohort study of adults with mTBI and persistent symptoms (n=180) used self-report questionnaires to assess physical activity levels pre- and post-injury. The authors examined how many patients self-reported meeting Canadian physical activity guideline suggestions of 150 minutes of MVPA/week, finding that 85% and 28% of their sample self-reported meeting said guidelines pre- and post-injury, respectively. Moreover, in this cohort, post-concussion self-reported sedentary behaviour was associated with reduced quality of life and increased symptoms, depression, and anxiety. In contrast, those who did participate in more than 150 minutes of MVPA/week post-injury had less fatigue, depression, anxiety, and functional impact of headache (Mercier et al., 2021).

These studies provide early data which suggest that increasing the time spent being physically active post-brain injury (upwards of 150 minutes/week) may be beneficial. Combined with the results of Chapter 4, wherein an accelerometer-measured physical activity deficit was observed post-concussion in children, the *second wave* of concussion research should consider studying interventions that increase overall daily physical activity. This first requires determining the amounts of LPA, MPA, and VPA that lead to optimal outcome in pediatric concussion. Subsequently, patients can be provided with equivalent step and/or activity targets to help them meet empirically-derived physical activity goals, as has successfully been done in the past (Colley et al., 2012). Overall, further research is required to better understand the appropriate time of exercise to prescribe post-concussion.

Type

A recent meta-analysis showed that interventions that involve only sub-maximal aerobic exercise have more than twice the effect of “multi-modal” programs, or those that incorporate exercise with balance, vestibular, or other cognitive tasks (Carter et al., 2021). However, multi-modal studies to date have largely been case-series or involved smaller cohorts; data on such interventions should still be collected in the *second wave* of exercise-concussion research using more rigorous designs. Further, data from Chapter 5 of this thesis showed that intra-network connectivity of the DMN is associated with participation in subsequent physical activity. Therefore, future multi-modal interventions can investigate the impacts of therapies such as mindfulness, which is associated with DMN health (Doll et al., 2015), and thus potentially and ultimately physical activity levels. Adjunctive interventions that address the depression and anxiety that is often co-morbid in concussion should also be considered, given that these mental health issues are implicated with reduced participation in physical activity and can also contribute to increased sedentary time in otherwise healthy individuals (Allen et al., 2019; Zhai et al., 2015).

Building towards F.I.T.T. informed exercise interventions is important to help make exercise prescription more personalized following concussion. The *second wave* of exercise and physical activity concussion research should prioritize research in this area.

Exploring the relation between brain activity and physical activity

Chapter 5 bridged concepts and methodologies from the former two Chapters, by examining whether intra-network connectivity of four rs-fMRI networks was associated with subsequent accelerometer-measured activity in children with concussion. Intra-network connectivity of the DMN–but not SMN, SA, or FPN–predicted subsequent levels of LPA, MPA, and VPA, but not sedentary time. Given that DMN impairment is a common pathological feature of concussion (as shown in `Chapter 3`), this may partly explain the reduced levels of physical activity of children with concussion (as observed in `Chapter 4`). The *second wave* of exercise and physical activity concussion research should expand our understanding of the associations between brain activity and physical activity.

Targeting the functional neuropathology of concussion

The final chapter of the thesis was the most exploratory, partly because of its sample size (n=14) and also because there was no precedent for such analysis in pediatric or adult concussion. To our knowledge, this was the first study to apply both accelerometry and neuroimaging in a single concussion cohort. Because of this, the preliminary findings from this chapter are, arguably, also the most exciting. They provide the first insight into a potential link between resting state brain activity (of the DMN, specifically), and subsequent accelerometer-measured physical activity. This suggests that the physical activity deficit observed in concussion (per `Chapter 4`) may be related to an underlying functional neuropathology.

If additional research corroborates these findings, this would further emphasize the importance of developing interventions that help restore the functional abnormalities observed in concussion. In addition to our findings which show that rs-fMRI disturbances in children with concussion are associated with reduced levels of physical activity, other studies have reported a similar negative relationship between rs-fMRI disturbance and symptoms, sleep, cognition, and mood (Gornall et al., 2021; Iyer et al., 2019a; Iyer et al., 2019b; Kaushal et al., 2019). Together, these data underscore that many of the most pressing and problematic symptoms and co-morbidities of concussion are rooted in a common functional neurological disturbance. This disturbance should, in turn, be the target of intervention rather than individual symptoms themselves.

Relating brain activity and physical activity

Data from other populations, including older adults, suggests that exercise has a positive impact on brain function (Bray et al., 2021). Our data would suggest that this relationship is bidirectional, with brain function also predicting physical activity. Such a relationship could reasonably be expected, given that there are many cognitive processes that need to be performed to engage in physical activity and/or exercise (i.e., executive functions related to planning, task initiation, and goal-directed behaviour). These cognitive processes have neural underpinnings, which would suggest that brain activity can drive exercise behaviour. If so, and because executive function impairment is common in pediatric concussion (Howell et al., 2013), this may explain the physical activity deficit that we observed and reported in Chapter 4.

However, based on our data, impairment to executive function alone is unlikely to be the driver of reduced physical activity in pediatric concussion. We reported that intra-network connectivity of the DMN, but not networks implicated with executive functions such as the FPN, were related to subsequent levels of accelerometer-measured physical activity. Additional research is required to better understand the relationship between brain activity and physical activity, though our work is the first to suggest this exciting link in pediatric concussion.

General considerations for future research

In the sections above, many specific future research directions were identified as they related to particulars reported in this thesis. However, in general, based on findings from this thesis and the broader exercise-concussion evidence-base, there are four general considerations for future research:

1. Future exercise-concussion studies need to be of more rigorous designs. Chapter 2 of this thesis, a systematic review on data from randomized trials on the effects of exercise on cognitive and neuroimaging outcomes following brain injury, identified only 6 relevant articles. Of the nearly 6000 articles originally identified by our comprehensive search of 6 health sciences databases, less than 0.1% were eligible for inclusion, with most on-topic articles excluded for not

being the appropriate study design (i.e., an RCT). Even symptom-based exercise studies in concussion that form the majority of our evidence-base are comprised largely of cohort studies. Of the 23 studies that were meta-analyzed in the most recent review of exercise effects on symptoms, only 8 (or 35.8%) employed a randomized design; 2 of these studies were based on one cohort of participants and 3 others had total samples ≤20 (Carter et al., 2021). Therefore, there is not only a need for studies that examine outcomes other than symptoms, but broadly, there is also a need for more rigorously designed prospective exercise intervention research in pediatric concussion.

2. Exercise interventions need to study outcomes beyond symptoms. The broader literature has established that concussion neuropathologies can persist beyond the point of symptom resolution. The *second wave* of exercise and physical activity concussion research needs to understand the impact of exercise on other important concussion outcomes, including functional brain activity, physical activity levels, mental health, among others.

3. Sex-based analyses are critical to include in future exercise-concussion research studies. Chapters 3 and 4 demonstrate that there are differences with respect to rs-fMRI and accelerometer-measured activity, respectively, between males and females with

concussion. The broader literature and multiple recent reviews (Gupte et al., 2019; Merritt et al., 2019; Valera et al., 2021) have made it clear that sex effects have been understudied in brain injury, and create a compelling argument for the need for prospective research to include sex as a biological variable in their analyses. This thesis supports that this notion.

4. There needs to be more “exercise” in exercise-concussion research. There is opportunity for exercise interventions in concussion to become more F.I.T.T. and physiologically informed as we move towards personalized medicine and optimized exercise protocols. Further, the effects of physical activity, and not only exercise, need to be studied in pediatric concussion. To date, many studies examining the impact of activity on concussion outcome have used self-report measures of physical activity. Chapter 4 and 5 show that accelerometry is a powerful outcome for understanding physical activity and sedentary time in children with concussion. Future studies can aim to develop physical activity interventions and guidelines for pediatric concussion informed by accelerometer and other clinical data.

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APPENDICIES

Appendix A: Sample search strategy for Chapter 2, as optimized for OVID Medline.

1 exp Exercise Movement Techniques/ (6445)

2 exp Movement/ (461153)

3 exp Exercise Therapy/ (39103)

4 exp Physical Exertion/ (55302)

5 exp Motor Activity/ (238505)

6 exp Sports/ (153575)

7 exp Sports Medicine/ (10473)

8 exp Games, Recreational/ (50)

9 exp Locomotion/ (202007)

10 exp Running/ (16910)

11 exp Swimming/ (21547)

12 exp Walking/ (42314)

13 exp Health Behavior/ (144801)

14 exp Health Promotion/ (64566)

15 exp Physical Endurance/ (29078)

16 exp Physical Fitness/ (25152)

17 exp Exercise/ (150454)

18 exp "Activities of Daily Living"/ (58887)

19 exp Dance Therapy/ (257)

20 exp Early Ambulation/ (2406)

21 exp Recreation Therapy/ (90)

22 exercis*.mp. (311343)

23 sport*.mp. (82085)

24 fitness.mp. (70247)

25 physical fitness.mp. (28330)

26 active rehab*.mp. (362)

27 Physiotherapy.mp. (14907)

28 aerobic exercise.mp. (7069)

29 anaerobic exercise.mp. (442)

30 exertion.mp. (64287)

31 resistance training.mp. (8853)

32 physical conditioning.mp. (12567)

33 gym*.mp. (9547)

34 strengthen*.mp. (60495)

35 gymnastic*.mp. (3241)

36 locomotion.mp. (37954)

37 treadmill.mp. (27375)

38 walking.mp. (64356)

39 running.mp. (56133)

40 cycling.mp. (46283)

41 jogging.mp. (1819)

42 (play and playthings).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7993)

43 (physical* adj3 activ*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (89774)

44 (active adj (play or playing or living or lifestyle*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2259)

45 (activity adj2 level*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (39209)

46 ((physical* or cardio* or musc* or weight* or strength* or resistance or endurance or treadmill) adj2 (train* or conditioning or activit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (149807)

47 (physical adj2 (rehab* or therap*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (50622)

48 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (1303227)

49 exp Brain Injuries/ (57569)

50 exp Brain Concussion/ (6213)

51 exp Craniocerebral Trauma/ (138935)

52 TBI*.mp. (20328)

53 craniocerebral trauma.mp. (21787)

54 ((head or crani* or brain* or intercran* or intracran*) adj3 (injur* or trauma* or damag* or lesion* or wound* or contusion* or concus*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (166101)

55 traumatic brain injur*.mp. (26882)

56 concuss*.mp. (9072)

57 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 (232999)

58 randomized controlled trial.pt. (446593)

59 controlled clinical trial.pt. (91788)

60 randomized.ab. (389533)

61 placebo.ab. (183731)

62 drug therapy.fs. (1928290)

63 randomly.ab. (270776)

64 trial.ab. (409355)

65 groups.ab. (1671133)

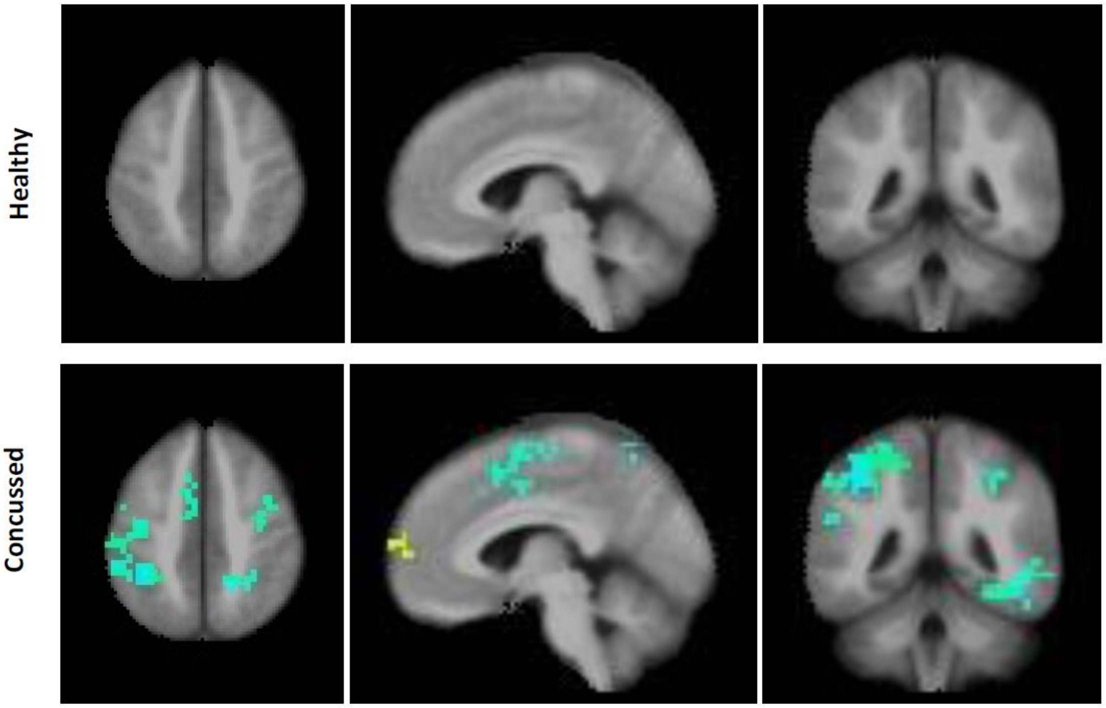
66 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (3973066)

67 exp animals/ not humans.sh. (4311358)

68 66 not 67 (3433878)

69 48 and 57 and 68 (2398)

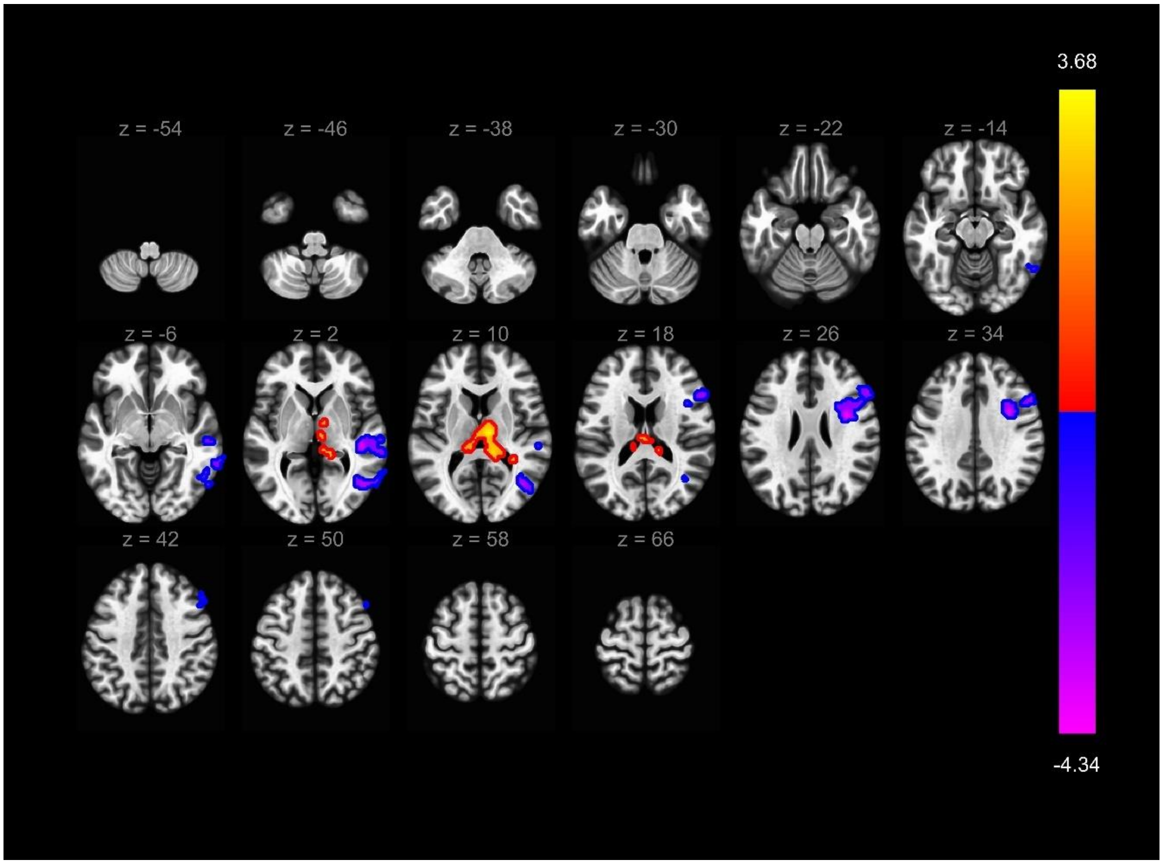
Appendix B: Preliminary data on pre-post exercise rs-fMRI changes in children with concussion compared to healthy controls.



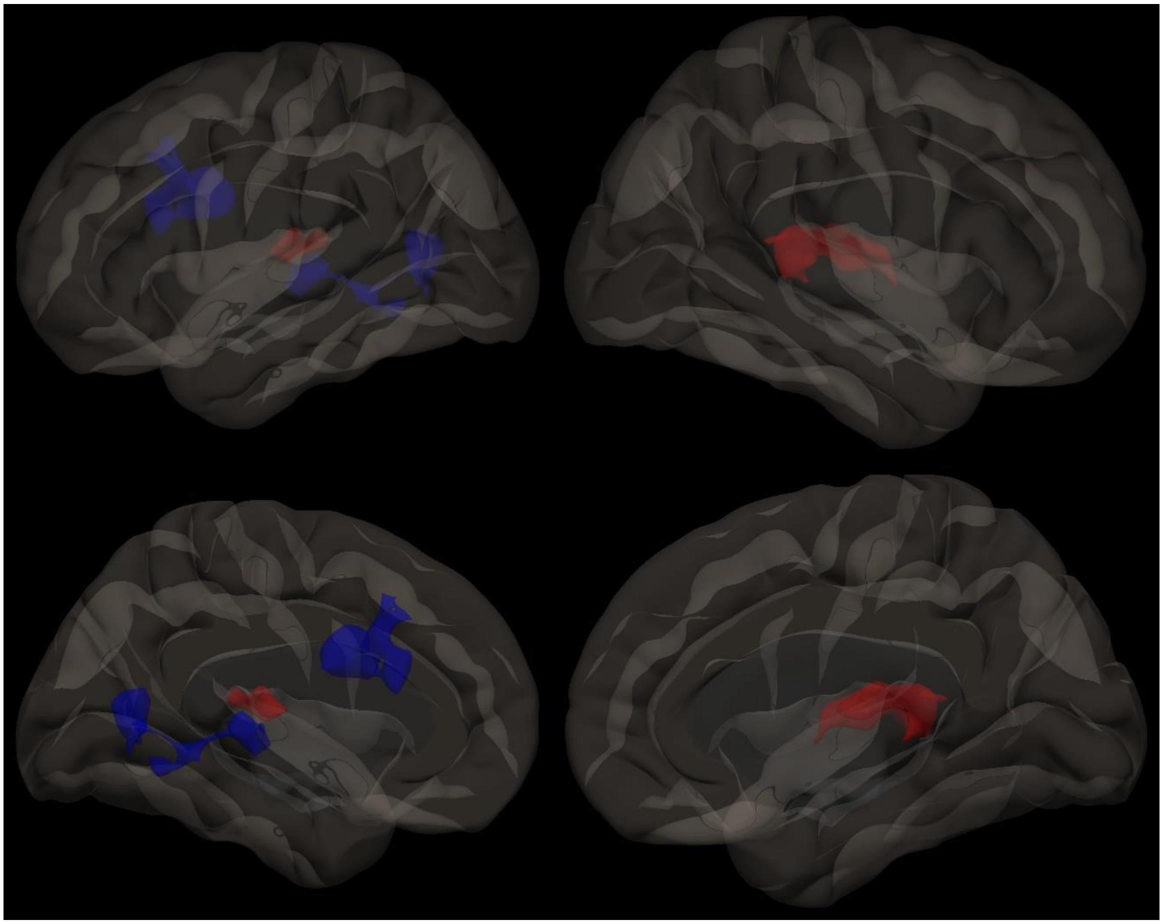
Appendix C: Exercise-induced changes in resting state functional activity in healthy (n=4) and concussed (n=5) children. Group results are overlaid on a standard anatomical atlas. Warm and cool colours represent areas of increased and decreased activity. Maps are thresholded to show voxels that survive t=2.776 at p=0.05. There were **no** changes in pre- to post-exercise functional activity in healthy children. However, there were both **increases** and **decreases** in functional activity in children with concussion, suggesting neurological vulnerability.

Appendix C: Preliminary data on rs-fMRI activity of children with concussion at <1 month vs. >1 month post-injury.

The data from Panels A and B (which represent the same data, but in 2D and 3D visualizations, respectively) provide early evidence of both hyper- and hypo-connectivity in children >1 month post-injury vs. children <1 month post-injury. This suggests a persistent functional neuropathology in symptomatic children with concussion.



Panel A: rs-fMRI differences in children with concussion imaged <1 month post-injury (n=12) vs. those imaged >1 month post-injury (n=9). Warm and cool colours represent patterns of hyper- and hypo-connectivity, respectively.



Panel B: rs-fMRI differences in children with concussion imaged <1 month post-injury (n=12) vs. those imaged >1 month post-injury (n=9) represented on a 3D glass brain. Warm and cool colours represent patterns of hyper- and hypo-connectivity, respectively.

CONCLUDING REMARKS

The multi-disciplinary study of exercise in concussion has created a new research frontier. We are beginning to understand more about how exercise and physical activity can be used to manage concussion (and brain injury more broadly). These disciplines have met with the momentum to push the field forward and in new directions.

While writing this thesis, one of the books on my “read pile” was *Range* by David Epstein, who builds an argument for why facilitating cross-talk between disciplines can lead to impactful invention. With respect to the sciences, Epstein references a study which shows that articles in which citations from two separate disciplines first appear are meekly cited soon after publication, yet in the long-term, they can become some of the most influential and paradigm shifting publications of the field. We have just started to see spillover between concussion and exercise medicine. My thoughts of how the discoveries of today may change the thinking of tomorrow are piqued.

This thesis was aimed at reinforcing the multi-disciplinary bridge between concussion and exercise medicine that has recently been built. Chapter 5 of this thesis was the first to use both accelerometry and neuroimaging in concussion, providing the first insights into the advancements that can be made when combining key outcomes from different disciplines. Continued cross-talk between disciplines and shared implementation of their methodologies, outcomes, research practices, and perspectives can lead to meaningful new research questions that previously may not have been thinkable.

In closing, this thesis was written with excitement about the work presented herein, and an eager eye towards the discoveries of tomorrow made possible by the joining of disciplines today.