Neural Correlates of Resilience in Pediatric Concussion and the Influence of a Mindfulness-Based Intervention

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Abstract

Concussion is the most common form of brain injury. It disproportionately affects children and adolescents, as they face heightened risk of head injury. Emerging evidence suggests psychological resilience mitigates clinical symptom burden from pediatric concussion. Mindfulness-based interventions (MBIs) may enhance resilience, thereby affecting recovery trajectories. More advanced imaging research of pediatric concussion is required to better understand the neural correlates of resilience in this context as well as whether MBIs moderate associations between resilience and neural outcomes. This dissertation presents an evidence-based framework depicting mechanisms by which resilience may affect neural outcomes following concussion, as well as ways that MBI may influence resilience and moderate neurofunctional correlates of resilience.

This work includes three studies from multi-site pediatric concussion trials. Studies 1 and 2 were based on data from the Pediatric Concussion Assessment of Rest and Exertion trial (Clinicaltrials.gov identifier: NCT02893969). Study 1, a case-control study, examined associations between resilience and white matter microstructure in adolescents with acute concussion (n=66) and orthopedic injury (n=29). Resilience was measured by the Connor-Davidson Resilience Scale 10 at baseline, reflecting experiences over the preceding 30 days, and white matter microstructure (fractional anisotropy, mean, axial, and radial diffusivity) was assessed via diffusion tensor imaging at baseline and follow-up. Results revealed negative correlations between baseline resilience and fractional anisotropy, and positive correlations between baseline resilience and both mean and radial diffusivity in the concussion group. Study 2, also a case-control study (concussion n=67, orthopedic injury n=30), examined associations between resilience and resting-state functional connectivity of the default mode network (DMN), salience network (SN), and central executive network (CEN) at baseline and follow-up. Seed-to-voxel analyses showed a positive correlation between resilience and CEN connectivity in the concussion group, with group moderating associations involving SN and DMN connectivity. Study 3, a study from the Mindfulness-Based Intervention for Mild Traumatic Brain Injury trial (ClinicalTrials.gov identifier: NCT05105802), explored whether an MBI influenced resilience trajectories and moderated the association between baseline resilience and functional connectivity at 4 weeks post-injury (MBI *n*=16, cognitive sham control *n*=20). While MBI did not significantly impact resilience trajectories, significant group-by-resilience interactions were observed in relation to connectivity of the DMN (intention-to-treat and per-protocol), SN (per-protocol), and CEN (per-protocol). Together, these studies provide a foundation for understanding the neural underpinnings of resilience following pediatric concussion, providing evidence of significant associations of resilience with white matter microstructure and functional connectivity, as well as the moderating role of MBI. The findings explored in this dissertation support an empirical evidence-based framework of resilience and MBI in pediatric concussion outcomes, warranting future initiatives to improve our understanding of the potentially beneficial effects that resilience may have on brain health of children and adolescents with concussion.

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Preface

Ethics Statement

All studies included in this dissertation were approved by the Research Ethic Board at the Children's Hospital of Eastern Ontario. All eligible children and adolescents capable of consenting provided written informed consent, while those unable to consent provided assent and parental consent.

Thesis Format

This thesis is submitted in article format. At the time of submission of the thesis for written evaluation, two of the three articles were published, and the remaining one was submitted for publication.

Contributions of Authors

All written works contained in this dissertation were produced by Olivier Brown with the support of co-supervisors Drs. Andra Smith and Andrée-Anne Ledoux.

Study 1: Associations between psychological resilience and metrics of white matter microstructure in pediatric concussion (Published in *Human Brain Mapping*, 2023)
Author contributors included conception and study design (OB, AS, RZ, AAL), data collection or acquisition (KH, RZ, AAL), statistical analysis (OB, ZF, AAL), interpretation of results (OB, AS, AAL), drafting the manuscript work (OB, AS, AAL), and approval of final version to be published (All authors).

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List of Abbreviations

A-CAP	Advancing Concussion Assessment in Pediatrics
AD	Axial diffusivity
BOLD	Blood-oxygen level dependent
CAMM	Child and Adolescent Mindfulness Measure
CD-RISC	Connor-Davidson Resilience Scale
CD-RISC 10	Connor-Davidson Resilience Scale 10
CES-D-10	Center of Epidemiologic Studies Depression Scale 10-Item
CEN	Central executive network
CHEO	Children's Hospital of Eastern Ontario
CT	Computerized tomography
DMN	Default mode network
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging
GAD-7	General Anxiety Disorder-7
HBI	Health Behaviour Inventory
hrs / h	Hours
IQR	Interquartile range
MBI	Mindfulness-based interventions
MBI-4-mTBI	Mindfulness-Based Intervention for Mild Traumatic Brain Injury
MD	Mean diffusivity
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
PECARN	Pediatric Emergency Care Applied Research Network
PedCARE	Pediatric Concussion Assessment of Rest and Exertion
PedsQL	Pediatric Quality of Life Inventory
PSaC	Persistent symptoms after concussion
RD	Radial diffusivity
REDCap	Research Electronic Data Capture
ROI	Regions of interest
SN	Salience network
TBI	Traumatic brain injury
TE	Echo time
TFCE	Threshold-free cluster enhancement
TR	Repetition time

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Chapter 1: General Introduction

1. Pediatric Concussion

Concussion, also known as a mild traumatic brain injury (mTBI) is a direct result of traumatic biomechanical injury to the head, triggering a neurometabolic cascade that is associated with common symptomatology (Duquette & Spotts, 2021; Halstead et al., 2018; Rose et al., 2015). The traumatic injury disrupts neuronal membranes, leads to axonal stretching and swelling, and mechanoporation of cellular membranes opening voltage-gated ion channels (see Giza & Hovda [2014] for a review). The resulting nonspecific neuronal depolarization signals release of the excitatory amino acid glutamate, triggering a mass efflux of potassium. Sodium-potassium pumps become hyperactive to reestablish electrochemical homeostasis, demanding an abnormal increase in the metabolism of glucose, or hyperglycolysis. After the hyperglycolysis phase, there is a decrease in glucose metabolism, accompanied by other neurophysiological changes such as a depression of cerebral blood flow. This neurometabolic cascade is likely associated with the acute clinical outcomes that follow injury.

Pediatric mTBI is a particularly concerning issue. Approximately 10% of youth report experiencing a traumatic brain injury (TBI) in the past year (Daugherty et al., 2024). Children and adolescents have among the highest rates of TBI-related emergency department visits (Taylor et al., 2017). Although approximately 70-90% of TBI cases seen in the emergency departments are mild (Cassidy et al., 2004; Lumba-Brown et al., 2018), children and adolescents that sustain mTBI can experience a variety of post-concussive symptoms (PCS). Several common acute somatic, emotional, and cognitive symptoms exist (Anderson et al., 2001; Carroll et al., 2004; Patricios et al., 2023; Willer & Leddy, 2006). Somatic symptoms include headaches, confusion, nausea, vomiting, balance problems/dizziness, and sensitivity to light. Emotional symptoms include drowsiness, fatigue/lethargy, sadness/depression, nervousness/irritability, sleeping more than usual, and trouble falling asleep. Cognitive symptoms include feeling 'slowed down', feeling 'in a fog' or 'dazed', difficulty concentrating, and difficulty remembering. Children and adolescents may also be more vulnerable than adults to sustain neuronal injury from mTBI (Keightley et al., 2012; McCrory et al., 2004). This increase in vulnerability may stem from pathophysiological differences in children relative to adults. More specifically, the increased vulnerability is thought to be associated with differences in brain water content, degree of myelination, skull geometry, suture elasticity, and neck strength (Keightley et al., 2012).

Previous accounts of TBI consider the term *concussion* to be a subset of mTBI, while others suggest it to be synonymous with mTBI (Mayer, 2021; McCrory & Berkovic, 2001; Sussman et al., 2018). Based on new diagnostic criteria, 93.8% of established expert panel members agreed that concussion may be used interchangeably with mTBI in instances when neuroimaging outcomes are considered as normal or otherwise not clinically indicated (Silverberg et al., 2023). The works of this dissertation are largely concerned with pediatric concussion.

1.1 Recovery

Children and adolescents take longer to recover from concussion than adults (Guskiewicz & McLeod, 2011). Although most cases of pediatric concussion are resolved after two to three weeks (Ledoux et al., 2019; Purcell et al., 2016), approximately 30-35% of cases experience concussion symptoms beyond one month (Barlow et al., 2010; Chadwick et al., 2022; Davis et al., 2017; Yeates et al., 2012; Zemek et al., 2016). This clinical presentation is now referred to as *persisting symptoms after concussion* (PSaC), a term that replaces the formerly used persistent post-concussive symptoms (Broshek et al., 2022). When a child or adolescent sustains a concussion, the consequences often extend well beyond the resolution of acute clinical symptoms (Johnson et al., 2015; Sinopoli et al., 2014; Westfall et al., 2015). The persistence of somatic, emotional, and cognitive symptoms can disrupt academic functioning and limit engagement in daily activities (Gornall et al., 2020; Russell et al., 2016). Prolonged recovery can negatively affect psychological well-being and delay the re-establishment of daily routines, underscoring the importance of identifying effective interventions to mitigate the multifaceted burden of pediatric concussion (Gornall et al., 2020).

While acute injury characteristics have some predictive value for concussion recovery, emerging evidence indicates that pre-injury characteristics may have a stronger influence on recovery trajectories. For instance, Zemek et al. (2016) developed a predictive model that determines the estimated likelihood of prolonged clinical recovery, which significantly outperformed physician judgment in predicting PSaC. Notably, while the model includes some acute clinical symptoms, many of its key variables such as age, sex, prior concussion history and symptom resolution, and migraine history reflect pre-injury characteristics. Maladaptive coping strategies provide further evidence for the predictive power of pre-injury characteristics in concussion. Silverberg et al. (2018) showed that fear avoidance behaviour, a maladaptive coping strategy, correlated with greater symptom severity, functional disability, and risk for depression and anxiety disorders. This is further supported by Cairncross et al. (2021), who developed and validated a fear avoidance measure for children with concussion and reported it as significantly associated with emotional distress and reduced quality of life. Additionally, Ledoux et al. (2022) conducted a retrospective cohort study and demonstrated that, compared to orthopedic injury controls, rates of post-concussion mental health visits in children and adolescents without mental health visits in the year before were higher in a concussion group and correlated with new mental health problems. While this may reflect the psychological impact of concussion itself, it also raises the possibility that pre-injury psychosocial factors may contribute to recovery outcomes.

Akin to this, rate of recovery is also associated with pre-injury characteristics such as age (Covassin et al., 2012; Davis et al., 2017; Iverson et al., 2017; Kostyun & Hafeez, 2015; Ledoux et al., 2019; Zemek et al., 2016); biological sex (Colvin et al., 2009; Covassin et al., 2012; Iverson et al., 2017; Kostyun & Hafeez, 2015; Ledoux et al., 2019; Zemek et al., 2016); history of concussion (Aggarwal et al., 2020; Colvin et al., 2009; Eisenberg et al., 2013; Zemek et al., 2016); ADHD (Aggarwal et al., 2020); and migraine history (O'Reilly et al., 2025; Zemek et al., 2016). Age and biological sex, for example, influenced symptom improvement timeframe in Ledoux et al. (2019). Ledoux et al. found that symptom improvement in children aged 5 to 7 years occurs primarily within two weeks post-concussion, while in preadolescents aged 8 to 12 years and male adolescents ages 13 to 18 years it occurred only within 4 weeks post-concussion. Female adolescents, however, appeared to have protracted recovery. Most adolescent females in Ledoux et al.'s study did not recover by week 12. Relatedly, Aggarwal et al. (2020) sought to identify clinical and demographic factors that may be predictive of concussion recovery in adolescents aged 13 to 19 years with a retrospective observational cohort study and identified history of concussion and diagnostic history of ADHD as significant predictors of protracted recovery.

Other pre-injury characteristics, such as a history of depression and/or anxiety diagnosis are also associated with prolonged recovery. Children and adolescents aged 5 to 18 years with pre-existing anxiety, for example, took at least twice as long to be cleared for all activities than patients without anxiety (Corwin et al., 2014). The authors reported that this also applied to children and adolescents with pre-existing depression. In a controlled study of pediatric mTBI, pre-injury risk factors including lifetime psychiatric disorder; high versus low family psychiatric history; and lower socio-economic status were each significantly associated with a higher frequency of novel psychiatric disorder post-injury (Max et al., 2021). O'Reilly et al. (2025) stated that 75.9% of concussion patients with PSaC experienced symptoms attributable to non-concussion factors, including migraines, anxiety, depression, and other psychiatric disorders. Certain pre-injury characteristics may thus be related to increased vulnerability to a slower rate of recovery, or symptom resolution. Beyond influencing recovery duration, pre-injury characteristics also significantly predict symptom burden. Another recent study on pediatric concussion claimed that pre-injury factors accounted for 23-40% of variance in acute mental health outcomes; 32-38% of variance in post-acute mental health outcomes; and 47-69% of total variance when incorporating acute mental health into the statistical model (Gornall et al., 2024). In their study, Gornall et al. identified lower psychological resilience, pre-injury learning difficulties, pre-injury concussive symptoms, psychiatric diagnoses, and family history of psychiatric illness as strong predictors of heightened mental health difficulties after concussion.

1.2 Imaging Techniques

Concussion diagnosis is largely dependent on self-report assessment of symptoms, neuropsychological testing, and, in some cases, conventional structural imaging techniques (Rivara & Graham, 2014). Although computerized tomography (CT) is efficient at detecting skull fractures, hemorrhages, or lesions, evidence suggests that it may be insufficient in detecting brain microstructural changes following concussion (Fiser et al., 1998; Rose et al., 2017; Suskauer & Huisman, 2009). In addition, the amount of radiation required for CT should be limited. Increased use of CT in children heightens the risk of developing cancer (Miglioretti et al., 2013). According to the PECARN (Pediatric Emergency Care Applied Research Network) Pediatric Head Injury Prediction Rule, performing a CT scan is not necessary for diagnostic purposes of concussion (Kuppermann et al., 2009). Following the PECARN rule, CT may be recommended for minor head trauma cases only after signs of skull fractures (Kuppermann et al., 2009). Standard clinical magnetic resonance imaging (MRI), albeit more sensitive in detecting hemorrhages and volumetric changes of grey and white matter than CT, may also underestimate the neuropathology of mTBI (Lee et al., 2008). Further, clinical CT and clinical MRI sequences are not designed to measure alterations in brain functioning and cerebral blood perfusion. More advanced imaging techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI) may be more effective for studying microstructural and neurofunctional effects of concussion.

DTI uses radio frequency pulses in conjunction with a series of magnetic gradients to measure water diffusivity in the microstructural tissue of the brain's white matter. Isotropic diffusion implies that water molecules diffuse in all directions equally, with little to no constraints (Figure 1). Anisotropic diffusion, however, implies a restriction of molecular movement due to physical barriers (e.g., axonal membranes) with differential patterns of diffusivity dependent on the properties of such barriers. DTI provides several measures of diffusivity including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). FA delineates the degree of directional diffusion, whereby a value of 0 indicates complete isotropic diffusion and a value of 1 indicates complete anisotropic diffusion. Increased FA across white matter tracts may be considered an indicator of white matter structural integrity, as restricted molecular movement is associated with myelination and axonal density

(Song et al., 2002).

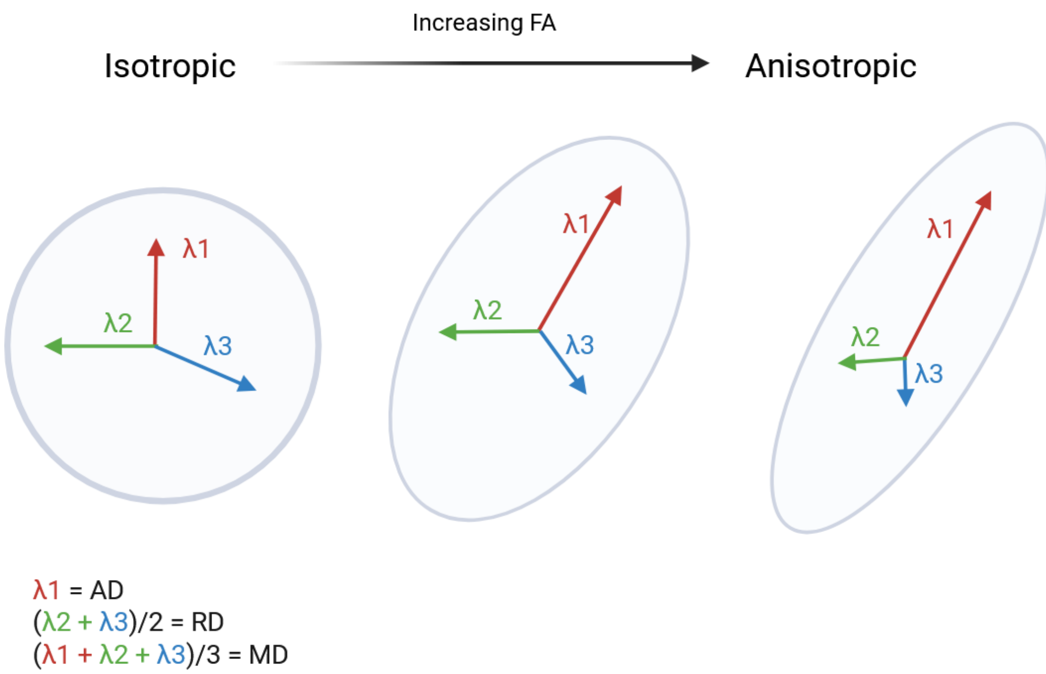

Figure 1. Illustration of isotropic and anisotropic diffusion
A visual representation of isotropic (low fractional anisotropy) to anisotropic (high fractional anisotropy) diffusion, including eigenvalues reflecting axial, radial, and mean diffusivity.

In instances of brain injury, increased FA may also be indicative of axonal swelling or cytotoxic edema, as such conditions might also be associated with restricted molecular movement (Bigler & Bazarian, 2010). It is evident that FA alone as a metric of white matter integrity might lead to contradictory interpretations of significant results in the context of brain injury (i.e., greater myelination and axonal density vs. axonal swelling and edema). To construct a clear, robust, and accurate interpretation of white matter microstructure, studies should carefully consider additional metrics of diffusion. MD, or the apparent diffusion coefficient, is a metric that describes the magnitude of diffusion. AD refers to the rate of diffusivity along the longitudinal plane of diffusion, while RD refers to the rate of diffusivity across or perpendicular to the axis of diffusion. Together, DTI measures of diffusivity can be used to characterize the microstructural properties of white matter in the brain.

fMRI measures fluctuations in magnetic fields within the brain reflecting the blood-oxygen level dependent (BOLD) contrast to indirectly measure local neuronal activity. Oxygen and glucose are imperative to the functioning of neurons. However, neurons do not contain reserves for glucose and oxygen, thus relying on an adaptable source of oxygenated blood flow. Naturally, the hemodynamic response supplies increased oxygen and glucose to active regions of the brain relative to inactive regions. BOLD contrast captures signal changes corresponding to these fluctuations of the oxyhemoglobin to deoxyhemoglobin ratio in the brain, thus indirectly measuring local neuronal activity. This imaging technique is used, for example, to identify resting-state functional neural networks.

Resting-state neurofunctional networks are functionally connected regions of the brain identified during rest, where functional connectivity (FC) refers to the correlations between spatially remote regional activity (Figure 2). While some networks, such as the default mode network (DMN), typically deactivate during tasks, others, like the central executive network (CEN), become more active during cognitive tasks or external demand. Resting-state fMRI research commonly examines the DMN, CEN, and salience network (SN). The main components of the DMN include the dorsal and ventral medial prefrontal cortices, posterior cingulate cortex, and the lateral parietal cortex (Raichle, 2015). This network is related to self-referential processes, emotional processing, and biographical memory (Frewen et al., 2020; Raichle, 2015). Dysfunction of the DMN correlated with the pathophysiology of some psychiatric illnesses, such as depression (Broyd et al., 2009; Greicius et al., 2007). The CEN is comprised of functionally connected neocortical regions, including dorsolateral frontal and parietal cortices (Seeley et al., 2007). This network correlates negatively to activity of the DMN and is influences executive functioning; sustained attention and working memory; as well as behavioural selection and inhibition (Seeley et al., 2007). The SN includes the ventrolateral prefrontal cortex, paralimbic anterior cingulate and frontoinsular cortices, and supramarginal gyri, with connectivity to subcortical regions and components of the limbic system (Goulden et al., 2014; Seeley et al., 2007). This network processes salient stimuli, and studies suggest the SN influences transient, selective switching between DMN and CEN activation (Goulden et al., 2014; Seeley et al., 2007).

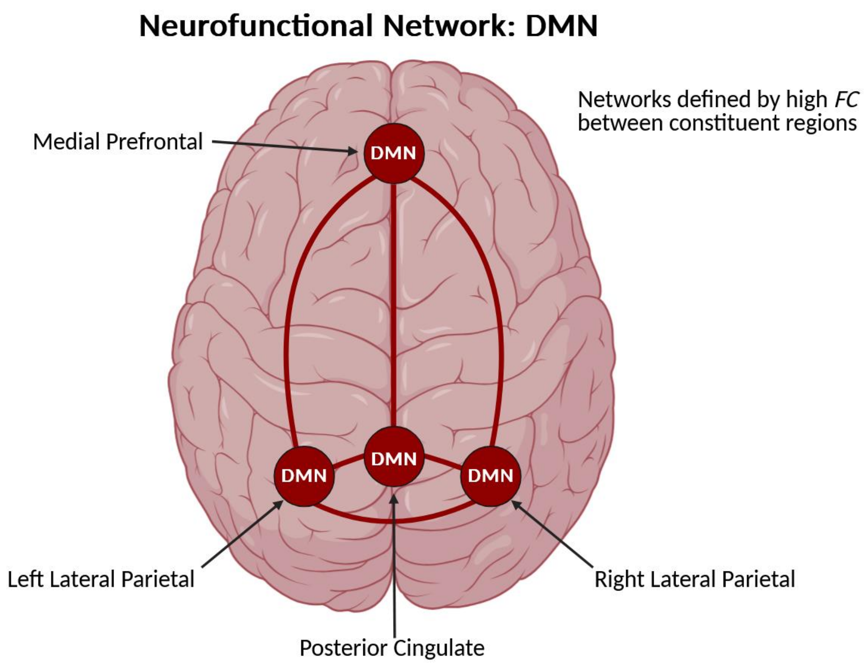

Figure 2. Illustration of a neurofunctional network
A visual representation of the default mode network (DMN). Neurofunctional networks are identified by high functional connectivity (FC) between constituent regions, correlations in activity between spatially remote brain areas.

1.3 White Matter and Resting-State Network Changes in Concussion

The neurological effects of concussion frequently persist even after clinical symptoms have resolved (Johnson et al., 2015; Hagen et al., 2024; Manning et al., 2017; Sinopoli et al., 2014; Westfall et al., 2015). These neural outcomes of pediatric concussion manifest through alterations in global brain white matter, cerebral blood flow and perfusion, as well as resting-state network connectivity, ultimately impacting brain structure and function. A meta-analysis by Roberts et al. (2014) explored a plethora of research that identified both widescale increases in FA within white matter tracts and overall decreases in FA in concussed children. The authors explain that all selected articles examining the sub-acute phase of recovery (one to four weeks post-injury) report large and significant increases in FA compared to controls across the many major white matter tracts. Researchers postulated that, in the context of acute brain injury, increased FA as well as a decreased in MD reflect axonal swelling and cytotoxic edema in the sub-acute phase of recovery (Bigler & Bazarian, 2010). Meanwhile, studies investigating the medium to long term phases of recovery in children found moderate to very large decreases in FA across numerous white matter tracts (Henry et al., 2011; Ware et al., 2022). The reported decrease in FA, and increase in MD, identified in the medium to long term phases of recovery may reflect axonal degeneration after axonal swelling.

Studies also identified complex alterations in resting-state FC following concussion, particularly affecting the DMN, SN, and CEN. In pediatric populations, Plourde et al. (2021) demonstrated decreased DMN FC in children with multiple concussions compared to those with single concussion or orthopedic injury, while other studies reported increased DMN FC in children with concussion (Abbas et al., 2015; Newsome et al., 2016). Adult studies further confirm this complex pattern, revealing dynamic alterations in FC characterized by acute phase hyperconnectivity, such as increased FC between DMN hubs and non-hubs (Bouchard et al., 2024) and increased spectral connectivity associated with persistent symptoms (Dunkley et al., 2018), followed by chronic phase hypoconnectivity within the DMN with only partial recovery by one-month post-injury (Zhu et al., 2015). The significant FC alterations following concussion extends beyond the DMN, and may be detected in the SN and CEN. There are numerous reports of increased within- and between-network FC of both the SN and CEN (Borich et al., 2015; Healey et al., 2022, Liu et al., 2020b; Marusak et al., 2017, Orr et al., 2016).

Any heterogeneity in advanced imaging findings may be at least partly attributable to methodological differences in studies. A systematic review by Dodd et al. (2014) revealed that studies examining anisotropic diffusion within the semi-acute phase of mTBI report mixed findings, with some showing increased FA and others decreased FA. The authors concluded that the direction of findings were partially influenced by methodological factors such as the number of diffusion-weighted directions acquired. Dodd et al. (2014) continued to suggest, for example, that varying inclusion criteria, sample sizes, and data acquisition parameters complicate predictions regarding the directionality of findings. Nuanced findings pertaining to concussion extend beyond diffusion weighted techniques to resting-state FC. For example, Borich et al. (2015) reported both increases and decreases in FC of certain DMN and CEN nodes. Although evidence suggests that the acute phase of concussion is generally characterized by increased FC (hyperconnectivity; Boshra et al., 2020; Bouchard et al., 2024; Dunkley et al., 2018) while the sub-acute to chronic phase is characterised by decreased FC (hypoconnectivity; Borich et al., 2015; Plourde et al., 2021; Zhu et al., 2015), more research is needed to fully understand these nuanced findings, particularly in the acute to sub-acute phase in pediatric populations. Despite the increasing understanding of the acute neurometabolic cascade and the diverse symptomatology following concussion, current management strategies would benefit from integration of targeted therapeutic approaches that consider these neural outcomes. More research using advanced imaging techniques is necessary for understanding how to optimally support long-term neural recovery, particularly with interventions that enhance adaptive coping mechanisms.

1.4 Interventions

Traumatic biomechanical forces of concussion do not transect axons; hence, effective treatment may be crucial in decreasing the likelihood of progression to axonal degeneration, diminishing overall axon loss (Alisafaei et al., 2020; Armstrong et al., 2016). Yet, current treatment approaches may not yet be fully optimized (Comper et al., 2005; Prince & Bruhns, 2017). The 2022 Concussion in Sport Group consensus statement recommends a stepwise return to physical activity 24 to 48 hours post-injury (Patricios et al., 2023). This stepwise progression encourages the individual to engage in daily physical activity, beginning with light aerobic exercise and progressing through increasing levels of intensity at each subsequent stage. The individual should stop the activity and attempt to exercise on the next day if more than mild exacerbation of concussion-related symptoms occurs during physical exertion. While current concussion management practices emphasize a stepwise return to activity, there remains an opportunity in exploring additional psychological-based interventions. Although physical activity has established benefits for diminishing symptoms and promoting recovery, some children and adolescents might not be able to readily engage in light aerobic exercises following acute concussion due to symptom severity, fear avoidance behaviours, or mental health problems. Psychological-based interventions may be an accessible and effective alternative by targeting mental health-related contributors to persistent symptoms (i.e., anxiety and depression) while promoting adaptive behaviours, enhancing resilience, in these children and adolescents.

2. Resilience

Psychological resilience reflects achieving favorable outcomes, adjusting successfully, or reaching developmental goals despite facing considerable stress or hardship. (Naglieri et al., 2013). Although resilience was previously construed as a trait, or a stable, unchanging characteristic (Wagnild & Young, 1993), this account might be considered as constricted and even potentially damaging for pediatric populations (Masten & Barnes, 2018; Wright et al., 2013). Alternative approaches to defining the construct seek to understand it in terms of processes, or a dynamic continuum of adaptation in response to stress (Connor & Davidson, 2003). Some measures of resilience were developed with an explicit operationalization of resilience as a malleable phenomenon (Campbell-Sills & Stein, 2007; Wright et al., 2013). Among the most established measures of resilience is the Connor-Davidson Resilience scale, which conceptualizes the construct as an individual's capacity to successfully cope with stressors that might otherwise threaten healthy functioning or development (Campbell-Sills & Stein, 2007; Connor & Davidson, 2003). Research conducted using this assessment showed that resilience can be modified, with evidence supporting the efficacy of resilience-targeted interventions (Connor & Davidson, 2003; O'Connor et al., 2023). In essence, resilience-targeted interventions employ healthy coping strategies that could increase the likelihood of successful coping from stress that might threaten normal development (i.e., resilience). Ongoing studies continue to investigate methods of enhancing resilience, including interventions based on physical activity, cognitive behavioural therapy, social support, psychoeducation, and mindfulness (see Liu et al. [2020a] for a review). This account of resilience in terms of processes capable of improvement encourages further research to investigate the behavioural, but also neurological implications of resilience-targeted interventions in clinical environments.

Previous studies suggest that resilience affects clinical outcomes of concussion. In adults with mTBI, pre-injury resilience influenced severity of post-injury anxiety and PCS (McCauley et al., 2013) In adults with recent mTBI, Sullivan et al. (2015) found that lower psychological resilience significantly predicted greater severity of PSaC. In adolescents and young adults with concussion, Bunt et al. (2021) showed that lower resilience at the initial clinical assessment correlated with more numerous and severe symptoms, elevated levels of anxiety and depression, a decreased probability of clinical recovery after three months, and heightened symptom aggravation in response to physical and cognitive activity. In adolescent and young adult athletes with sport-related concussion, Ernst et al. (2021) showed that lower psychological resilience correlated with prolonged recovery duration, greater affective symptoms, and more severe vestibular-ocular impairments. Notably, resilience was the only significant predictor of protracted recovery, emphasizing its potential prognostic utility in clinical concussion outcomes.

These clinical findings are further supported by concussion research using pediatric samples. In a recent study, low resilience in children and adolescents assessed at two weeks post-concussion corelated significantly with increased mental health difficulties (Gornall et al., 2024). Durish et al. (2018) examined the relationship between psychological resilience and PSaC in children aged 8 to 18 years with single or multiple concussions. In this study, a history of concussion and lower psychological resilience was associated with severity of PSaC symptoms. Additionally, psychological resilience correlated negatively with child-reported total PSaC. This finding, however, was not significant in the parent-reported total PSaC. Even so, psychological resilience correlated with both child-rated and parent-rated emotional and fatigue symptoms. Therefore, psychological resilience may be more closely related to emotional and fatigue symptoms than somatic and cognitive symptoms. Likewise, Durish et al. (2019) reported evidence in support of a mediation in adolescents aged 13 to 18 years with concussion, whereby by anxiety and depressive symptoms mediated the relationship between psychological resilience and recovery. The authors suggested that interventions targeted towards increasing psychological resilience may contribute to preventing or alleviating PSaC, though additional empirical evidence is necessary to support this claim.

More recently, a substudy of the Advancing Concussion Assessment in Pediatrics study (A-CAP; Yeates et al., 2017), the largest completed multi-site longitudinal study of pediatric concussion to date, found that resilience correlated negatively with child-reported PCS, emphasizing the potential of resilience as a protective factor of recovery from pediatric injury (Dharsee et al., 2024). Another recently published A-CAP substudy found that resilience both affected and was affected by PCS in children with either concussion or orthopedic injury (Hassan et al., 2024). Specifically, parent-reported cognitive symptom severity at 1-week post-injury correlated positively with resilience at 3 months; resilience at 3 months correlated negatively with total symptoms at 6 months; higher resilience at 3 months correlated negatively with child-reported symptoms at 6 months; and child-reported symptoms at 3 months correlated negatively with resilience at 6 months. The authors proceed to suggest that resilience-targeted interventions may promote recovery following pediatric injury, namely concussion.

Previous studies also suggest that resilience relates to metrics of white matter microstructure and FC. For example, psychological resilience correlated positively with FA in the corpus callosum of healthy adolescents (Galinowski et al., 2015). Resilience-promoting factors such as intact intellectual functioning; access to community resources; supportive caregivers; and prosocial influences correlated with FA and MD in complicated mild, moderate and severe TBI (Schmidt et al., 2021). Nevertheless, more research is required to understand the white matter microstructural correlates of perceived resilience in the early phases of pediatric concussion. As for neurofunctional correlates, resilience correlated negatively with DMN, SN, and CEN FC (Altinok et al., 2021; Bolsinger et al., 2018; Hemington et al., 2018; Iadipaolo et al., 2017, 2018; Van der Werff et al., 2013). Miyagi et al. (2020) also reported an association between resilience and changes in FC, specifically when engaging in a cognitive task. That is, higher scores of resilience related to stability and homeostasis of FC in the DMN when initially engaging in cognitively demanding conditions. Additionally, resilience was linked to dynamic states of DMN-CEN connectivity in children and adolescents exposed to significant sociodemographic adversity, suggesting that these network interactions may reflect adaptive neurofunctional reorganization in response to environmental stressors (Iadipaolo et al., 2018). Importantly, interpretations of these neurofunctional findings in the context of concussion should consider commonly reported injury-related disruptions that may confound resilience-FC associations, such as acute hyperconnectivity and complex connectivity changes throughout recovery (Bouchard et al., 2024; Boshra et al., 2020; Liu et al., 2020b; Mayer et al., 2011; Zhu et al., 2015). Few studies, however, have directly addressed the neurofunctional correlates of resilience following pediatric concussion.

Some research suggests that resilience might decrease following TBI. In a recent study, children with mTBI reported significantly lower resilience scores than orthopedic injury controls, particularly at 1-weeks, 3 months, and 6 months post-injury (Hassan et al., 2024). Marwitz et al. (2018) found a significant decrease in resilience during the first-year post-injury of moderate to severe TBI, though only after controlling for race, education, preinjury substance abuse, anxiety, satisfaction with life, and disability level. In a study of traumatic physical injury-related factors, only the Glasgow Coma Scale ratings correlated significantly with resilience at either baseline or one year follow-up (Rainey et al., 2014). Given that resilience may decline following concussion and considering its critical role in clinical outcomes as well as its potential influence on neural outcomes, it is paramount to identify effective strategies to foster this capacity in children and adolescents. Mindfulness practices are among the current evidence-based interventions for enhancing psychological resilience, which cultivate attentional and regulatory skills relevant to adaptive behaviours that present a valuable therapeutic approach in this context.

3. Mindfulness

Mindfulness research is becoming increasingly prevalent in both the scientific and clinical community, exploring the effects of a psychological process when implemented as an intervention in clinical populations. Operationalization of mindfulness as a construct is a necessary precursor for scientific advancement in explaining the implications of such phenomenon in clinical environments. While Davids (1881) first translated the Pali concept of sati into mindfulness, subsequent scholars have attempted to translate the concept into contemporary psychology research. Influenced by the original conception of sati, which may be characterized as a way of paying attention (Davids & Davids, 1910) or keeping something in mind (Gethin, 2015), Kabat-Zinn (2003) defined mindfulness as “awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment” (p. 145). Similarly, Brown et al. (2007) defined mindfulness as a “receptive attention to and awareness of present events and experience” (p. 212). The authors further outlined overlapping and mutually supportive core concepts to further conceptualize mindfulness, including clarity of awareness; nonconceptual, non-discriminatory awareness; flexibility of awareness and attention; empirical stance towards reality; present-oriented consciousness; and stability or continuity of attention and awareness (Brown et al., 2007). Although these definitions of mindfulness provoked contention among scholars (Vervaeke, 2022), some authors reconcile disparities in the definitions by acknowledging that accounts will always differ based on context (e.g., psychological, clinical, or spiritual) and perspective (e.g., researcher, clinician, practitioner; Singh et al., 2008). Other authors suggest that formulating an absolute definition of mindfulness is insurmountable, as phenomenological components of the construct remain ineffable and can only be understood on an experiential plane (Shonin et al., 2014). Despite the nuanced conceptualizations of mindfulness as a construct, there is a growing convergence of results across methods that suggest mindfulness and, by extension, mindfulness-based interventions (MBIs) can foster healthy, adaptive behaviours.

MBIs are psychological-based interventions that include a collection of mindfulness practices, demonstrating contemporary efforts towards its application in a scientific setting. An increasing volume of research applying MBI with healthy and clinical populations alike demonstrates distinctly positive behavioural effects. In a recent systematic review and meta-analysis, Zhou et al. (2020) found that the mindfulness-based stress reduction program, a clinically established MBI (Baer, 2003; Kabat-Zinn, 1990), significantly and reliably reduced anxiety symptoms in young people relative to various control conditions including a didactic lecture course; didactic seminar and cognitive behavioural program in young people with anxiety symptoms; health education; and treatment as usual. In youth, MBI related significantly to improved attentional focus, cognitive flexibility, depression, anxiety, self-concept, resiliency, and academic achievements as well as decreased emotional reactivity and fear (Dunning et al., 2019). In healthy children, MBI correlated with a significant improvement in the emotional and psychological components of the Pediatric Quality of Life Inventory (PedsQL; Bazzano et al., 2018). In a pilot study of adults with mild to moderate TBI, Bédard et al. (2003) reported an increase in quality of life and a decrease in depression symptoms following an MBI. Azulay et al. (2013) reported improvements in perceived self-efficacy, positive problem-solving orientation, and central executive aspects of attention and working memory in mTBI participants after completing an MBI. Supporting this, a recent systematic review and meta-analysis reported that meditation, yoga, and MBIs significantly improved a range of chronic symptoms in patients with mTBI, including mental health, physical health, cognitive performance, quality of life, and self-related processing, with the most pronounced improvements to fatigue and depression (Acabchuk et al., 2021).

Recent evidence also demonstrated neural effects of mindfulness practices across various stages of training. It is theorized (Zeidan, 2015) that early stages of mindfulness meditation training (e.g., <1 week of training) support top-down regulation of emotional processing, indicated by greater activation of cortical regions including prefrontal and anterior cingulate cortices (Zeidan et al., 2011) as well as deactivation of subcortical regions including the amygdala and thalamus (Goldin & Gross, 2010; Taylor et al., 2011; Zeidan et al., 2011). Later stages of training (e.g., >1,000 hours of training) are accompanied by a decoupling between brain regions underlying appraisals of sensory processing, indicated by greater activation of regions including the anterior insula and somatosensory cortices as well as deactivation of the prefrontal cortex (Gard et al., 2012; Grant et al., 2011). Meanwhile, studies show decreases in DMN activity in both early stages (Farb et al., 2010; Farb et al., 2007; Taylor et al., 2013; Zeidan et al., 2011) and later stages (Grant et al., 2011) of training. In a recent systematic review, MBIs generally increased DMN, SN, and CEN FC (Jande et al., 2025). For instance, Bauer et al. (2020) observed that MBIs enhanced FC between the posterior cingulate cortex of the DMN and the dorsolateral prefrontal cortex of the CEN, with these neural changes linked to improvements in sustained attention. Hafeman et al. (2020) also found MBI enhanced resting-state FC between the posterior cingulate cortex and dorsolateral prefrontal cortices following MBI, which was associated reductions in mood lability and emotion suppression. Patsenko et al. (2019) found that MBI increased resting-state FC between the dorsolateral prefrontal and inferior parietal cortices, which correlated with enhanced attention task performance. Lastly, Mishra et al. (2020) reported that MBI enhanced FC between the dorsal anterior cingulate cortex of the SN and the cingulo-opercular network, which was associated with better sustained attention, decreased hyperactivity, and improved academic outcomes. Collectively, these reports highlight MBIs as potent interventions capable of eliciting both behavioural and neurobiological changes across levels of experience or training, underscoring their potential relevance for enhancing adaptive capacities such as resilience across diverse populations.

4. Mindfulness and Resilience

MBIs are among the most common strategies for enhancing resilience. As an example, a recent study of young adults found that mindfulness practices directly increased resilience as well as psychological well-being (Oh et al., 2022). Additionally, a systematic review and meta-analysis examining MBI in school systems found promising evidence for application of MBI in children and youth for improving resilience (Zenner et al., 2014). Another recent systematic review by O'Connor et al. (2023) found MBIs to be effective in promoting resilience in randomized controlled trials, outperforming both inactive control conditions (waiting list or no treatment) and active control condition (designed to control for nonspecific effects of activity and attention). Therefore, MBIs were deemed efficacious in enhancing resilience, with similar efficacy relative to comparison interventions.

Mindfulness practices taught in MBI are essential for diminishing discursive thoughts, expressive suppression, and rumination while promoting non-reactive awareness, and non-judgmental acceptance of present moment experiences. This, in turn, may be linked to successfully coping with trauma and consequently increased resilience. Rumination is a common coping mechanism that is often associated with symptoms of depression and anxiety (Michl et al., 2013). Mindfulness was found to correlate negatively with rumination and positively with resilience, suggesting that reduced rumination may partially mediate its beneficial emotional effects (Shi et al., 2023). Rumination processes were also shown to mediate the association between mindfulness and depression, whereby mindfulness improved cognitive reappraisal and diminished expressive suppression, worry, and rumination (Parmentier et al., 2019). Decentering, where individuals learn to observe their thoughts and emotions from a detached perspective, was also proposed as a key psychological mechanism for the reported effects of MBI (Bernstein et al., 2015). Given that decentering fosters adaptive emotional regulation (Feldman et al., 2010), it may also play a role in the resilience-enhancing effects of MBIs. These potential mechanisms suggest that MBIs not only alleviate maladaptive cognitive patterns but may also promote healthy coping techniques that are necessary for enhancing resilience.

MBIs might enhance resilience by leveraging mechanisms that reduce overidentification with stressors and symptoms. Together, skills utilized in MBIs such as attention retention, decentring, and non-judgmental acceptance might establish a psychological space to regulate emotion and stress response. This capacity to observe distress without avoidance, suppression, or overidentification could foster adaptive behaviours and mitigate affective reactivity. The reduced affective reactivity may reflect healthy nervous system functioning in the presence of stressors or traumas, thereby supporting resilience.

At a neurobiological level, MBI may support resilience by enhancing top-down regulatory processes in the brain. Structural and functional neuroimaging studies link mindfulness training to increased activity and connectivity in prefrontal cortical regions involved in cognitive control and emotion regulation (Hölzel et al., 2007; Tomasino & Fabbro, 2016; Zeidan et al., 2015). Such neurobiological changes are often associated with decreased stress-related connectivity between the amygdala and anterior cingulate cortex, reducing physiological stress reactivity (Creswell & Lindsay, 2014; Creswell et al., 2016; Taren et al., 2017). Relatedly, in a controlled study examining the effects of meditation on resilience and resting-state FC, the meditation group showed sustained increases in resilience, which were mediated by enhanced resting-state connectivity between the rostral anterior cingulate cortex and the dorsomedial prefrontal cortex (Kwak et al., 2019). Notably, the increase in FC significantly mediated changes in both self-reported mindfulness and resilience scores, suggesting a potential neurofunctional mechanism of meditation practices and adaptive behaviours. Research also consistently indicates that MBIs are linked to increased FC within and between the DMN, SN, and CEN in youth populations (Bauer et al., 2020; Bremer et al., 2022; Hafeman et al., 2020; Jande et al., 2025; Mishra et al., 2020; Patsenko et al., 2019; Tang et al., 2015; Taren et al., 2017). Given that the coordinated interaction among these networks is implicated in self-regulatory processes, it is posited that MBIs may facilitate behavioural outcomes, such as resilience, by fostering functional reorganization across these neurofunctional networks (Jande et al., 2025; Melis et al., 2022; Young et al., 2018). Additionally, structural changes following MBI, such as increased grey matter density in the hippocampus (Hölzel et al., 2011) and white matter microstructural changes (Mioduszewski et al., 2020), may further support adaptive stress responses. Together, these psychological and neurobiological findings may provide a foundation for understanding the resilience-enhancing effects of MBI, equipping individuals with a greater capacity for adaptive behaviours and successful coping in the face of trauma or adversity.

5. Theoretical Foundation for Evidence-Based Framework

As outlined in preceding sections, resilience is a dynamic, malleable process that supports positive adaptation following adversity and may be implicated in mitigating clinical outcomes of concussion. As noted in Section 4, MBIs are empirically supported approaches for enhancing resilience in healthy populations. Building on this theoretical foundation, this dissertation presents an evidence-based framework that outlines potential mechanisms by which baseline resilience, reflecting participants' experiences over the preceding 30-day period, may be implicated in concussion outcomes along with the incorporation of MBIs as resilience-targeted interventions (see Figure 2). Neural outcomes refer to changes in brain structure and function, including white matter microstructure (e.g., FA, MD, AD, RD) and resting-state FC, while clinical outcomes refer to PCS as well as recovery time and, relatedly, PSaC. Concussion-related outcomes are theorized to be closely intertwined, with influences of neural outcomes on clinical symptomatology. Empirical evidence indicates that neurological disruptions may persist beyond the resolution of clinical symptoms (Johnson et al., 2015; Sinopoli et al., 2014), while clinical symptom severity may be associated with such disruptions (Duquette & Spotts, 2021; Halstead et al., 2018; Rose et al., 2015). Furthermore, both factors are likely affected in part by pre-injury characteristics. For example, certain demographics (age and sex) and diagnostic history (anxiety and depression) are associated with recovery trajectory and risk for post-concussive mental health difficulties (Gornall et al., 2024; Max et al., 2021; Zemek et al., 2016).

Resilience is related to clinical outcomes following pediatric concussion, with lower resilience associated with greater PCS and PSaC severity, longer recovery duration, and increased emotional dysregulation (Bunt et al., 2021; Durish et al., 2018, 2019; Ernst et al., 2021; Hassan et al., 2024). Conversely, emerging evidence suggests that resilience itself may be shaped by PCS, with longitudinal studies indicating bidirectional associations between resilience and symptoms across time points (Hassan et al., 2024). These findings support this dissertation's framework depicting of a bidirectional association between resilience and clinical outcomes, particularly PCS, suggesting that resilience-targeted interventions may support recovery. This dissertation's proposed framework also depicts the hypothesized association between resilience and neural outcomes of concussion. Studies in non-injured and complicated mild, moderate and severe TBI populations have demonstrated associations between resilience and indices of white matter microstructure (Galinowski et al., 2015; Schmidt et al., 2021), as well as FC within and between the DMN, SN, and CEN (Altinok et al., 2021; Iadipaolo et al., 2017). Given that concussion is linked to hyper- and hypoconnectivity of these same networks (Bouchard et al., 2024; Borich et al., 2015), resilience may moderate FC of these networks and promote neurofunctional recovery.

In addition to its potential direct effects on concussion-related outcomes, MBIs may enhance resilience and influence the association between resilience and outcomes. MBIs could support resilience by reducing maladaptive coping strategies (e.g., fear avoidance, rumination, and emotional reactivity) and strengthening top-down regulatory processes (Zeidan et al., 2015; Creswell & Lindsay, 2014). Moreover, MBIs are related to FC changes in the same neurofunctional networks implicated in both resilience and concussion-related brain alterations (Bauer et al., 2020; Jande et al., 2025). Thus, this dissertation's proposed framework suggests that MBIs may have both direct and indirect effects on concussion recovery: directly by promoting clinical improvement and enhancing network efficiency, and indirectly by enhancing resilience and moderating its effects on neural outcomes.

Taken together, this dissertation's proposed framework and its components considers reports of empirical evidence-based findings while also outlining opportunities for future research. To support this framework, the dissertation presents three studies that examine hypothesized mechanisms: (1) the direct effects of resilience on neural outcomes, specifically white matter microstructure and FC; (2) the effects of an MBI on resilience trajectories in pediatric concussion; and (3) the moderating effects of MBI on the association between resilience and neurofunctional outcomes (see Figure 3).

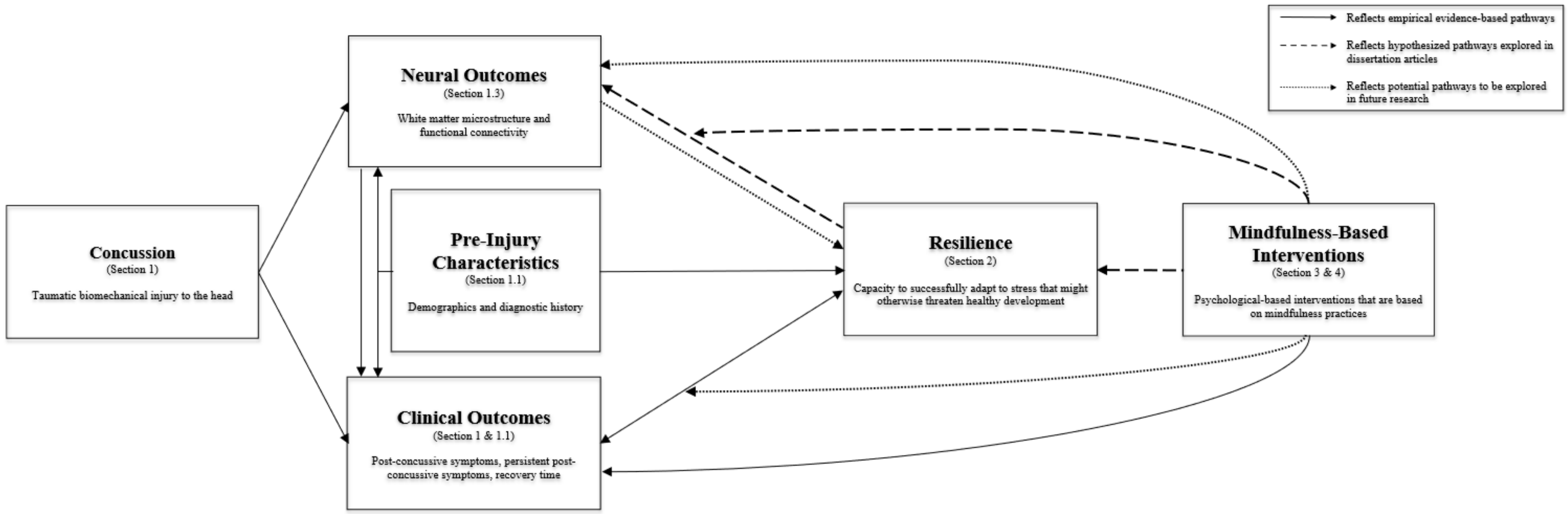

Figure 3. Evidence-based framework of resilience

An evidence-based framework that reflects the pathways by which resilience might influence concussion outcomes, and how MBI might enhance such effects. Solid arrows reflect empirical evidence-based pathways; dashed arrows reflect hypothesized pathways to be addressed in this dissertation; while dotted arrows reflect potential pathways advised for future research initiatives.

6. Purpose of Current Research

Building upon the established importance of psychological resilience in mitigating post-concussion symptoms and the potential of MBIs to enhance this capacity, more research is needed to explore the neurobiological underpinnings of resilience and resilience-targeted interventions in the proposed evidence-based framework.

Specifically, there is a significant paucity of research directly investigating the neural correlates of resilience following pediatric concussion, particularly within the acute to sub-acute phase (<=1 month post-injury), and how MBIs may moderate these neural pathways. As pediatric concussion triggers a neurometabolic cascade (Giza & Hovda, 2014), it is probable that the several of the neural correlates of resilience identified in non-injured samples are incongruent to those in brain injured samples. It is crucial to understand the neural correlates of resilience following brain injury in children as a prerequisite for researching resilience-targeted interventions that may effectively support recovery. Investigations of this sort have the potential to improve not only clinical outcomes, but also brain health and overall well-being for children with concussion.

It also remains unclear whether resilience can be increased following pediatric concussion with the application of resilience-targeted interventions, particularly MBI, and whether such interventions can improve both clinical and neural outcomes. Consequently, if children and adolescents with concussion and low resilience are more susceptible to adverse clinical symptoms and neural alterations, then the early implementation of MBIs as a targeted approach to enhance resilience could effectively mitigate these negative outcomes, thereby fostering improved brain health and long-term well-being. MBI can be designed to teach children healthy coping skills to deal with their concussion symptoms, thereby increasing resilience and reducing the risk of worsened concussion symptoms for affected children.

This line of investigation needs to be considered by concurrent guidelines for treatment following pediatric concussion. The current proposed guidelines are limited to a recommended 24-48 hours (hrs) rest after concussion followed by a stepwise return to activity with no indication of early implementation of psychological interventions (Patricios et al., 2023). Children that follow an MBI in conjunction with the guidelines may experience the additional benefits to brain health. If positive results from these investigations are demonstrable, future generations of children that sustain a concussion could benefit from updated consensus statement guidelines that incorporate early implementation of resilience-targeted interventions.

No studies to date explicitly examined perceived resilience as a predictor of neural outcomes following pediatric concussion, nor the effects of MBI on these associations. Hence, there is insufficient empirical evidence to explain whether resilience is associated with white matter microstructure and FC following pediatric concussion, as well as whether MBI enhances resilience in this context or moderates such effects. Here we will address these questions with a series of studies examining the effects of resilience, as well as MBI, on neural outcomes in concussed children. This dissertation provides a unique and valuable contribution to the literature by empirically combining psychosocial and neurobiological models, specifically investigating both the structural (white matter microstructure) and functional (FC) neural correlates of resilience in acute pediatric concussion. The evidence-based framework will produce findings that directly inform future research for clinical practice by using established methods to identify neural correlates of a measurable, modifiable factor (resilience) in acute pediatric concussion and assessing the effects of an implemented MBI.

The primary research objective addressed in this dissertation is to investigate whether resilience predicts neural outcomes (DTI and fMRI metrics) following acute pediatric concussion. Additionally, we will assess whether injury type (concussion vs. orthopedic injury) moderates the association between resilience and neural outcomes. The secondary research objective is to investigate whether an app-based MBI enhances resilience and moderates the effects of baseline resilience on neural outcomes. The primary objective is based on an initial larger study which investigated the effects of gradual return to physical activity at 72 hrs post-injury on symptom burden in children with concussion. The secondary objective is based on a second larger study which investigated the feasibility of a randomized controlled trial for an app based MBI in pediatric concussion.

7. Research Protocol

This research project consists of three studies based on data collected from two larger studies. Specifically, Chapters 2 and 3 are based on the first study, while Chapter 4 is based on the second study.

Study 1, presented in Chapter 2, sought to identify white matter microstructural correlates of resilience, reflecting experiences over the preceding 30 days, in pediatric concussion at baseline (72hrs post-injury) and follow-up (4 weeks post-injury). This study simultaneously aimed to identify differences in such correlates between samples of children with concussion and orthopedic injury. We hypothesized that resilience scores were associated with DTI metrics in both groups (i.e., concussion and orthopedic injury) at both timepoints, with no interactions between group and resilience when predicting outcomes.

Study 2, presented in Chapter 3, sought to identify longitudinal and cross-sectional associations between resting-state FC and resilience in pediatric concussion. This second study also aimed to identify differences in these associations between children with concussion or with orthopedic injury. We hypothesized that longitudinal and cross-sectional resilience was negatively correlated with DMN, SN, and CEN FC within both groups. We further anticipated that such correlations were moderated by group.

Study 3, presented in Chapter 4, sought to identify whether the implementation of an MBI affected resilience trajectories and moderated associations between baseline resilience (1-day post-recruitment) and follow-up resting-state FC (4 weeks post-injury). We hypothesized that the MBI group would show greater improvements in resilience scores relative to the control group. We also hypothesized that MBI would moderate associations between baseline resilience and DMN, SN, and CEN FC at follow-up.

Data for Studies 1 and 2 was derived from a randomized clinical trial entitled Pediatric Concussion Assessment of Rest and Exertion with MRI (Clinicaltrials.gov identifier: NCT02893969; Ledoux et al., 2019). This study investigated the effects of gradual resumption of physical activity commencing 72hrs post-injury on symptom burden, neurophysiological and neuropsychological indicators. Participants were randomly assigned to one of two groups: the experimental group (1); the control group (2). The experimental group commenced a gradual resumption of daily physical activity at 72hrs post-injury even if symptomatic. The control group underwent gradual resumption of physical activity once asymptomatic; McCrory et al. [2013]). Concussed participants' behavioural movement was tracked for 14 consecutive days (24hrs/day) with an accelerometer. Orthopedic injury participants were included as a control, representative of a non-concussed child population. The orthopedic injury group did not have a targeted intervention to follow. Given the minimal differences in moderate to vigorous physical activity between groups, participants were pooled into a single group for analyses in Studies 1 and 2, with adjustment for group assignment. Imaging acquisition occurred at two timepoints: 72hrs post-injury and 4 weeks post-injury. Self-report measures of resilience, symptomatology, and other pertinent variables were assessed at both timepoints.

Data for Study 3 was derived from a Health-Canada regulated randomized clinical trial entitled Mindfulness-Based Intervention in Mild Traumatic Brain Injury (ClinicalTrials.gov ID: NCT05105802; Ledoux et al., 2024). Participants aged 12-17.99 with concussion were enrolled from the emergency department at the Children's Hospital of Eastern Ontario (CHEO) or the 360 Concussion Care clinic. Concussions were defined based on the modified American Congress of Rehabilitation Medicine criteria (Silverberg et al., 2023). This involved including adolescents who reported at least one 'highest certainty' symptom or two 'higher certainty' symptoms either immediately or within an hour of their injury. Additionally, all participants needed to score above 4 on the Predicting and Preventing Post-Concussive Problems in Pediatrics clinical risk score, which classifies the likelihood of developing PSaC after acute concussion in children and adolescents (Zemek et al., 2016) and be proficient in English. Participants were then randomly assigned to one of two groups: the experimental group (1); the control group (2). The experimental group completed an app based MBI over four weeks. The control group was assigned to a sham app, where they had to engage in a simple arithmetic task. The control group was offered the opportunity to undergo the MBI upon completion of the study. Both groups followed current standard of care, whereby patients were recommended to gradually return to cognitive and physical activity after a rest period of 24 to 48 hrs post-injury. The patients were to begin with a low to moderate level of cognitive and physical activity that did not result in recurrence or exacerbation of symptoms (Patricios et al., 2023; Reed et al., 2020). Imaging acquisition occurred at two timepoints: 72hrs post-injury (1); 4 weeks post-injury (2). Self-report assessments of resilience, symptomatology, and other pertinent variables were assessed in the emergency department, at 1-day post-recruitment, and at 4 weeks post-recruitment.

7.1 MBI

The mobile app MBI was designed with careful consideration in collaboration with Mobio Interactive Pte Ltd (Singapore), the host of the digital therapeutic platform AmDTx. The personalized MBI was co-developed by study investigators Drs. Andrée-Anne Ledoux and Molly Cairncross, based on previously validated AmDTx MBI app protocols (Ledoux et al., 2024; Subnis et al., 2020; Walsh et al., 2019) as well as team expertise in youth MBI, and was also peer reviewed by relevant experts and parent engagement leaders. The AmDTx app lists the MBI as a Concussion Recovery Journey, consisting of several modules each containing a variety of sessions for the duration of four to eight weeks. This program is organized into modules specifically designed to help participants manage emotions, respond to stress, and cope with concussion-related difficulties through psychoeducation and mindfulness exercises. The program incorporates a variety of components. For instance, audio-recorded lectures provide psychoeducational components, while guided practices include meditations, such as body scans, and exercises for mindful breathing. Moreover, the app features optional interactive components that involve setting intentions, a mood check-in, and a function for journalling. Participants in the MBI group were instructed to use the app-based program for a minimum of 10 minutes daily, 4 days a week, for 4 weeks following their enrollment. The pilot study evaluating the personalized MBI found the intervention to be acceptable, usable, and credible based on validated and reliable measures, including the Credibility and Expectancy Questionnaire, Client Satisfaction Questionnaire, System Usability Scale, Working Alliance Inventory for guided Internet Interventions, and qualitative semi-structured interviews (Sicard et al., 2024). Moreover, adolescents developed a strong therapeutic alliance and a sense of social presence through engagement with the self-guided digital MBI, with qualitative findings suggesting that this experience was influenced by developing a genuine connection, sensing real people, as well as the usage of personal backgrounds and voices (O'Kane et al., 2024).

An app-based platform to administer the MBI allows for optimal accessibility, feasibility, and integration. The accessibility of an intervention administered through an app also allows for participants to access the guided sessions daily at any given time as opposed to scheduled, in-person appointments with certified guides. The app offers a series of scripted practices pre-recorded by both a male and female guide, guaranteeing consistency in how the intervention is administered. The app collects usage data, allowing for consideration of intervention adherence prior to statistical analysis. The mobile app is also the host of the cognitive sham intervention. Although the sham intervention is provided on the same host app, participants in the control group did not have access to the MBI or any mindfulness-based activities hosted by AmDTx. This sham intervention consisted of daily engagement with a simple arithmetic task, or the game 2048, which was applied as a cognitive sham intervention in another study of app-based mindfulness meditation on well-being (Walsh et al., 2019). More specifically, participants in the control group were instructed to engage in the sham intervention for 10 minutes daily, four days a week, for four weeks. The sham intervention was only made accessible in-app for 10 minutes per day. Moreover, the game 2048 was not found to reduce concussion symptoms at 4 weeks following pediatric concussion, further supporting its use as a suitable sham intervention (Teel et al., 2021).

In sum, pediatric concussion poses a clinical problem with potentially long-lasting neural and clinical outcomes. There is emerging evidence indicating that psychological resilience is associated with diminished clinical symptom severity and improved recovery trajectories. More empirical findings regarding the neural underpinnings of resilience in the context of pediatric concussion are needed to better understand its implications for brain health. Considering that resilience may be enhanced through MBIs, it is probable that children and adolescents with concussion that are assigned to an MBI would present improvements in resilience and resilience-related neural outcomes. This dissertation seeks to advance our understanding of resilience and MBI as a resilience-targeted intervention on neural outcomes in pediatric concussion by contributing empirical evidence derived from three advanced imaging studies, along with a general discussion concerning overlapping findings and opportunities for future research initiatives.

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Chapter 2: Study 1

Associations between psychological resilience and metrics of white matter microstructure in pediatric concussion

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Abstract

This study investigated associations between psychological resilience and characteristics of white matter microstructure in pediatric concussion. This is a case control study and a planned substudy of a larger randomized controlled trial. Children with an acute concussion or orthopedic injury were recruited from the emergency department. Participants completed both the Connor–Davidson Resilience Scale 10 and an MRI at 72 h and 4 weeks post-injury. The association between resiliency and fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) at both timepoints were examined. We examined whether these associations were moderated by group. The association between resiliency captured at 72 h and diffusion tensor imaging metrics at 4 weeks was also investigated. Clusters were extracted using a significance threshold of threshold-free cluster enhancement corrected $p < .05$. A total of 66 children with concussion (median [IQR] age = 12.88 [IQR: 11.80–14.36]; 47% female) and 29 children with orthopedic-injury (median [IQR] age = 12.49 [IQR: 11.18–14.01]; 41% female) were included. A negative correlation was identified in the concussion group between 72 h resilience and 72 h FA. Meanwhile, positive correlations were identified in the concussion group with concussion between 72 h resilience and both 72 h MD and 72 h RD. These findings suggest that 72 h resilience is associated with white matter microstructure of the forceps minor, superior longitudinal fasciculus, and anterior thalamic radiation at 72 h post-concussion. Resilience seems to be associated with neural integrity only in the acute phase of concussion and thus may be considered when researching concussion recovery.

Introduction

Children and adolescents are among those with the highest rates of traumatic brain injury related emergency department visits, with increased vulnerability to neuronal damage (Keightley et al., 2012; McCrory et al., 2004; Taylor et al., 2017). Although concussions are considered as mild traumatic brain injuries, those with a concussion can experience a variety of somatic, emotional, and cognitive symptoms, that can last for months to years, impacting quality of life. (Beauchamp et al., 2019; McCrory et al., 2017; Novak et al., 2016; Yeates, 2010). Concussion is characterized by neural deficits such as decreases in white matter structural integrity, altered patterns of brain activity, dysfunctional autoregulation and impaired vascular reactivity, as well as depressed cerebral blood flow (Bigler & Bazarian, 2010; Choe et al., 2012; Johnson et al., 2012; Maugans et al., 2012; Mayer et al., 2011; Roberts et al., 2014; Werner & Engelhard, 2007).

Psychological resilience is defined as an individual's ability to adapt or thrive in the face of trauma or adversity that may threaten healthy functioning or development (Masten & Barnes, 2018). The construct of resilience is an abstraction of all adaptive capacities available to an individual to successfully cope with various stressors or traumas (Masten & Barnes, 2018). High levels of negative stress can impact children's emotions, behaviour, physical health, and socialization (Barnes, 2016). Highly resilient children are more likely to successfully cope with stress, decreasing its effects on their functioning (Barnes, 2016). Thus, resilience may be considered as a measure of the ability to cope with stress (Connor & Davidson, 2003). Resilience has also been characterized as a process, and not a trait. Measures such as the Connor–Davidson Resilience Scale (CD-RISC), were designed with the intention to assess the modifiability of resilience. Previous studies using this assessment demonstrated that resiliency scores can be modifiable and can improve with appropriate treatments (Connor & Davidson, 2003; Davidson et al., 2005). Hence, children that follow such treatments may experience the benefits of high resilience on well-being. If highly resilient children have differential white matter integrity following concussion, treatments targeted toward enhancing resilience may bolster brain structure post-concussion. This provides an opportunity for further studies to investigate whether specific treatments enhance resilience in pediatric concussion, and to examine such effects on brain health.

There is emerging evidence that would suggest psychological resilience is associated with favorable behavioural and, possibly, neural outcomes in clinical pediatric cases, particularly traumatic brain injury. Two recent studies of children with acute concussion, have demonstrated that low resilience was associated with high post-concussion symptom severity and was often accompanied by both high depressive and anxiety symptoms (Bunt et al., 2021; Durish et al., 2018). The association between resilience and concussion symptomatology was also determined to be mediated by depressive and anxiety symptoms (Durish et al., 2019). With regards to neural outcomes, a recent report indicated that fractional anisotropy (FA) and mean diffusivity (MD), measures of white matter integrity, were associated with resilience-promoting factors (i.e., intact intellectual functioning, access to community resources, presence of a warm and supportive caregiver, and prosocial peer influences) in complicated mild, moderate and severe TBI (Schmidt et al., 2021). Currently, no studies have examined the white matter microstructural correlates of resilience in pediatric concussion, or mild traumatic brain injury, in the acute and subacute phase (<1-month post-injury). The subacute phase of concussion is often associated with significant changes in FA, MD, and other measures of white matter integrity (Borich et al., 2013; Mayer et al., 2012; Roberts et al., 2014; Wu et al., 2010). The neural correlates of resilience may be a protective factor in this critical phase of the pediatric concussion recovery process. If highly resilient children experience diminished neural deficits following concussion, it may be postulated that resilience-targeted treatments may alleviate such deficits in children with lower resilience and improve brain health. Investigating both behavioural and neural correlates of resilient children might help further our understanding of recovery processes in the subacute phase of pediatric concussion.

Diffusion tensor imaging (DTI) may serve as an effective technique to identify white matter correlates of resilience in children with concussion (Bigler & Bazarian, 2010; Gardner et al., 2012; Roberts et al., 2014). Alterations in microstructural white matter integrity following pediatric concussion can be detected immediately following the injury (acute phase; Roberts et al., 2014) and can persist beyond 3 months post-injury (chronic phase; Roberts et al., 2014; Ware, Yeates, Geeraert, et al., 2022; Ware, Yeates, Tang, et al., 2022). The most common measure used to assess white matter integrity with DTI is FA, a normalized measure of the directionality of molecular diffusion. An increase in myelination or axonal density decreases intercellular water diffusion, thus increasing FA (see Feldman et al., 2010 for a review). Additional information for the characterization of white matter microstructure can be extracted from DTI measures, including axial diffusivity (AD), that is diffusivity parallel to the axis of diffusion, radial diffusivity (RD), that is diffusivity perpendicular to the axis of diffusion, and MD, the magnitude of diffusion. Traumatic brain injury animal model research provides further insight to DTI metric correlates of white matter microstructure. In mouse models of white matter injuries, increased FA with decreased AD and RD is thought to reflect axonal degeneration, while decreased FA with increased RD alongside unchanged AD may reflect demyelination (Budde et al., 2008, 2009).

Healthy children and adolescents experience ongoing microstructural development of fiber tracts, including myelination progression (Asato et al., 2010). Such microstructural development of white matter can be detected using DTI metrics. Several studies reported a gradual decrease in MD alongside a gradual increase in FA across numerous major fiber tracts in developing brains (see Qiu et al., 2015 for a review). Maximal levels of FA along various fiber tracts are achieved at different ages (Lebel et al., 2008). Hence, differences in DTI metrics are detectable in pediatric samples that are still undergoing white matter development. Children and adolescents are thought to have increased risk of neuronal injury from concussion, partly due to ongoing myelination (Keightley et al., 2012; Kirkwood et al., 2006; McCrory et al., 2004). Fiber tracts that are not fully developed, or with lower extent of protective myelin, likely have diminished shear resistance (Thibault & Margulies, 1998). Although the developing brain was thought to be more adaptive due to its plasticity and myelination, some evidence suggests that deficits in white matter microstructure can persist for years following concussion (Caeyenberghs et al., 2011; Roberts et al., 2014).

In pediatric and young adult concussion samples, however, some research has detected an increase in FA in the acute phase following concussion, which might reflect axonal swelling or cytotoxic edema (Bigler & Bazarian, 2010; Gardner et al., 2012; Roberts et al., 2014; Wu et al., 2010). This variability in the interpretation of what FA values indicate suggests that FA alone is not sufficient to characterize microstructural white matter integrity, at least within the context of concussion. A meta-analysis conducted by Roberts et al. (2014) reports a trend of increases in FA and decreases in MD within the acute and subacute phases of pediatric concussion. In chronic pediatric concussion, however, global decreases in FA and increases in MD can be identified, suggesting depressed integrity of white matter. Such changes in DTI measures were also associated with increases in pediatric concussion-related symptoms (Bartnik-Olson et al., 2014). Further research is required to accurately assess the implications of the direction of changes in DTI metric values, particularly in pediatric concussion, while also considering whether resilience is associated with the outcomes as such.

Exploring the neural correlates of resilience in pediatric concussion is a necessary precursor to understanding the capacity of resilience-targeted treatments for improving brain health following concussion. It is paramount for studies to first explain the effects of resilience on brain structure and function after a concussion, as research has already demonstrated positive effects of resilience on clinical outcomes (Durish et al., 2018; Durish et al., 2019). If high resilience is associated with different neural outcomes in the event of a concussion, resilience-targeted treatments may further benefit current guidelines for optimal concussion recovery.

The objectives of this article were to investigate self-reported resiliency as a correlate of FA, MD, AD, and RD maps assessed at both 72-h and 4 weeks post-injury in pediatric and orthopedic-injured children. We also sought to determine whether these correlates were moderated by type of pediatric injury (concussion or orthopedic). A secondary objective was to assess 72 h resiliency as a correlate of 4-week FA, MD, AD, and RD maps in the concussion group.

Associations between resilience promoting factors and DTI metrics were previously identified in youth with concussion (Schmidt et al., 2021). Similarities in DTI metric alterations following injury were reported between children with concussion and orthopedic-injured children, likely attributable to premorbid or injury-risk-related factors (Hulkower et al., 2013). Consequently, we hypothesized that resilience scores are associated with DTI metrics in both groups at both timepoints. Specifically, we anticipated that resilience was positively correlated with FA and AD values, while negatively correlated with MD and RD values in both groups at each timepoint. We also hypothesized that associations of resilience and DTI metrics at both timepoints would not differ between groups. In other words, there are no interactions between group and resilience when predicting DTI metrics.

Methods

Design

This was a substudy of the randomized clinical trial entitled Pediatric Concussion Assessment of Rest and Exertion (PedCARE; Ledoux et al., 2019), where a subsample of children and adolescents with a concussion received an MRI at <72 h (±48 h) and at 4 weeks (±5 days) from enrolment in the emergency department, post-injury. PedCARE studied two groups of participants with a concussion based on rest until asymptomatic or exertion after 72 h of rest instruction but found no differences in the overall group means of physical activity (Ledoux et al., 2021). For this reason, the current study combined both concussion groups together. Participants with an orthopedic injury were also included as a comparison group, allowing for comparisons both within as well as between groups. Participants were included in this substudy only after satisfying inclusion and exclusion criteria, as well as having complete data for all variables included in listed analyses. This study was approved by the Research Ethic Board at the Children's Hospital of Eastern Ontario.

Participants

Children and adolescents with a concussion were only included if they were deemed eligible according to the following criteria: sustained a concussion within 48 h prior to the emergency department visit; were 10 through 17.99 years of age; and proficient in English. Participants with a concussion were excluded if they met any of the following criteria: Glasgow

Coma Scale rating of <=13; abnormality or incidental findings on standard imaging; required neurosurgical operative intervention, intubation, or intensive care; required sedation; incapable of resuming physical activity; history of trauma preceding injury.

Orthopedic-injured participants were included as a comparison group. Children and adolescents with orthopedic injuries are a suitable comparison group, as statistical comparisons with healthy non-injured children fails to eliminate confounds related to the experience of injury trauma. Although previous research identified similar alterations in DTI metrics in the acute phase of injury (i.e., <96 h post-injury; Wilde et al., 2019) between concussion and orthopedic-injured participants relative to healthy children, such similarities may be attributable to premorbid or predisposing risk factors (Ware, Yeates, Geeraert, et al., 2022; Wilde et al., 2019). Further, differences in DTI metrics between concussion and orthopedic-injured samples have been reported in the in the subacute and chronic phases (Roberts et al., 2014; Ware, Yeates, Tang, et al., 2022). Orthopedic-injured participants were included if they were 10 through 17.99 years of age; sustained an orthopedic injury isolated to the upper extremity within 48 h prior to the emergency department visit; and were proficient in English. Orthopedic-injured participants were excluded if they had a concussion within the past year or required sedation or surgical operation. As such, orthopedic-injured participants were eligible if they had a concussion over 1 year from the date of enrolment.

Any participants, concussion or orthopedic-injured, were excluded if they presented: communication difficulties from severe chronic neurological developmental delay; a history of neurological disorder; intellectual disability; intoxication during the emergency department visit or imaging session; documented sedation prior to the emergency department visit; history of hospitalization for psychiatric illness; incapability of resuming physical activity; incapability of providing consent/assent; absent legal guardian; unavailable for data collection at both time points; medical contraindications to MRI; braces or metal implants. A total of 129 participants qualified for the MRI portion of the PEDCare study, 95 of which were included in this study after meeting set conditions.

Diagnostic history of depression and anxiety (i.e., history of psychiatric illness) and reported mechanism of injury was collected during the emergency department visit, while additional self-report data such as the Health Behavior Inventory (HBI; symptom scale) and Connor–Davidson Resilience Scale 10 were collected at both 72 h and 4-weeks post-injury. Each participant of this substudy underwent MRI scanning including a DTI sequence at both time points.

Connor–Davidson Resilience Scale 10

The CD-RISC 10 (Campbell-Sills & Stein, 2007) is a 5-point Likert scale with 10 items, a shortened version of the original 25-item CD-RISC (Connor & Davidson, 2003). This scale computes a degree of resilience in the past month. This scale measures resilience by assessing characteristics such as the ability to adapt, maintain secure relationships, manifest confidence in face of new challenges, successfully cope with stress, and bounce back after hardship. As such, 72 h resilience may serve as a measure of pre-injury and acute resilience, while 4-week resilience may serve as a measure of acute and subacute resilience. The computed sum of all items on the CD-RISC 10 serves as a measure of psychological resilience, whereby higher scores indicate high resilience, and lower scores indicate low resilience. The CD-RISC 10 has good internal consistency, convergence, and content validity (Kuiper et al., 2019; Windle et al., 2011). Further, it has satisfactory construct validity with evidence of greater validity relative to the 25-item version when used in pediatric concussion populations (Durish et al., 2018). The scale has been previously used to assess longitudinal changes in resilience (Okuyama et al., 2018). For this study, the computed sum of all items on the scale, completed by the participant, was used.

DTI acquisition

The DTI used a multi-slice 2D spin echo EPI sequence with the following parameters: resolution = 2.2 × 2.2 × 2.2 mm3; slices = 57, FOV = 22 × 22 cm2, TR = 6300 ms, TE = 55 ms; 5 b = 0 s/mm2, datasets, 30 directions at b = 900 s/mm2, 30 directions at b = 2000 s/mm2. Each DTI analysis incorporated volumes collected with b = 0 s/mm2, b = 900 s/mm2, and b = 2000 s/mm2 (Pines et al., 2020). The DTI scan duration was 7 min; identical sequences were used at both time points (72-h and 4-weeks post-injury).

The FMRIB software (FSL; Smith et al., 2004; Woolrich et al., 2009) was used to process the imaging data. A careful visual inspection of the images for signs of distortion determined that field distortion correction was not necessary for our sample. FA, AD, RD, and MD were all assessed from the DTI data. FA was used to indirectly measure fiber density and organization. Although FA is highly sensitive to detecting structural changes in white matter, it lacks specificity as a biomarker of neuropathology and for the characterization of microstructure (Alexander et al., 2007). Thus, AD was used to assess axial microstructure, which is sensitive to axonal degeneration (Song et al., 2002). Meanwhile, RD was used to assess radial microstructure, which is sensitive to myelination (Song et al., 2002). MD, the mean of eigenvalues representative of AD and MD, was used to indirectly characterize changes in diffusion tensors (i.e., AD and RD). All DTI marker comparisons were computed using a voxel-wise statistical repeated measures analysis with a threshold-free cluster enhancement correction (TFCE) for regions of interest.

Tract-based spatial statistics processing

Voxel-wise analyses of FA, MD, AD, and RD data were computed using tract-based spatial statistics following guidelines provided in the FMRIB software (Smith et al., 2006). All generated FA, MD, AD, and RD images were registered into a standard space using the mean FA/MD/AD/RD image and mean skeleton derived from the mean of all participants in each analysis. A mean skeleton image threshold of 0.2 was applied to each data set. All results were projected onto the MNI152_T1_1mm template. The Johns Hopkins University White-Matter Tractography Atlas was used to identify and label significant regions (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007). Specifically, the FSL software's automated atlasquery (autoaq) was used to identify the structures in the provided atlas to which the significant cluster peaks belong. If no structures were identified for a significant cluster, the cluster was not reported.

Statistical analyses

Independent samples *t* tests were conducted to compare differences in age, resilience, and HBI scores between both groups. A chi-square test was used to determine whether the proportion of sex differed between groups. Paired samples *t* tests were conducted to differences in resilience and HBI scores between 72 h and 4-weeks post-injury. Outliers for resilience scores were defined as 2.48 standard deviations above or below the mean ($Z = + - 2.48$), based on recommendations following the effect of sample size on outlier detection (Cousineau & Chartier, 2010; van Selst & Jolicoeur, 1994). One outlier was identified within the concussion group for scores of 72 h resilience. One other outlier was identified within the concussion group for scores of 4-week resilience. The outliers were Winsorized to the nearest data point within their respective group (Dixon & Yuen, 1974). A total of three cases of 4-week resilience were missing within the concussion group. The 4-week resilience data were considered missing completely at random ($\chi 2 = 4.26[5, n = 66]$, $p = .512$), and the expectation–maximization algorithm was applied to impute the missing 4-week resilience values (Dong & Peng, 2013). A total of 20 cases of 4-week HBI data were missing within the concussion group. The 4-week HBI data were considered missing at random ($\chi 2 = 1.19[5, n = 66]$, $p = .946$) and was also imputed using expectation–maximization (Dong & Peng, 2013).

Nonparametric permutation testing was conducted on whole-brain FA, MD, AD, and RD values using FSL's randomize command with 5000 permutations in conjunction with a TFCE for each DTI metric (Winkler et al., 2014). The randomize command runs a permutation script that includes modeling and inferencing with the general-linear model design using the specified number of iterations per metric. The demeaning option was selected to demean the variables in the design matrices within each group. Clusters were extracted using a significance threshold of $p < .05$ TFCE corrected for multiple comparisons across space using nonparametric permutation testing (Smith & Nichols, 2009). Significant clusters were extracted with a cluster-extent threshold of ≥50 voxels.

The two-sample randomized pipeline was modeled to investigate the association between resilience and DTI metrics at both time points and whether group moderates the association. Further, this pipeline was used to examine whether 72 h resilience was associated to 4-week DTI metrics. These sets of analyses included the following covariates: (1) age, (2) sex, (3) history of concussion, and (4) history of psychiatric illness. Handedness was not included as a covariate due to insignificant differences in FA maps between healthy right- and left-handed children (López-Vicente et al., 2021). Covariates were entered jointly across the two groups to control for differences in white matter microstructure between groups. If significant interactions were detected in any of the statistical models, the relationships between resilience and the specified outcome (i.e., the regression slopes) were examined in each group separately on the corresponding white matter tract to further explain the interaction. The two-sample randomized pipeline was also used to investigate the association between resilience and DTI metrics within both groups separately. The analysis for the concussion group included the following covariates: (1) age, (2) sex, (3) history of concussion, and (4) history of psychiatric illness. Meanwhile, the analysis for orthopedic-injury group included only (1) age and (2) sex as covariates due to the smaller sample size.

Results

Demographics

Of the 129 participants enrolled in the MRI component of the PedCARE study, 6 were excluded based on having left the emergency department without receiving instructions to join the study, 10 were excluded for missing behavioural data, 15 were excluded for missing imaging data, and 3 were excluded due to clinically significant incidental imaging findings (see Figure 1).

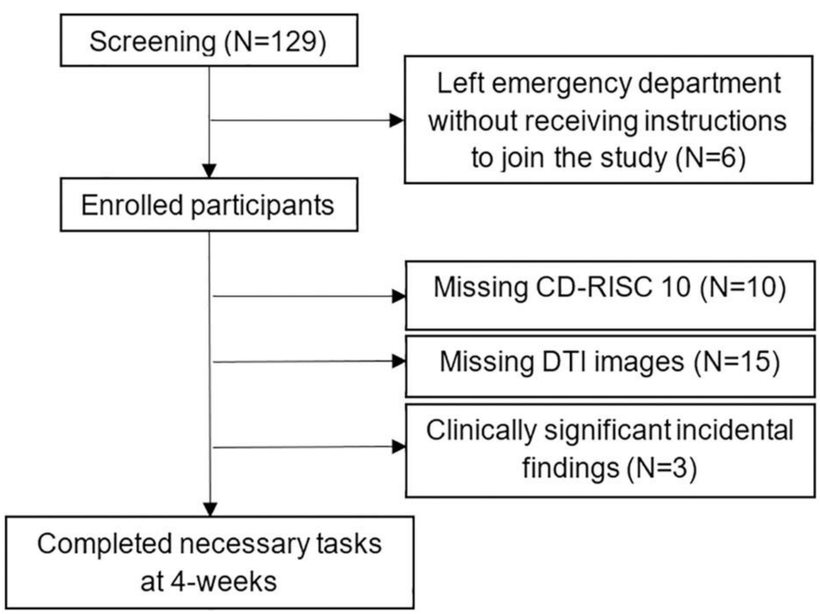

Figure 1. Participant flow chart

A total of 95 participants were included in this study, 66 of which were included as part of the concussion group (47% female, median age = 12.88 [IQR: 11.80–14.36]) while 29 were included as part of the orthopedic-injured comparison group (41% female, median age = 12.49 [IQR: 11.18–14.01]). The main mechanism of injury was sports for both the concussion group (n = 37) and the comparison group (n = 19). Both groups did not differ on age, history of concussion, sex, handedness, diagnostic history, 72 h post-injury resiliency scores, and 4 weeks post-injury resiliency scores (Table 1).

Table 1. Demographic data

	Concussion N (%)	Orthopedic Injury N (%)	Group Differences *p*-value
Age, *median(IQR)*	12.88(11.80 – 14.36)	12.49(11.18 – 14.01)	.265
History of concussion	16(24.40)	6(20.69)	.409
Sex			.614
Male	35(53)	17(59)	
Female	31(47)	12(41)	
Handedness			.102
Left	9(14)	8 (28)	
Right	57(86)	21(72)	
Diagnostic History			
Anxiety	11(17)	3(10)	.423
Depression	4(6)	1(3)	.600
Attention-deficit/hyperactivity disorder	10(15)	4(14)	.863
Mechanism of Injury			
Fall from elevation	1	1	
Fall down stairs	2	0	
Sport	37	19	
Fall from standing/walking/running	7	2	
Ran into stationary object	7	0	
Bike collision/fall while riding	0	1	
Other mechanism	12	6	

IQR: Interquartile range

Table 1. Demographic data *continued*

	Concussion N (%)	Orthopedic Injury N (%)	Group Differences *p*-value
Resilience 72hrs post-injury, *median(IQR)*	28(20.75 – 31.25)	27(21.50 – 30.50)	.621
Resilience 4 weeks post-injury, *median(IQR)*	28(21.00 – 33.25)	28(20.50 – 33.00)	.917
HBI at ED, *median(IQR)*	23(16.00 – 30.25)	13(7.50 – 23.00)	< .001
HBI at 72hrs post-injury, *median(IQR)*	24(17.00 – 32.00)	12(3.00 – 20.50)	< .001
HBI at 4 weeks post-injury, *median(IQR)*	10.5(1.75 – 17.50)	11(3.00 – 18.50)	.893
Hours between ED and 72hrs scan, *median(IQR)*	75.38(53.26 – 93.69)	100(68.77 – 119.96)	
Days between ED and 4 week scan, *median(IQR)*	30.24(28.35 – 32.09)	30.70(27.98 – 32.61)	

ED: Emergency department; HBI: Health Behaviour Inventory; IQR: Interquartile range

Independent samples *t* test found a significant difference in emergency department and 72 h HBI scores between groups, whereby the concussion group had higher scores than the comparison group ($t[93] = 3.85$, $p < .001$), ($t[93] = 5.34$, $p < .001$). No significant difference in 4-week HBI scores between groups group was found ($t[93] = 0.13$, $p = .893$). HBI scores at 72 h post-injury were significantly greater than HBI scores at 4 weeks post-injury in the concussion group ($t[65] = 9.07$, $p < .001$). No significant differences were detected between HBI scores at 72 h post-injury and 4 weeks post-injury within the orthopedic-injured group ($t[28] = .45$, $p = .655$). Paired-samples *t* tests found no significant differences in 72 h post-injury and 4-week post-injury resiliency scores within the concussion group ($t[65] = -1.35$, $p = .181$) and the orthopedic-injured group ($t[28] = -0.155$, $p = .878$).

Permutation testing of between-group differences in DTI metrics found no significant cluster differences between the concussion group and orthopedic injury group at both 72 h and 4 weeks post-injury.

Associations between resilience and DTI metrics

Analyses identified one significant inverse association between 72 h resilience and 72 h FA along the forceps minor (cluster size = 35,953; MNI x y z = 17 −16 −11; TFCE-corrected $p = .003$; β = −2.60E-03; 95% CI = −5.37E-03, 1.62E-04; Figure 2). Two significant direct associations were identified between 72 h resilience and 72 h MD along the right superior longitudinal fasciculus (cluster size = 31,823; MNI x y z = 20 −2 12; TFCE-corrected $p = .006$; β = 1.80E-06; 95% CI = −1.23E-07, 3.71E-06; Figure 3) and right anterior thalamic radiation (cluster size = 426, MNI x y z = 7 −32 −14, TFCE-corrected $p = .048$, β = 2.00E-06, 95% CI = −1.22E-07, 4.13E-06; Figure 3). Analyses also detected one significant direct association between 72 h resilience and 72 h RD along the right superior longitudinal fasciculus (cluster size = 41,079; MNI x y z = 37 −36 8; TFCE-corrected $p = .004$; β = 2.24E-06; 95% CI = −7.48E-08, 4.55E-06; Figure 4). No significant associations were identified between resilience and AD.

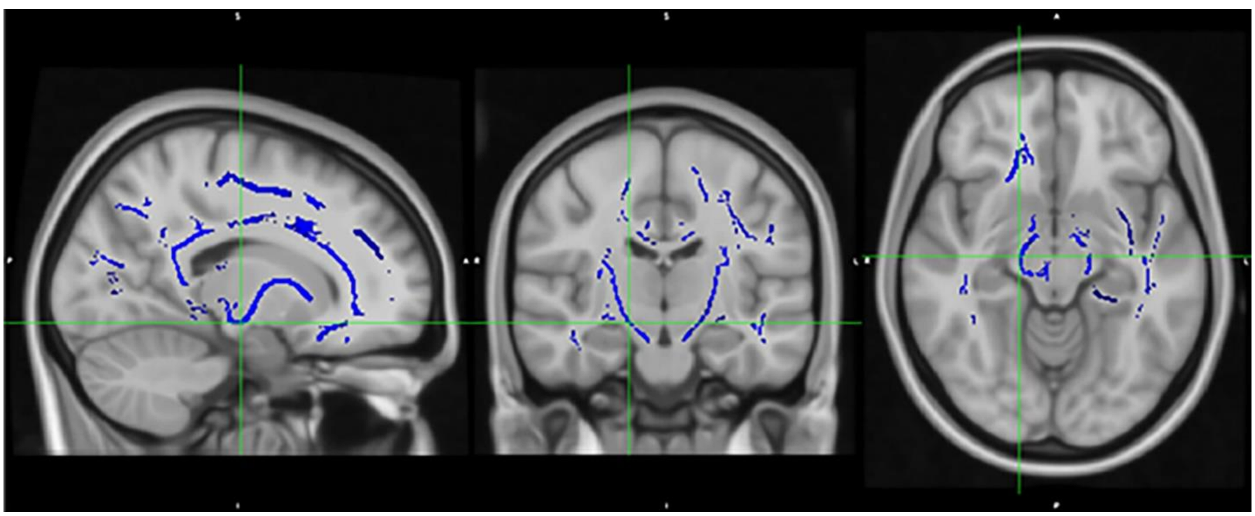

Figure 2. Associations between 72 h resilience and 72 h fractional anisotropy (FA) in concussion group: Associations between 72 h resilience and 72 h fractional anisotropy (FA) in concussion group. Areas in blue reflect significant voxels at threshold-free cluster enhancement (TFCE)-corrected p < .05, whereby 72 h post-injury resilience is inversely associated with 72 h post-injury FA values. Cursor is on the maximum intensity voxel of the cluster, located on the right cerebral peduncle.

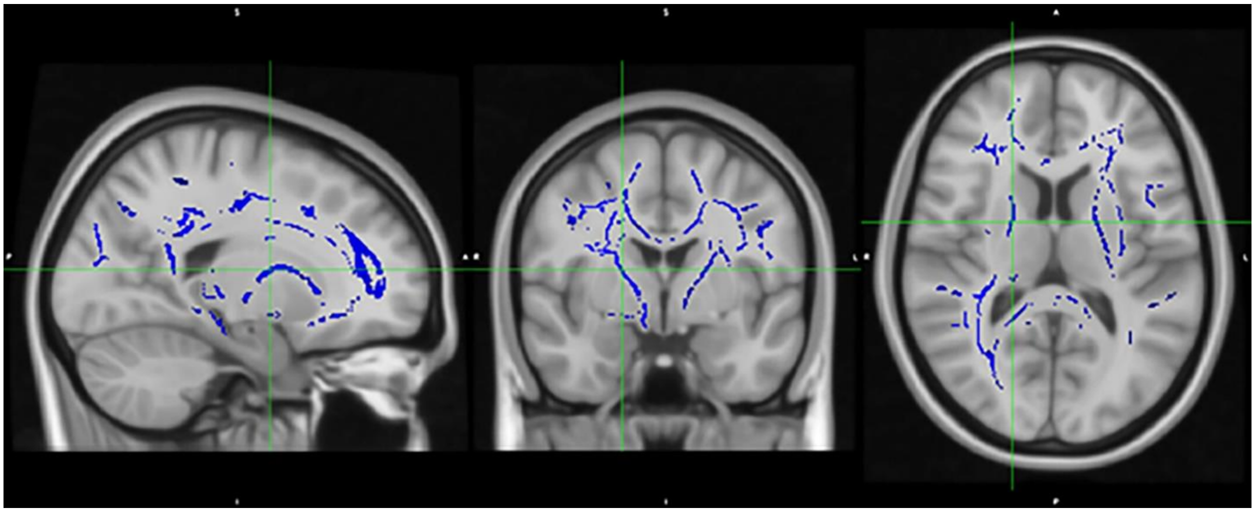

Figure 3. Associations between 72 h resilience and 72 h mean diffusivity (MD) in concussion group: Areas in blue reflect significant voxels at threshold-free cluster enhancement (TFCE)-corrected $p < .05$, whereby 72 h post-injury resilience is directly associated with 72 h post-injury MD values. Cursor is on the maximum intensity voxel of the cluster, located on the right posterior limb of the internal capsule.

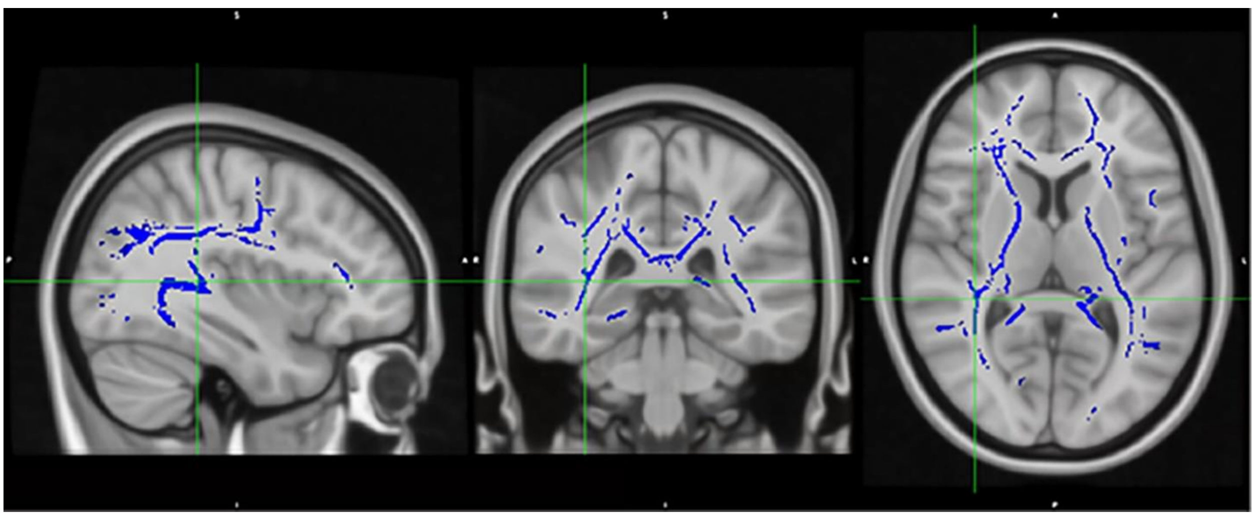

Figure 4. Associations between 72 h resilience and 72 h radial diffusivity (RD) in concussion group: Areas in blue reflect significant voxels at threshold-free cluster enhancement (TFCE)-corrected $p < .05$, whereby 72 h post-injury resilience is directly associated with 72 h post-injury RD values. Cursor is on the maximum intensity voxel of the cluster, located on the right retrolenticular part of the internal capsule.

Groups did not moderate the association between 72 h resilience and 72 h DTI metrics, as well as 4-week resilience and 4-week DTI metrics. There were no significant clusters within orthopedic-injured children between 72 h resilience and each 72 h DTI metric following multiple corrections. There were no significant clusters within the concussion group between 72 h resilience and each 4-week DTI metric following multiple corrections. There were no significant clusters within the concussion group between 4-week resilience and each 4-week DTI metric following multiple corrections. There were no significant clusters within the orthopedic-injury group between 4-week resilience and each 4-week DTI metric following multiple corrections.

Discussion

In this study, we found significant associations between 72 h resilience and 72 h DTI metrics within children and adolescents with a concussion. We found no significant associations between 72 h resilience and 4-week DTI metrics, as well as between 4-week resilience and 4-week DTI metrics. There were no associations between 72 h resilience and 72 h DTI metrics in the orthopedic-injured group, nor were there associations between 4-week resilience and 4-week DTI metrics. We did not find any significant interactions between group and resilience when predicting DTI metrics at both timepoints.

Our results suggest that injury type (i.e., concussion or orthopedic injuries) was not a significant moderator of associations between resilience and DTI metrics. Although resilience at each time point did not differ between groups, within-group comparisons of DTI metrics are not reported in this study. Schmidt et al. (2021) demonstrated that DTI metrics did not differ between young participants with concussion and orthopedic injury. Nonetheless, in support of our findings, the authors indicate that there were significant associations between resilience promoting factors and DTI metrics observed in the concussion group that were not identified in the orthopedic-injury group (Schmidt et al., 2021). Common pre-injury and injury-related factors between children with a concussion and orthopedic injuries may influence DTI metrics and ambiguate concussion-related alterations to white matter integrity. It follows that identified associations between resilience and DTI metrics might not be inherently unique to children with a concussion. Further research with a sample of healthy non-injured children is warranted to determine whether significant interactions exist between healthy controls and children with concussion or orthopedic injury when predicting outcome.

In partial support of our hypotheses, we found several associations between 72 h resilience and 72 h DTI metrics (FA, MD, and RD) within the sample of children with a concussion. Higher resilience was associated with higher MD and RD along the right superior longitudinal fasciculus. The superior longitudinal fasciculus connects regions of the temporoparietal junction and parietal cortex with the frontal cortex and is theorized to be implicated in language function (Dick & Tremblay, 2012; Wang et al., 2016). Higher resilience was associated with lower FA values along the forceps minor. The forceps minor connects regions of the frontal lobes by crossing the midline structures (Catani & Thiebaut de Schotten, 2008; Mamiya et al., 2018). Higher resilience was associated with higher MD along the right anterior thalamic radiation. The anterior thalamic radiation is a white matter bundle that connects regions of the frontal lobe to the thalamus and limbic system, thought to be implicated in executive functioning and negative emotion (Catani & Thiebaut de Schotten, 2008; Mamiya et al., 2018; Panksepp, 2005). These findings are consistent with a previous study reporting associations between resilience-promoting factors and both FA and MD in youth with a concussion, albeit in different white matter tracts (Schmidt et al., 2021). Schmidt et al. (2021) reported a positive correlation between resilience promoting factors and FA of the left sagittal stratum. The authors also report negative correlations between resilience promoting factors and MD of the anterior corona radiata and anterior limb of the internal capsule (Schmidt et al., 2021). There are few, if any, studies examining the associations between resilience and RD. We suggest that the reported associations between 72 h resilience and 72 h DTI metrics might be indicative of improved neural outcome in participants with higher resiliency. However, there is insufficient consistency in the literature pertaining to white matter injury progression in pediatric concussion to provide accurate inferences as to the integrity of white matter microstructure. Although FA, MD, AD, and RD are powerful indicators of white matter characteristics, including orientation and density, the variable effects of pediatric concussion on such metrics render it challenging to infer improved or worsened tract integrity (see Roberts et al., 2014 for a review). Here, we merely report that 72 h resilience is associated with the degree of directional diffusion (FA), magnitude of diffusion (MD), and degree of diffusivity across the axis of diffusion (RD) in white matter tracts in the acute phase of pediatric concussion.

Despite the significant clusters between 72 h resilience and 72 h DTI metrics in the concussion group, we did not find support for our hypothesis that 4-week resilience is associated with 4-week DTI metrics in either group. We also did not find any significant associations between 72 h resilience and 4-week DTI metrics in the concussion group. This might suggest that pre-injury/acute resilience is only an indicator of white matter microstructure in the acute phase of concussion. It is possible that concussion injury-related alterations to white matter microstructure in the subacute phase of concussion, including axonal swelling (Giza & Hovda, 2014; Roberts et al., 2014), ambiguate or eliminate the associations between resilience and 4-week DTI metrics. Longitudinal studies are thus required to examine whether time since injury is a significant moderator of resilience and DTI metrics in pediatric concussion. Unfortunately, the nonparametric permutation methods applied in this study are designed for independent measures and are often not well-equipped for repeated measures (Winkler et al., 2014). The DTI data included in our study are inherently limited to nonparametric tests, as they do not meet the assumption of normality required for parametric tests. Hence, a longitudinal model was not feasible for our study but is advised for future investigations of resilience and white matter microstructure.

Limitations

There is a paucity of consistency in DTI literature pertaining to directionality of FA, MD, AD, and RD outcomes following pediatric concussion. Directionality of DTI metric findings in pediatric concussion often varies when considering time since injury (Roberts et al., 2014). There is also considerable heterogeneity in methodology or timing of MRI acquisition in pediatric concussion research, further complicating predictions of findings (Dodd et al., 2014). Hence, caution is warranted when interpreting significant DTI findings regarding children with concussion. Future research should implement additional measures for the characterization of microstructural white matter integrity. Neurite orientation dispersion and density imaging, or NODDI, uses diffusion MRI to provide additional information regarding dendrites and axons such as the orientation dispersion index—a measure of angular variation across neurites (Zhang et al., 2012). This method of analysis was proven effective when investigating white matter microstructure following mild traumatic brain injury in adult samples (Churchill et al., 2017; Palacios et al., 2020). However, this method has yet to be used in a pediatric concussion sample. Future research is needed to address these limitations, offering evidence to demystify the complex relationship between resilience and white matter integrity following the shearing forces of concussion.

Healthy children and adolescents experience significant developmental changes in white matter integrity, including ongoing changes in myelination (Asato et al., 2010). Subtle differences in degree of myelination, axonal density, or fiber organization across developmental stages might be associated with changes in DTI metrics. In a study investigating the changes in white matter development from childhood to adulthood, Lebel et al. (2008) found that maximal levels of FA are established at different rates in different tracts. Most maximal levels of FA, for example, are established by 11 years of age in the corpus callosum and inferior longitudinal fasciculus (Lebel et al., 2008). While our groups were matched on age and the interquartile range for both groups was narrow, a large age range of 10–17.99 years may be considered as a potential limitation to our study. Structural differences, as measured with DTI metrics, can also be detected between male and female pediatric samples. White matter volume develops at a faster rate in boys than in girls, reflected by differences in FA (Johnson et al., 2014; Lawrence et al., 2023; Schmithorst et al., 2008; Wang et al., 2012). In short, children of different age and sex at time of scanning likely demonstrate differences in FA, MD, AD, and RD maps. To control for such effects on our results, we implemented both age and sex as separate covariates in our statistical models. The comparison group of orthopedic-injured children was also matched to the concussion group in age and sex.

The self-reported resiliency data in our samples might be influenced by a diagnostic history of anxiety or depression. Some studies report that resilience was associated with decreased rates of depression in adults with adverse childhood experiences (Poole et al., 2017; Schulz et al., 2014). It follows that individuals with low levels of resilience have heightened risk of depression following adverse experiences. As such, cases of depression and anxiety in our pediatric sample might demonstrate lower self-reported resilience. Moreover, preexisting mental health conditions may influence the association between resilience and clinical outcomes following concussion (Gornall et al., 2021). As shown in a previous study, anxiety and depression were a significant moderator of the effects of resilience on post-concussion symptom severity in a sample of children with concussion (Durish et al., 2019). Our study did not discard cases with a diagnostic history of anxiety or depression, which may have influenced self-reported scores of resilience at each timepoint. However, our analyses of resilience as a correlate of DTI metrics across all timepoints within children with concussion included preexisting mental health conditions as a covariate, controlling for the effects of anxiety or depression as a confounding variable on the reported results. Further, it remains a possibility that pediatric injury type may impact self-reported resiliency. Truss et al. (2017) found that most children are resilient to post-traumatic stress symptoms following concussion, which might suggest that pediatric concussion might not have a significant impact on resiliency. In our study, resilience scores did not differ between orthopedic-injured children and children with concussion at both timepoints. This lack of differences in resilience scores within- and between-groups also restricts our interpretations of the results, inherently limiting the scope of this study. Further research with other samples (e.g., children with psychiatric illness) is required to determine whether there are meaningful differences in resilience scores that can be moderated by resilience-targeted clinical interventions.

Conclusion

In this study, we identified significant associations between 72 h resilience and 72 h DTI metrics within children with a concussion. No interactions were identified between group and resilience when predicting DTI metrics at both timepoints. These findings warrant further longitudinal studies exploring the associations between resilience and white matter microstructure in the acute and subacute phase of pediatric concussion. Although DTI is a powerful tool, implementing additional imaging techniques, including functional connectivity and cerebral blood perfusion rates, may further clarify the interaction between injury type and resilience on white matter integrity. Future research should seek to further investigate associations between resilience and white matter microstructure, particularly whether resilience is associated to improved neural recovery following pediatric injury.

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Compliance with Ethical Standards

This study received approval by the Research Ethic Board and the Children's Hospital of Eastern Ontario. All eligible children and adolescents capable of consenting on their own behalf provided written informed consent, while those unable to consent on their own behalf provided assent and parental consent.

Conflict of Interest Statement

Roger Zemek has received competitively funded research grants from Canadian Institutes of Health Research (CIHR), Ontario Neurotrauma Foundation (ONF), Physician Services Incorporated (PSI) Foundation, CHEO Foundation, Ontario Brain Institute (OBI), and Ontario SPOR Support Unit (OSSU), and the National Football League (NFL) Scientific Advisory Board, and he is supported by a Clinical Research Chair in Pediatric Concussion from University

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Chapter 3: Study 2

Associations Between Changes in Psychological Resilience and Resting-State Functional Connectivity Throughout Pediatric Concussion Recovery

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Abstract

Purpose: This study investigated the association between psychological resilience and resting-state network functional connectivity of three major brain networks in pediatric concussion. *Methods*: This was a substudy of a randomized controlled trial, recruiting children with concussion and orthopedic injury. Participants completed the Connor–Davidson Resilience 10 Scale and underwent magnetic resonance imaging at 72 h and 4 weeks postinjury. We explored associations between resilience and connectivity with the default mode network (DMN), central executive network (CEN), and salience network (SN) at both timepoints and also any change that occurred over time. We also explored associations between resilience and connectivity within each network. *Results*: A total of 67 children with a concussion (median age = 12.87 [IQR: 11.79–14.36]; 46% female) and 30 with orthopedic injury (median age = 12.27 [IQR: 11.19–13.94]; 40% female) were included. Seed-to- voxel analyses detected a positive correlation between 72-h resilience and CEN connectivity in the concussion group. Group moderated associations between resilience and SN connectivity at 72 h, as well as resilience and DMN connectivity over time. Regions-of-interest analyses identified group as a moderator of longitudinal resilience and within-DMN connectivity. *Conclusions*: These results suggest that neural recovery from concussion could be reliant on resilience. Resilience was related to functional connectivity with three of the main networks in the brain that are often impacted by concussion. Improving resilience might be investigated as a modifiable variable in children as both a protective and restorative in the context of concussion. Clinical Trial Registration Identifier: NCT05105802. PedCARE+MRI team (see Supplementary Appendix S1)

Introduction

Concussion affects the wellbeing and quality of life of children (Novak et al., 2016). Children with concussion who are highly resilient, defined as one's ability to adapt when faced with adversity (Connor and Davidson, 2003), are more likely to report decreased post-concussion symptoms than less resilient children in the chronic phase of injury (Bunt et al., 2021; Durish et al., 2018b; Hassan et al., 2023), and higher scores of quality of life (Durish et al., 2018a). Resilience has been associated with several neurofunctional networks (Iadipaolo et al., 2018, 2017), while the same networks have been found to be disrupted post-concussion (Abbas et al., 2015; Borich et al., 2015; Brett et al., 2022; Iyer et al., 2019; Johnson et al., 2012; Mayer et al., 2011; Meier et al., 2017; Newsome et al., 2016; Plourde et al., 2021; Sours et al., 2015, 2013). Limited evidence exists on whether resilience can be protective to the neurophysiological deficits of concussion.

Resilience reflects an individual's accessible adaptive capacities for the successful coping of trauma or adversity that may otherwise threaten healthy functioning or development (Masten and Barnes, 2018). The most common functional networks associated with measures of resilience in children are the Default Mode Network (DMN; Iadipaolo et al., 2017, 2018), Central Executive Network (CEN; Iadipaolo et al., 2018), and Salience Network (SN; Iadipaolo et al., 2017). The DMN supports self-referential processes, emotional processing, and recollection of past experiences (Raichle, 2015). The CEN plays a role in executive functioning, sustained attention and working memory, response selection, and response suppression (Seeley et al., 2007). The SN is theorized to integrate, identify, and prioritize the most relevant incoming stimuli, as well as switching between activation of the DMN and CEN (Goulden et al., 2014; Seeley et al., 2007). Greater psychological resilience has been associated with decreased within-network DMN functional connectivity (FC) in healthy adults (Hemington et al., 2018). Within- and between-network FC of the DMN and SN have also been reported as inversely associated with resilience (Altinok et al., 2021; Bolsinger et al., 2018; Hemington et al., 2018; Van der Werff et al., 2013). In healthy children and adolescents, decreased resilience has been associated with increased FC of the DMN to the anterior cingulate cortex, a key node of the SN (Iadipaolo et al., 2017). A negative correlation was also identified in children and adolescents between resilience and a dynamic state of FC between the DMN and CEN (Iadipaolo et al., 2018). Dynamic state describes discrete patterns of FC or time-varying patterns of resting-state FC. These reports indicate evidence of an inverse association between resilience and FC to the DMN, CEN, and SN in healthy individuals. However, the DMN, CEN, and SN FC have been shown to be altered post-concussion (Abbas et al., 2015; Borich et al., 2015; van der Horn et al., 2023; Iyer et al., 2019; Johnson et al., 2012; Mayer et al., 2011; Meier et al., 2020; Newsome et al., 2016; Plourde et al., 2021; Sours et al., 2015, 2013).

Considering the empirical findings indicating that concussion alters neurofunctional networks associated with resilience, it remains unclear whether the functional correlates of resilience are altered post-concussion. As such, the functional correlates of resilience might be unique to pediatric concussion when compared to children without brain injury. Children with orthopedic injuries serve as an appropriate comparison group, as they control over various nonspecific effects of traumatic injury (Wilde et al., 2018). An investigation of the neurofunctional correlates of resilience in pediatric concussion is vital for developing a clear comprehension of resilience’s impact on neural components of recovery following brain injury . The present study investigated cross-sectional and longitudinal associations between resilience and resting-state FC of DMN, SN, and CEN, and whether these associations were moderated by pediatric injury type (concussion or orthopedic injury). Given that resilience can be malleable (Connor and Davidson, 2003), we examined the associations between resilience and FC over time and at each timepoint separately. Secondary objectives were to investigate cross-sectional and longitudinal associations between resilience and patterns of within-network DMN, SN, and CEN FC. In other words, we examined the association of resilience and clusters of connections between nodes belonging to each network respectively, or within-network FC.

We hypothesized that changes in resilience are inversely associated with FC to each network within both groups, and that these associations are moderated by pediatric injury type. We also hypothesized that resilience is inversely associated with patterns of within-network FC in both groups, and that these associations are moderated by pediatric injury type.

Methods

Study Design

This is a secondary analysis of a larger randomized clinical trial, Pediatric Concussion Assessment of Rest and Exertion (PedCARE; Ledoux et al., 2019), where a subsample of children with a concussion or orthopedic injury underwent an MRI scan at 72hrs (+/- 48hrs) and 4 weeks (+/- 5 days) post-injury (Ledoux et al., 2019). This study received approval by the Research Ethic Board and the Children's Hospital of Eastern Ontario. All eligible children and adolescents capable of consenting on their own behalf provided written informed consent, while those unable to consent on their own behalf provided assent and parental consent.

Participants

Children with a concussion or an orthopedic injury (OI) were included in the study if they sustained a concussion or OI < 48hrs from their emergency department visit, were 10 to 17.99 years of age, and proficient in English. Concussion participants were excluded from the study if they presented with a Glasgow Coma Scale score of <= 13, had abnormalities on standard imaging, underwent intubation, or had a history of trauma prior to the injury. Children with an orthopedic injury were excluded if their injury was isolated to the lower extremity or if they experienced a concussion within the past year.

Any participants from either group were excluded if they met any of the following criteria: communication difficulties as a result of severe chronic neurological developmental delay; history of neurological disorder; intellectual disability; intoxication at the emergency department or during the imaging session; required sedation at or prior to the emergency department visit; required surgical operation; history of hospitalization for psychiatric illness; incapable of resuming physical activity; incapable of providing consent or assent; absent legal guardian; unavailable for data collection at both timepoints; medical contraindications to the MRI scanner; equipped with braces or metal implants.

Symptoms were assessed with the validated and reliable Health Behavior Inventory (HBI; Ayr et al., 2009), a 20-item, 4-point Likert self-report scale of symptomatology, with higher total scores indicating increased symptom severity. The validated and reliable Pediatric Quality of Life Inventory (PedsQL) version 4.0, a 23-item, 5-point Likert self-report scale, was used to assess quality of life. Each item is reverse scored and transformed to a linear 0-100 scale, with higher scores reflecting higher quality of life based on the past seven days. The Connor-Davidson Resilience Scale 10 (CD-RISC 10) is a validated 10-item, 5-point Likert self-report scale of resilience, scores ranging from 0 through 40 (Campbell-Sills and Stein, 2007). The sum of every item on the scale is interpreted as the degree of psychological resilience in the past 30 days, with higher scores indicating increased resilience and lower scores indicating diminished resilience. These assessments and MRI scanning were recorded at 72hrs and 4 weeks post-injury.

MRI Acquisition

The fMRI acquisition used a 3-Tesla Siemens PET-MRI with a 12-channel head coil. A resting-state fMRI sequence was applied as part of the acquisition protocol. Participants were tasked with fixating on a crosshair and instructed to relax and try not to think of anything specific. The gradient-echo echoplanar pulse sequence parameters were as follows: resolution= 3.6x3.6x3.6 mm^3, slices = 36, FOV= 23x23 cm^2, TR = 2000 ms, TE = 30 ms, measurement total = 241. The duration of this sequence was 8 minutes and 10 seconds. The high-resolution T1-weighted images acquisition parameters were as follows: TE = 2.21, 4.09, 5.97, and 7.85 ms; TR = 2300 ms; an inversion time of 1.16 s; an 8° flip angle; a slice thickness of 1 mm; a voxel size of 0.9 × 0.9 × 1 mm3; FOV = 230 mm; and a resolution of 230 × 230 × 176 mm. The duration of this sequence was 5 minutes and 52 seconds. These sequences were identical for both scan sessions.

Statistical Analyses

Between-group differences in age and resilience were tested using independent samples t-tests. Within-group differences in resilience at both time points were tested using paired samples t-tests. Group differences in both proportion of biological sex at birth and history of concussion were computed using a chi-square test. Pearson correlations were conducted to assess correlations between CD-RISC 10 scores and both HBI and PedsQL scores (Bonferroni corrected alpha value at $\alpha = .013$). Outliers were defined as being 2.48 standard deviations from the mean (Cousineau and Chartier, 2010) and were Winsorized to the nearest score within their group. Two cases of 4 week resilience were missing from the concussion group and were imputed using expectation maximization (Dong and Peng, 2013).

Structural image quality checks were conducted based on guidelines proposed by Backhausen et al. (2016). The CONN toolbox, a Matlab-based software, was used for the preprocessing and both seed-to-voxel and ROI-to-ROI analyses of the resting-state data (Whitfield-Gabrieli & Nieto-Castanon, 2012). The default data preprocessing pipeline for volume-based analyses (direct normalization to MNI-space) was used for the data preprocessing, which includes functional realignment and unwarp; slice-timing correction; outlier detection; segmentation and normalization; and smoothing (Gaussian kernel of 8mm). The CONN toolbox quality assurance plot was used to identify and exclude potential subject outliers based on automated measures of valid scans and average framewise displacement, or motion (Morfini et al., 2023). The functional outlier detection threshold was set to 97th percentiles in normative samples. The default denoising pipeline, combining linear regression of confounding effects in blood-oxygen level dependent signal and temporal band-pass filtering, was used for the denoising the data. Regarding temporal band-pass filtering, temporal frequencies below 0.008 Hz or above 0.09 Hz were removed. All region labels were based on the CONN toolbox default structural atlas derived from the Harvard-Oxford Cortical atlas (Desikan et al., 2006). The network seeds were based on CONN's default clustering and ordering procedures applied to Cambridge 1000-connectomes resting state dataset.

A seed-to-voxel approach was used to analyze FC between DMN, SN, and CEN seeds and every voxel of the brain. The seed-based connectivity maps reflect FC between the specified seed and each voxel across the brain. The seed-based connectivity maps were based on the CONN toolbox provided seeds corresponding to the DMN, CEN, and SN. These networks were selected based on significant findings reported in literature pertaining to concussion (Abbas et al., 2015; Borich et al., 2015; van der Horn et al., 2023; Iyer et al., 2019; Johnson et al., 2012;

Mayer et al., 2011; Meier et al., 2017; Plourde et al., 2021; Sours et al., 2015, 2013) and resilience (Altinok et al., 2021; Bolsinger et al., 2018; Goulden et al., 2014; Hemington et al., 2018; Iadipaolo et al., 2018, 2017; Seeley et al., 2007; Van der Werff et al., 2013). The DMN seeds included: the medial prefrontal cortex; the bi-lateral parietal cortex; and the posterior cingulate cortex. The CEN seeds included: bi-lateral prefrontal cortex, as well as the left and right posterior parietal cortex. The SN seeds included: the anterior cingulate cortex; the bi-anterior insula; the left and right rostral prefrontal cortex; as well as the left and right supramarginal gyrus. All significant clusters were defined following the CONN toolbox application of the Random Field Theory (Worsley et al., 1996), using a voxel height threshold of $p < .001$ uncorrected and a cluster height threshold of $p < .05$ corrected for false discovery rate (FDR). The corrected alpha value for analyses concerning seeds of the DMN was Bonferroni corrected at $\alpha = .013$. The alpha value for analyses concerning the seeds of the CEN was corrected at $\alpha = .013$. The alpha value for analyses concerning the seeds of the SN was corrected at $\alpha = .007$.

Based on previous reports suggesting an inverse association between resilience and resting-state FC (Altinok et al., 2021; Bolsinger et al., 2018; Hemington et al., 2018; Iadipaolo et al., 2017; Van der Werff et al., 2013), we pursued a priori region-of-interest (ROI) analyses of within-network DMN, SN, and CEN FC. The ROI connectivity maps measure FC between pre-determined pairs of ROIs. The ROIs selected for our analyses included each of the listed CONN toolbox provided DMN, SN, and CEN seeds. We used parametric multivariate statistics for cluster-based inferences. A series of t-statistics for all connections in a matrix of selected ROIs were computed. The selected ROIs were then sorted by a hierarchical clustering procedure based on the CONN toolbox default weight (0.05) for ROI-to-ROI anatomical proximity (1 =

proximal) or functional similarity (0 = functional). Significant clusters were defined using a connection threshold of $p < .05$ uncorrected and a cluster threshold of $p < .05$ corrected for FDR among connections across all ROIs included in the analysis. A significant cluster is a similar pattern of FC within a set of connections between ROIs, irrespective of whether the association with individual connections is significant. The within-network analyses of DMN, SN, and CEN FC included only ROIs from their respective network.

Multiple regressions were used to examine interactions between resilience change scores, group, and time points when predicting FC (longitudinal). These three-way interactions were analyzed to explore how group moderates the associations between resilience change scores and changes in FC over time. Multiple regressions were also used to examine interactions between resilience and group at each time point separately when predicting FC (cross-sectional). Meaning, our regression models measured the associations between resilience and FC across time (from 72hrs to 4 weeks) and at each timepoint (72hrs and 4 weeks), and whether these associations were dependent on group. Resilience change scores were imported into the CONN toolbox as a second-level covariate, while the scans (72hrs scans and 4-week scans) were entered as two contrasting conditions into the model. An interaction term between group and resilience change score was created using the CONN toolbox calculator and implemented to investigate whether there was an interaction between group and resilience change scores when predicting changes in FC. The multiple regression model for the longitudinal analyses is represented as follows:

$$FC_{ij} = \beta_0 + \beta_1(Resilience_{ij}) + \beta_2(Group_j) + \beta_3(Time_i) + \beta_4(Resilience_{ij} \times Group_j \times Time_i) + \sum\nolimits^{n}_{k=1} \beta_{covk}\, Covariate_{ijk} + \epsilon_{ij} \quad (1)$$

where FC_{ij} represents the functional connectivity between the specified seed and each voxel across the brain for participant i at time point j. $Resilience_{ij}$ represents the resilience score for participant i at time point j. $Group_j$ is a binary variable representing the group (concussion or orthopedic injury) at time point j. $Time_i$ is a binary variable representing the time point (72 hours or 4 weeks) for participant i. β_0 is the intercept term. β_1 through β_6 are the regression coefficients representing the effects of resilience, group, time, and their interactions on functional connectivity. $Covariate_{ijk}$ represents the kth covariate for participant i at time point j. β_{covk} represents the regression coefficient for the kth covariate. n represents the total number of covariates. ϵ_{ij} represents the error term.

The multiple regression model for cross-sectional analyses is represented similarly, but without the time-related terms:

$$FC_{ij} = \beta_0 + \beta_1(Resilience_{ij}) + \beta_2(Group_j) + \beta_3(Resilience_{ij} \times Group_j) + \sum\nolimits^{n}_{k=1} \beta_{covk}\, Covariate_{ijk} + \epsilon_{ij} \quad (2)$$

where the variables are defined as before.

Analyses using both groups included the following covariates entered jointly across groups: age, sex, handedness, and history of psychiatric illness. Within-group analyses of the concussion group included the following covariates: age (Alarcón et al., 2015; Zemek et al., 2016), sex (Alarcón et al., 2015; Zemek et al., 2016), handedness (Saenger et al., 2012), and history of psychiatric illness (Durish et al., 2018b; Hahn et al., 2011). Meanwhile, due to a smaller group size, within-group analyses of the orthopedic injury group included age and sex as covariates.

Results

Demographics

A total of 67/92 (73%) children with concussion (median age= 12.81[IQR: 11.79 – 14.36]; 46% female) and 30/46 (65%) children with orthopedic injury (median age=12.27 [IQR: 11.18 – 13.94]; 46% female) were included in this study (Figure 1). All demographic and clinical data met assumptions for parametric testing, including normality and homogeneity of variance. Sports was identified as the main mechanism of injury for both the concussion (38/67 [57%]) and orthopedic injury (19/30 [63%]) group. There were no significant differences between groups with respect to age, sex, history of concussion, handedness, diagnostic history, 72hrs resilience, 4-week resilience, and resilience change scores (Table 1 and Table 2). There were no significant differences between 72hrs resilience and 4-week resilience scores within the concussion (t[66] = -1.58, p = 119) and orthopedic injury groups (t[29] = -.527, p = .602).

Table 1. Demographic data

	Concussion N(%)	Orthopedic Injury N (%)	Group Differences *p*-value
Age, *median(IQR)*	*12.87(11.79 – 14.36)*	*12.27(11.19 – 13.94)*	.292
Record of a previous concussion diagnosis	16(24.40)	6(20.69)	.726
Sex			.566
Male	36(54)	18(60)	
Female	31(46)	12(40)	
Handedness			.113
Left	9(13)	8 (27)	
Right	58(87)	21(73)	
Diagnostic History			
Anxiety	10(15)	3(10)	.510
Depression	3(5)	1(3)	.793
Attention-deficit/hyperactivity disorder	9(13)	4(13)	.989
Mechanism of Injury			
Fall from elevation	1	1	
Fall down stairs	2	1	
Sport	38	19	
Fall from standing/walking/running	8	2	
Ran into stationary object	7	0	
Bike collision/fall while riding	0	1	
Other mechanism	12	6	

IQR: Interquartile range

The total emergency department self-reported HBI scores were significantly higher in the concussion group compared to the orthopedic injury group, $t(95) = 3.80$, $p < .001$. The total 72hrs self-reported HBI scores were also significantly higher in the concussion group, $t(95) = 5.62$, $p < .001$. There was no significant difference in total 4-week HBI scores between groups. There were no significant correlations between HBI and resilience scores at either timepoint.

Table 2. Demographic data *continued*

	Concussion median(IQR)	Orthopedic Injury median(IQR)	Group Differences *p*-value
CD-RISC 10			
Resilience 72hrs post-injury	28(21 – 31)	27.5(22 – 30)	.557
Resilience 4 weeks post-injury	28(21.5 – 34)	28(21.5 – 33)	.987
Resilience change scores	1(-3 – 5)	0(-2 – 2)	.483
HBI			
HBI at ED	23(16.5 – 29.5)	14(8.5 – 21)	< .001
HBI at 72hrs post-injury	24(17 – 31.5)	12(2.5 – 20)	< .001
HBI at 4 weeks post-injury	12(2.76 – 18.80)	10(3 – 18)	.898
PedsQL			
PedsQL at 72hrs post-injury	75(64.7 – 83.2)	80.4(75.3 – 93.2)	.002
PedsQL at 4 weeks post-injury	83.7(82.6 – 95.1)	86.4(74.2 – 94)	.036
Time Between ED and Scan			
Hours between ED and 72hrs scan	75.50(53.43 – 90.75)	108.5(69.77 – 120.11)	
Days between ED and 4-week scan	30.25(28.56 – 32.08)	30.38(27.92 – 32.25)	

ED: Emergency department; HBI: Health Behaviour Inventory; IQR: Interquartile range; PedsQL: Pediatric Quality of Life Inventory

The total 72hrs PedsQL scores were significantly higher in the concussion group compared to the orthopedic injury group, $t(95) = 3.21$, $p = .002$. There were no significant differences in total 4-week PedsQL scores between groups. The correlation between 72hrs CD-RISC 10 scores and 72hrs PedsQL scores group did not reach significance after correction for multiple comparisons within both the concussion ($r[66] = .29$, 95% CI [0.054, 0.5], $p = .017$; $\alpha = .013$) and orthopedic injury groups ($r[29] = .25$, 95% CI [-0.12, 0.56], $p = .180$). A significant positive correlation was identified between 4 week CD-RISC 10 scores and 4 week PedsQL within the concussion group ($r[66] = .33$, 95% CI [0.098, 0.53], $p = .006$). This correlation did not reach significance within the orthopedic injury group after correction for multiple comparisons ($r[29] = .37$, 95% CI [0.011, 0.64], $p = .042$; $\alpha = .013$).

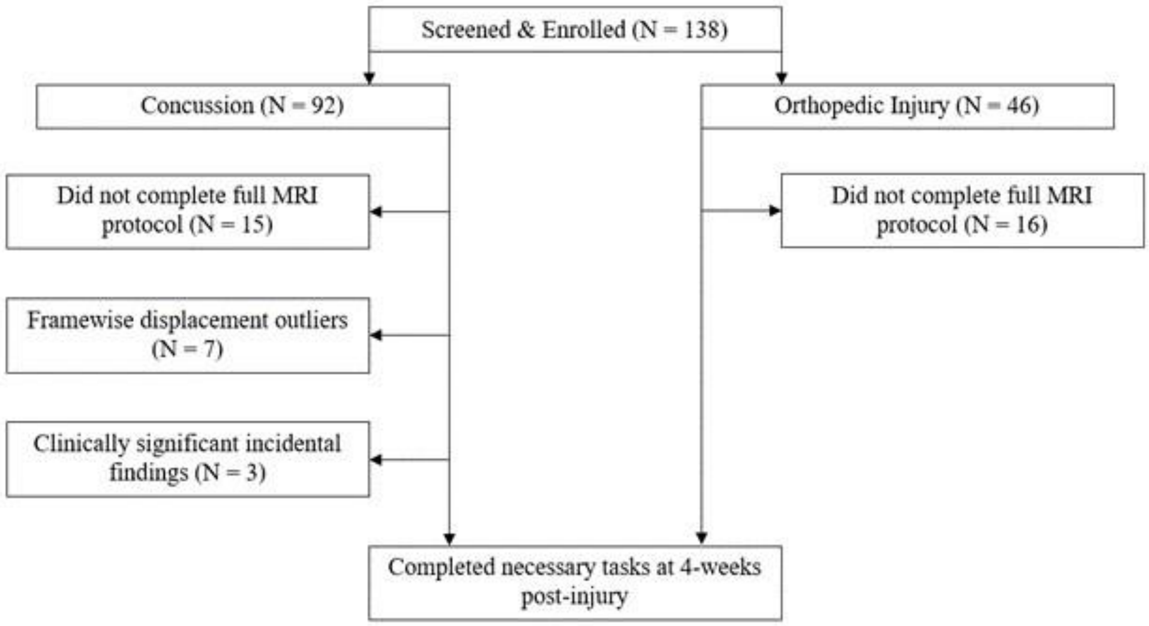


Figure 1. Participant flow chart. Information regarding participant enrollment and attrition.

Seed-to-Voxel Analyses

Longitudinal Resilience and FC.

A significant three-way interaction (group*resilience*time) with the right lateral parietal cortex seed of the DMN was identified along the right cerebellum (cluster size = 237, MNI x y z = +02 -72 -34, $F[1\ 89] = 30.69$, FDR corrected $p = .012$; Figure 2). Group was a moderator of longitudinal resilience and DMN FC with the right cerebellum. Within this cluster, the concussion group showed a negative correlation between longitudinal resilience and FC ($F[1\ 89] = 15.59$, FDR corrected $p = <.001$, $\beta = -0.003$). Meanwhile, orthopedic injury group showed a positive correlation between longitudinal resilience and FC ($F[1\ 89] = 29.41$, FDR corrected $p = <.001$, $\beta = 0.033$).

Within the orthopedic injury group, longitudinal resilience was positively correlated with FC between the right lateral parietal cortex seed of the DMN to the right cerebellum (cluster size

= 327, MNI x y z = +02 -76 -28, $F[1\ 26] = 39.92$, FDR corrected $p < .001$, $\beta = 0.033$). Within the concussion group, no significant associations between longitudinal resilience and FC were detected.

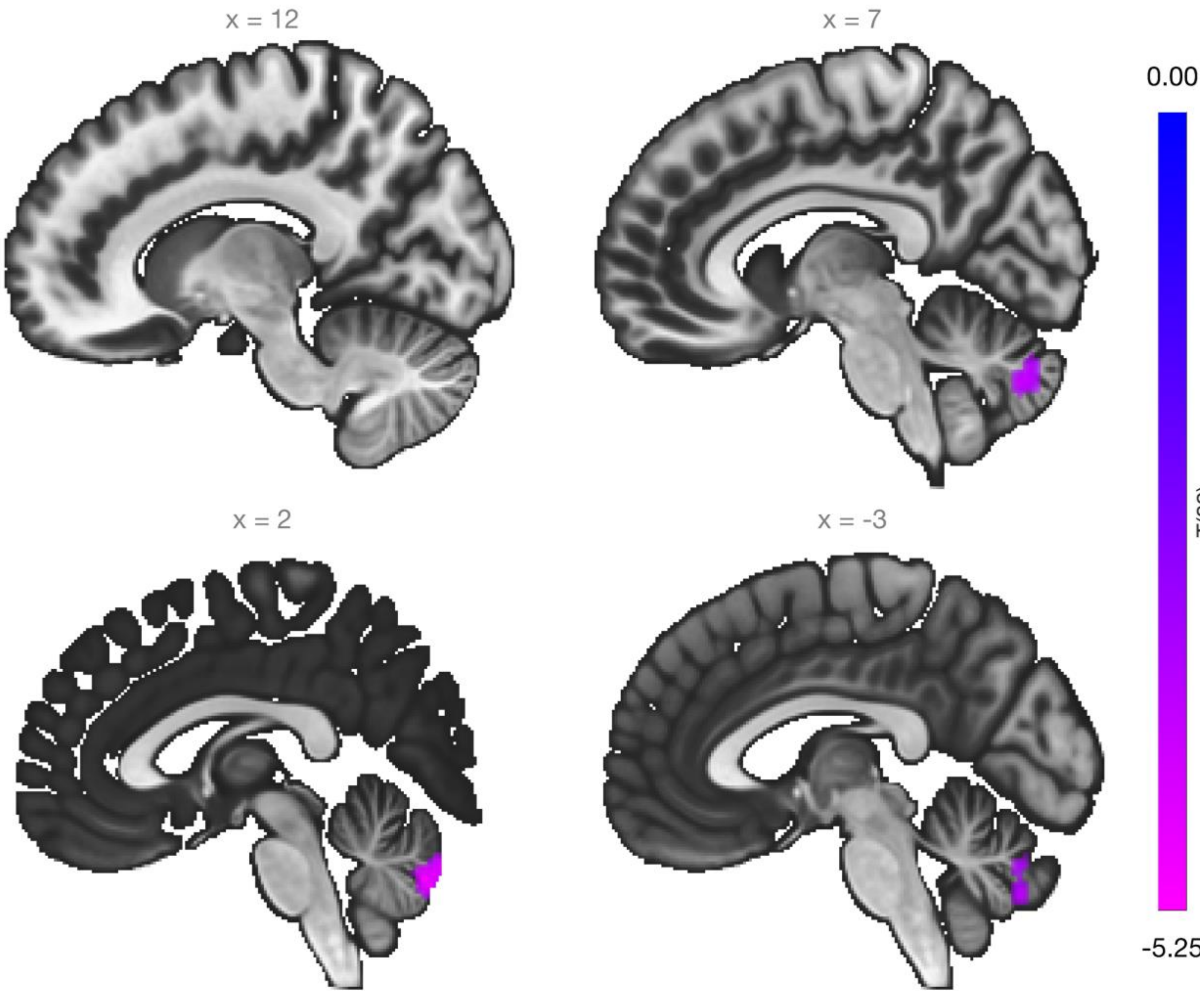


Figure 2. Group as a moderator between longitudinal resilience and FC: Sagittal slices displaying the significant cluster within the right cerebellum, color-coded by voxel statistic, indicating an interaction between group and changes in resilience when predicting changes in FC to the right lateral parietal cortex of the DMN. Associations between longitudinal resilience and connectivity values within this cluster differed significantly between groups, whereby the concussion group showed a negative correlation, whereas the orthopedic injury group showed a positive correlation. DMN, default-mode network.

Cross-Sectional Resilience and FC.

A significant two-way interaction (group*resilience) with the left anterior insula seed of the SN was identified along the posterior division of the cingulate gyrus (cluster size = 407, MNI x y z = +02 -30 +28, $F[1\ 89] = 19.33$, FDR corrected $p < .001$; Figure 3). Group was a moderator of 72hrs resilience and SN FC with the posterior cingulate gyrus. Within this cluster, the concussion group showed a positive correlation between 72hrs resilience and FC ($F[1\ 89] = 9.69$, FDR corrected $p = <.001$, $\beta = 0.006$). Meanwhile, orthopedic injury group showed a negative correlation between longitudinal resilience and FC ($F[1\ 89] = 15.33$, FDR corrected $p = <.001$, $\beta = -0.019$).

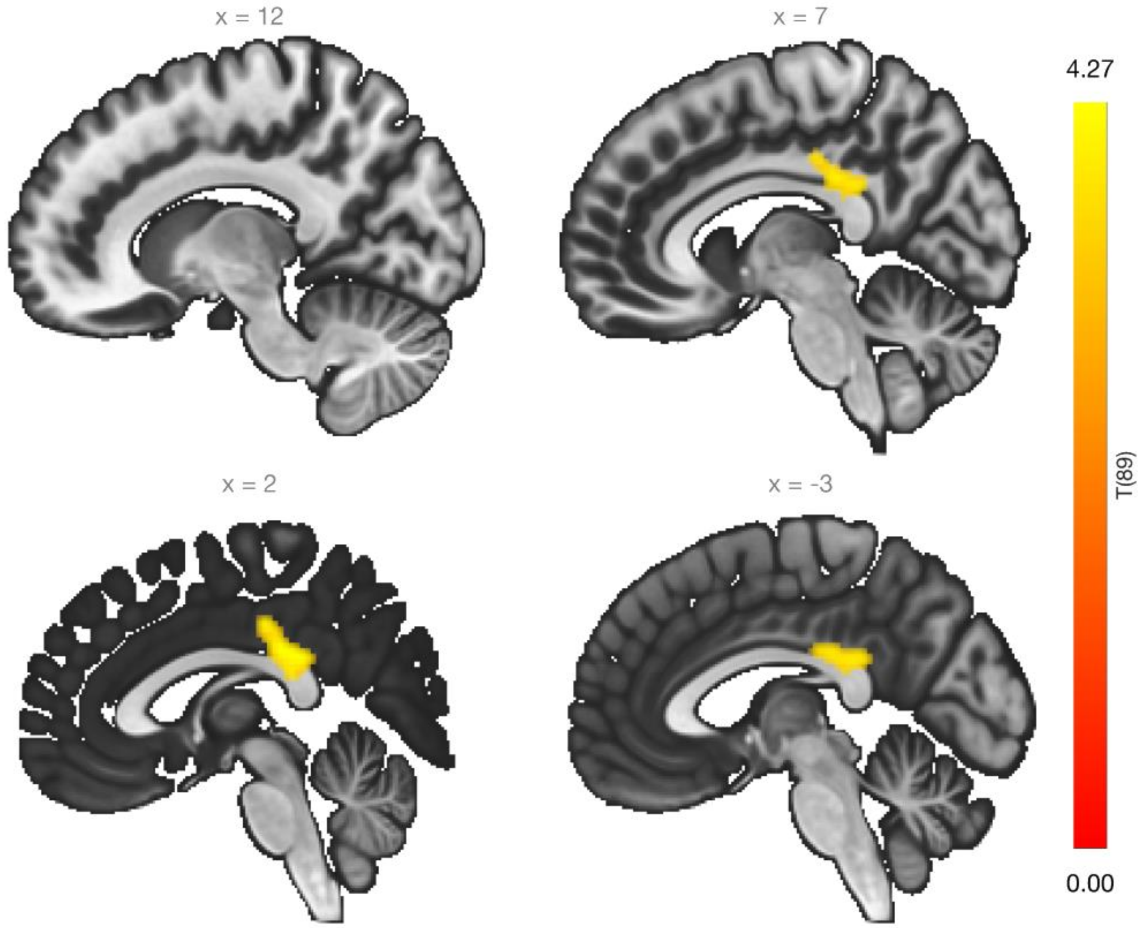


Figure 3. Group as a moderator between 72 h resilience and FC.: Sagittal slices displaying the significant cluster within the posterior division of the cingulate gyrus, color-coded by voxel statistic, indicating an interaction between group and 72 h resilience when predicting 72 h FC to the left anterior insula of the SN. Associations between longitudinal resilience and connectivity values within this cluster differed significantly between groups, whereby the concussion group showed a positive correlation, whereas the orthopedic injury group showed a negative correlation. SN, salience network.

Within the concussion group, 72hrs resilience was positively correlated with FC between the left lateral prefrontal cortex seed of the CEN and the left lateral occipital cortex (cluster size = 307, MNI x y z = -26 -70 +62, $F[1, 61] = 29.92$, FDR corrected $p = .003$, $\beta = 0.015$; Figure 4).

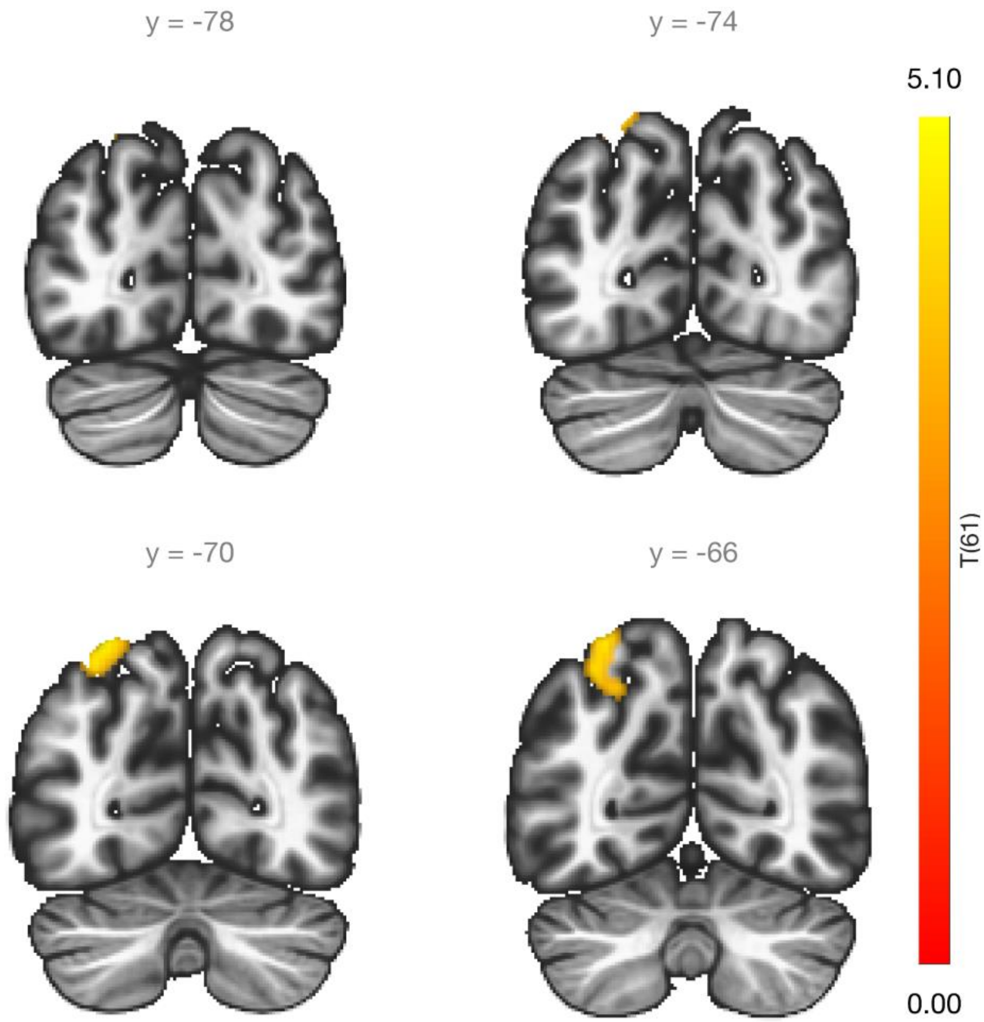


Figure 4. Associations between 72 h resilience and FC within concussion group: Coronal slices displaying the significant cluster within the left lateral occipital cortex, color-coded by voxel statistic, indicating a positive correlation between 72 h resilience and 72 h FC to the left lateral prefrontal cortex of the CEN. CEN, central executive network.

Within the orthopedic injury group, 72hrs resilience was positively correlated with FC between the left anterior insula seed of the SN and the right superior parietal lobule (cluster size = 416, MNI x y z = +44 -38 +54, $F[1, 26] = 52.28$, FDR corrected $p < .001$, $\beta = 0.018$; Figure 5).

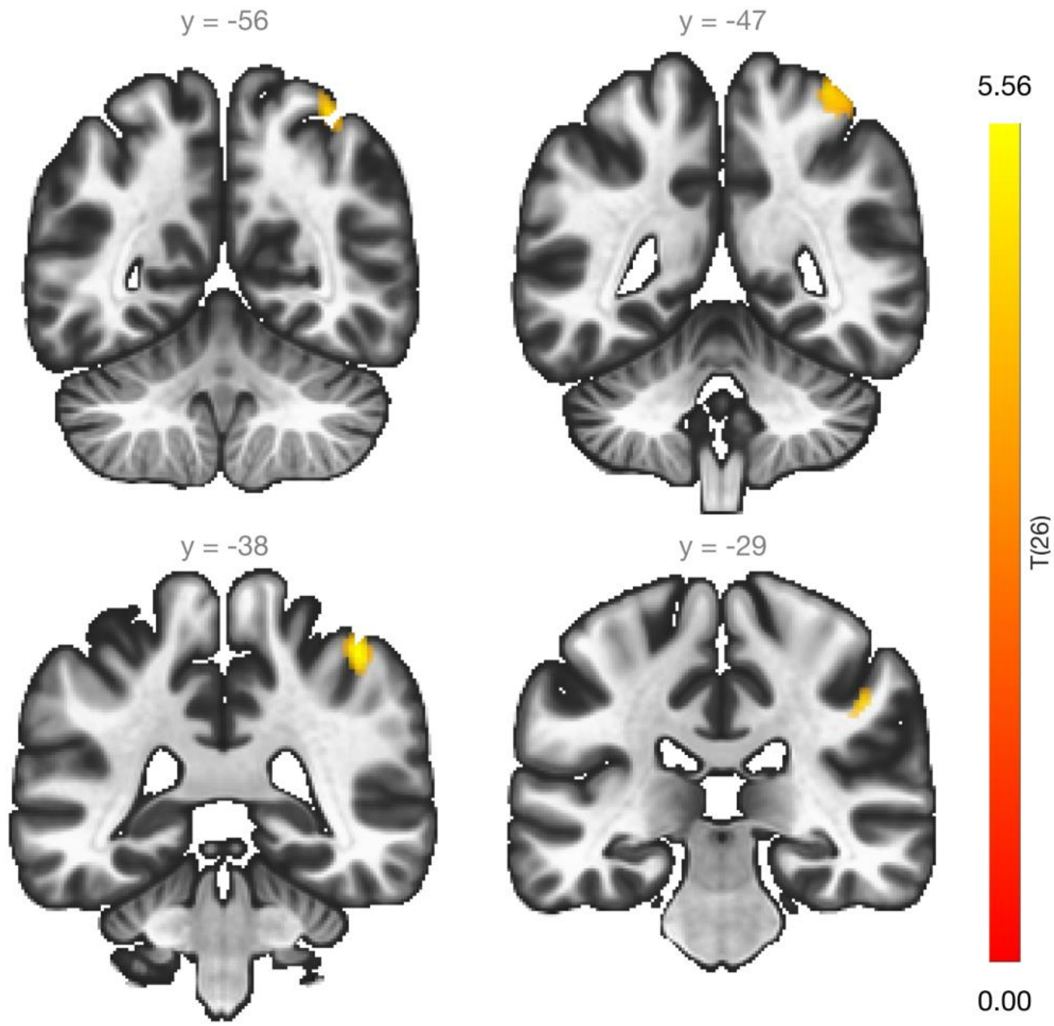


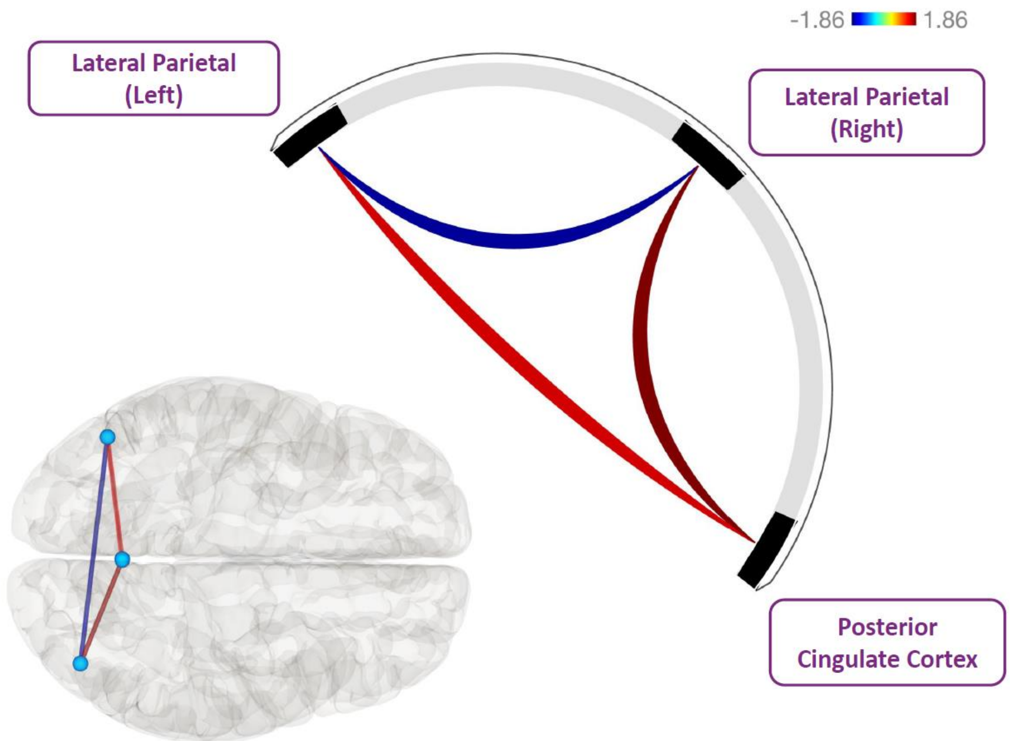
Figure 5. Associations between 72 h resilience and FC within orthopedic injury group: Coronal slices displaying the significant cluster within the right superior parietal lobule, color-coded by voxel statistic, indicating a positive correlation between 72 h resilience and 72 h FC to the left anterior insula of the SN. SN, salience network.

Seed-to-voxel analyses did not detect any significant interactions or associations between 4-week resilience and FC.

ROI-to-ROI Analyses

Longitudinal Resilience and FC.

A significant three-way interaction (group*resilience*time) was identified among connections between DMN seeds ($F[2, 88] = 4.56$, p-FDR = .026; Figure 6). Group was a moderator of longitudinal resilience and patterns of FC between DMN nodes. The interaction cluster included three ROIs and three connections among them. The first connection between bilateral lateral parietal cortices was a positive correlation in both the concussion group (β = 0.001) and the orthopedic injury group (β = 0.018). The second connection between the right lateral parietal cortex and posterior cingulate cortex was a negative correlation in both the concussion group (β = -0.002) and the orthopedic injury group (β = -0.021). The third connection between the left lateral parietal cortex with the posterior cingulate cortex was a positive correlation in the concussion group (β = 6.80E-05) and a negative correlation in the orthopedic injury group (β = -0.015).



F[2, 88] = 4.56, p-FDR = .026

Figure 6. Group as a moderator between longitudinal resilience and within-DMN FC: Ring plot demonstrating the connectivity differences between DMN seeds of the identified cluster, color-coded by connection statistic. The orthopedic injury group had an overall greater effect size relative to the concussion group, suggesting that injury type interacts with longitudinal resilience when predicting within-DMN connectivity. DMN, default-mode network.

Within the orthopedic injury group, longitudinal resilience was associated with longitudinal within-network DMN FC ($F[2, 25] = 4.99$, p-FDR = .030; Figure 7). The significant cluster comprised of three ROIs and three connections among them: a positive correlation between the right and left lateral parietal cortex (β = 0.018); a negative correlation between the right lateral parietal cortex and posterior cingulate cortex (β = -0.021); as well as a negative correlation between the left lateral parietal cortex and the posterior cingulate cortex (β = -0.015). Within the concussion group, no significant associations between longitudinal resilience and within-network FC were detected.

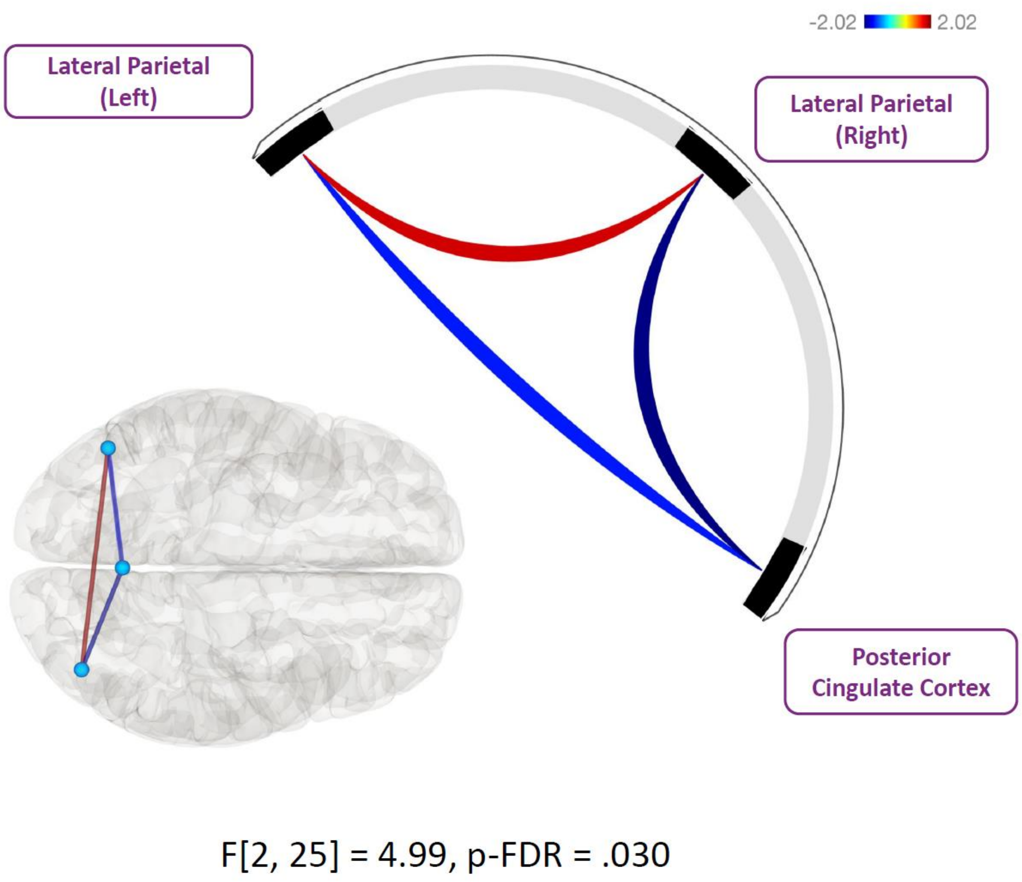


Figure 7. Orthopedic injury associations between longitudinal resilience and within-DMN FC: Ring plot demonstrating the associations between longitudinal resilience and within-DMN connectivity of the identified cluster, color-coded by connection statistic. The orthopedic injury group had a significant association between resilience and patterns of within-DMN cluster-based connectivity over time. DMN, default-mode network.

Cross-Sectional Resilience and FC.

Within the orthopedic injury group, analyses of within-network SN FC identified one significant cluster (*F*[1, 26] = 8.98, *p*-FDR = .036; Figure 8). The cluster included three ROIs and three connections among them: a negative correlation between 72hrs resilience and FC of the right anterior insula with the anterior cingulate cortex (β = -0.012); a negative correlation between 72hrs resilience and FC of the left and right anterior insula (β = -0.016); and a negative correlation between 72hrs resilience and FC of the left anterior insula with the anterior cingulate cortex (β = -0.015). No two-way interactions (group*resilience) were detected for within-network FC. Within the concussion group, analyses did not detect any significant associations between 72hrs resilience and FC.

ROI-to-ROI analyses did not detect any significant interactions or associations between 4-week resilience and FC.

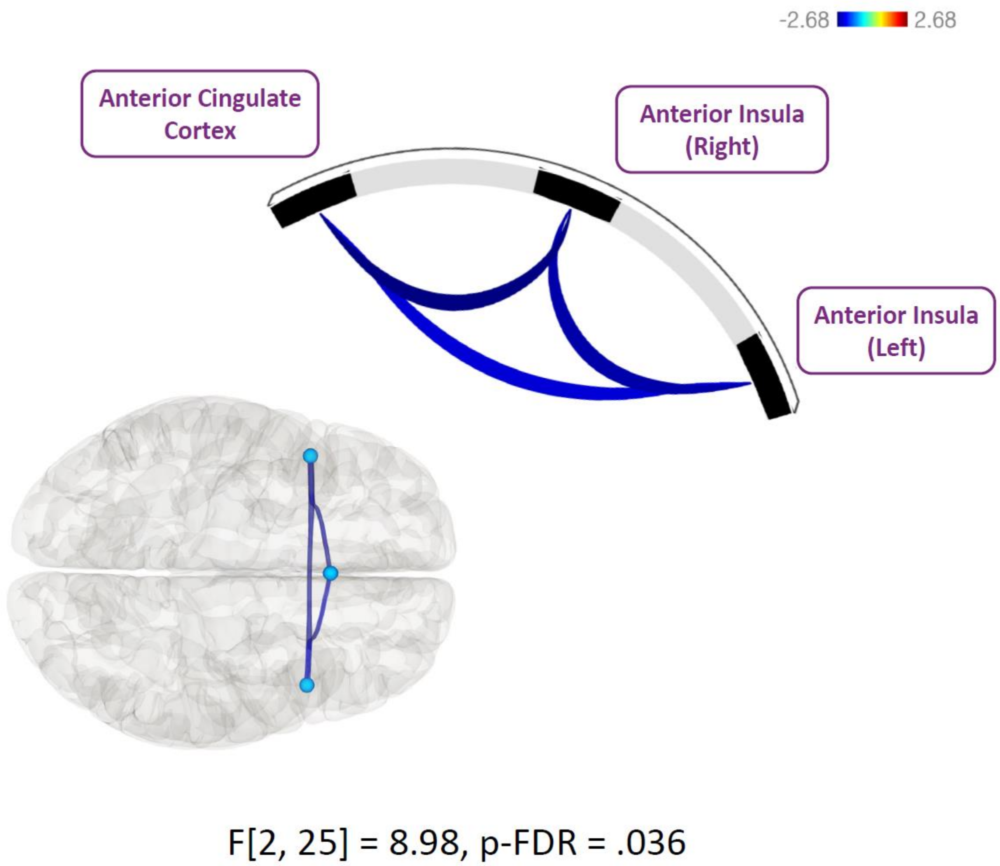


Figure 8. Orthopedic injury associations between 72 h resilience and within-SN FC: Ring plot demonstrating the associations between 72 h resilience and within-SN connectivity of the identified cluster, color-coded by connection statistic. The orthopedic injury group had a significant association between resilience and patterns of within-SN cluster-based connectivity at 72 h postinjury. In this study, all identified connections were negatively correlated with resilience scores. SN, salience network.

Discussion

Results showed that with higher resilience, there was greater FC with the CEN in children with acute concussion. Heightened resilience over time was related to decreased FC with the DMN in children with concussion, however, was related to increased FC in children with orthopedic injury. Resilience over time was also related to differential patterns of within-DMN FC in children with concussion compared to children with orthopedic injury. Also, highly resilient children had greater quality of life at 4 weeks post-concussion.

Results for our primary objective suggest that pediatric injury type moderates the associations between longitudinal resilience and DMN FC, that is FC of the right lateral parietal cortex with the right cerebellum. Within the concussion group, there was a negative correlation between longitudinal resilience and FC within the identified cluster in the right cerebellum. Meanwhile, within the orthopedic injury group, there was a positive correlation between longitudinal resilience and FC within the same cluster. The lateral parietal cortex plays a role in various cognitive processes including attention, working memory, spatial cognition, and social cognition (Cabeza et al., 2012; Desmurget et al., 2009; Humphreys & Lambon Ralph, 2015; Tumati et al., 2019). A recent fMRI study identified the cerebellum and corticocerebellar connections as being integral to episodic memory for emotionally arousing visual information (Fastenrath et al., 2022). Furthermore, this study found a significant positive correlation between longitudinal resilience and FC with the same regions within orthopedic-injured children. As longitudinal resilience did not differ between our samples of concussion and orthopedic injury children, perhaps the difference of associations between groups may be attributed to concussion-related changes to FC. Our secondary analyses indicate that associations between longitudinal resilience and within-DMN FC are also moderated by pediatric injury type. The association within the cluster of ROIs was stronger in the orthopedic injury group when compared to the concussion group. Our results similarly found that such associations were significant in orthopedic-injured children. The effects of pediatric concussion might thus contribute towards a diminished association between longitudinal resilience and within-DMN FC.

Moreover, our primary analyses indicate the associations between 72hrs resilience and SN FC are moderated by pediatric injury type. This significant moderation was identified in FC between the left anterior insula of the SN and the posterior division of the cingulate gyrus, a node of the DMN. Within the concussion group, there was a positive correlation between 72hrs resilience and FC within the identified cluster. In the orthopedic injury group, there was a negative correlation between 72hrs resilience and FC within the same cluster. This finding of differential functional FC with the DMN is consistent with a recent study that reported an association between pediatric mild traumatic brain injury and decreased time spent in a default mode brain state with altered FC within midline cortical regions (van der Horn et al., 2023). In a study investigating whether damage to white matter tracts of the SN disrupts regulation of associated networks, structural connectivity within the SN was a significant predictor of DMN function (Bonnelle et al., 2012). Specifically, integrity of a tract connecting the right anterior insula to the presupplementary motor area and dorsal anterior cingulate cortex was correlated with abnormal posterior cingulate cortex activation in traumatic brain injury patients. The authors concluded that structural integrity of the SN is imperative for regulation of DMN activity. Pediatric concussion might diminish the association between resilience and SN FC to the DMN, contributing to a deregulation of DMN activity. This might, in turn, partially explain the discrepancy of significant DMN FC associations between our samples of children with concussion and orthopedic injury.

A significant positive correlation was reported between 72hrs resilience and FC of the CEN, specifically the left lateral prefrontal cortex, with the left lateral occipital cortex in children with concussion. Interestingly, a recent study identified increased FC between the right lateral prefrontal cortex and right occipital pole in youth with concussion with resolved headache symptoms when compared to youth with concussion showing persisting headache symptoms (Lemme et al., 2021). This recent study, however, did not incorporate a measure of resilience. It is possible that their sample of youth with concussion showing resolved headache symptoms had increased resilience relative to those showing persisting headache symptoms. This warrants further investigation into the associations between resilience and CEN FC in concussion. Meanwhile, in orthopedic-injured children, 72hrs resilience was positively correlated with SN FC. Secondary analyses found that 72hrs resilience was also significantly associated with within-SN FC in orthopedic-injured children. This is consistent with previous reports of negative correlations between resilience and within-SN FC in healthy populations (Altinok et al., 2021; Bolsinger et al., 2018). As suggested by Altinok et al. (2021), highly resilient individuals might have decreased switching of the SN between networks responsible for processing self-relevant information. Highly resilient individuals might thus maintain a reasonable emotional response to injury, allowing for an increased capacity to focus on their current mental state and successfully cope without interference from internal and external stressors. Unfortunately, these results were not identified in the concussion group, which might suggest that biomechanical injury to the head contributes to a disruption of this association otherwise identified in non-concussed individuals. As such, only results from the orthopedic-injury group, as opposed to the concussion group, are largely consistent with the resilience literature using non-injured participants.

Additional research is necessary to understand the effects of such associations on clinical symptoms post-injury in both orthopedic injury and concussion groups.

There were no significant results to report with respect to 4-week resilience and FC. Associations between resilience and resting-state FC might thus only be pertinent or detectable within the acute phase of injury. Research using non-injured pediatric samples reported various associations between resilience and resting-state FC of the SN with the DMN and CEN (Iadipaolo et al., 2018). Considering this, the underlying mechanism that may explain the progressive changes in associations between resilience and FC during pediatric concussion recovery remain unclear.

CD-RISC 10 scores were previously identified as being positively correlated with PedsQL in children with concussion in the chronic stage of injury (> 4 weeks post-injury; Durish, 2018a). Our results are consistent with this finding and demonstrate an association between resilience and quality of life at 4 weeks post-concussion using identical metrics to Durish (2018a). Although the association between resilience and quality of life at 72hrs did not reach significance, this may be the result of diminished statistical power and differential report instructions in the acute phase of injury. The computed confidence intervals suggest that the association between resilience and quality of life at 72hrs could potentially reach significance after multiple comparisons if statistical power were to be increased. Further, the CD-RISC 10 instructs the participant to complete the report based on the past 30 days, while the PedsQL is based on the past seven days. It remains a possibility that the acute injury event had a greater impact on quality of life scores than resilience scores at the time of reporting (72hrs post-injury), consequently altering the association between the two metrics. These findings, along with the reported associations between resilience and functional connectivity, suggest that self-reported resilience maybe implicated in both neural and functional outcomes following pediatric concussion. Conversely, our results suggest that resilience is not correlated with symptom burden at any timepoint, contradicting prior research reporting a significant association between resilience and post-injury symptom burden in the chronic phase of concussion (Hassan et al., 2023). Further research of resilience-targeted interventions is needed to assess the effects of such an intervention on the outcomes reported here.

Although this study provides insight as to the associations between resilience and DMN, CEN, and SN FC following pediatric concussion, the identified patterns in resting-state FC might be affected by our selection of spatial seeds in the seed-based correlations. It is known that subtle differences in selection of spatial seed voxel locations for seed-based correlation analyses of resting-state networks can have a significant effect on the variability of resulting associations in network FC (Buckner et al., 2008; Cole et al., 2010; Hayasaka and Laurienti, 2010). Future research of this sort should seek to apply similar spatial seeds as the ones selected for this study to replicate these findings. It is also important to note that this study applied the CONN toolbox default weight for the hierarchical clustering. Although the significant results reported here are based on a combined weighting of function and proximity, a different approach (e.g., modified weight to reflect only functional or only proximal clustering) may influence results. More research comparing the effects of prioritizing either clustering method is required to discuss its implications on cluster-based inferential analyses in this context. Furthermore, the analyses conducted in this study might be constrained by diminished statistical power. Although the sample size may be considered adequate for fMRI research, the complexity of our models (i.e., three-way interaction multiple regressions with the implementation of several covariates) may have limited the power of our statistical analyses. Future studies should seek to mitigate this potential limitation by increasing sample size and constricting the number of predictors and/or covariates of the statistical models.

Conclusions

Our results provide insight of the associations between resilience and FC in the sub-acute phase of pediatric concussion. Highly resilient children with concussion had heightened FC with the CEN at 72hrs post-injury. We report several differences between our samples of children with orthopedic-injury and concussion, whereby significant associations between resilience and FC were identified in the former but not the latter. Resilience was also associated with quality of life in the concussion group, whereby highly resilient children reported higher quality of life at 4 weeks post-injury. These findings indicate that resilience might play a role in both the functional neuroimaging results and quality of life following pediatric concussion and should be further examined to determine its potential usefulness in clinical settings as a protective or restorative element after injury. Additional investigations are warranted to determine the potential of resilience as a factor linked to optimal recovery from pediatric concussion.

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Compliance with Ethical Standards

This study received approval by the Research Ethic Board and the Children's Hospital of Eastern Ontario. All eligible children and adolescents capable of consenting on their own behalf provided written informed consent, while those unable to consent on their own behalf provided assent and parental consent.

Conflict of Interest Statement

Roger Zemek has received competitively-funded research grants from Canadian Institutes of Health Research (CIHR), Ontario Neurotrauma Foundation (ONF), Physician Services Incorporated (PSI) Foundation, CHEO Foundation, Ontario Brain Institute (OBI), and Ontario SPOR Support Unit (OSSU), and the National Football League (NFL) Scientific Advisory Board, and he is supported by a Clinical Research Chair in Pediatric Concussion from University of Ottawa. He is the co-founder, Scientific Director and a minority shareholder in 360 Concussion Care, an interdisciplinary concussion clinic. All other co-authors have no conflict of interest.

Supplementary Appendix S1

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Chapter 4: Study 3

Investigating a Mindfulness-Based Intervention as a Moderator of Resilience on Functional Connectivity in Pediatric Concussion

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Abstract

Psychological resilience may be associated with neurofunctional outcomes after concussion. While mindfulness-based interventions (MBIs) may enhance resilience, their specific effects on both resilience and functional connectivity (FC) following concussion remain unknown. This study examined whether MBI influences resilience trajectories and moderates the association between baseline resilience and follow-up resting-state FC in adolescents with concussion. This substudy of a randomized clinical trial (ClinicalTrials.gov ID: NCT05105802) randomly assigned participants to a four-week digital program: either a custom-made MBI or a cognitive sham. Resilience was assessed in the full sample using the Connor-Davidson Resilience Scale 10, whereas fMRI data was collected from a partial sample at 72 hours and 4 weeks post-injury. Linear mixed effect models were applied to the full sample to test group differences in resilience trajectories. Seed-to-voxel regressions were applied to the partial sample to test Group × Resilience (Baseline) interactions when assessing FC at 4 weeks across the default mode network (DMN), salience network (SN), and central executive network (CEN). Ninety-five participants were included in the resilience analysis (MBI $n = 47$; Sham $n = 48$), while 36 participants (MBI $n = 16$; Sham $n = 20$) were included in the FC analysis. There were no significant group differences in resilience trajectories. Significant interactions were identified in FC across the DMN, SN, and CEN (FDR $p < .05$). While MBI did not enhance self-reported resilience, the identified interactions in FC suggest that neuroimaging may be more sensitive than self-report in detecting early MBI effects on resilience after concussion.

Introduction

Concussion is the most common type of traumatic brain injury among youth, with approximately 10% reporting a traumatic brain injury in the past year (Daugherty et al., 2024; McCrory et al., 2017; Taylor et al., 2017). While most children and adolescents recover from concussion within weeks, approximately one-third experience persisting symptoms after concussion (PSaC), which are associated with reduced physical and psychosocial health-related quality of life (Chadwick et al., 2022; Novak et al., 2016; Yeates et al., 2012; Zemek et al., 2016). Emerging evidence suggests that psychological resilience, the ability to adapt effectively to adversity or trauma that could disrupt healthy development, may be associated with pediatric concussion recovery trajectories (Bunt et al., 2021; Durish et al., 2018b; Ernst et al., 2021; Gornall et al., 2024). Importantly, research suggests that resilience measured at initial clinical assessment, or baseline, may be associated with clinical outcomes assessed at a later phase of injury recovery. In adults with mild traumatic brain injury (mTBI), pre-injury resilience influenced the severity of concussion symptoms and post-injury anxiety (McCauley et al., 2013). Similarly, in adolescents and young adults with concussion, lower resilience during the initial clinic visit correlated with greater symptom count and severity, higher anxiety and depression, reduced likelihood of recovery at three months, and increased symptom aggravation from physical and cognitive activity (Bunt et al., 2021). In adolescent and young adult athletes with sport-related concussion, lower psychological resilience predicted protracted recovery, while also correlating with longer recovery duration, greater affective symptoms, and more severe vestibular-ocular impairments (Ernst et al., 2021). In adults with recent mTBI, lower psychological resilience significantly predicted greater severity of PSaC (Sullivan et al., 2015). In a recent prospective longitudinal cohort study, lower resilience correlated with greater externalizing symptoms at 2 weeks following pediatric concussion (Gornall et al., 2024). In adolescents, lower resilience correlated with PSaC and greater anxiety/depressive symptoms beyond one month post-injury (Durish et al., 2018b). These findings highlight the potential clinical impact of developing and implementing resilience-targeted interventions to enhance resilience in vulnerable patients and, in turn, reduce the negative effects that contribute to prolonged recovery after pediatric concussion.

These clinical findings are supported by emerging resting-state functional magnetic resonance imaging (rs-fMRI) evidence linking resilience to functional connectivity (FC) of major networks involved in cognitive and emotional regulation. These include the default mode network (DMN), associated with self-referential processing, mind-wandering, and rumination (Raichle, 2015); the central executive network (CEN), which mediates attention, working memory, and cognitive control (Seeley et al., 2007); and the salience network (SN), which detects relevant stimuli to coordinating switching between the DMN and CEN activation (Goulden et al., 2014; Seeley et al., 2007). In acute pediatric concussion, FC between the lateral prefrontal cortex of the CEN and the lateral occipital cortex correlated positively with resilience (Brown et al., 2024). Resilience correlated with dynamic states of DMN-CEN FC in children and adolescents with significant sociodemographic risk, suggesting potential adaptive reorganization of these networks in response to frequent adversity (Iadipaolo et al., 2018). Conversely, in healthy populations, resilience correlated negatively with FC of the DMN, SN, and CEN (Altinok et al., 2021; Bolsinger et al., 2018; Hemington et al., 2018; Iadipaolo et al., 2017; van der Werff et al., 2013). It is important to consider these results in the context of acute concussion. Concussion often disrupts neural network FC, including transient patterns of hyperconnectivity, particularly in the early post-injury phase (Bouchard et al., 2024; Boshra et al.

2020; Liu et al., 2020; Mayer et al., 2011; Zhu et al., 2015). Over time, these changes can evolve in bidirectional or regionally specific ways depending on recovery phase (Abbas et al., 2015; Borich et al., 2015; Bouchard et al., 2024; Healey et al., 2022; Johnson et al., 2012; Marusak et al., 2017; Newsome et al., 2016; Orr et al., 2016; Plourde et al., 2021; Sours et al., 2013, 2015; Zhu et al., 2015). These dynamic alterations may influence or confound the observed associations between resilience and FC. A recent report, for example, found that acute pediatric concussion moderated the association between resilience and SN FC (Brown et al., 2024). Given the emerging evidence linking resilience to both clinical and neurofunctional outcomes, interventions that enhance psychological resilience may offer a promising avenue for optimizing concussion recovery.

Mindfulness-based interventions (MBIs) are psychological interventions that systematically implement mindfulness practices of intentional, non-judgmental awareness of present moment experiences, thereby promoting adaptive coping behaviours They often involve practices such as focused breathing, body awareness, and meditation to support emotional regulation and foster adaptive coping strategies (Kabat-Zinn, 1990). A meta-analysis of randomized controlled trials on MBIs delivered via smartphone application (app) to adults reported significant improvements in perceived stress, depressive and anxiety symptoms, quality of life, psychological well-being, and positive affect when compared to control groups, waitlists, or other interventions (Gál et al., 2021). Notably, emerging evidence suggests that MBI may enhance resilience by improving individuals’ capacity to manage stress and recovery from adversity. MBIs effectively promote resilience with medium effect sizes (O'Connor et al., 2023; Zenner et al., 2014) and were identified as a key factor in enhancing resilience (Oh et al., 2022).

Given the emerging evidence linking resilience at initial clinical assessment, or baseline, to both psychological and neurofunctional outcomes, interventions that promote resilience may offer a promising avenue for supporting concussion recovery. Among these, MBIs are increasingly studied for their reported effects on brain network connectivity. In healthy youth, MBIs are typically associated with post-intervention increased FC within and between the DMN, SN, and CEN (Bauer et al., 2020; Bremer et al., 2022; Hafeman et al., 2020; Jande et al., 2025; Mishra et al., 2020; Patsenko et al., 2019; Tang et al., 2015; Taren et al., 2017). In clinical populations presenting network hyperconnectivity, MBIs might be linked to restored network connectivity patterns rather than uniform increases in connectivity. For instance, reductions in DMN FC were reported following MBI in individuals with major depressive disorder, where DMN hyperconnectivity is implicated in rumination and maladaptive behaviours (Sezer et al., 2022). Specifically, decreased FC between the rostral anterior cingulate cortex and DMN was interpreted as a potential mechanism underlying the antidepressant effects of MBI (Sezer et al., 2022; Yang et al., 2016). Researchers postulate that coordinated activity of the DMN, SN, and CEN supports self-regulatory functions, suggesting that MBIs may contribute to resilience through functional reorganization, potentially restoring network dynamics disrupted by concussion rather than indiscriminately increasing FC (Jande et al., 2025; Melis et al., 2022; Sezer et al., 2022; Young et al., 2018). However, limited evidence exists regarding whether engaging with an MBI following concussion influences resilience trajectories or the associations between resilience and FC.

The primary objective of this study was to examine whether randomization to an MBI, compared to a cognitive sham group, influences the trajectory of resilience among adolescents recovering from acute concussion. The secondary objective was to examine whether MBI moderates associations between baseline resilience when predicting resting-state FC of key neurofunctional networks (DMN, SN, and CEN) at follow-up, 4-weeks post-concussion. We hypothesize that adolescents allocated to an MBI will show a greater increase in resilience from baseline to follow-up compared to those in the sham group. This is consistent with literature suggesting that MBIs are effective in enhancing resilience (O'Connor et al., 2023; Oh et al., 2022; Zenner et al., 2014). We also hypothesize that MBI will significantly moderate the association between baseline resilience and follow-up FC. Specifically, we expect that higher resilience will correlate with lower FC of the DMN, SN, and CEN in the MBI group, but not in the sham group. This aligns with previous findings of negative correlations between resilience and FC in healthy populations (Altinok et al., 2021; Bolsinger et al., 2018; Hemington et al., 2018; Iadipaolo et al., 2017; van der Werff et al., 2013), suggesting that greater resilience is associated with reduced hyperconnectivity among the main neurofunctional networks. Given that acute concussion involves pathological hyperconnectivity (Bouchard et al., 2024; Boshra et al., 2020; Liu et al., 2020), MBI-enhanced resilience may promote neurofunctional recovery by normalizing elevated FC consistent with natural recovery patterns (Bouchard et al., 2024; Zhu et al., 2015).

Methods

Study Design

This is a substudy of the Health Canada-regulated randomized, sham-controlled clinical trial *Mindfulness-Based Intervention for Mild Traumatic Brain Injury* (MBI-4-mTBI; Ledoux et al., 2024). MBI-4-mTBI is a trial that investigated the feasibility and acceptability of conducting a large, multi-site randomized controlled trial of MBI in pediatric concussion by measuring recruitment efficiency, intervention credibility and adherence, and retention. The program design and curriculum are detailed in the study protocol (Ledoux et al., 2024).

MBI-4-mTBI included a nested magnetic resonance imaging (MRI) component, in which a subpopulation underwent MRI scanning at 72 hours (± 72 hours) and 4 weeks (± 5 days) post-injury. The secondary objective is based on the MRI component and is comprised only of randomized participants that underwent both MRI scans. MBI-4-mTBI was approved by the Research Ethics Board of the Children's Hospital of Eastern Ontario (CHEO). Eligible and willing parents, along with adolescents who were able to consent on their own behalf, were asked to provide written informed consent. Adolescents who were unable to provide consent themselves were asked to provide assent.

Participants

This study included adolescents aged 12 to 17.99 years who presented to the emergency department at CHEO or 360 Concussion Care, an interdisciplinary specialty concussion care clinic, within seven days of a concussion. Concussions were defined according to the adapted American Congress of Rehabilitation Medicine framework (Silverberg et al., 2023), whereby adolescents with either 1 *highest level of certainty* symptom or 2 *higher level of certainty* symptoms immediately or within 1 hour of injury were included. Participants required a score above 4 on the Predicting and Preventing Post-Concussive Problems in Pediatrics clinical risk score (Zemek et al., 2016) and English proficiency.

Participants were excluded if they had a Glasgow Coma Scale score of 13 or lower, abnormal neuroimaging results, required neurosurgical intervention, intubation, or intensive care, or had multisystem injuries necessitating hospitalization, surgery, or procedural sedation. Other exclusions included severe chronic neurological or developmental conditions impairing communication, intoxication at the time of the emergency visit, no clear traumatic event as the cause of injury (e.g., seizure, syncope, or migraine), prior psychiatric hospitalization, inability to provide informed consent or assent, absence of a legal guardian, lack of internet or mobile/tablet access, or currently receiving psychotherapeutic services. Treatment for other medical conditions (e.g., psychiatric medication) or for concussion (e.g., physical therapy) was recorded but not considered an exclusion criterion. Likewise, prior diagnoses of attention deficit hyperactivity disorder, anxiety, or depression were documented but not exclusionary.

The MRI component had additional exclusions: a history of neurological or neurodevelopmental disorders such as epilepsy, intellectual disability, or autism, a prior stroke or transient ischemic attack, sedation medication administered before or during the emergency visit, inability to attend both the 72-hour and 4-week MRI sessions, or medical contraindications such as claustrophobia, pregnancy, or the presence of metal implants.

Procedures

The study was conducted at CHEO and the 360 Concussion Care clinic, while the MRI component took place at the Brain Imaging Centre of the Royal Ottawa Mental Health Centre. Once participants were enrolled, research assistants (RAs) administered a series of electronic surveys via the Research Electronic Data Capture system (REDCap; Harris et al., 2009) in the emergency department, 1 day (baseline) and 4 weeks post-recruitment (follow-up), collecting patient demographics, pre-injury and injury details, symptoms, and diagnostic history. On the day following enrollment, RAs randomized participants via REDCap to one of two groups: the app-delivered MBI or a cognitive sham intervention delivered on the same app. Both groups also followed usual care (Reed et al., 2023). The RAs responsible for randomization were the only ones among the research team that were unblinded, while patients and families remained blinded.

The following assessments were administered at baseline and follow-up to characterize the sample: Health Behaviour Inventory (HBI; Ayr et al., 2009); Child and Adolescent Mindfulness Measure (CAMM; Greco et al., 2011); Center of Epidemiologic Studies Depression Scale 10-Item Version (CES-D-10; Andersen et al., 1994); General Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006); and Pediatric Quality of Life Inventory version 4.0 (PedsQL; Varni et al., 2001). Participants also completed the Connor-Davidson Resilience Scale 10 (CD-RISC 10; Campbell-Sills & Stein, 2007) at baseline and follow-up, which reflects experiences over the preceding 30 days, at baseline and 4 weeks follow-up. The CD-RISC 10 is a validated 5-point Likert self-report scale of psychological resilience; higher cumulative scores reflect increased resilience. The CD-RISC 10 is a clinically validated scale used in pediatric concussion research (Durish et al., 2018b) with good internal consistency, convergence, and content validity, with satisfactory construct validity (Durish et al., 2018a; Kuiper et al., 2019; Windle et al., 2011).

MRI Acquisition and Image Processing

A 3-Tesla Biograph Siemens PET-MRI scanner with a 32-channel head coil was used to acquire brain scans from a resting-state fMRI sequence. Participants were instructed to keep their eyes open and fixated on a crosshair, remain still, think of nothing, and relax. A single rs-fMRI sequence was collected with the following parameters: resolution = $3.0mm^3$; slices = 40; FOV = 204mm; repetition time (TR) = 2160ms; echo time (TE) = 25ms; flip angle = 70^o; acceleration factor = 2; 334 volumes; scan time = 12min 8sec. A high-resolution T1-weighted anatomical image was acquired for registration based on the following parameters: resolution = $1.0mm^3$; slices = 192; FOV = 256mm; TR = 2500ms; TE = 1.69ms, 3.55ms, 5.41ms, and 7.27ms; flip angle = 7^o; inversion time = 1050ms; phase FOV = 100%; scan time = 5min 48sec (van der Kouwe et al., 2008). Both the rs-fMRI and 3D T1-weighted anatomical scans were acquired along the anterior commissure and posterior commissure line (AC-PC) with whole head coverages.

Structural image quality checks were performed based on methods outlined by Backhausen et al. (2016). fMRI data were preprocessed using fMRIPrep (Esteban et al., 2019), AFNI (Cox, 1996), and CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012). The fMRIPrep processing pipeline included tissue segmentation, realignment, susceptibility distortion correction, structural and functional normalization to the MNI152 space at 2mm resolution, and computation of relevant confound regressors. Participant scans were excluded if the mean framewise displacement value exceeded 0.3 mm, a cutoff value previously used in pediatric samples (DeSerisy et al., 2020; Frew et al., 2022; Ofoghi et al., 2021; Smith et al., 2022). The AFNI software was then used for spatial smoothing at a full width at half-maximum value of 6 mm, aligning with kernel sizes commonly used in fMRI studies involving youth populations (DeSerisy et al., 2020; Ofoghi et al., 2021). The global signal, cerebrospinal fluid, white matter, framewise displacement, and motion parameter (rotation and translation x-, y-, and z-axes) regressors were then imported into the CONN toolbox for subsequent denoising, first-level, and second-level analyses. The global signal was included as a regressor to reduce non-neuronal noise influences, in line with approaches adopted in recent pediatric fMRI studies (Aguirre et al., 1997; Fox et al., 2005; Macey et al., 2004; Ofoghi et al., 2021; Power et al., 2017). The denoising pipeline included both linear regression of confounding effects of signals and temporal band-pass filtering, removing frequencies < 0.008 Hz or > 0.009 Hz. Brain region labelling was based on the Harvard-Oxford Cortical atlas (Desikan et al., 2006).

Statistical Analyses

All primary and secondary objectives were addressed using both intention-to-treat and per-protocol analyses. The intention-to-treat analyses included all randomized participants, regardless of adherence to the intervention. The per-protocol analyses included participants who met the defined criteria for sufficient adherence to the study protocol, as defined by 10 minutes per day with a minimum of four days per week, over a period of four weeks. Adherence to the study protocol was assessed with device-recorded engagement metrics (i.e., duration of active session in the assigned intervention, in seconds). All analyses addressing the research objectives were conducted with covariates of age and biological sex. Age and biological sex were selected as covariates due to their documented effects on recovery from pediatric concussion (Ledoux et al. 2019).

We conducted a series of independent *t*-tests and chi-square tests to describe group differences in demographic variables across timepoints (alpha value: $\alpha = .05$). Item scores of 2.48 standard deviations from the mean were deemed as outliers (Cousineau & Chartier, 2010). Missing behavioural data were imputed with expectation maximization (Dong & Peng, 2013).

The primary objective was addressed with the following linear mixed model, based on the full MBI-4-mTBI sample, including participants who did not enroll in the MRI component. The model accounted for repeated measures of CD-RISC scores (baseline and follow-up) for each participant:

$$CD\text{-}RISC_{ij} = \beta 0 + \beta 1 Time_{ij} + \beta 2 Group_i + \beta 3 Time_{ij} \times Group_i + \beta 4 Age_i + \beta 5 Sex_i + u_{0i} + \epsilon_{ij}$$

where $CD\text{-}RISC_{ij}$ represents the CD-RISC 10 scores for participant i at time j. $\beta 0$ is the fixed intercept. $\beta 1$ is a variable representing the time point. $\beta 2$ is a binary variable representing the group (MBI or sham). $\beta 3$ is the interaction term between time and group. $\beta 4$ and $\beta 5$ are the regression coefficients representing the effects of age and biological sex on outcome. u_{0i}

represents the random intercept for participant *i*, accounting for the individual differences in baseline resilience. ϵ_{ij} represents the residual error. The model was estimated using restricted maximum likelihood, and degrees of freedom for fixed effects were computed using Satterthwaite's approximation. The critical value was set to $\alpha = .05$.

The secondary objective was addressed with the following regression model, based on the MBI-4-mTBI MRI component, only including participants who completed the rs-fMRI sequence:

$$FC = \beta 0 + \beta 1 CD\text{-}RISC + \beta 2 Group + \beta 3(CD\text{-}RISC \times Group) + \beta 4 Age + \beta 5 Sex + \epsilon$$

where *FC* represents the represents the FC values at follow-up. This model was estimated separately for each of the three major resting-state networks: DMN, SN, and CEN. $\beta 0$ is the intercept term. $\beta 1$ is a continuous variable representing baseline resilience. $\beta 2$ is a binary variable representing the group (MBI or sham). $\beta 3$ represents an interaction between baseline resilience and group. $B4$ and $\beta 5$ are the regression coefficients representing the effects of age and sex on outcome. ϵ represents the error term.

A seed-to-voxel approach was used to examine FC between seeds from the DMN, SN, and CEN with every voxel in the brain. Seed-based connectivity maps were generated to reflect FC between each specified seed and the entire brain. These maps were derived using seeds provided by the CONN toolbox for the DMN, CEN, and SN. The selection of these networks was informed by significant findings in the literature on concussion (Abbas et al., 2015; Borich et al., 2015; Iyer et al., 2019; Johnson et al., 2012; Mayer et al., 2011; Meier et al., 2017; Plourde et al., 2021; Sours et al., 2013, 2015; van der Horn et al., 2023), mindfulness (Bremer et al., 2022; Brewer et al., 2011; Doll et al., 2015; Farb et al., 2007; Taylor et al., 2011; Zhang et al., 2023), and resilience (Altinok et al., 2021; Bolsinger et al., 2018; Hemington et al., 2018;

Iadipaolo et al., 2017, 2018; van der Werff et al., 2013). The DMN seeds included the medial prefrontal cortex, bilateral parietal cortex, and posterior cingulate cortex. The CEN seeds included the bilateral prefrontal cortex and the left and right posterior parietal cortex. The SN seeds included the anterior cingulate cortex, bilateral anterior insula, left and right rostral prefrontal cortex, and the left and right supramarginal gyrus. Significant clusters were identified using the CONN toolbox's application of Random Field Theory (Worsley et al., 1996), with a voxel-level uncorrected height threshold of $p < .001$ and a cluster-level threshold corrected for False Discovery Rate (FDR) at $p < .05$.

Results

Demographics

Ninety-five participants were included in the intention-to-treat analysis (MBI $n = 47$, 40% female, age median [IQR]: 14.92 [13.66 – 16.14]; sham $n = 48$, 43% female, age median [IQR]: 15.00 [13.37 – 16.74]); Figure 1 for flow chart). Sports was identified as the most common injury setting for both groups (MBI: 35/47 [74%], sham: 32/48 [67%]; Table 1). Fifty-four participants were included in the per-protocol analysis (MBI $n = 29$, 52% female, age median [IQR]: 14.91 [13.99 – 15.93]; sham $n = 25$, 48% female, age median [IQR]: 15.05 [13.39 – 16.73]). There were no significant within- or between-groups differences in age, sex, diagnostic history, and concussion history in either the intention-to-treat or per-protocol analyses at baseline or follow-up ($p > .05$; Table 1).

Demographics, MRI Component

Thirty-six participants were included in the intention-to-treat analysis (MBI $n = 16$, 31% female, age median [IQR]: 14.23 [13.52 – 15.65]; sham $n = 20$, 45% female, age median [IQR]: 14.05 [13.13 – 16.26]). Twenty-three participants were included in the per-protocol analysis

(MBI *n* = 10, 40% female, age median [IQR]: 14.90 [14.01 – 15.66]; sham *n* = 13, 46% female, age median [IQR]: 14.66 [13.61 – 16.59]).

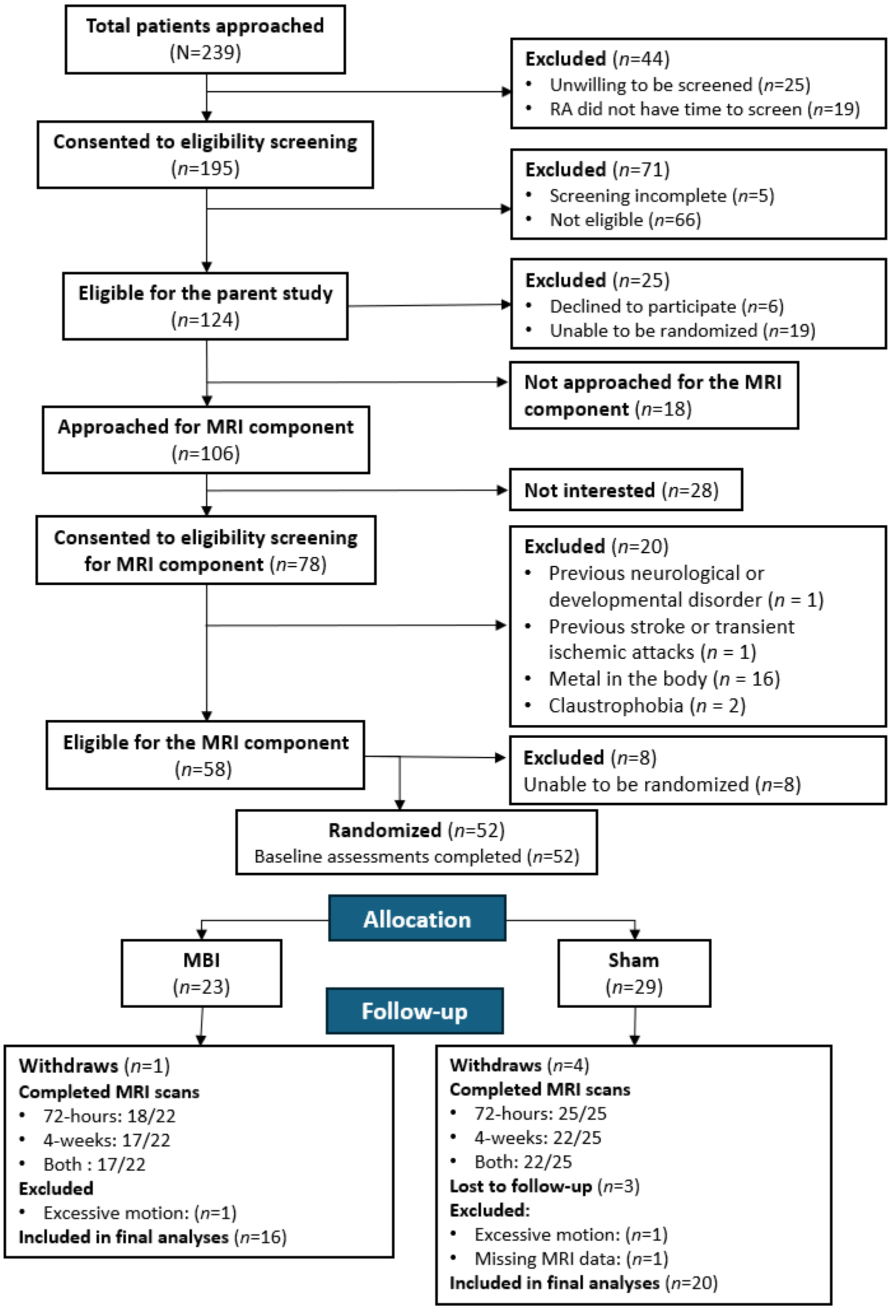

Figure 1. Flow chart: Illustrative chart depicting participant enrolment, randomization, and completion data.

Table 1*: *Demographics

Variables	Intention-to-Treat MBI (*n*=47)	Intention-to-Treat Sham (*n*= 48)	Per-Protocol MBI (*n*=29)	Per-Protocol Sham (*n*=25)
Age; Median (*IQR*)	14.92 (*13.65 – 16.14*)	15.00 (*13.37 – 16.74*)	14.91 (*13.99 – 15.93*)	15.05 (*13.39 – 16.73*)
Sex *n*(%)				
Male	28 (60%)	28 (58%)	14 (48%)	13 (52%)
Female	19 (40%)	20 (42%)	15 (52%)	12 (48%)
Diagnostic History *n*(%)				
Depression	4 (9%)	1 (2%)	3 (10%)	0
Anxiety	5 (11%)	8 (17%)	14 (6%)	6 (24%)
Prior Concussion *n*(%)	20 (43%)	22 (46%)	13 (45%)	14 (56%)
Mechanism of Injury *n*(%)				
Motor Vehicle Collision	0	1 (2%)	0	0
Fall Down Stairs	1 (2%)	1 (2%)	0	0
Sport	35 (74%)	32 (67%)	23 (79%)	17 (68%)
Fall from Standing/Walking/ Running	3 (6%)	5 (10%)	2 (7%)	2 (8%)
Ran into Stationary Object	0	2 (4%)	0	2
Other Mechanism	7 (15%)	7 (15%)	3 (10%)	4 (16%)

***Table 2**: Self-report measures at baseline and follow-up*

Variables	Intention-to-Treat MBI (*n*=47)	Intention-to-Treat Sham (*n*= 48)	Per-Protocol MBI (*n*=29)	Per-Protocol Sham (*n*=25)
Baseline				
CAMM; Median (*IQR*)	33.00 (*27.00 – 37.00*)	31.00 (*25.00 – 38.00*)	32.00 (*27.00 – 37.00*)	28.00 (*22.00 – 36.00*)
CES-D-10; Median (*IQR*)	7.00 (*3.50 – 10.00*)	7.00 (*5.00 – 9.50*)	7.00 (*4.00 – 10.00*)	8.00 (*6.00 – 11.00*)
CD-RISC 10; Median (*IQR*)	28.00 (*24.00 – 32.00*)	29.00 (*25.00 – 31.00*)	28.00 (*24.00 – 33.00*)	28.00 (*26.00 – 31.00*)
GAD-7; Median (*IQR*)	4.00 (*1.00 – 9.00*)	4.50 (*1.00 – 9.25*)	5.00 (*1.00 – 10.00*)	6.00 (*2.05 – 9.00*)
HBI; Median (*IQR*)	26.00 (*17.50 – 34.00*)	25.00 (*13.00 – 32.00*)	26.00 (*18.00 – 34.00*)	25.00 (*17.00 – 30.00*)
PedsQL; Median (*IQR*)	79.35 (*72.28 – 91.30*)	80.98 (*72.83 – 89.60*)	81.52 (*72.83 – 91.30*)	80.43 (*72.83 – 89.13*)
Follow-up				
CAMM; Median (*IQR*)	33.00 (*25.00 – 38.00*)	31.84 (*27.00 – 36.00*)	33.00 (*26.00 – 38.00*)	30.00 (*23.00 –35.00*)
CES-D-10; Median (*IQR*)	7.00 (*5.00 – 10.50*)	7.00 (*5.74 – 10.00*)	7.00 (*4.00 – 10.00*)	8.00 (*6.00 – 11.00*)
CD-RISC 10; Median (*IQR*)	27.00 (*20.50 – 30.00*)	27.33 (*20.00 – 32.00*)	24.00 (*18.00 – 29.00*)	26.00 (*20.00 – 32.00*)
GAD-7; Median (*IQR*)	3.00 (*1.50 – 9.50*)	5.00 (0.00 – *9.00*)	3.00 (*1.00 – 8.00*)	6.00 (*1.00 – 9.00*)
HBI; Median (*IQR*)	16.00 (*10.00 – 22.50*)	13.59 (*7.00 –22.25*)	15.00 (*7.00 – 22.00*)	13.00 (*9.00 – 22.00*)
PedsQL; Median (*IQR*)	82.61 (*70.11 –89.13*)	84.78 (70.65 – *92.39*)	85.87 (69.57 – *90.22*)	84.78 (*73.91 –93.48*)

CAMM: Child and Adolescent Mindfulness Measure; CD-RISC 10: Connor Davidson Resilience Scale 10; CES-D-10: Center for Epidemiologic Studies Depression Scale – 10 Item Version; GAD-7: Generalized Anxiety Disorder 7-Item Scale; HBI: Health Behaviour Inventory; PedsQL: Pediatric Quality of Life Inventory

Effect of MBI on Resilience

Intention-to-Treat

There was a significant main effect of time (β = –2.08, SE = 0.99, *t*[93] = –2.09, *p* = .039, 95% CI [–4.03, –0.13]; Figure 2), indicating that overall resilience scores decreased over time (Table 2). There was no significant main effect of group (β = 0.31, SE = 1.48, *t*[141] = 0.21, *p* = .833, 95% CI [–2.59, 3.22]), nor a significant group-by-time interaction (β = 0.12, SE = 1.40, *t*[93] = 0.09, *p* = .931, 95% CI [–2.62, 2.86]).

Per-Protocol

There was a significant main effect of time was found, with resilience scores decreasing over time (β = –3.29, SE = 1.22, *t*[56] = –2.69, *p* = .009, 95% CI [–5.68, –0.89]; Table 2). No significant main effect of group (β = 0.07, SE = 1.96, *t*[78.96] = 0.03, p = .973, 95% CI [–3.77, 3.90]), nor a significant group-by-time interaction (β = 2.11, SE = 1.73, *t*[56] = 1.22, *p* = .227, 95% CI [–1.28, 5.51]) were found.

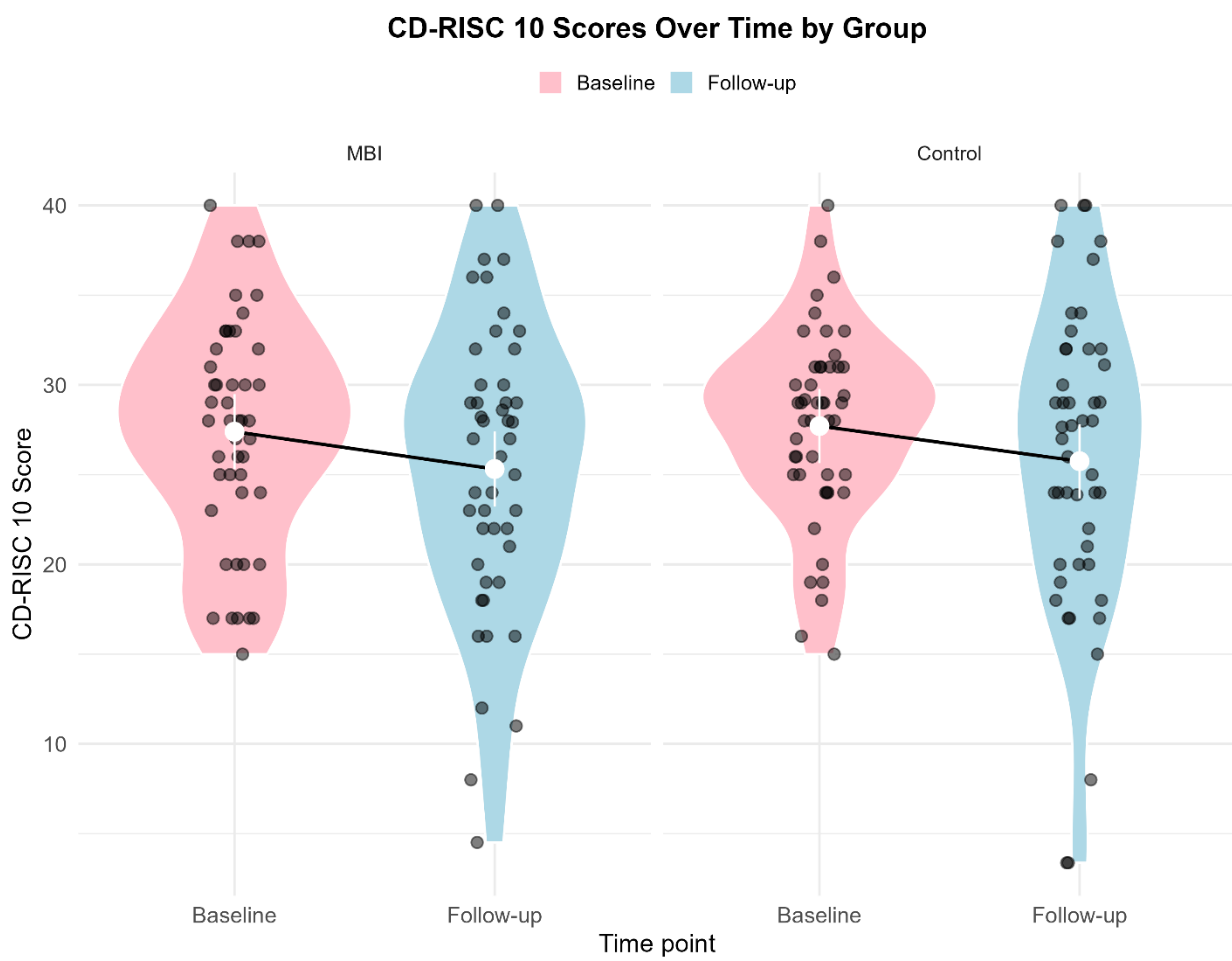

Figure 2. Change in resilience scores over time by group: Violin plot depicting the resilience trajectory post-recruitment assessments by group in the intention-to-treat approach. Connor-Davidson Resilience Scale 10 (CD-RISC 10); mindfulness-based intervention (MBI).

Group-by-Resilience Interaction Effects on FC Outcomes

Intention-to-Treat

There was a significant interaction between baseline resilience and group in relation to follow-up FC within the DMN. Specifically, the association between resilience and FC of the right lateral parietal seed with the posterior cingulate gyrus differed significantly across groups (cluster size [voxels] = 102; MNI [x, y, z] = +00, -24, +28; interaction effect $F[1, 30] = 25.42$; FDR $p = .011$; Figure 3). Within this cluster, resilience was negatively correlated with FC in the MBI group ($\beta = -0.01$) but positively correlated with FC in the sham group ($\beta = 0.02$).

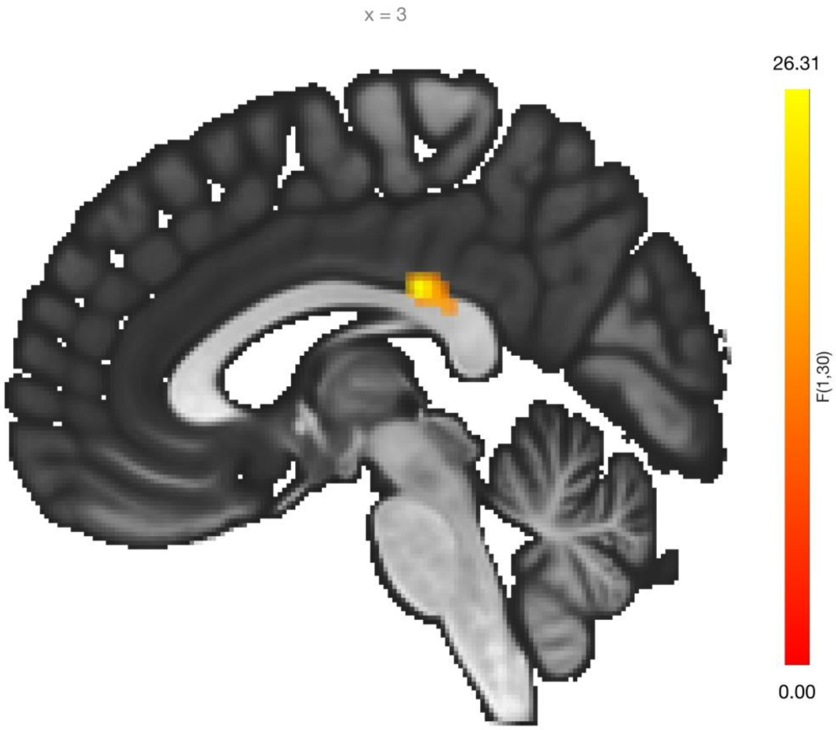

Figure 3. Resilience x Group interaction in the default mode network: Sagittal brain slice overlaid on an MNI template, highlighting a significant cluster (cluster size = 102) within the posterior cingulate gyrus that showed an interaction between baseline resilience and group allocation. The heatmap represents F-values, demonstrating that the association between resilience and functional connectivity of the right lateral parietal seed of the default mode network and posterior cingulate gyrus differed significantly between groups. Specifically, resilience was negatively correlated with functional connectivity in the mindfulness-based intervention group (β = -0.01) and positively correlated in the sham group (β = 0.02).

Per-Protocol

There was a significant interaction between baseline resilience and group in relation to follow-up FC within the DMN. Specifically, the association between resilience and FC of the right lateral parietal seed with the posterior cingulate gyrus differed significantly across groups (cluster size = 208; MNI [x, y, z] = +10, -46, +20; interaction effect $F[1, 17] = 44.89$; FDR $p < .001$; Figure 4). Within this cluster, resilience was negatively correlated with changes in FC in the MBI group (β = -0.01) but positively correlated with changes in FC in the sham group (β = 0.02).

Figure 4. Resilience x Group interaction in the default mode network, per-protocol: Sagittal brain slice overlaid on an MNI template, highlighting a significant cluster (cluster size = 208) within the posterior cingulate gyrus that showed an interaction between baseline resilience and group allocation. The heatmap represents F-values, demonstrating that the association between resilience and functional connectivity of the right lateral parietal seed of the default mode network and posterior cingulate gyrus differed significantly between groups. Specifically, resilience was negatively correlated with functional connectivity in the mindfulness-based intervention group (β = -0.01) and positively correlated in the sham group (β = 0.02).

There was a significant interaction between baseline resilience and group in relation to follow-up FC of the SN. Specifically, the association between resilience and FC of the anterior cingulate cortex seed with the right occipital pole differed significantly across groups (cluster size = 79; MNI [x, y, z] = +22, -94, +12; interaction effect $F[1, 17] = 34.61$; FDR $p = .017$; Figure 5). Within this cluster, resilience was negatively correlated with FC in the MBI group (β = -0.03) but positively correlated with FC in the sham group (β = 0.01).

Two significant interactions emerged between baseline resilience and group allocation in relation to follow-up FC of the CEN. In the first interaction, the association between resilience scores and FC of the left posterior parietal cortex seed and right inferior temporal gyrus differed significantly across groups (cluster size = 65; MNI [48,-2,-36]; interaction F[1,17] = 54.37; FDR

p = .042; Figure 6a). Resilience correlated positively with FC in the MBI group (β = 0.02) but negatively in the sham group (β = -0.01). In the second interaction, the association between resilience and FC of the right lateral prefrontal cortex seed and left middle temporal gyrus differed significantly across groups (cluster size = 69; MNI [-56,-22,-22]; interaction $F[1,17]$ = 33.01; FDR p = .015; Figure 6b). Similarly, resilience correlated positively with FC in the MBI group (β = 0.02) but negatively in the sham group (β = -0.01).

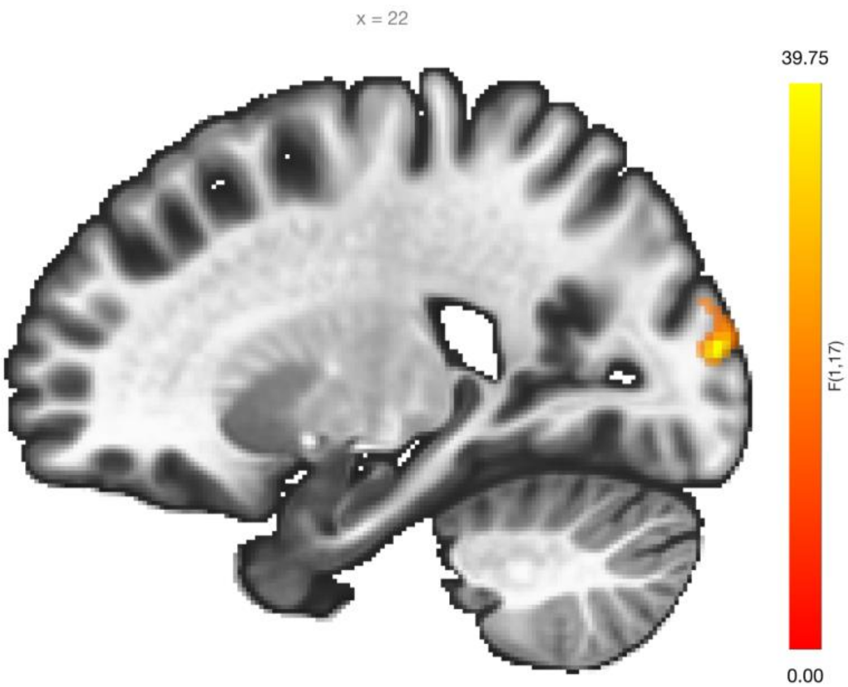

Figure 5. Resilience x Group interaction in the salience network: Sagittal brain slice overlaid on an MNI template, highlighting a significant cluster (cluster size = 79) within the right occipital pole that showed an interaction between baseline resilience and group allocation. The heatmap represents F-values, demonstrating that the association between resilience and functional connectivity of the anterior cingulate cortex seed of the salience network and right occipital pole differed significantly between groups. Specifically, resilience was negatively correlated with functional connectivity in the mindfulness-based intervention group (β = -0.03) and positively correlated in the sham group (β = 0.01).

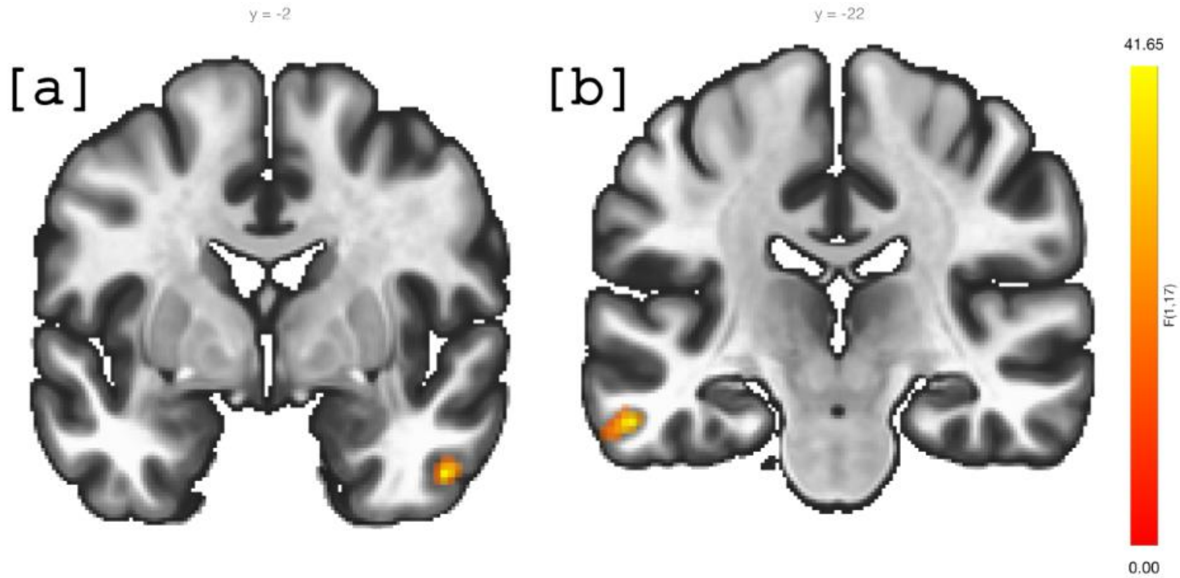

Figure 6. Resilience x Group interaction in the central executive network: Coronal brain slices overlaid on an MNI template, highlighting significant clusters that showed an interaction between baseline resilience and group allocation. The heatmap represents F-values. **a)** Interaction between resilience and functional connectivity of the left posterior parietal cortex seed of the central executive network (CEN) and right inferior temporal gyrus. Specifically, resilience was negatively correlated with functional connectivity (FC) in the mindfulness-based intervention (MBI) group (β = 0.02) and positively correlated in the sham group (β = -0.01). **b)** Interaction between resilience and functional connectivity of the right lateral prefrontal cortex seed of the CEN and left middle temporal gyrus. Specifically, resilience was negatively correlated with FC in the MBI group (β = 0.02) and positively correlated in the sham group (β = -0.01).

Discussion

In this study, we investigated the effects of an MBI on resilience and FC in adolescents with acute concussion. MBI did not lead to greater changes in resilience compared to the sham condition. However, the results indicate that MBI moderates the association between baseline resilience and FC of the DMN, SN, and CEN at the follow-up. These results suggest that MBI influences how baseline resilience relates to neurofunctional outcomes following a concussion.

Despite previous research indicating that MBIs can enhance resilience in other populations (O'Connor et al., 2023; Oh et al., 2022), our study did not find a significant direct influence of the MBI on self-reported resilience during the 4-week study period. Both groups showed a statistically significant decline in resilience scores over time, contrary to our hypothesis of a group-by-resilience interaction. Few, if any, published reports define clinically significant changes on the CD-RISC 10, making it unclear whether the observed statistically significant decrease is also clinically meaningful. However, the median resilience scores at both baseline and follow-up for each group are within normal range when considering normative data (Davidson, 2018). Comparable findings were reported in a pediatric sample aged 10–15 years, which showed a mean CD-RISC 10 score of 29.3 (SD = 7.3; Skrzypiec et al., 2018). This decline in resilience is also consistent with recent evidence suggesting that pediatric concussion, relative to orthopedic injury, is associated with lower resilience during recovery (Hassan et al., 2024). As such, the MBI group may attenuate the natural decrease in resilience that follows concussion, but our study potentially lacked the statistical power to fully capture such effects. This could be due to the relatively small sample size of this feasibility trial and consequent limitation in statistical power to detect subtle changes in resilience. Future research with larger sample sizes and potentially more sensitive measures could further investigate the impact of MBIs on resilience in this population.

Our findings indicate that MBI significantly moderated the association between resilience and FC in the DMN (intention-to-treat and per-protocol), SN (per-protocol), and CEN (per-protocol). These interactions suggest that the associations between baseline resilience and follow-up FC differ by group, with MBI potentially impacting how resilience predicts neurofunctional patterns during recovery from pediatric concussion. In the DMN and SN, higher resilience in the MBI group was associated with lower within-network FC, a pattern opposite to that of the sham group and consistent with healthy populations (Altinok et al., 2021; Bolsinger et al., 2018). This convergence with healthy population patterns suggests that MBI may facilitate a restoration of typical patterns of resilience-related connectivity in adolescents recovering from concussion. While MBIs are often associated with increased FC in healthy populations, and resilience is negatively correlated with FC of these networks, these effects are not inherently contradictory. In clinical populations such as major depressive disorder, where hyperconnectivity is observed, MBIs might reduce FC toward normative levels (Sezer et al., 2022; Yang et al., 2016). Group-level increases or decreases in FC would reflect the mean shift associated with the intervention, whereas individuals with higher resilience continue to show relatively lower DMN and SN FC, preserving the negative correlation. While the clinical significance remains unclear, these results raise the possibility that MBIs may promote neurofunctional recovery by restoring neurofunctional connections underpinning resilience that are disrupted by concussion (Brown et al., 2024). Although MBI did not directly enhance self-reported resilience, the unique baseline resilience-FC associations in the MBI group suggest that mindfulness may promote connectivity patterns more consistent with those seen in healthy populations. This could indicate that neuroimaging may be more sensitive than self-report measures for detecting early MBI effects in concussion recovery.

In contrast, in the CEN, higher resilience was associated with greater FC in the MBI group, particularly involving the inferior and middle temporal gyri, whereas in the sham group, higher resilience was linked to lower FC. While negative resilience–CEN FC correlations were reported in other populations (Altinok et al., 2021), the positive correlations observed here indicate that, within the MBI group, higher resilience is linked to greater FC in frontoparietal regions often influenced by MBI (Bauer et al., 2020; Bremer et al., 2022; Patsenko et al., 2019). The middle and inferior temporal gyri contribute to semantic processing and the integration of perceptual information (Binder et al., 2009), which may interact with the CEN to support context-sensitive regulation of emotional and cognitive responses. Given that these group-specific CEN FC patterns contrast with those observed in the DMN and SN, they likely reflect network-specific individual differences, with effects that are not uniform across networks. This highlights the potential heterogeneity in the association between resilience and FC in clinical populations compared with healthy populations.

Alternatively, given the significant interactions when assessing FC at follow-up, these findings may also be interpreted as reflecting resilience moderating the effect of MBI on FC. That is, baseline resilience may affect the extent to which individuals benefit from MBI, reflecting treatment response. This interpretation is consistent with frameworks positioning resilience as a moderator of intervention responsiveness and recovery trajectories. Conversely, MBI and resilience may represent complementary mechanisms, whereby resilience influences the neurofunctional effects of MBI following acute pediatric concussion.

Our findings also suggest that the interaction between MBI and resilience on FC may be network- and adherence-dependent. In the intention-to-treat analysis, we observed a significant group-by-resilience interaction only within the DMN, suggesting that MBI may influence DMN connectivity even with varying levels of participant engagement. Meanwhile, per-protocol analysis of the DMN revealed both a larger cluster and stronger interaction effect relative to the intention-to-treat analysis. Moreover, in the per-protocol approach, we reported significant group-by-resilience interactions across all three examined networks. These findings may suggest that stricter adherence to the MBI protocol could amplify network-specific effects. The absence of intention-to-treat effects for the SN and CEN might also reflect reduced sensitivity due to variable adherence to the protocol. However, randomized controlled trial research on dose-response associations in MBIs remains limited (see Creswell et al. [2017] for a review). Future studies should explore dose and adherence thresholds and their impact on resilience and FC to inform the design of MBIs for pediatric concussion.

Limitations

A potential limitation is that the MBI was delivered via a custom, app-based platform specifically designed for the youth concussion sample. Consequently, the generalizability of these findings to other populations or different MBI formats may be limited. The custom MBI program activities and psychoeducational components were tailored to this sample; thus, the reported effects may not directly translate to different age groups with acute concussion or to individuals with different clinical profiles. Future work with other MBIs formats and broader populations is needed to determine whether similar effects would be detected, and to clarify the scope of applicability for app-based MBIs in concussion recovery.

Another consideration is that the MRI component focused solely on a group-by-resilience interaction to predict FC at 4 weeks post-injury rather than employing a longitudinal design modeling a three-way interaction between time, group, and resilience. There are, however, inherent limitations to the longitudinal approach in this substudy of the MBI-4-mTBI feasibility trial due to the susceptibility of low statistical power from sample size. The implementation of repeated measures analyses alongside the group-by-resilience interactions reduces statistical power. This, along with the incorporated covariates and correction for multiple comparisons, can increase the likelihood of Type II errors. Alternatively, a mediation model could be proposed to examine whether the effects of resilience on outcome are mediated by MBI. However, mediation models generally require more statistical power than moderation models, consequently increasing the likelihood of Type II errors in a smaller sample feasibility trial. This is especially relevant in fMRI research, where high-dimensional data, small effect sizes, and motion artifacts are known to amplify statistical challenges (Marek et al., 2022). Future studies with much larger samples are needed to examine within-subject changes in FC over time, including both early (e.g., 72 hours) and later (e.g., 4 weeks) post-injury scans, to better understand how MBIs may influence neural recovery trajectories following concussion.

Furthermore, while this study identified associations between resilience and FC, there were no significant between-group differences of resilience trajectories. This may reflect early assessment timing or insufficient power. It is also possible that neural changes precede measurable behavioural effects. However, without clear associations between FC and clinical outcomes, the functional relevance of these changes remains uncertain. Future work should thus examine whether FC changes mediate or predict diminished symptom burden or quality of life with larger samples over longer follow-up periods.

Conclusions

Overall, while the primary hypothesis that the MBI would improve resilience was not supported, the secondary objective showed that baseline resilience influenced the impact of MBI on neurofunctional outcomes, indicating that individual differences in resilience predicts treatment response in pediatric concussion recovery. These results further explain the associations between MBI, resilience, and brain function in pediatric concussion. In the era of precision-based intervention, future research should explore how resilience-targeted interventions may be optimized to enhance brain function in pediatric concussion populations. It may be worthwhile for future studies to consider implementing resilience-targeted interventions, such as MBI, in children and adolescents before the occurrence of a traumatic brain injury. By fostering resilience proactively, such interventions could potentially buffer against the negative impacts of concussion should one occur, acting as a protective factor for brain function. Future research should explore how preventative MBI could potentially improve resilience and mitigate the effects of concussion in pediatric populations. Ultimately, this study underscores the critical role of enhancing resilience early in life to enhance recovery and ensure lasting well-being following pediatric concussion. While the study did not find evidence that MBI directly enhances short-term self-reported resilience, it remains a potential tool for supporting neural recovery and promoting long-term health outcomes in children and adolescents after a concussion.

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Chapter 5: General Discussion

1. Summary of Findings

1.1 Study 1

In Study 1, we sought to explore associations between baseline resilience and metrics of white matter microstructure in children with pediatric concussion and orthopedic injury at multiple timepoints (Brown et al., 2023). First, analyses detected a significant negative correlation between resilience and FA within the sample of children with concussion. This significant cluster was identified along the forceps minor. Second, analyses detected significant positive correlations between resilience and MD as well as RD within the sample of children with concussion. The significant MD clusters were identified along the right superior longitudinal fasciculus and right anterior thalamic radiation. The significant RD cluster was identified along the right superior longitudinal fasciculus.

1.2 Study 2

In Study 2, we explored the associations between baseline resilience and resting-state FC in children with pediatric concussion and orthopedic injury both longitudinally and at separate timepoints (Brown et al., 2024). Seed-to-voxel analyses identified a significant positive correlation between resilience and CEN FC in the sample of children with concussion. Analyses also identified a significant positive correlation between resilience and SN FC in the sample of children with orthopedic injury, also significantly moderated by group. Group was a significant moderator of longitudinal between-DMN FC. ROI analyses identified a significant association between resilience and within-SN FC in the sample of children with orthopedic injury. Analyses also identified a significant association between longitudinal resilience and within-DMN FC in the sample of children with orthopedic injury, an association that was significantly moderated by group.

1.3 Study 3

In Study 3, we investigated whether participation in an MBI effects resilience, and whether MBI moderates the association between baseline resilience and resting-state FC at follow-up in pediatric concussion. We identified a significant interaction between resilience and FC within the DMN, reflecting distinct associations between resilience and DMN FC in the MBI group compared to the control group. Analyses detected significant group-by-resilience interactions for the SN and CEN. Allocation to an MBI did not significantly affect resilience trajectories.

2. Neural Correlates of Resilience in Pediatric Concussion

Findings from Studies 1 and 2 provide converging evidence that resilience is associated with neural outcomes in the acute phase of pediatric concussion. In Study 1, resilience correlated with metrics of white matter microstructure (i.e., FA, MD, and RD). Specifically, greater resilience predicted lower FA along the forceps minor, higher MD along the right anterior thalamic radiation, as well as higher MD and RD along the right superior longitudinal fasciculus. It is important to note that these significant associations were not identified in the orthopedic injury group. Complementary evidence from Study 2 reinforces the notion that resilience is associated with neural outcomes in pediatric concussion. Baseline resilience correlated positively with resting-state FC of the left lateral prefrontal cortex (CEN) and the left lateral occipital cortex (Figure 1), while group moderated associations between resilience and DMN FC as well as SN FC. As with Study 1, analyses did not identify a significant resilience-by-CEN FC association in the group of children with orthopedic injury.

These findings could suggest that in the context of acute pediatric concussion, the white matter microstructural (e.g., superior longitudinal fasciculus, anterior thalamic radiation, and forceps minor) and neurofunctional (e.g., CEN, particularly the lateral prefrontal cortex) correlates of resilience converge on regions implicated in executive function and top-down emotion regulation, and adaptive coping. For instance, the lateral prefrontal cortex as part of the CEN is implicated in cognitive reappraisal to regulate emotions and has been suggested as a potential target for clinical intervention (Scult et al., 2017, 2019). Aberrant FC of the dorsolateral prefrontal cortex was directly associated with increased fear avoidance in a sample of patients with chronic pain, further supporting the CEN's role in adaptive behaviours (Ihara et al., 2019). In a comprehensive overview, Merchant (2018) stated that the superior longitudinal fasciculus connects frontal with parietal and temporal regions, implicating it in frontoparietal networks such as the CEN. Structural integrity of the superior longitudinal fasciculus and anterior thalamic radiation was shown to be inversely associated with depression (Lai & Wu, 2014). Specifically, young adults with major depressive disorder showed lower FA than controls in these tracts, along with higher RD in the superior longitudinal fasciculus and lower AD in the anterior thalamic radiation. The authors further reported a significant negative correlation between FA along the superior longitudinal fasciculus and depression severity. Significant decreases in FA and increases in MD in the superior longitudinal fasciculus were also identified in patients with major depressive disorder relative to healthy controls (Ota et al., 2019). Furthermore, the forceps minor connects regions of the frontal lobes and might indirectly support functions linked to the CEN (Catani & Thiebaut de Schotten, 2008). For example, FA of the forceps minor was directly linked to performance on the Stroop task in bilingual young adults, indicating that integrity of this tract might be implicated in executive function skills (Mamiya et al., 2018).

Together, our results, along with these findings, might suggest that baseline resilience in acute pediatric concussion influences white matter microstructural and neurofunctional mechanisms that are linked to cognition, emotional processing and mental health, as well as adaptive behaviours. This warrants further inquiry as to whether these neural correlates can be indicators of improved clinical outcome following injury or evidence of fewer neural deficits typically associated with concussion.

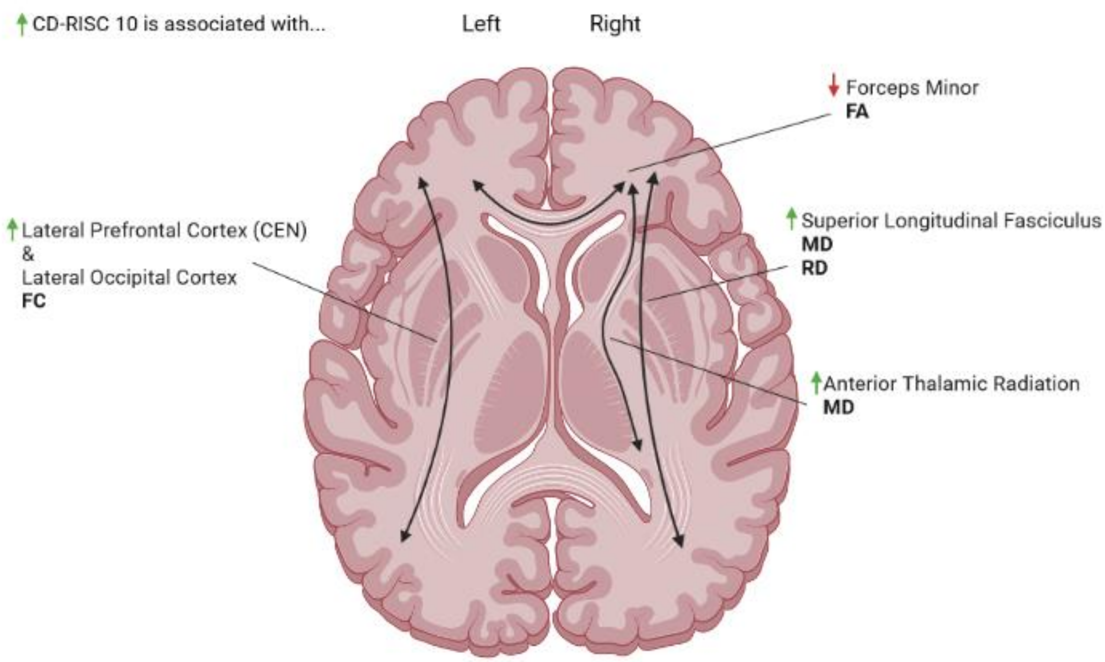

Figure 1. Neural correlates of baseline resilience in acute concussion: Axial slice of the brain displaying significant positive and negative correlations between resilience and imaging outcomes represented with green and red arrows respectively. Abbreviations: central executive network (CEN), Connor-Davidson Resilience Scale 10 (CD-RISC 10), fractional anisotropy (FA), functional connectivity (FC), mean diffusivity (MD), radial diffusivity (RD)

3. Moderating Role of Concussion in Resilience and Neural Outcomes

The investigation of white matter microstructural correlates of resilience, or Study 1, found that pediatric injury type (i.e., concussion vs. orthopedic injury) was not a significant moderator of outcome in our sample. Yet, the results from Study 2 suggest that pediatric injury type was a significant moderator between resilience and FC (Figure 2). Specifically, clusters of resilience-by-FC associations differed significantly between groups. Within these significant clusters, resilience only correlated significantly with FC in the orthopedic injury group. As suggested in Study 2, these results could reflect a process whereby significant associations between resilience and neurofunctional outcomes identified in non-concussed participants might be weakened in children that sustain a brain injury.

Given this discrepancy, whereby concussion moderated resilience related neural outcomes in Study 2 but not in Study 1, concussion might significantly impact neurofunctional correlates of resilience but fail to produce detectable effects on white matter microstructural correlates of resilience. Since concussion does not transect axons (Alisafaei et al., 2020; Armstrong et al., 2016), it may be that the injury-related effects on white matter microstructural correlates of resilience only surpass statistically significant thresholds in more severe injury cases, such as moderate to severe TBI. However, it is possible that the moderation effect in Study 1 did not reach a statistically significant result due to number of diffusion weighted directions, or restrictions in statistical power from sample size, conservative correction for multiple comparisons, and whole-brain analysis approach over tract-specific analyses. Still, the findings from Study 2, specifically the moderation effect in the DMN and SN, suggest that pediatric concussion likely disrupts white matter microstructure along tracts implicated in these networks. In a study of pediatric concussion, Mayer et al. (2012) detected significant widespread white matter microstructural changes in a concussion group relative to controls. These included increased FA along the corona radiata, internal capsule, cerebral peduncle, superior longitudinal fasciculus, and corpus collosum. Such widespread white matter disruptions may thus affect neurofunctional correlates of resilience involving the DMN and SN, even if they do not directly affect tract clusters underpinning resilience as identified in Study 1. More targeted, multi-modal imaging research is required to deduce whether the effects of concussion on resilience neural correlates is uniquely detectable with certain metrics, such as FC.

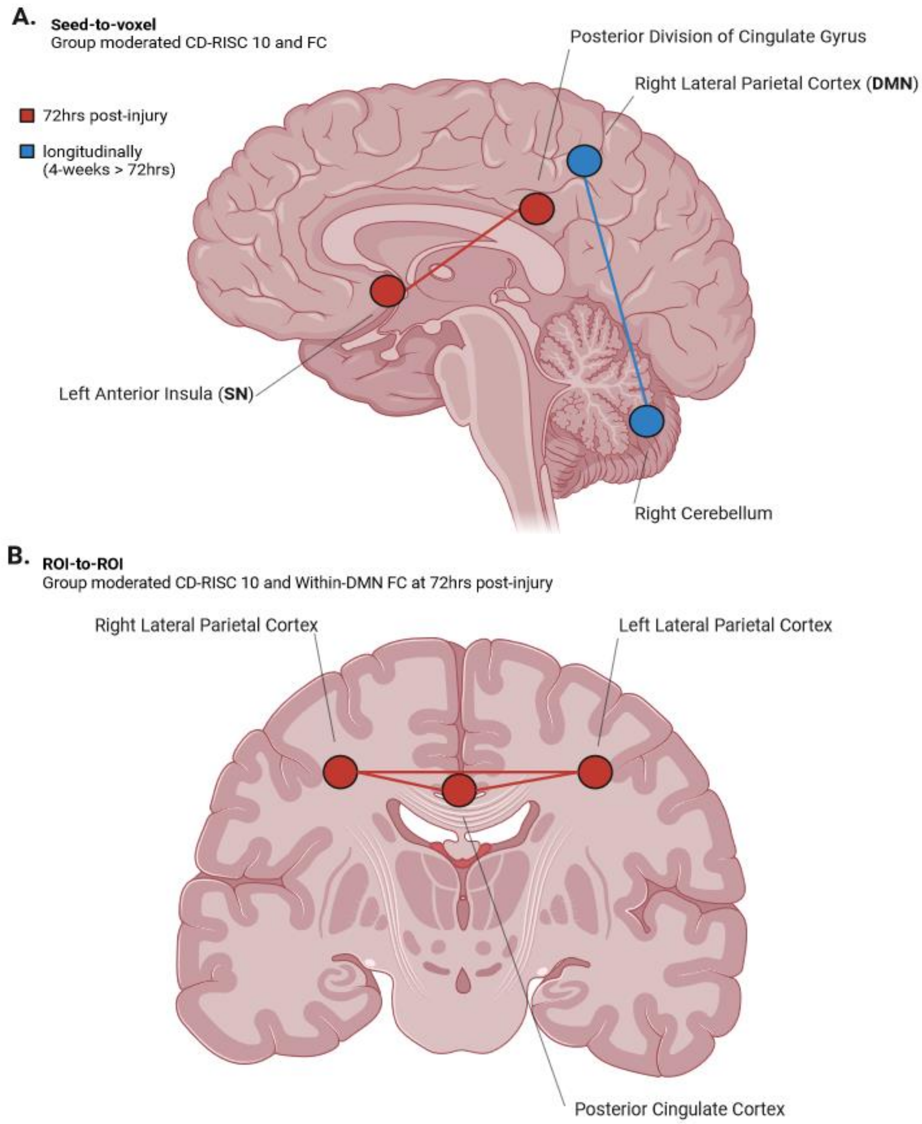

Figure 2. Pediatric injury type moderates neurofunctional outcomes post-injury: A. Seed-to-voxel results displaying two significant clusters: (1) moderation of resilience (CD-RISC 10) and salience network (SN) functional connectivity (FC); (2) moderation of resilience and default mode network (DMN) FC. **B.** Region of interest (ROI) analyses displaying one significant cluster: a moderation of resilience and within-DMN FC comprising of three connections between the bilateral lateral parietal cortices and posterior cingulate cortex.

4. Moderating Role of MBI in Resilience and Neural Outcomes

Although MBI did not directly affect resilience scores, as discussed in Study 3, it significantly moderated associations between resilience and resting-state FC. There are several factors to consider that may explain these findings. While numerous studies suggest that MBIs are effective in enhancing resilience (O'Connor et al., 2023), the lack of a significant effect in Study 3 may stem from methodological considerations. These include the limited sample size inherent to a feasibility trial and reliance on a subjective, 10-item scale of perceived resilience, which may not have sufficient sensitivity to fully capture MBI effects. Therefore, it is plausible that the MBI does bolster resilience, but the study may have lacked sufficient statistical power or sensitivity in its measure for these effects to surpass the significance threshold.

Despite the absence of a significant direct effect, the interactions between baseline resilience and MBI on FC of the DMN, SN, and CEN suggest that MBI affects brain connectivity patterns implicated in resilience following pediatric concussion. In other words, MBI may influence the neural mechanisms underlying resilience, rather than merely increasing self-reported resilience scores. It is probable that advanced neuroimaging techniques are more sensitive than self-report metrics in capturing the early effects of MBI. From a neurobiological perspective, MBIs were linked to top-down regulation of emotional processing, connectivity patterns across large-scale brain networks, and structural changes that support cognitive control and emotional regulation (Hölzel et al., 2007; Creswell & Lindsay, 2014; Taren et al., 2015). These interaction effects, particularly pertaining to the CEN, overlapped with a significant region identified in the concussion group from Study 2, the lateral prefrontal cortex. Given that the lateral prefrontal cortex and other CEN hubs are implicated in cognition and emotion regulation, moderation by MBI might reflect an adaptive mechanism through which mindfulness practices may influence neural correlates of resilience. Since the DMN, SN, and CEN play a key role in self-referential processes, salient or emotional stimuli processing, and executive functions respectively, the impact of MBI on FC of these networks may reflect its role in promoting adaptive stress responses through functional reorganization across each network (Jande et al., 2025; Melis et al., 2022; Young et al., 2018).

Taken together, findings from Study 3 directly inform and extend those of Studies 1 and 2 by suggesting that the neural correlates of resilience in pediatric concussion are not only identifiable in early phases of injury but may also be modifiable through targeted intervention. Whereas Studies 1 and 2 identified associations between baseline resilience and neural outcomes, Study 3 introduced evidence that these associations may be influenced by implementation of an MBI. Specifically, the moderation effects of MBI on the associations between resilience and FC of the DMN, SN, and CEN imply that connectivity of these networks may be susceptible to changes from engaging in mindfulness practices in the early phases of concussion recovery. The overlap of these moderated networks with those previously identified in Study 2, particularly the lateral prefrontal cortex of the CEN, reinforces the notion that the neurofunctional correlates of baseline resilience can be altered through MBI. This converges with the findings from Study 1 regarding the structural tracts underpinning resilience, specifically the superior longitudinal fasciculus, anterior thalamic radiation, and forceps minor, which connect various DMN, SN, and CEN nodes. These effects may be especially relevant in the context of acute pediatric concussion, as the observed effects from Studies 1 and 2 were significant in the concussion group, but not among children with orthopedic injury. In pediatric concussion, MBI may thus facilitate the reorganization of network-level connectivity necessary for adaptive behaviours, as indicated by the white matter and neurofunctional correlates of resilience identified throughout this dissertation. These findings warrant future investigation into whether MBI-related changes in neural outcomes contribute to clinical recovery and capacity to engage in adaptive behaviours.

5. Implications and Future Research

The findings from Studies 1 through 3 support this dissertation's evidence-based framework proposed in Chapter 1, Section 5, whereby resilience is a significant factor when assessing neural outcomes (i.e., white matter microstructure and FC) and MBI is a significant moderator of resilience and neurofunctional outcomes. These studies thus contribute evidence towards the supported framework and warrants consideration of resilience and resilience-targeted interventions when optimizing concussion management. Still, more research is needed to advance this framework, providing opportunities for future initiatives.

For instance, replication studies with larger samples are essential to increase the generalizability and robustness of the reported associations based on advanced imaging techniques. In addition, while the findings from Studies 1 and 2 suggest resilience as a significant predictor of neural outcomes, future studies should address the potential for neural disruptions from concussion to influence resilience trajectories while considering whether a significant bidirectional association exists. Although Study 3 highlights MBI as a moderator of resilience and neural functioning, additional investigation is also warranted to determine whether MBI similarly moderates the link between resilience and clinical outcomes. Research should also evaluate the direct effects of MBI on neural outcomes, regardless of perceived resilience, thereby offering additional pathways through which mindfulness practices may support concussion recovery. A series of large-scale, multi-site randomized controlled trials designed to address these possibilities may inspire collaborative efforts towards refining and expanding upon the presented framework and consequently evolving concussion management research and practices.

6. Considerations

This research presents several limitations which are partly discussed within each article, including the usage of a retrospective resilience scale in the context of acute concussion; the inherent restrictions to advances imaging techniques; generalizability of a custom, app-based MBI; and an inability to adequately enforce compliance.

Instructing participants to complete the CD-RISC 10 in the acute phase of pediatric concussion presents considerations regarding reporter bias. The CD-RISC 10 requires participants to reflect on their experiences over the past 30 days yet was administered within days of concussion within these studies. A relevant reporter bias worth consideration is the "Good Old Days" bias, whereby individuals who sustain injury retrospectively underestimate pre-injury symptoms (Gunstad & Suhr, 2001). Such bias could influence the accuracy of retrospective resilience assessments in acute concussion. However, evidence from Teel et al. (2019) suggests that children and adolescents can reliably recall their pre-injury symptoms over time, particularly when initial assessments are conducted acutely. This supports the early post-injury implementation of the CD-RISC 10 as seen in Studies 1–3, which might reduce the likelihood of Good Old Days bias influencing responses. These further supports implementing the CD-RISC 10 in pediatric populations, as Good Old Days bias was not identified in children and adolescents in the Teel et al. study. Furthermore, it is important to clarify that the Good Old Days bias pertains specifically to recall of pre-injury symptoms, and not necessarily to perceived resilience over a 30-day period. As such, while reporter bias is a valid concern, its impact on resilience measurement in our studies is likely limited.

Moreover, instructing participants to complete the CD-RISC 10 in both acute and sub-acute phases of injury introduces overlap in measurement timeframes, which may obscure the interpretation of results in distinct phases of injury. The CD-RISC 10 items are designed to be completed based on the past 30 days. The 30-day reporting of the CD-RISC 10 suggests that the follow-up assessments overlap with the initial assessments in Studies 1 through 3. Although the overlap may contribute to some ambiguity in resilience across acute and subacute recovery phases, it is unlikely to have meaningfully influences the reported associations. The CD-RISC-10 operationalizes resilience as a modifiable construct, so temporal overlap is expected during recovery and may reflect the evolving nature of resilience rather than a measurement error.

In studies using MRI and fMRI data, there is often a substantial divergence in methodological approaches. This heterogeneity in advanced imaging methods limits the capacity for replication studies, or consistent results. As such, a contradiction in results across studies might be attributable to different decisions pertaining to image acquisition, processing software and parameters, as well as seed selection (Poldrack et al., 2017; Teves et al., 2023). These limitations are further compounded by low statistical power from low sample sizes often reported in fMRI studies (Poldrack, 2017). The typical sample size of $n = 25$ likely overestimates effect sizes and is less likely to produce in replicable results (Marek et al., 2022). However, measurement precision (e.g., longer resting-state sequences as well as multi-band and multi-echo acquisition with adequate denoising techniques) may mitigate constraints of statistical power in imaging research (Nebe et al., 2023). Although the sample size of the study in Study 3 (intention-to-treat: MBI $n = 16$, control $n = 20$; per-protocol: MBI $n = 10$, control $n = 13$) was limited relative to those of Study 1 (concussion $n = 66$, orthopedic injury $n = 29$) and Study 2 (concussion $n = 67$, orthopedic injury $n = 30$), the resting-state scan sequence used was 12 minutes and 8 seconds, which is longer than most sequences and could improve reliability of results (Birn et al., 2013). Nonetheless, replication efforts of our findings using a precision approach with advanced imaging techniques are warranted.

Furthermore, the app-based MBI only reflects the effects of that specific intervention on resilience and neural outcomes. As aforementioned, the MBI is a customized app-based intervention that combines core mindfulness practices designed specifically for the target sample, which might not reflect the effects of an in-person, potentially group-based program. On a similar note, participants might not adequately comply with the practices enforced by the MBI. However, compliance was monitored with app data and self-report ratings, while protocol-specified efforts were made to increase adherence with reminders and check-ins by treatment coaches. This is crucial considering that, as shown in Study 3, some significant interaction clusters between MBI and both resilience and FC outcomes were only detected in per-protocol analyses that included participants who sufficiently adhered to the intervention. Future works using resilience-targeted interventions should also examine whether the magnitude of intervention-related effects is contingent on the extent of participant engagement, as potential dose-dependent associations could dilute effects in intention-to-treat analyses.

7. Conclusion

Together, these studies contribute novel insight into the neurobiological underpinnings of resilience and the potential mechanisms through which MBI may support neural recovery. In doing so, this dissertation puts forth an integrative model of resilience and MBI in concussion recovery that includes neurobiological processes supported by advanced imaging techniques while also outlining opportunities for future research projects. Concussion care guidelines should consider integrating resilience and resilience-targeted interventions into standard management recommendations, particularly during the early phases of pediatric concussion recovery. Doing so may not only reduce symptom burden and improve long-term clinical outcomes but also foster adaptive brain changes that support children and adolescent healthy development following brain injury. By targeting resilience in children and adolescents, we not only support concussion recovery but also provide a foundation for broader well-being benefits that could reach beyond clinical and neural outcomes, ultimately strengthening long-term adaptive capacity and developmental health for a brighter future.

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