Resting state functional connectivity in pediatric concussion

RESTING STATE FUNCTIONAL CONNECTIVITY

IN PEDIATRIC CONCUSSION

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Lay Abstract

Your brain at rest is not resting. In fact, your many brain regions are continuously communicating even during rest to maintain important communication between them. This communication between brain regions is termed *functional connectivity*. When you receive a blow to the head, face, neck, or another part of your body that senses a biomechanical force to your brain, the functional connectivity (i.e., communication lines) between your brain regions may be altered. A blow of this nature is considered a concussion, also known as a mild traumatic brain injury. With disruptions to the typical functional connectivity between your brain regions following a concussion, you may experience difficulty in managing cognitive tasks, emotions, and body coordination. Among those most vulnerable to the effects of concussion are children and adolescents whose brains have yet to develop fully.

The goal of this thesis was to evaluate the functional connectivity between brain regions of children and adolescents to determine how brain communication might be disrupted following concussion. These evaluations were done using functional magnetic resonance imaging (fMRI) of the brains of children and adolescents ages 10-18 years old. It was discovered that the functional connectivity of the frontal lobe is related severity of post-concussion symptoms such that individuals with worse symptoms had reduced functional connectivity in the frontal lobe compared to individuals who reported less severe symptoms. Further, children and adolescents with longer recovery periods have a different level of functional connectivity in the temporal lobe compared to youth with relatively shorter recovery periods. This might suggest that both of these regions could

provide prognostic value in determining who might have worse symptoms or a longer recovery time following injury.

In comparison to children and adolescents who have not had a concussion, children and adolescents experiencing a concussion are more likely to have abnormal functional connectivity between the hippocampus and cerebellum, which are particularly involved in processing sensory information and navigation. This was interpreted to mean that the brain responded to the concussion by increasing the communication between regions that might help a child with a concussion coordinate their bodies so that they can move from place to place. This was additionally supported by a further investigation which showed that children and adolescents have reduced communication between areas of the brain that might allow them to process information about the self (*e.g.,* memories, sensations, relationships with others, *etc.*).

Overall, the results demonstrated that following a concussion, children and adolescents may have a deficit in the functioning of the frontal lobe in a specific region that allows them to process cognitive and sensory information. This might explain why concussion leads to poor memory, body coordination, sensitivity to light and sounds, and even difficulty sleeping. Their brains might then compensate for the disruption by increasing alternate pathways of communication. Together these findings open gateways for future researchers to look more deeply at the specific regions affected by concussion in youth. It draws attention to the many neurocognitive, emotional, and somatic symptoms a child with a concussion exhibits and their symptoms' underlying neurological processes.

Abstract

Children and adolescents with concussion display aberrant functional connectivity in some of the major neurocognitive networks. This includes the Default Mode Network, Central Executive Network and Salience Network. Using resting state fMRI, the purpose of this thesis was to explore the functional connectivity of cognition-related networks in youth experiencing concussion. With a prospective cohort study, the functional connectivity (defined as the temporal coherence between spatially separated brain regions) of children and adolescents ages 10-18 years old was evaluated in relation to a number of demographic and injury-specific factors including recovery length, age at the time of injury, symptom severity, and neurocognitive performance.

The results showed two general trends: (1) a reduction in connectivity (*i.e.*, hypoconnectivity) between the regions of the Default Mode Network, and (2) an increase in connectivity (*i.e.*, hyperconnectivity) between additional sensory related regions like the cerebellum and hippocampus. The Default Mode Network, which processes self-referential information, has a long-protracted development across childhood through adulthood. Given that the participants in this cohort exhibited reduced functional connectivity within the Default Mode Network and between the Default Mode Network and other neurocognitive networks suggests that this is an area of vulnerability in youth in the event of concussion. Increased connectivity between the Central Executive Network and Salience Network, and between cognitive- and sensory-related regions such as the hippocampus and cerebellum might be interpreted as a compensatory mechanism to supplement deficits of the Default Mode Network.

This thesis sheds light on important concussion-related regions for future research to investigate further and delves into the possible neural mechanisms contributing to the cognitive, sensory, mood, and sleep disturbances in children and adolescents with concussion.

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From the early childhood days of making Medieval castles and writing speeches about pandemics, to the undergraduate days of late evening library pick-ups and home-made lunches, to the hurdles of research and the many feelings of fear and excitement over the course of graduate school, to my next steps and beyond. There was never a time that my parents did not believe that I was capable of everything I have done today and their steadfast belief in me is what has surmounted all forms of self-doubt that I ever had. To my Grandma for showing me that a young female in the '50s / '60s can be a member of the British bar and see only possibilities rather than hurdles. To my siblings (Larissa, Stephanie, Mathias, and Elizabeth) for being the closest friends I have in life. To my cousin Nicole: for your constant care, friendship and support that I am so lucky to have. To my little cousin Cianna: for being such an active and kind listener. To my aunt (Nicole's mom): for being so caring and supportive of me over so many years.

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List of Abbreviations

ABIDE	Autism Brain Imaging Data Exchange
ACC	Anterior cingulate cortex
aI	Anterior insula
AI-L	Anterior insula (left)
AI-R	Anterior insula (right)
ANCOVA	Analysis of covariance
BOLD	Blood oxygen level dependent
CEN	Central Executive Network
DAN	Dorsal Attention Network
DMN	Default Mode Network
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FPN	Frontoparietal Network
FWE	Family-wise error
ICA	Independent component analysis
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing

LP-L	Lateral parietal (left)
LP-R	Lateral parietal (right)
LPFC-L	Lateral prefrontal cortex (left)
LPFC-R	Lateral prefrontal cortex (right)
mPFC	Medial prefrontal cortex
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MVPA	Multivariate pattern analysis
PCC	Posterior cingulate cortex
PCSS	Post-Concussion Symptom Scale
PET	Positron emission tomography
PFC	Prefrontal cortex
PPC-L	Posterior parietal cortex (left)
PPC-R	Posterior parietal cortex (right)
ROI	Region of interest
rPFC-L	Rostral prefrontal cortex (left)
rPFC-R	Rostral prefrontal cortex (right)

SD	Standard deviation
SE	Standard error
SMG-L	Supramarginal gyrus (left)
SMG-R	Supramarginal gyrus (right)
SN	Salience Network
TFCE	Threshold-free cluster enhancement

Dedication

To the children and families impacted by brain injury and other childhood disabilities.
And to my childhood music teacher, Mrs. Lola Hinton,
who told me to study the brain when I grow up.

Chapter 1:

Introduction

Concussion, once thought to be an easily recoverable, transient brain injury (McCrory & Berkovic, 2001), is a physical insult to the head or body that results in neurobiological dysfunction (Bramlett & Dietrich, 2015; Katayama et al., 1990; Macfarlane & Glenn, 2015; Stillo et al., 2021) and possible immediate and long-term consequences (Ahman et al., 2013; Chamard et al., 2016; Doroszkiewicz et al., 2021; McCrory et al., 2013). The range of signs and symptoms can consist of difficulty concentrating, trouble with balance, poor hand-eye coordination, difficulties with sleep, sensitivity to light and sound, and issues with mood, among several other cognitive, emotional and sleep-related symptoms (McCrory et al., 2013). While adults and youth experience similar deficits following concussion, children and adolescents have been reported to be particularly vulnerable to its effects (Karlin, 2011; McCrory et al., 2004; Ommaya et al., 2002).

Following a concussion, children often report feeling dissociated from social groups, display academic difficulties, and experience lower self-worth (Cassilo & Sanderson, 2019; Gibson et al., 2013; Ransom et al., 2015; Rieger et al., 2019; Valovich McLeod et al., 2017; M. N. Yang et al., 2019). These symptoms may go unnoticed by parents, teachers and coaches or are unreported by the students (McCrea et al., 2004). Misconceptions about concussion suggest a gap in public understanding of how concussion may impact a child's current and future experiences in school, sport and social settings (DeMatteo et al., 2010; McKinlay & Buck, 2019; Valovich McLeod et al., 2007). A focus on child and adolescent concussion is especially crucial now as new evidence suggests

that concussion can be associated with diagnoses of psychiatric illness later in life (Chrisman & Richardson, 2014; Doroszkiewicz et al., 2021; Fralick et al., 2016; Pryor et al., 2016; Rapoport et al., 2003; J. Yang et al., 2015).

Contributing to child and adolescent susceptibility to concussion sequelae are the ongoing developmental changes in the brain. Children and adolescents have neuroplasticity mechanisms that allow for morphological and functional changes to occur (Anderson et al., 2011). A concussion during childhood or adolescence could impact critical periods during which important neural circuits form to allow for complex skills and behaviours (Anderson et al., 2011; Yurgelun-Todd, 2007). While research about traumatic brain injury effects on critical periods is limited to pre-clinical studies (Diaz-Chávez et al., 2020; Kochanek et al., 2017; Prins & Hovda, 2003), animal model research suggests that early-life stressors can alter critical brain periods which may impact future development (Marco et al., 2015; Murgatroyd & Spengler, 2011; van Bodegom et al., 2017). To date, current conceptual frameworks and models of early-life stress do not include concussion data, but given the psychosocial stress that may arise following concussion, as discussed previously, one might suspect that concussion could lead to similar outcomes exhibited by other forms of traumatic events.

Our current understanding of pediatric concussion is supported by both clinical and experimental research. By nature of experimental research, scientists have relied on inferences made about how humans respond to traumatic brain injury through mostly animal models (Giza et al., 2005). With the advancement of technology, clinical research has propelled the investigations of concussions on the human brain. This has been beneficial in identifying how children and adolescents differ from adult populations (Moser et al., 2018) and has prompted further research into the special population of pediatric concussion.

A recent field in neuroscience that has application to pediatric concussion is the study of brain networks, their development, and function and dysfunction. Using cerebral blood flow to identify where neurons are activated, brain imaging research has been able to study in vivo brain function. Such advances to the field of neuroscience have stemmed from the advancements of brain imaging technology. A number of brain imaging technologies have been used to study brain function such as positron emission tomography (PET) scanners and magnetic resonance imaging (MRI) scanners. The detection of blood flow to supply oxygen to areas where neurons are active is termed the BOLD (blood oxygen level-dependent) effect (Ogawa et al., 1990). It provides a proxy for our neurophysiological activity, relying on the coupling between blood flow and neuronal firing. By evaluating the BOLD effect, researchers observed temporally synchronized activity between multiple brain regions (Raichle, 1998), giving rise to the field of functional human brain mapping. While much of this earlier work was completed using PET scanners, non-invasive technology like MRI or, more specifically, functional MRI (fMRI) has contributed to a substantial amount of research on brain function.

From this body of functional brain research, we have learned that brain regions work in concert. To carry out complex human behaviours, emotions and cognitive processes, the brain relies on interconnected networks of regions that not only work together within a network but also with other networks (van den Heuvel & Hulshoff Pol, 2010). To illustrate the organization of functional neural activity, one could use the analogy of a professional orchestra that plays one symphony together (analogous to a complex human behaviour) but is composed of several sections of players (*e.g.*, the string section, brass section, etc.). While each section plays in synchrony (analogous to the temporal coherence between functionally connected brain regions), each section has a different set of melody lines that it is responsible for (analogous to the modality of functional networks). Each

section can be further divided into subsections (*e.g.*, the first and second violin sections) with harmonizing but separate lines of music (analogous to subnetworks within a larger network that processes different pieces of information).

A well-organized orchestra takes years to develop, much like our brain networks. A less organized or practiced orchestra might be less equipped to manage mishaps and disturbances to the orchestra structure, akin to the developing brain compensating for neurological disturbances. If, for example, some instruments of the orchestra (e.g., the trumpets) were to suddenly break (analogous to injury), related subsections (e.g., other brass instruments) might be able to fill in for the missing players, but, perhaps, with a negative impact on the sound of the symphony (analogous to abnormal behaviour) and/or with a greater effort from all musicians maintain the musical performance (analogous to aberrant network efficiency).

A concussion is much like having many broken instruments across different sections of an orchestra—it is a global injury affecting widespread functionality of the brain. As we will discuss throughout this thesis, a concussion is a traumatic brain injury with distributed effects on behaviour and neurophysiology. In a developing child or adolescent, a concussion may present greater immediate and long-term deficits in behaviour, cognition, mood. With a specific lens on the functional connectivity following concussion in adolescents, we will address how the communication between brain regions is impacted.

The overall purpose of this thesis is to further explore the effects of concussion on the child and adolescent brain. Using a network approach, I have evaluated the resting state networks of a cohort of children and adolescents with a current diagnosis of concussion.

In the following chapters, we explore functional connectivity in a sample of adolescents experiencing concussion. A cohort of 34 adolescents diagnosed with concussion were recruited and

scanned for a 6-minute resting state fMRI scan. Using methods established to categorize and represent brain networks, we evaluate connectivity correlates of concussion outcomes such as recovery length, neurocognitive performance, and symptom severity. This is achieved through an investigation of the following questions:

1) Are resting state networks associated with symptom severity and recovery status? Through this exploration in Chapter 3, adolescents who reached symptom resolution within a six-month period were compared to adolescents who continued to experience post-concussion symptoms past six months to determine whether functional connectivity provides prognostic value for adolescents with long-term symptoms. 29 of the participants of the 34 full sample who had follow-up recovery information were included in this study.
2) Is the functional connectivity of the anterior and posterior hippocampus associated with neurocognitive function? Chapter 4 (n=34), explores the neurocognitive correlates of functional connectivity to evaluate hippocampal involvement in concussion presentation. All 34 participants were included in this sample.
3) What is the nature of the dynamic relationship between the Default Mode, Central Executive, and Salience Networks? Chapter 5 (n=34), evaluates the intra- and inter-network functional connectivity of adolescents with concussion compared to healthy controls to assess the integration of important regions involved in emotional and cognitive processing. All 34 participants were included in this sample.

This thesis is divided into six chapters in total: three theoretical and literature-focused chapters (Chapters 1, 2, 6) and three data-focused chapters (Chapters 3, 4, 5). Chapter 2 will

introduce functional brain networks and the theories surrounding brain injury and neurodysfunction. Chapters 3-5 provides the novel findings of research on our sample of adolescents with concussion. Chapter 6 offers a cumulative perspective of the findings presented in the previous three chapters, discusses areas of future research, and summarizes the major contributions of this thesis to the literature on pediatric brain injury.

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Chapter 2:

Brain network development & dysfunction: a theoretical approach

2.1 Introduction

Childhood concussion has age-related effects (Chrisman & Richardson, 2014; Howell et al., 2013; Moser et al., 2018; Ransom et al., 2015). Because brain development is spread across years of childhood and even early adulthood, the age of injury may be an important factor in the emotional, cognitive, and physical symptoms presented post-injury (Kaldoja & Kolk, 2012; McCrory et al., 2013; Zuckerman et al., 2012). In fact, research suggests that the signs and symptoms of concussion during childhood may be reflective of the underlying neurodevelopmental status of the brain networks (Anderson et al., 2005; Sisk & Zehr, 2005).

To elucidate the neurobiological processes during childhood and adolescence that might be impacted by concussion, we first discuss the discovery and purpose of functional brain networks and the emergence of these networks from infancy to adulthood. With an understanding of the neurobiological processes associated with functional brain networks, researchers have offered theories and models of dysfunction. How these theories might apply to and offer insight into pediatric concussion is also described below.

2.2 Network Discovery & Characterization

Brain regions that are co-activated are considered functionally connected, along which connection information is transferred between structures. In other words, functional connectivity describes the temporal dependencies between brain regions that are spatially separated (Friston et al., 1993). The field of neuroscience bloomed with the fortuitous discovery of measuring brain activation, and therefore, functional connectivity, using the BOLD signal on a PET or MRI scanner. Given a task, the brain regions that are functionally connected would be active at the same time, or in temporal synchrony (van den Heuvel & Hulshoff Pol, 2010). These regions are interpreted to be part of the same network as both structures need to communicate for a task to be carried out.

Biswal (1995) was among the first researchers to make use of the BOLD signal to identify brain networks using an MRI scanner. From this seminal work, Biswal et al. (1995) noted that brain regions visible during a motor task were also present when participants were not doing the task or thinking of anything in particular. This wakeful rest condition was intended initially to be a control condition to the task. Instead, it revealed that the brain networks are still active and communicating during rest, spontaneously producing neural signals. These networks that were visible in the absence of a task became known as resting state networks.

Given that task-based stimulation accounts for under 10% of BOLD signal change (Raichle & Mintun, 2006; Roland et al., 1987),the spontaneous and intrinsically generated neural signals exhibited in resting state scans contribute to the majority of the metabolic signal we detect in fMRI (Raichle & Mintun, 2006). Therefore, the presence of active functional networks during rest is hypothesized to serve a purpose (Biswal et al., 1995). Maintenance of functional networks during rest demonstrates the brain's readiness to recruit entire networks of brain structures when required

(van den Heuvel & Hulshoff Pol, 2010). Research suggests that resting state networks are not constantly active during rest. In fact, they fluctuate and switch configuration across time (Corbetta & Shulman, 2002; Fox et al., 2005; Uddin et al., 2011).

Three of these networks have been key players in research because of their involvement in emotional, cognitive and behavioural outcomes. They are the Default Mode Network (DMN), Central Executive Network (CEN), and Salience Network (SN). Research suggests that the Default Mode Network, Salience Network, and Central Executive Network work in unison to allow for the transition between cognitive states (Menon & Uddin, 2010) and form Menon's triple network framework of neurodysfunction (Menon, 2013), discussed below.

The Default Mode Network has been the subject of several studies as it commonly displays aberrations in neuropathological conditions (Menon, 2011). Largely centered on the ventral medial prefrontal cortex/precuneus, posterior cingulate cortex and lateral parietal cortex, the DMN is typically active during wakeful rest and suppressed under cognitive load (Greicius et al., 2003). For this reason, the DMN is often termed the "task-negative" network, but researchers have argued that it is indeed involved in a number of cognitive processes (Fox et al., 2005; Spreng, 2012).

Researchers evaluating the purpose of this "default" state have noted that the DMN also subserves unconstrained, undirected self-referential thoughts (Buckner, 2013; Buckner & Carroll, 2007). These cognitive processes can include autobiographical memory recall (Andreasen et al., 1995; Bado et al., 2014; Philippi et al., 2015; Yang et al., 2013), social judgements (Knyazev et al., 2020; Reniers et al., 2012), ideation about one's future (Okuda et al., 2003; Schacter et al., 2007), and mind-wandering (Andrews-Hanna et al., 2010). This has led to the hypothesis that an overarching purpose of the Default Mode Network is the processing of internally-oriented cognitions (Buckner, 2010).

The Central Executive Network, on the other hand, is typically involved in the presence of cognitive demands and is suppressed during rest (Seeley et al., 2007). A lack of consistency concerning what regions are included in the CEN throughout the literature is a challenge faced by connectome researchers. The CEN is often used to describe either one or both of the Dorsal Attention Network and Lateral Frontoparietal Network (Uddin et al., 2019). While these two networks overlap in function—both involved in attention (Uddin et al., 2019) – the Dorsal Attention Network includes the intraparietal sulcus, frontal eye field areas of the precentral gyrus, premotor regions, and superior parietal cortex (Fox et al., 2005; Yeo et al., 2011). For the purposes of this thesis, we will follow with the regions described by Menon (2013) in which the CEN aligns more closely with the Lateral Frontoparietal Network, comprising the lateral prefrontal cortex and lateral inferior parietal cortex (Seeley et al., 2007; Uddin et al., 2019).

The Central Executive Network demonstrates an opposite activation trend to that of the Default Mode, which is further accentuated with increasing attentional demands (Fox et al., 2005; Sridharan et al., 2008). It is activated when an individual is engaged in inhibitory control, working memory, and set-shifting (Chatham et al., 2011; Corbetta & Shulman, 2002; Lemire-Rodger et al., 2019). Improvements in these higher-order processes parallel age-related increases in functional connectivity within the Central Executive Network in children and adolescents (Sherman et al., 2014).

The third network in Menon's triple network framework is the Salience Network, also known as the Midcingulo-insular Network (Uddin et al., 2019). Much like the CEN, the literature surrounding the SN lacks consistency in naming convention and is often referred to as the Ventral Attention Network, but we will follow the anatomical characterization of the SN described in Menon (2013), which anchors the Salience Network in the anterior insula and posterior parietal

cortex. The SN is involved in the detection of information that is of importance to the individual, whether it is an internally-derived (e.g., an anxious thought) or externally-derived (e.g., a fire alarm) stimulus (Seeley et al., 2007). Research suggests that the anterior insula is integral in communicating with the DMN and CEN to activate the network as needed, allowing flexible transitions between cognitive states (Chand & Dhamala, 2016; Uddin, 2015).

2.3 Development of Resting State Networks

Children undergo protracted network development (Giedd et al., 1999; Gogtay et al., 2004). In a series of cumulative changes, the functional connections between the brain regions of a network, or the nodes, become more adult-like. Much like the small steps an individual takes to become a professional musician in an orchestra, the brain demonstrates incremental development towards well-functioning and mature networks.

Research suggests an evolutionary advantage for the long development of resting state networks, as non-human primates also exhibit resting state networks in primitive states (Levitt, 2003; Liu et al., 2019; Vendetti & Bunge, 2014). The differences in the functional connectivity of resting state networks between humans and non-human primates may underlie a number of cognitive differences between them too. These findings suggest that the long developmental trajectory of resting states demonstrated by humans (but not non-human primates) may have an adaptive advantage for human cognition.

The developmental trajectory of resting state networks begins even prior to birth, as evidenced by observable networks in preterm babies (Fransson et al., 2007; Smyser et al., 2010). The evaluation of in utero and premature babies shows that important inter-region communication

has already begun to form early versions of networks like the Default Mode Network, Sensorimotor Network, and Central Executive Network (Doria et al., 2010; Smyser et al., 2010). The functional connectivity observed in preterm babies illustrates the experience-expectant maturational process of resting state networks as their formation primes the infants to rapidly learn about their environment once they are born.

Babies and children demonstrate rapid connectivity change in the first years of life (Alcauter et al., 2014; Blakemore & Choudhury, 2006; Durston et al., 2006; Fair et al., 2008); however, not all connections mature at a similar rate (Lin et al., 2008; Menon, 2013; Stevens et al., 2009). Connections subserving lower-order processes (e.g., sensory information) exhibit earlier development both functionally and structurally (Gogtay et al., 2004). Accordingly, the networks that process sensory and motor functions are among the first networks to emerge and mature (Alcauter et al., 2014; Lin et al., 2008). The development of networks involved in higher-order cognition (e.g., working memory, response inhibition) and emotional processes continue to span from early childhood into adulthood (Fair et al., 2008; Uddin et al., 2010).

Here we will discuss the various simultaneous changes in the functional organization of the brain through childhood and adolescence and how it relates to observable functions and behaviours. The following discussion involves results from functional and graph theory metrics to describe the typical development of children and adolescents, highlighting the incremental but complex changes across the brain that support behavioural advances in cognitive and emotional processing. Consideration for the numerous ongoing developmental processes is essential to the prediction and interpretation of brain injury outcomes in youth.

2.3.1 Hierarchical organization through development

To have a well-organized brain network or orchestra, hierarchical organization is important. For example, the structure of the orchestra follows that each instrument type has a designated sitting area with the conductor at the head of the entire orchestra. Within each grouping of musicians, there is further hierarchical organization. Not only are the violins all clustered to one area of the orchestra, they are also divided into "first" and "second" violins. First violins are typically responsible for the melody line and are, therefore, given the best-skilled musicians, while the second violins provide supporting harmonies to the first violins. The most skilled violinist of the entire first violins section is considered a leader of the first violins. The second violins have a skilled individual that leads them as well. These leaders are much like the major nodes of a network with connections to a subgroup of brain regions with which they function.

As this analogy illustrates, hierarchical structure is beneficial to an orchestra. If you were to build an orchestra from scratch, you might infer which individuals are the most important players to identify first (*e.g.*, the conductor, leader of the first violins, etc.). Then each leader could help develop their smaller community of musicians. They are highly connected to each individual musician within their own community, and they communicate with other major leaders of the orchestra.

Research on the development of functional brain networks suggests that the brain exhibits hierarchical formation as well. Children first develop stable "cortical hubs" (Menon, 2013), some of which are already present by the time of full-term birth (Smyser et al., 2010). These cortical hubs are described as regions that have a higher degree of connections to other brain areas (analogous to leaders of a section of musicians) and form the basis of a network (Hagmann et al., 2008). Hubs

are often involved in directing information transfer between brain regions of a network (Fransson et al., 2007; Menon, 2013; van den Heuvel et al., 2012). In infants, the hubs with the greatest number of connections are motor and sensory regions (Fransson et al., 2007). As children develop into adults, the strongest cortical hubs shift from sensorimotor areas to the regions along the anterior-posterior axis of the brain, which coincides with regions of the Default Mode Network (Fransson et al., 2007; Hagmann et al., 2008).

Along with the development of cortical hubs, children form "small-world" architecture which describes the strong, short-range connections between neighbouring brain structures (de Asis-Cruz et al., 2016; Smyser et al., 2010; Uddin et al., 2010). Small world topography also describes high interconnectedness within a hemisphere (i.e., intrahemispheric) rather than between hemispheres (i.e., interhemispheric) (Gao et al., 2011). During the first two years of life, rapid pruning occurs to reduce the high density of intrahemispheric connections in favour of long-range interhemispheric connections (Fransson et al., 2007; Gao et al., 2011). This process of building stronger connections across spatially disparate brain regions is an energy- and resource-demanding process (Tau & Peterson, 2009), spanning across childhood and even into early adulthood (Giedd et al., 1999; Petanjek et al., 2011).

The formation of long-range connections and the pruning of short-range connections are not random, however. In fact, research suggests that these processes are targeted for the formation of networks (Supekar et al., 2009), allowing for the functional differentiation of each network (Fair et al., 2008). As networks begin to separate, the number of regions young children recruit to complete cognitive tasks is reduced (Durston et al., 2006). This narrowing in the number of recruited regions to fewer, more relevant regions is interpreted as an increase in cognitive efficiency (Fair et al., 2008; Uddin et al., 2010). Disruptions to this process of network integration and

separation can therefore impact network efficiency by reducing the specificity of network activation (Wylie et al., 2014). Lack of network specialization and differentiation is seen in children with autism spectrum disorder and is associated with behaviour inflexibility (Keown et al., 2017; Uddin, 2015).

Children also demonstrate a bias in the recruitment of subcortical regions like the basal ganglia and amygdala (Casey et al., 2019). Compared to adults who have stronger cortical-cortical connections, children have a greater number of subcortical-cortical connections (Supekar et al., 2010), suggesting a tendency to engage emotion and reward-seeking regions. This is in concordance with other studies that have cited higher engagement of subcortical regions during cognitive tasks in children (Kelly et al., 2009; Supekar et al., 2009). This also matches the behavioural data in children showing poor inhibition for task-irrelevant stimuli (Rueda et al., 2004). The shift from subcortico-cortical connectivity to higher cortico-cortical connectivity occurs in adolescence and parallels the development of emotion regulatory behaviours (Casey et al., 2019).

2.3.2 Development of neurocognitive networks

As discussed above, several concurrent developmental processes allow for the emergence of functional networks. While the sensorimotor network matures early in life, evidence suggests that areas involved in cognitive and emotional processing have longer protracted development (Casey et al., 2005), including the three most commonly cited networks involved in neuropathology: the DMN, CEN and SN (Menon, 2013). Disruptions during childhood or adolescence (e.g., injury, trauma, illness) could potentially impair network connectivity developmental trajectories and lead to immediate or long-term behavioural deficits.

The Default Mode Network development begins during gestation (Cui et al., 2017). It is detectable at 2 weeks of age with the prominent features of the network like the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) present (Gao et al., 2009). By 2 years, the gross structural layout of the Default Mode Network can be found in a stable form (Uddin et al., 2010) with a higher degree of connections between the network structures (Gao et al., 2009). As early life is a critical period of neurodevelopment and vulnerability, brain injury during this window of time may negatively impact the microstructural development of the cingulum, the connecting nerve tract between the mPFC and PCC (Cui et al., 2017).

Mid-childhood is the period during which the DMN exhibits the most change. Between 6-12 years old, improvements in DMN efficiency and strength occur particularly in the connectivity of midline structures (F. Fan et al., 2021; Sherman et al., 2014), which is subject to the slow development of the cingulum (F. Fan et al., 2021; Supekar et al., 2010). In investigating the individual connections between the structures of the Default Mode Network, it is the cingulum that undergoes the most change between mid-childhood (7-9 years) and early adolescence (10-13 years) (Sherman et al., 2014; Supekar et al., 2010). These ages translate to late elementary school and/or middle school years, during which has been shown to be associated with the advancement of skills in reorienting attention, executive attentional control, and alerting in addition to structural and functional changes of the mPFC and PCC (Konrad et al., 2005; Supekar et al., 2010).

Structural data showing the slow increase in white matter density (and pruning of grey matter) in areas involved in the Default Mode Network may describe why cognitive processes are slow to develop as well (Sowell et al., 2003). Increases in interhemispheric connections (which are typically lower in children) show little change between age 8 to adulthood, which suggests that

further developments in white matter in the Default Mode Network are due to myelination beyond age 8 (Fair et al., 2008).

Simultaneous development of the Central Executive Network also parallels cognitive advancements in children and adolescents and demonstrates susceptibility to neurocognitive deficits in the event of brain injury (Ryan et al., 2021). While childhood development of the CEN is not as well-studied as the development of the DMN, research suggests that cognitive enhancements may be related to CEN maturation. Maturation of the CEN is displayed through increased internetwork connectivity and increased anti-correlation with the DMN, which is interpreted as greater network segregation between the neurocognitive networks (Sherman et al., 2014). Although there is a myriad of measures of cognitive performance, IQ scores have been positively associated with greater segregation of the DMN-CEN (DeSerisy et al., 2021) and greater intra-CEN connectivity by a number of studies of children and adolescents from late childhood to mid-adolescence (Langeslag et al., 2013; C. Li & Tian, 2014; Sherman et al., 2014).

The developmental trajectories of the DMN and CEN parallel the development of cognitive and emotional processes. Cognitive abilities such as executive functioning (Rueda et al., 2004), reasoning (Wendelken et al., 2017), and reaction time and accuracy (Rueda et al., 2004) all demonstrate major improvement during this age range. One research lab investigated lying in children (which incorporates mentalizing an episodic memory, understanding the difference in mentalization between the self and other, and the creation of a false but rational story). They found that age at which children began generating and maintaining consistency in their false stories was around age 7 (Talwar & Lee, 2008). This is similar to another study that found that children were introspective and aware of their own thoughts much like adults by age 8 whereas 5-year-olds were less aware of their mental activities (Flavell et al., 2000). Six-year-olds demonstrated the greatest

improvement in reasoning skills with smaller increases seen in adolescence and adulthood (Wendelken et al., 2017). Adult-like performance in tasks such as working memory and inhibitory control, however, only occurs in mid-to-late adolescence (Luna et al., 2004).

The transition between these three networks is hypothesized to demonstrate the maturity of brain networks (Menon, 2013; Menon & Uddin, 2010). Compared to adults, children and adolescents exhibit fewer transitions between network states (Ryali et al., 2016), which is due, in part, to the development of the Salience Network.

The development of the Salience Network is not as well-studied as the previous two, but research cumulatively suggests it is involved in error detection and response inhibition (Menon & Uddin, 2010; Sridharan et al., 2008). Much like the Central Executive Network, higher functional connectivity within the SN is associated with maturity as children demonstrate weaker intra-network connectivity compared to adults (Fair et al., 2007; Uddin et al., 2011). The anterior insula has been shown to be particularly critical in the SN, activating the switch between the DMN and CEN (Goulden et al., 2014; Sridharan et al., 2008). To achieve efficient transitioning between the network states, the anterior insula communicates with the DMN and the CEN for rapid access to the appropriate cognitive processors (Goulden et al., 2014). Compared to adults, children not only display weaker intra-network connectivity; they also show weaker between-network functional connectivity between the anterior insula and the PCC from the DMN, and dorsolateral PFC from the CEN (Uddin, 2014; Uddin et al., 2011). Increased connectivity between the SN and the DMN and CEN is associated with improved cognitive performance.

2.4 Theories and Models of Neurodysfunction

A number of theories have been developed to aid our understanding of neurodysfunction. Three relevant theories are described below as they pertain to 1) specific networks that are theorized to be impacted by neurological dysfunction, 2) a generalized response of hyperconnectivity in the brain, and 3) the vulnerability of pediatric populations to concussion symptoms.

2.4.1 Triple network model

The triple network model describes the three major networks involved in a widespread of neuropathological disorders and diseases. Introduced by Menon (2011), the model focuses on the functional brain networks that are involved in neurocognitive and emotional processing, namely the Default Mode Network, the Salience Network, and Central Executive Network, as previously described. Research surrounding the behaviour of these networks in healthy populations and their common presentation following neuropathology provides a conceptual framework with which we can generate hypotheses and identify underlying mechanisms of specific clinical populations.

Evidence from healthy populations suggests that the ability to transition between functional networks such as the DMN, CEN and SN is associated with cognitive flexibility and higher executive function, as shown by the correlation between performance on neuropsychological testing and the number of transitions between network states (Douw et al., 2016; Kelly et al., 2008; Nomi et al., 2017). In fact, age-related increases in variation to brain signals during a cognitive task may suggest increases in signal complexity as networks differentiate and specialize from childhood to adulthood (McIntosh et al., 2008). Clinical populations demonstrating atypical cognitive and

emotional functions such as schizophrenia and Alzheimer's disease show reduced ability to transition between states. These findings suggest that evaluating network interactions may be a transdiagnostic approach to multiple neurodevelopmental disorders and injuries (Uddin, 2021).

The triple network model is built primarily on the schizophrenia, Alzheimer's disease, and autism literature. As previously discussed, the DMN is involved in self-referential thought processes including autobiographical recall (Ino et al., 2011) and reward- and value-based decision making (Koch et al., 2018; Maresh et al., 2014). Deficits in these processes are associated with several neurological disorders such as depression, obsessive-compulsive disorder, social anxiety, and Alzheimer's, all of which also demonstrate abnormal intra-DMN functional connectivity (Bluhm et al., 2009; el Haj et al., 2015; J. Fan et al., 2017; Rabany et al., 2017). Similarly, the CEN and SN—which are linked with executive functioning—also demonstrate aberrant intra-network functional connectivity in patients with neuropathological disorders and diseases (Menon & Uddin, 2010; Uddin, 2021).

The strength of the triple network model comes from the between-network dynamics of the DMN, SN, and CEN. As an overview, Menon posits that the SN detects salient stimuli and delegates either the CEN or DMN to process the stimuli. Abnormalities in the functioning of the networks alone (*e.g.*, dysfunctional within-network communication, aberrant nodal structural properties) can alter how accessible any one of the networks is to process incoming information. For example, microstructural abnormalities in the mPFC have been noted in patients with depression (Drevets et al., 2008). As an important node of the DMN, the mPFC plays an important role in the activities of the DMN including its communication with nodes of the SN (Goulden et al., 2014). Evidence suggests that the relationships between the DMN to the SN and CEN are indeed abnormal in patients with depression as well (Manoliu et al., 2014). In particular, researchers

have found a reduced influence of the SN on the DMN in negatively-valenced conditions, but a greater influence of the DMN on the SN in positively-valence conditions, which might contribute to poor executive control and an attentional bias towards negative stimuli in patients with depression (Guha et al., 2021). Similarly, individuals with anxiety disorders demonstrate functional and structural aberrations in the connections between the nodes of the SN (Baur et al., 2013). Dysfunction within the SN may contribute to the weakened CEN-SN connectivity in individuals with anxiety. As the SN and CEN allow for executive functioning, reduced CEN-SN connectivity might suggest poorer cognitive control in anxiety disorders (Geng et al., 2016). Together, these results demonstrate that abnormalities in the structure or function of any of the three networks can transcend to a myriad of symptoms pertaining to the other networks (Menon, 2011).

A budding area of research in addition to the functional connectivity between these networks and individual brain regions is the effectivity connectivity between them. Effective connectivity describes the influence one brain region has on another and, while scarcely researched in the field of brain injury, may shed light on the directionality of the connectivity. One study (Rangaprakash et al., 2018) that evaluated a sample of active military personnel who were diagnosed with both mild traumatic brain injury and post-traumatic stress disorder and reported lower variability in connectivity compared to individuals with post-traumatic stress disorder in the absence of a concussion. More interestingly, they reported reduced effective connectivity between the mPFC and anterior insula, meaning that there was less of an influence of the mPFC on activities of the insula, which was interpreted to impact the activity of subcortical regions like the amygdala and hippocampus. With reduced information flow between the mPFC and insula, the insula lacks signals to inhibit the activity of subcortical regions, leading to possible over-activity of the emotion-related regions.

Comparisons between clinical populations reveal that dynamics between the DMN, SN and CEN may also determine neurobiological differences between the disorders (*e.g.*, schizophrenia vs. depression (Shao et al., 2018) and even between clinical presentations within a disorder (e.g., adolescents with depression who self-harm vs. those that do not self-harm (Ho et al., 2021). Although Menon does not include concussion in his framework, emerging evidence suggests that adults and children with concussion also demonstrate similar abnormalities in the intra- and inter-network functional connectivity of the DMN, CEN, and SN (Bharath et al., 2015; Churchill et al., 2021; Muller & Virji-Babul, 2018).

Characterizing the roles of each of the three major networks involved in clinical psychopathology allows researchers to understand the overlap in the symptoms and clinical presentations of patients with different diagnoses. Concussion is one such condition that is sometimes undetected or misdiagnosed, especially in adolescence (Iverson, 2006). An exploration of the intra- and inter-network functional connectivity may provide novel insights into the multitude of neurological and clinical effects of concussion during childhood.

2.4.2 Hyperconnectivity Hypothesis

A common response to brain injury of hyperconnectivity. The theory of hyperconnectivity suggests that brain injury specifically leads to compensation for dysfunction by increasing connectivity (Hillary & Grafman, 2017). It may, perhaps, be in response to a lack of efficiency of the brain to process and transfer information to their appropriate locations. As seen in the initial stages of Parkinson's disease (Gorges et al., 2015; Stoffers et al., 2008; Tuovinen et al., 2018), mild cognitive impairment and Alzheimer's disease (Bonanni et al., 2021; Jie et al., 2016; Yao et al., 2021),

concussion and other traumatic brain injuries also exhibit a general response of heightening functional connections shortly after injury (Abbas et al., 2015; Iraji et al., 2016; Roy et al., 2017).

These resting state functional connectivity results aligned with task-related studies where more distributed areas of activity are detected following concussion. These findings might suggest that the post-concussion brain compensates with increased connectivity to peripheral brain areas in efforts to preserve normal processing.

Hillary and Grafman (2017) hypothesized that the brain's goal is to maintain the efficiency of network functioning while reducing the cost of maintenance. The efficiency of a network is determined by how easily accessible one brain region is to another. It is an evaluation of efficient information transfer between brain areas. If, for example, node A needs to communicate to node B, the most efficient route of communication would be a direct transfer from node A to B. A less efficient network would be one where node A must first transfer information to an intermediate node before information can be passed to node B. In the event of brain injury, dysfunction to a node might result in reduced efficiency if that node is the intermediate node in between two others.

Minimizing costs refers to keeping the number of connections low so as to reduce the resources needed to supply the connection (Chen et al., 2013). In our orchestra metaphor, balancing the efficiency-cost tradeoff would be similar to hiring highly experienced musicians while keeping the hiring budget to a minimum.

The response to neurological disruption with enhanced communication between brain areas allows the brain to keep up with the demands from the environment. Thus, hyperconnectivity may be adaptive as an initial reaction to neurodysfunction. As demonstrated by patients with Alzheimer's, however, prolonged hyperconnectivity may have negative consequences due to the neurometabolic demand to maintain heightened connectivity (Matsuda et al., 2019). The

hyperconnectivity hypothesis posits that chronic hyperconnectivity indeed comes at a cost and can result in long-term dysfunction of major network nodes (*e.g.*, the posterior cingulate cortex of the Default Mode Network). Evidence of the long-term costs of chronic hyperconnectivity is demonstrated by the progression of healthy aging to mild cognitive impairment to Alzheimer's disease in adults, which may be the expense of hyper-metabolic processes to supply connections (Agosta et al., 2012; Matsuda et al., 2019).

The hyperconnectivity hypothesis suggests that the penalty of chronic hyperconnectivity is not random. In fact, the major network nodes are the targets of dysfunction due to metabolic stress (Hillary & Grafman, 2017). These major network nodes are vulnerable because they are considered "rich-club hubs". Rich-club hubs are dense in connections and communicate to other network regions or to other networks (van den Heuvel & Hulshoff Pol, 2010). One could imagine that, in the structure of an orchestra, the conductor is a rich-club hub since the conductor coordinates and communicates with all other musicians. An overworked conductor might be ineffective in communicating with the players. In this case, there may be a greater reliance on the musicians to communicate with one another by listening more closely to the parts played by other sections to maintain the performance of the symphony. This is representative of the major network nodes demonstrating dysfunction, leading to increased connections between subnodes of the network.

Concussion research has also noted hyperconnectivity following injury. One study found increased functional connectivity within the DMN as the number of sub-concussive hits increased (as determined by an accelerometer placed in the helmets of the athletes) (Champagne et al., 2019). Another study reported that functional connectivity between subcortical regions to the DMN increased shortly after injury (Sours et al., 2015), suggesting greater input of extraneous regions in DMN functioning. In children and adolescents within a six-month period of injury, however,

reported decreased functional connectivity between the anterior and posterior nodes of the DMN (Plourde et al., 2020).

Together, these findings suggest that the hyperconnectivity of accessory regions to support network functionality is a possible early response to injury, followed by potential hypoconnectivity of major network nodes. The hyperconnectivity hypothesis may offer insights to the work presented here as our sample of children and adolescents with concussion demonstrate clinically significant aberrations in connectivity.

2.4.3 Reserve theory

The brain reserve theory borrows literature from Alzheimer's disease to describe the resilience of the brain to withstand damage (Stern, 2002). It is similar to the cognitive reserve hypothesis that posits that higher cognitive stimulation through education in early life will protect against cognitive decline in late life (Tucker-Drob et al., 2009). These two theories are complementary to one another are sometimes used interchangeably throughout the literature; thus, they will hereafter be referred to collectively as the reserve theory.

According to the reserve theory, the brain has a finite reserve of resources to compensate for damage through compensatory mechanisms. Because the reserve has a finite capacity, an injury surpassing the threshold of which the brain is able to compensate will result in clinical impairments (Stern, 2006). The reserve theory allows us to interpret why we might see the abnormal brain activity that often presents in neuroimaging studies following neurotrauma. It also might enable us to postulate why children and adolescents are more vulnerable to concussion effects (Anderson et al., 2005), why some individuals might experience longer recovery times than others (Broshek et

al., 2015; Scopaz & Hatzenbuehler, 2013), and why concussion might be linked to other neurological disorders and diseases such as depression (Chrisman & Richardson, 2014; Kerr et al., 2012) and Alzheimer's disease (Calvillo & Irimia, 2020; Guskiewicz et al., 2005).

The capacity of the reserve is dependent on a number of protective and risk factors. In individuals with Alzheimer's disease, researchers have found both genetic and environmental factors that either increase, decrease, or preserve the reserve capacity (Stern, 2006). For instance, a retrospective identical twin study evaluating dementia risk and education levels found that twins who achieved higher education (environmental factor) were less likely to develop dementia compared to their sibling who received the legally-required basic levels of education (Gatz et al., 2007). In a similar vein, the presence of a particular risk allele (genetic factor) significantly increases the likelihood of Alzheimer's later in life (Reiman et al., 2004; Snowden et al., 2007). Protective factors included a list of environmental and genetic factors as well including working in complex environments where cognitive problem solving is rewarded (Andel et al., 2005) and neuroprotective genetics (Z. Li et al., 2020).

While the Alzheimer's literature has a much more comprehensive repertoire of genetic and environmental factors that might impact the brain reserve of an individual with Alzheimer's disease, how reserve theory applies to concussion is much less studied. Because the study of concussion has only recently become a more topical field of study, twin studies, genetic explorations, and pre-injury brain conditions are not as commonly accessible. This is particularly true of children and adolescents. From animal studies, researchers have been able to determine that early-life stress may reduce the brain reserve by way of increasing reactivity of the hypothalamic-pituitary axis and ultimately increase the likelihood that the individual will exhibit poor recovery if traumatic brain injury occurs later in life (Diaz-Chávez et al., 2020)

The reserve theory is compatible with the functional hyperconnectivity hypothesis. Hillary and Grafman (2017) propose that greater connectivity of major nodes of the brain may increase an individual's reserve, allowing the individual an abundance of connections that can be relied upon in the event of neurological disruption. It allows leeway for major pathways of the brain to be re-routed to maintain brain communication. Using our orchestra analogy, hyperconnectivity supports the reserve in a similar way that having a group of backup trumpeters would sustain the symphony performance if the original trumpeters were unable to play. Without backup trumpeters (i.e., if one had a low reserve), alternative brass instruments might need to take the place of the trumpeters with a higher probability of detriment to the performance (analogous to behavioural deficits).

Reserve theory can also help describe the clinical presentation of childhood concussion. For instance, it provides a clinical perspective as to why children and adolescents might have a lower threshold to tolerate trauma and may be more likely to experience prolonged recovery times (Williams et al., 2015), greater severity of symptoms (Willer et al., 2004), and increased likelihood of repeat injury (Eisenberg et al., 2013). Moreover, it offers a theoretical lens to the functional connectivity aberrations presented in this thesis and neuropathological research overall.

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Chapter 3

Connectivity and recovery time

Abstract

Background: Following concussion, prediction of who will go on to experience long-term symptoms is important for treatment plans, especially in children and adolescents. Evaluating resting state networks may provide early insight into persisting concussion symptoms. Our purpose is to investigate the functional connectivity of the Default Mode Network (DMN) and the Central Executive Network (CEN) in youth following concussion, in order to assess its relationship to symptom severity, identify regions that differentiate individuals with symptoms lasting beyond six months, and characterize the change in these networks across recovery. *Methods:* Youth with concussion between ages 10-18 years were recruited and scanned using resting state fMRI. Symptoms were tracked up to 6 months. "Resolvers" were defined as participants whose symptoms resolved within six months, whereas "Non-resolvers" were defined as participants with lingering symptoms beyond 6 months. *Results:* Connectivity of the frontal regions of the DMN was negatively related to symptom severity. Connectivity of the temporal regions was significantly different between the resolvers from the non-resolvers and showed an age-related trend. *Conclusion:* Connectivity of the DMN following concussion relates to both severity of reported symptoms and length of recovery in youth. Specifically, lower connectivity in the right superior frontal and medial

prefrontal gyri is correlated with greater symptomology. In addition, a positive relationship between the connectivity of the temporo-occipital regions and symptom severity was shown in participants who resolved their concussion. However, a negative relationship was identified in those experiencing symptoms beyond six months.

3.1 Introduction

Concussion is a mild traumatic brain injury that results in symptoms affecting behaviour, cognition, sleep and mood (McCrory et al., 2013). Since standard emergency room brain scans are unable to detect gross structural abnormalities following concussion, concussion diagnosis relies most commonly on symptom report and mechanism of injury. Measuring symptomology is a clinical challenge since it depends on self-report or reports of observable behavioural changes from others such as parents and coaches (Alla, Sullivan, & McCrory, 2012). Nevertheless, symptom reporting remains a key factor in determining diagnosis, severity of injury, and recovery even in children and adolescents who often take longer than adults to recover (Anderson, Spencer-Smith, & Wood, 2011; McCrory, Collie, Anderson, & Davis, 2004).

With 30-60% of children and adolescents continuing to experience concussion symptoms even one month following injury (Grool et al., 2016; Zemek et al., 2016; Zemek, Farion, Sampson, & McGahern, 2013), early prediction of which individuals might be susceptible to persistent long-term symptoms is important for the development of treatment plans. However, there is currently minimal evidence that behavioural and clinical tests are reliable predictors of concussion recovery beyond one month of injury in children (Babcock et al., 2013; Meehan, Mannix, Stracciolini, Elbin, & Collins, 2013; Zemek et al., 2016, 2013). In addition, models estimating the probability of

prolonged recovery to identify at-risk individuals need further development (Cnossen, van der Naalt, Spikman, Nieboer, & Yue, 2018).

An area of concussion research that might supplement the clinical and behavioural measures used to assess concussion is brain imaging. Although brain imaging such as magnetic resonance imaging (MRI) may not be necessary for concussion diagnosis, it shows promise in identifying brain abnormalities that might be useful for prognosis (Dona, Noseworthy, DeMatteo, & Connolly, 2017; Lancaster et al., 2018; Manning et al., 2017; Toledo et al., 2012). One study showed that individuals who were cleared to return to physical activity continued to exhibit abnormal brain activity compared to healthy controls with even more profound abnormalities seen in individuals with persistent concussion symptoms (Churchill, Hutchison, Graham, & Schweizer, 2018). A similar study in adolescents also found abnormal brain activity in adolescents with a history of concussion and no symptom complaints (Orr et al., 2016). Not only do these studies suggest that neurophysiological abnormalities may exist in the absence of symptoms, they show that these abnormalities exist even when the individual is not tasked with cognitive demands, also known as the resting state.

The resting state of the brain is also known as a task-negative condition because the individual is not focused on any particular activity. Even during resting state, the brain continues to be active in an organized manner, synchronizing activity across multiple networks of brain regions that mirror functional activity seen when the brain is engaged in various cognitive tasks (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007). These networks are known as resting state networks. Two robust resting state networks are the Default Mode Network (DMN) and Central Executive Network (CEN). These networks both demonstrate change from infancy to adulthood (Supekar et al., 2010) that parallels the advances seen developmentally in cognitive

performance (Blakemore & Choudhury, 2006). Moreover, these two networks are anticorrelated such that brain activity switches from the rest state of the DMN to the active state of the CEN when an individual is tasked with a cognitive demand (Fox et al., 2005).

Both networks have been studied in relation to concussion prognosis and recovery. Following concussion, the functional connectivity of the DMN appears altered in both adults and children relative to healthy controls (Borich, Babul, Yuan, Boyd, & Virji-Babul, 2015; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Militana et al., 2016; van der Horn et al., 2017; Zhou et al., 2012). However, whether connectivity of the DMN increases (Sharp et al., 2011) or decreases (Borich et al., 2015; Militana et al., 2016) following concussion is still under debate.

The Central Executive Network is a less-studied network following concussion, particularly in youth. The CEN is important for directing attention in a goal-oriented (or top-down) manner (Corbetta & Shulman, 2002) such that stimulating brain regions of the CEN leads to better sustained attention and attentional control (Esterman et al., 2017). Even in the absence of a cognitively demanding task, simultaneous activation of CEN structures are observable as low-oscillating fluctuations (Beckmann, 2005). Researchers have reported increased connectivity in attention networks following concussion (Borich et al., 2015) even when there are no detectable performance differences in executive functioning (Czerniak et al., 2015). Although adolescents with concussion show evidence of greater difficulty concentrating, decreased executive functioning (Conklin, Salorio, & Slomine, 2008; Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013), and poorer academic performance (Ransom et al., 2015), the functional connectivity of attention-related networks post-concussion in adolescents is poorly understood.

Since childhood and adolescence is a time of neurodevelopment, age at the time of injury may contribute to concussion outcome. In fact, research has shown that older adolescents are more

greatly affected by head injury compared to younger children as shown by higher symptom severity (Willer, Dumas, Hutson, & Leddy, 2004) and increased risk for future emotional issues following injury (Chrisman & Richardson, 2014). The developmental stage of an individual's networks can shed light on reasons why older adolescents might be more vulnerable to the effects of concussion.

Starting from infancy, the resting state networks including the DMN and CEN begin to emerge. Studies of preterm babies show that the DMN and CEN are already present prior to birth (Doria et al., 2010). These networks continue to mature through childhood and adolescence into their adult forms. This includes the differentiation of resting state networks from one another as a the brain's connections progress from more diffuse connections to more focal connections (Durston et al., 2006). This is the result of the retraction of short-range connections and the strengthening long-range connections to increase network differentiation and efficiency (Menon, 2013). By adolescence, the brain has a more fine-tuned recruitment of networks to meet task demands (Durston et al., 2006). These changes parallel a decrease in grey matter through later adolescence (Narvacan, Treit, Camicioli, Martin, & Beaulieu, 2017), and an increase in white matter as the myelination of long-range tracts ensues (Asato, Terwilliger, Woo, & Luna, 2010). The development of the CEN and DMN, in particular, are especially important for higher-order cognition as the brain's ability to flexibly and appropriately switch between the two states also improves from childhood to adulthood (Ryali et al., 2016). Given the on-going development of the resting state networks (Supekar, Musen, & Menon, 2009), evaluating neurobiological dysfunction following concussion during adolescence may shed light on the age-related effects of concussion on recovery.

The purpose of the current study was to explore functional connectivity in the DMN and CEN in symptomatic adolescents post-concussion within six months of their injury. In particular,

we examined: (1) whether self-reported symptom severity is associated with functional connectivity of the DMN and CEN during adolescence, (2) whether functional connectivity within the DMN and CEN is predictive of concussion recovery within a six-month period, (3) if age at the time of injury impacts functional connectivity following injury, and (4) if there is a change in connectivity from recruitment to follow-up.

To do this we recruited children and adolescents diagnosed with concussion, scanned them using resting state fMRI, and tracked their recovery progress for six months. Participants who resolved their concussion within six months were grouped separately from those who did not resolve their symptoms. We evaluated the differences in functional connectivity between groups to assess the relationship between connectivity and symptomology, and across time to investigate how networks change through recovery.

3.2 Methods

3.2.1 Participants

This study was approved by the Hamilton Integrated Research Ethics Board. All participants and their parents/guardians provided informed assent and consent before a child was enrolled in this study. Twenty-nine adolescents between the age of 10 and 18 (mean=14.0, SD=2.5) were recruited with the intention to collect MRI in participants at baseline (following recruitment) and follow-up (following symptom resolution or 6-months after baseline imaging in the event that a child did not reach symptom resolution within 6 months), as depicted in Figure 3.1. Thirteen participants declined to take part in the follow-up MRI session most commonly because of the participant's

experience of discomfort with the scanner following the baseline session or the time commitment to complete the study. As such only 16 participants completed both MRI sessions. Participants were recruited from physicians' offices, emergency rooms, or by self-referral from the study website. Inclusion criteria included (1) age of 10 to 18 years, (2) a diagnosis of a concussion by a physician within the past 2 months, (3) the experience of concussive symptoms at the time of recruitment. Participants were excluded if they had; (1) a complex system injury requiring surgery, resuscitation, or admission to the intensive care unit, (2) a diagnosis of a severe developmental disability, and/or (3) MRI contraindications (*e.g.*, claustrophobia, metal in the body). Table 3.1 describes the mechanism of injury, number of prior concussions, known loss of consciousness, location of impact, symptom severity score and any previous medical diagnoses including psychiatric disorders.

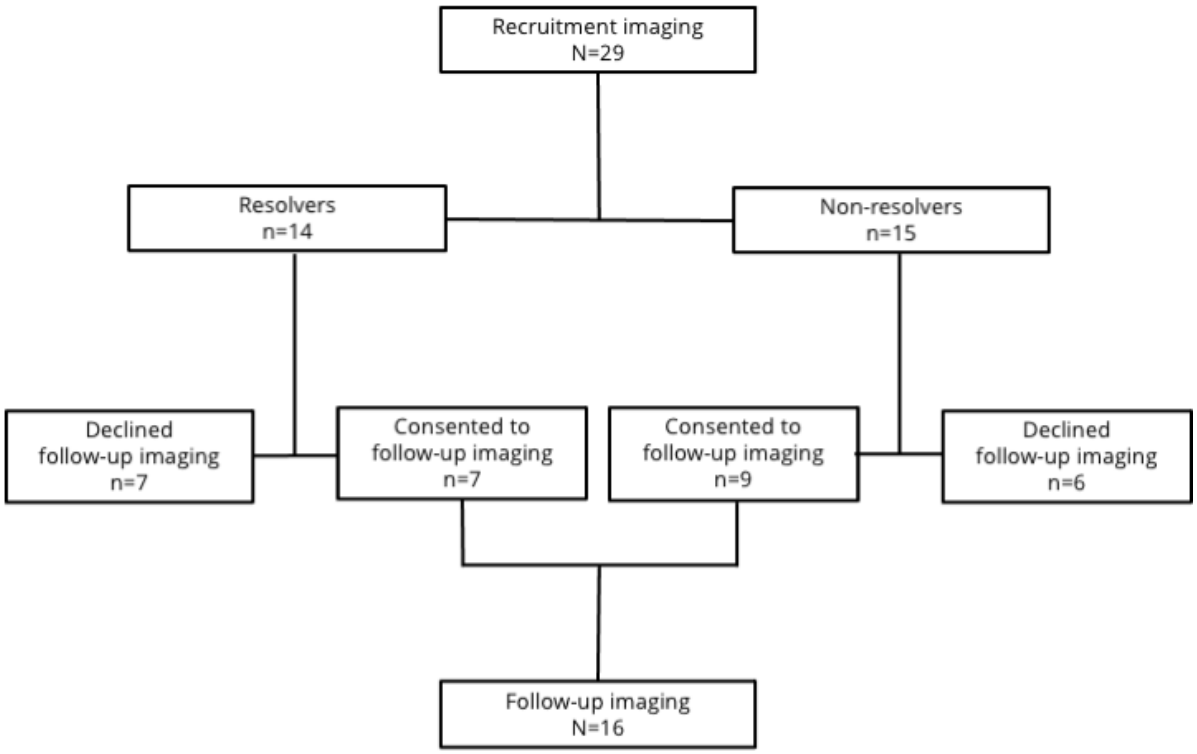


Figure 3.1. This study recruited 29 eligible participants and acquired resting state data upon recruitment. Of these participants, 13 had resolved their symptoms within six months of their injury (resolvers), whereas 15 had not (non-resolvers). Thirteen participants declined to complete a second MRI scan, resulting in 16 returning participants for a follow-up imaging session.

3.2.2 Procedure

To evaluate functional connectivity as a predictive factor in concussion recovery, participants were grouped based on the resolution of symptoms within a 6-month period of injury into two groups based on symptom report within six-months of recruitment: resolvers and non-resolvers. Depicted in Figure 3.2, participants whose symptoms resolved completely (*i.e.*, no remaining symptoms) within six months of their injury comprised the resolvers. Those with lasting symptoms beyond six months (i.e., participant continues to report at least one persistent symptom) comprised the non-resolvers. To evaluate age-related effects of injury, participants were also split into a subcategory based on age. A split-median of all ages was used to categorize younger (<14.06 years) and older (>14.07 years) adolescents.

Once participants were recruited, they were given the Post-Concussive Symptom Scale (PCSS; Lovell et al., 2006) and scanned in the MRI scanner. Length of time between injury and first scan varied greatly (mean=7.1 weeks, SD=7.6). The PCSS is a pediatric-adapted concussion symptom scale where the participant can rate which of the concussion symptoms are experienced and the severity of the symptoms using a scale of 0 (symptom not experienced) to 7 (very severe) on 22 different symptoms. Symptoms were continuously tracked for up to six months every 48 hours using an online survey that was sent to the participant's email until the participant indicated zero symptoms across two consecutive symptom surveys. When this occurred, the participant was considered to have reached symptom resolution. An identical follow-up scan was acquired three-months after the participant reported the complete resolution of symptoms. The participants who did not reach symptom resolution within a six-month period were scanned six-months post-injury.

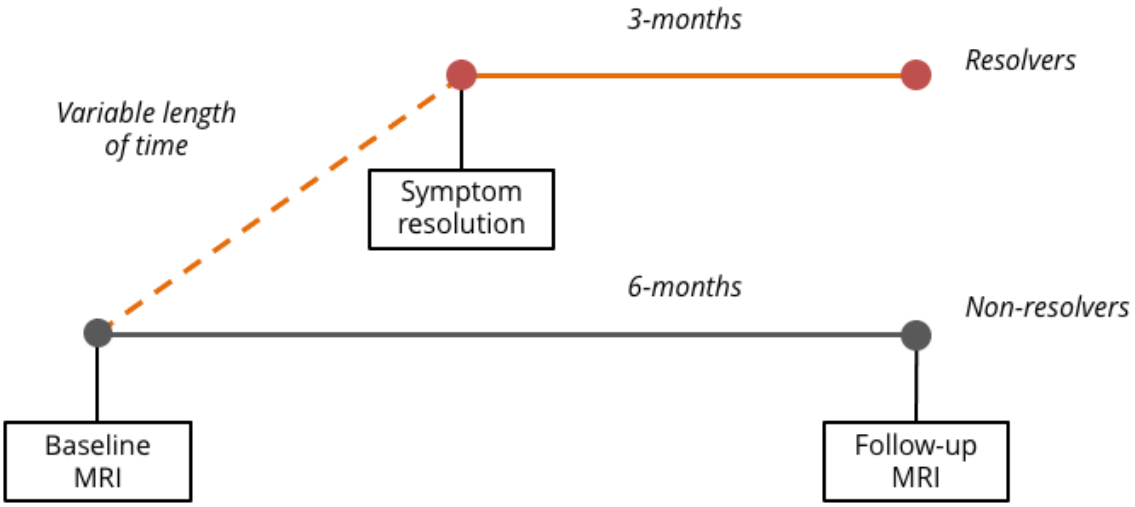


Figure 3.2 A depiction of how participants were grouped as resolvers or non-resolvers. Following recruitment (Baseline), participants completed the PCSS (Lovell et al., 2006) every other day. Resolvers are participants who reported having reached Symptom Resolution within a 6-month period. When this occurred, participants were given a follow-up scan 3 months after Symptom Resolution. Non-resolvers are participants whose symptom scores never reached zero.

3.2.3 MRI acquisition & pre-processing

Participants were scanned in a 3 Tesla magnetic resonance imaging (MRI) scanner using a 32-channel RF receiver coil (General Electric Healthcare, Milwaukee, WI). Following two routine scans (a 3-plane localizer and an ASSET calibration scan), a 3D T_1-weighted anatomical image (TE=4.25 ms, TR=11.36 ms, flip angle=12^O, image matrix=256x256, slice thickness=1mm, FOV=25.6 x 25.6cm) and whole-brain resting state functional images (echo planar imaging sequence, TE=35ms, TR=2000ms, temporal points=180, flip angle=90^O, image matrix=64x64, slice thickness=3mm, FOV=22 x 22cm, 35 slices) were acquired. Resting state data was collected over 6 minutes and 10 seconds. To ensure data processing was conducted on images collected after the scanner reached a steady state, the first four data points were discarded in each fMRI scan.

Field map corrections were applied to the functional BOLD data to account for image distortions due to magnetic field inhomogeneity. A processing pipeline was used to create the field map and apply corrections to the EPI (Davis & Noseworthy, 2016). The pipeline, using pre-processing tools from AFNI and FSL, was modified for brain data to incorporate skull stripping of the anatomical image.

Pre-processing was conducted in CONN Toolbox v19c using the default pre-processing pipeline (Whitfield-Gabrieli & Nieto-Castanon, 2012). Realignment and motion correction of the functional data was applied using SPM12 (Anderson et al., 2001). Anatomical and functional data were registered to MNI152 space. Functional smoothing was applied to increase signal-to-noise ratio using a spatial convolution with a Gaussian kernel of 5mm FWHM. Data denoising was applied in two steps: regression of confounding BOLD effects including physiological noise, motion artifacts, and scanner drift, and temporal high-pass filtering (>0.008 Hz).

3.2.4 Analysis of functional connectivity

All connectivity analyses were conducted using CONN Toolbox v19c (hppt://nitrc.org/projects/conn/). First, group-level independent component analysis (group-ICA) was used on the preprocessed data with non-linear FastICA to extract 20 independent components representing spatially separated but temporally correlated areas in the brain (Calhoun, Adali, Pearlson, & Pekar, 2001) based on our total sample (N=29). The DMN and CEN were identified using the Dice coefficient to determine which independent components most correlated with a network atlas (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2011). Networks that were split into two components (*i.e.*, the posterior-DMN and anterior-DMN, right-CEN and left-CEN) were combined. The regions identified as the DMN and CEN comprised of voxels surpassing a voxel-wise threshold of $p<.01$, FDR (false discovery rate)-corrected, and a cluster threshold of $p<.05$, FDR-corrected. The two networks were then converted into binary images and used as two separate masks in the subsequent analysis.

Second, to determine regions where connectivity is associated with symptom severity scores, we conducted a connectome-multivariate pattern analysis (MVPA; Whitfield-Gabrieli & Nieto-Castanon, 2012). This assesses connectivity at each voxel across the brain based on the temporal correlation between timeseries. MVPA has been recommended for heterogeneous populations such as those involving brain injury (Thompson, Thelin, Lilja, Bellander, & Fransson, 2016). It has been used widely in recent literature as a data-driven method for determining functional connectivity with masked regions and identifying regions-of-interest (ROIs) in clinical populations (Muehlhan et al., 2020; Thompson et al., 2016; Whitfield-Gabrieli et al., 2016) including concussion (Churchill et al., 2018). This method evaluates temporal coherence between

the timeseries at each voxel to every other voxel within the masked brain areas, and then the dimensionality is reduced using a principal component analysis to provide a resulting spatial correlation map representing a within-network connectivity map (Whitfield-Gabrieli & Nieto-Castanon, 2012).

We generated MPVA-derived maps that were masked by the DMN and CEN regions identified by group-ICA and constrained to four components. Each network was assessed separately. Only the first component was used in this analysis as the following three components as it accounted for the greatest explained variance (0.44% BOLD change). To determine ROIs within each network where connectivity values were associated with concussion severity scores, an omnibus F-test was used (Whitfield-Gabrieli & Nieto-Castanon, 2012). The results were thresholded using Gaussian Random Field Theory with a cluster-size threshold of $p<.05$ FDR-corrected, and voxel-threshold of $p<.01$ uncorrected (Worsley et al., 1996). The average connectivity of these regions-of-interest was determined by finding the mean correlation β-values produced by MVPA in our ROIs.

3.2.5 Statistical analyses

To determine whether connectivity within the DMN can predict concussion recovery, we created ANCOVA-maps based on the connectivity values derived from the MVPA β-values while accounting to severity of symptoms (connectivity ~ recovery group + symptom severity + interaction). This creates individual connectivity ANCOVA-maps. This method, similarly used in previous literature (Wang et al., 2019), identified regions where there is a significant interaction

effect between recovery groups (resolvers vs. non-resolvers) and connectivity when accounting for variance in symptom severity (cluster size p<.05 FDR-corrected).

An average ANCOVA-map was created per subject and used to explore the effect of age at the time of injury on recovery. The interaction between age at injury (older vs. younger adolescents) and recovery status at 6-months (resolvers vs. non-resolvers) was evaluated with a two-way between-subjects ANCOVA (connectivity ~ recovery group + symptom severity + age group + interaction terms) in R Studio (v.1.3.1056).

With the 16 participants who returned for the follow-up imaging session, the change in connectivity was evaluated using a mixed-factor ANOVA (connectivity ~ timepoint + recovery group + interaction) using the timepoint as a within-subject factor and recovery status as a between-group factor.

3.3 Results

3.3.1 Demographics

In total, 14 of 29 (48.2%) participants reported full resolution of concussion symptoms as reported on the Post-Concussion Symptom Scale (PCSS) within 6 months of injury, and 15 of 29 (51.7%) participants reported post-concussive symptoms at 6 months post-injury. As shown in Table 3.1, the recovery groups (resolvers vs. non-resolvers) did not differ significantly on a number of demographic items including age, sex, number of previous concussions, or symptom score at presentation. The average length of time from injury to symptom resolution in the resolvers was 6.9 weeks (SD=8.5).

Table 3.1. Demographic information for 29 participants at recruitment

Demographics	Total sample	Outcome group		Statistic
		Resolvers	Non-resolvers	
Sex				
N	29	13	15	
Male	10	4	6	$\chi^2(1, N=29)=0.66$, $p=.80$
Female	19	9	9	
Age (M, SD)	14.0 (2.5)	14.9 (1.9)	13.3 (2.7)	$t(25.1)=1.75$, $p=.10$
<14.06 years (n)	14	6	8	$\chi^2(1, N=29)=0.32$, $p=.57$
>14.07 years (n)	14	7	7	
PCSS score (M, SD)				
At recruitment	47.5 (20.4)	44.1 (23.2)	50.7 (17.4)	$t(24.3)=-0.85$, $p=.41$
At follow-up	9.4 (16.8)	0 (0)	18.2 (19.8)	$t(14)=-3.56$, $p=.003$
Loss of consciousness (n)				
No	18	7	11	
Yes	5	3	2	$\chi^2(2, N=29)=1.73$, $p=.42$
Unknown	6	4	2	
Previous concussions				
Number of concussions (M, SD)	1.1 (1.6)	1.4 (1.7)	0.8 (1.4)	$t(25.2)=0.94$, $p=.36$
Number of participants with previous concussion (n)	15	9	6	
Mechanism of injury (n)				
Sport/Recreational play	20	10	10	$\chi^2(3, N=29)=2.97$, $p=.40$
Non-sport fall	6	3	3	
Assault	2	0	2	
Other	1	1	0	
Prior diagnosis (n)				
Anxiety / Depression / Sleep disorder	4	4	0	$\chi^2(2, N=29)=3.65$, $p=.16$
Learning Disability	3	1	2	
ADHD	3	2	1	
Location of impact (n)				
Frontal	4	1	3	$\chi^2(4, N=29)=1.5$, $p=.83$
L/R Temporal	6	3	3	
Occipital	2	1	1	
L/R Parietal	12	7	5	
Body	5	2	3	
Time between injury & first MRI (average weeks, SD) N=28	7.1 (7.6)	4.5 (3.9)	9.5 (9.5)	$t(18.2)=-1.88$, $p=.08$
Time between injury & follow-up MRI (average weeks, SD) N=16	17.8 (6.5)	17.4 (6.4)	18.2 (7.0)	$t(13.6)=-0.24$, $p=.81$

3.3.2 Functional Connectivity

Functional connectivity was measured using a multivariate pattern analysis (MVPA), a voxel-wise evaluation of connectivity, with a significance threshold of p-corrected false discovery rate (FDR) voxel-wise < .01 and p-corrected FDR cluster-wise < .05. We evaluated the relationship between functional connectivity (as measured by MVPA) and symptom severity (as measured by the PCSS) in each recovery group based on symptom resolution within a six-month period (resolvers vs. non-resolvers) and age group based on a median split of age at the time of injury (younger vs. older adolescents). The creation of ANCOVA maps identified regions where there was a main effect of symptom severity, and regions where there was an interaction between our two groups (resolvers vs. non-resolvers) that signifies a different relationship between symptom severity and connectivity in each group. Individual connectivity values were submitted to a two-way ANCOVA to evaluate the interaction between connectivity, symptom scores, recovery groups and age groups (connectivity ~ symptom score + recovery group + age group + interactions). Age groups were determined using a median split where younger adolescents (<14.06 years) were compared to older adolescents (>14.07 years).

3.3.2.1 Main effect of symptom severity.

For voxels within the DMN, the right superior frontal gyrus and right medial prefrontal gyrus (shown in Figure 3.3a), as identified by Automated Anatomical Labelling (Rolls, Huang, Lin, Feng, & Joliot, 2020), were significantly correlated with symptom severity scores ($F(1, 25) = 16.60$, $p < .001$, $\eta^2_p = .40$). Individual connectivity values and symptom scores were plotted in in Figure 3.3b to depict a negative correlation between PCSS and connectivity in the right superior frontal

gyrus and right medial prefrontal gyrus (r(26) = -.66, p < .001) indicating that individuals with higher symptom severity had lower connectivity in the right superior frontal gyrus and right medial prefrontal cortex. There was also a difference between groups that approached significance (F(1, 25) = 3.34, p = .075, η^2_p = .12). However, the interaction effect between groups and symptom scores was not significant in these clusters. For voxels within the CEN, the correlation map revealed no voxels where connectivity was significantly correlated with symptom severity.

3.3.2.2 Interaction effect between groups.

The ANCOVA-map isolated regions where the relationship between connectivity and symptom severity was significantly different between recovery groups. For voxels within the DMN, the left temporo-occipital and left inferior temporal gyrus demonstrated a significant interaction effect (shown in Figure 3.3c).

The two-way ANCOVA revealed a three-way interaction between symptom score, recovery groups, and age groups that approached significance (F(1, 21) = 3.72, p = .068, η^2_p = .15). However, the three two-way interactions were all significant at p = .05.

The interaction effect between symptom score and recovery groups (resolver vs. non-resolver) was significant (F(1, 21) = 58.72, p < .001, η^2_p = .74), as shown in Figure 3.3d. The interaction was examined further by performing Pearson's correlations that evaluated the resolvers and non-resolvers separately. The resolvers show a positive relationship between connectivity and symptom score (r(11) = .81, p < .001), whereas non-resolvers show a negative relationship between connectivity and symptom score (r(13) = -.82, p < .001).

The interaction effect between symptom score and age group (younger vs. older) was significant (F(1, 21) = 4.47, p < .047, η^2_p = .18), as shown in Figure 3.3e. The interaction was

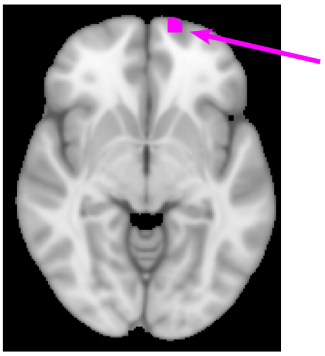
examined further by performing Pearson's correlations that evaluated the younger and older adolescents separately. The younger adolescents show a negative relationship between connectivity and symptom score ($r(12) = -.67$, $p = .01$), whereas older adolescents show a non-significant relationship between connectivity and symptom score ($r(13) = .41$, $p = .13$).

The interaction effect between recovery group (resolver vs. non-resolver) and age group (younger vs. older) was significant ($F(1, 21) = 5.17$, $p < .034$, $\eta^2_p = .20$), as shown in Figure 3.3f. This interaction was examined further by performing Welch's t-tests based on the a priori hypothesis that older adolescents might have poorer outcomes compared to younger adolescents as demonstrated in past research. In evaluation of the connectivity of the temporo-occipital clusters, the older non-resolvers had significantly lower connectivity compared to the younger non-resolvers ($t(12.26) = 2.92$, $p = .013$, $d = 1.47$), where there was no significant difference between age groups among the resolvers.

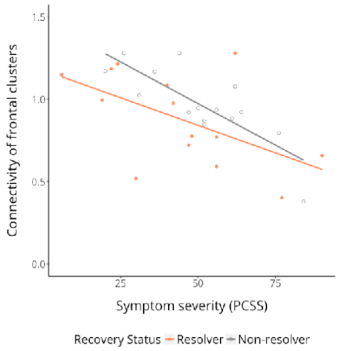
3.3.2.3 Change across recovery.

In evaluating the change in connectivity from baseline to follow-up (n=16), individual connectivity values for each the DMN and CEN were submitted to a mixed factor ANOVA that treated time of scanning (at recruitment and at follow-up) as the within-subjects factor and recovery status at six months (resolvers and non-resolvers) as the between-subjects factor. There were no significant effects detectable in the analysis of either network (as shown in Figure 3.4).

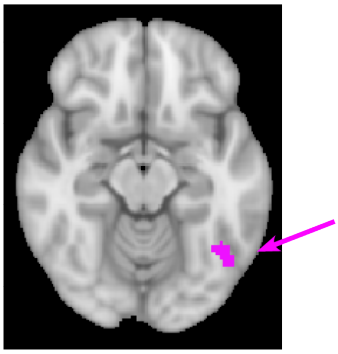
a. Frontal clusters



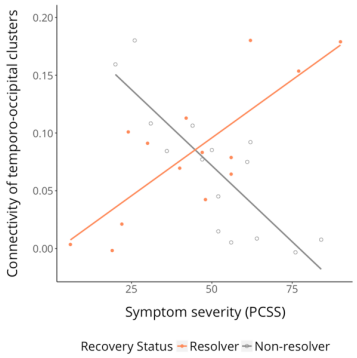
b. Effect of symptom severity



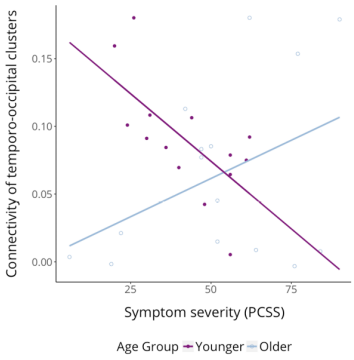
c. Temporo-occipital clusters



d. Interaction effect between recovery group and symptoms



e. Interaction effect between age group and symptoms



f. Interaction effect between age and recovery groups

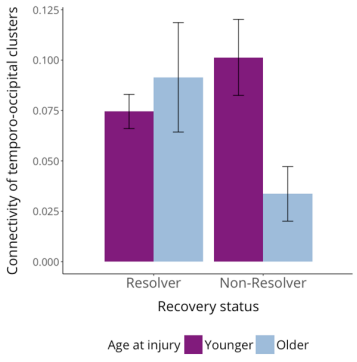


Figure 3.3. The results shown above represent the connectivity of group-based Default Mode Network (DMN) *a.* The effect of symptom severity was significant in right superior frontal and prefrontal gyri (thresholded at p=.05, cluster-size FDR-corrected). *b.* A graphical depiction of the negative relationship between connectivity of frontal clusters to symptom severity (p<.001). *c.* The interaction effect between recovery groups (resolvers vs. non-resolvers), symptom severity, and connectivity was significant in the temporo-occipital and inferior temporal gyri (thresholded at p=.05, cluster-size FDR-corrected). *d.* A graphical depiction of the interaction effect between recovery groups and symptom severity (p<.001). *e.* A graphical depiction of the interaction effect between age groups and symptom severity (p=.034). *f.* The interaction effect between age groups and recovery groups showed a significant interaction (p=.047) with a significant difference between older and younger non-resolvers (p=.01).

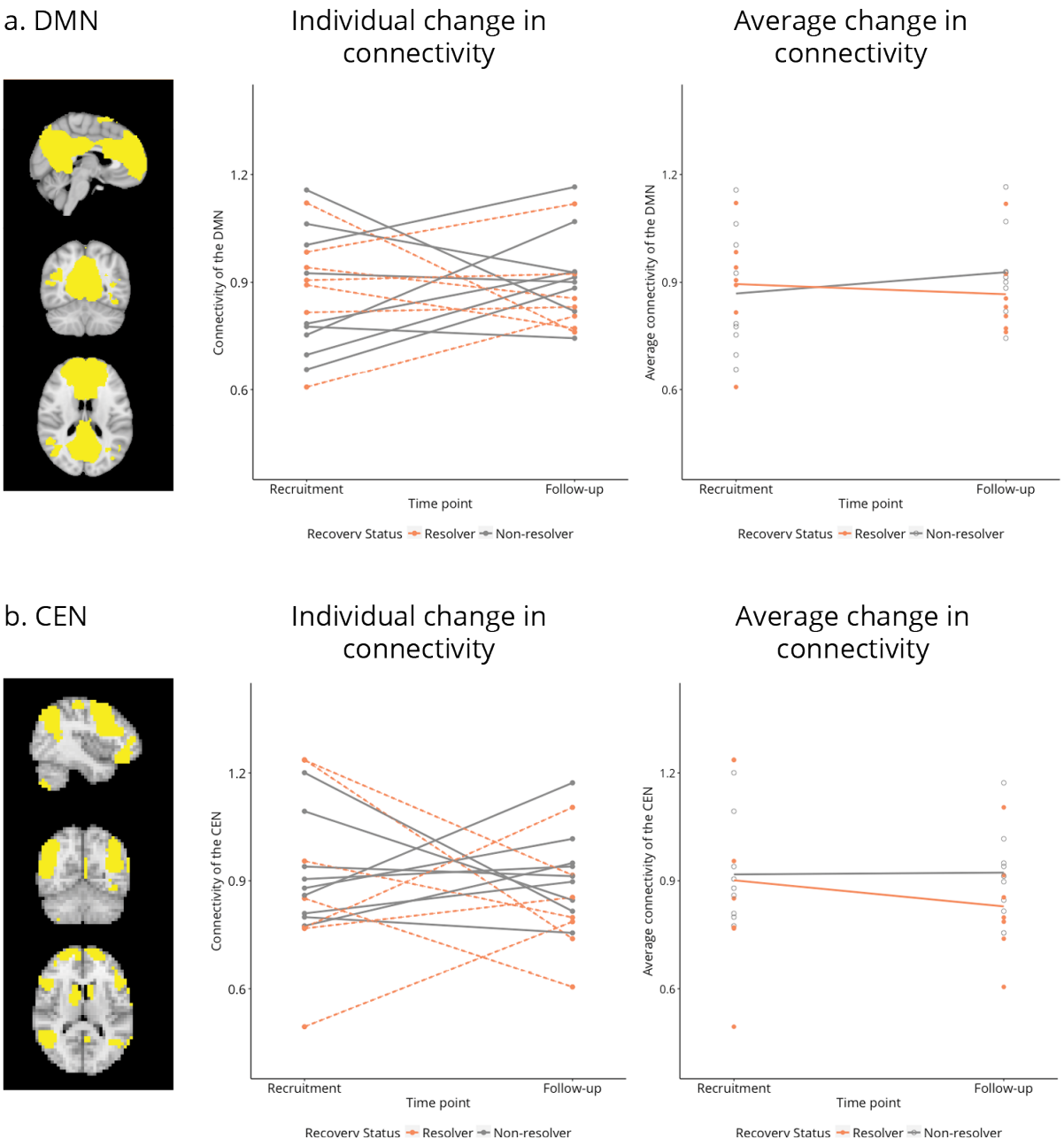


Figure 3.4. The results of within-subjects ANOVA depicting change in within-network connectivity from recruitment (time 1) to follow-up (time 2) for *a.* the Default Mode Network (left graph: lines show individual change, right graph: lines show average change), and *b.* the Central Executive Network (left graph: lines show individual change, right graph: lines show average change).

3.4 Discussion

We investigated vulnerable areas within the Default Mode Network and Central Executive Network where functional connectivity was associated with self-reported symptom severity. We found that the superior frontal cortex and medial prefrontal cortex were specific regions within the DMN where connectivity was significantly related to symptom severity. Higher symptom severity was associated with less frontal cortex connectivity. By comparing the resting state connectivity at the time of recruitment in adolescents that recovered within a six-month period to those that continued to have lingering post-concussion symptoms, we found an interaction in the temporal occipital cortex where connectivity and symptom severity had opposite trends in each of the groups. More specially, we observed that adolescents who recovered with six months had a positive correlation between temporo-occipital connectivity and symptom severity after injury. Adolescents with lingering symptoms had the opposite trend, displaying a negative correlation between temporo-occipital connectivity and symptom severity. This suggests that connectivity of the temporal occipital cortex may be indicative of long-term concussion recovery. In addition, we found that age at the time of injury may contribute to variation in connectivity in the temporal occipital cortex, showing that older adolescents who did not resolve their concussion with six months had greater symptom severity and lower connectivity compared to their younger counterparts at recruitment. This investigation looks at brain connectivity in the context of self-reported measures of post-concussive symptoms and offers insight to the prognostic ability of measures of connectivity after injury.

While our population included only adolescents, the results are comparable to those seen in adults. Similar to the negative relationship between connectivity and symptom severity reported

here, one study found that lower whole-brain connectivity in adults was related to worse symptom severity (Churchill et al., 2018). Looking more closely at specific network connectivity, one study reported that, much like our present study, the connectivity of the DMN but not the CEN was a biomarker for persistent post-concussion syndrome (van der Horn et al., 2017). Another study found increased within-network connectivity of the DMN in adults with concussion compared to healthy controls but the connectivity of the medial prefrontal cortex specifically was negatively related to symptoms such as fatigue, depression and anxiety (Zhou et al., 2012).

The above studies also highlight the prefrontal cortex as a region-of-interest, post-concussion. They reveal that the superior and inferior frontal cortices were specifically related to concussion severity reporting (Churchill et al., 2018) and the medial prefrontal cortex was inversely correlated with symptoms such as fatigue, depression and anxiety (Zhou et al., 2012). The association between lower frontal connectivity and worse concussion symptoms may suggest poorer executive functioning and emotion regulation, both of which are functions centralized to the prefrontal cortex (Bach, Happe, Fleminger, & Powell, 2000; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Because the frontal cortex undergoes developmental changes during adolescence including the proliferation of synapses until puberty, followed by cortical thinning (O'Donnell, Noseworthy, Levine, & Dennis, 2005) and synaptic pruning (Blakemore & Choudhury, 2006), the long-term effects of concussion during adolescence on the maturation of the connectivity of the frontal cortex and DMN warrants further investigation. One theory suggests that increased connectivity of the medial prefrontal cortex is a compensatory response to the injury to aid in neurocognitive tasks, and that the long-term usage of frontal regions may prolong post-concussion symptoms (Zhou et al., 2012).

The temporo-occipital and inferior temporal cortices may be other regions of interest for future research in concussion. We found that these regions may be early predictors of concussion recovery in adolescents, as shown by the opposing relationships between connectivity and symptom scores in the two groups. The different trends could also be an indicator of different strategies employed by the two groups to compensate for the injury. The temporo-occipital and inferior temporal cortices have been reported in other studies as areas showing early signs of traumatic brain injury (Czerniak et al., 2015; Lipton et al., 2013).

Interestingly, activity in the left inferior temporal gyrus has been reported to be negatively correlated with the anterior aspect of the DMN (Uddin, Kelly, Biswal, Xavier Castellanos, & Milham, 2009). Co-activation of the inferior temporal gyrus region with the DMN might suggest more widespread recruitment of brain regions as another potential compensatory mechanism following concussion. In fact, research suggests that the DMN is modular in its activity such that certain cognitive tasks (*e.g.*, autobiographical recall) activate the different regions of DMN (Spreng, 2012). This hypothesis suggests that the inferior temporal cortex might be activated more specifically in autobiographical recall and self-other reflection tasks (Fuentes-Claramonte et al., 2019), and thus these functions may be impacted following concussion.

Age at the time of injury may also contribute to within and between the network connectivity of the DMN. Here we found an age-related influence on concussion recovery. During adolescence, the brain consolidates networks such that there is greater connectivity within a network than between networks (Stevens, Pearlson, & Calhoun, 2009), thus younger adolescents may be more likely to engage additional brain regions in the DMN. From our results we suggest that younger adolescents have greater likelihood of over-recruiting regions of the temporal lobe compared to older adolescents. Hyperconnectivity in younger adolescents and hypoconnectivity in

older adolescents may each be a compensatory mechanism employed by different age groups in reaction to their injury.

Exploring the change in network connectivity from injury to follow-up revealed no significant effects. These results are similar Mayer et al. who were unable to detect a change in functional connectivity across a 4-month recovery time in adults in the DMN (Mayer et al., 2011); however, both our study and Mayer et al. were limited in sample size (n=14 to 16). Other longitudinal studies have found similar non-significant effects of time on the overall functional connectivity of resting state following concussion (Meier, Bellgowan, & Mayer, 2017; van der Horn et al., 2017). However, when investigating changes in local connectivity across time (by measuring the connectivity of a specific region relative to neighbouring regions), researchers noted significant changes in connectivity after one week compared to one day after injury (Meier et al., 2017).

Our inability to detect changes may also be due to the heterogeneity of development in children and adolescents since adult studies have shown trackable changes in connectivity through concussion recovery. One study with adults found changes in the connectivity of the DMN across recovery was more pronounced in the acute stages of the injury (Zhu et al., 2015). Another study found that decreases in functional connectivity within the DMN one year after injury (Acqua et al., 2017). This might indicate that adolescents have greater between-subject variability in response to concussion compared to adults and may require an even larger sample size to characterize group-level changes in connectivity.

In addition to the impact of concussion on connectivity, our study also addresses the high prevalence of children and adolescents experiencing one or more concussion symptoms at least 6 months following injury (51%). This is higher than prevalence of post-concussion syndrome rates reported in adults (Rose et al., 2015; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009), but

falls within the expected rates for children (Barlow et al., 2017; Eisenberg, Meehan, & Mannix, 2014). Research in this area is crucial as prolonged recovery may be associated with adverse mental health conditions in both children and adults (Deshpande et al., 2019; Stein et al., 2019).

3.4.1 Limitations

The current study was limited by a small sample size, but the number of participants falls within the average number of participants reported in previous MRI concussion studies in youth. The window of time between injury and the first MRI visit was also variable between participants, which will change the stage of recovery of each participant at the time of MRI scanning. The length of time between injury to the first scanning session was marginally significantly different between resolvers and non-resolvers, suggesting that non-resolvers might have been sampled from adolescents already struggling to recover from their concussion at the time of recruitment. Lastly, we used a conservative method of identifying participants with long-term post-concussive symptoms (the non-resolver group). With a lack of standardized methods of measuring post-concussive syndrome (Voormolen et al., 2018), participants were considered to have persisting symptoms if a minimum of one symptom persisted at any level of severity above zero past six months. This measurement was based on the participant's report of symptoms and thus, we are reliant on self-examination rather than a clinical judgement of impairment. We controlled for this by asking participants to rate their symptoms prior to the injury and to state whether they felt this symptom impacted their everyday life.

3.5 Conclusions

We evaluated the association between within-network connectivity and concussion symptom severity in adolescents. We reported three main findings: (1) the connectivity of the superior frontal gyrus and medial prefrontal cortex was negatively associated with symptom severity indicating that more severe concussion symptoms correlated with lower frontal connectivity, (2) connectivity in the temporo-occipital and inferior temporal cortex shows an interaction effect between groups such that adolescents with persisting concussion symptoms showed an anticorrelation between symptom severity scores and connectivity at the time of recruitment (and vice versa for adolescents who recovered within six months), and (3) the age at the time of injury may influence connectivity of the DMN to the temporo-occipital and inferior temporal regions. These results may contribute to both clinicians and researchers alike in the development of future evidence-based concussion management protocols.

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Chapter 4

Hippocampal and cerebellar connectivity

Abstract

Introduction: The hippocampus is susceptible to concussion, a biomechanical insult (DeRidder et al., 2006) which can lead to oxidative stress and neuronal death (Cho et al., 2013). The functions of the hippocampus are widespread across many cognitive functions (Poppenk et al., 2013) and it is involved in sensory integration needed for neurocognitive activities like spatial navigation and spatial memory (Bates & Wolbers, 2014). Disruption to normal signaling of either the anterior or posterior division of hippocampus can result in many of the symptoms typical of concussion. Although the hippocampus is involved in multiple functions and has high susceptibility to biomechanical brain injury, it is not well studied in concussion populations, with even fewer studies in pediatrics. *Methods*: 33 adolescents (10-18 years old, 11 males, 22 females) with a current concussion diagnosis were recruited and were assessed using Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Lovell et al., 2000) followed with resting state fMRI. ImPACT is a computerized test created to detect neurocognitive deficits in individuals with concussion through 4 composite scores: verbal memory, visual memory, visuomotor speed, and reaction time. Analyses were performed with the CONN Toolbox v20b (Whitfield-Gabrieli & Nieto-Castanon, 2012). ImPACT scores were correlated with whole-brain ROI-to-ROI analysis

using non-parametric cluster-level inference analysis, threshold free cluster enhancement with a connection threshold of p-FWE < 0.05. *Results:* Whole-brain ROI-to-ROI analysis evaluating the effect of each ImPACT neurocognitive score revealed that reaction time correlated with 38 connections. The posterior hippocampus accounted for 6 of these connections, such that longer response time was associated with higher connectivity between the posterior hippocampus to the cerebellum and posterior parahippocampus. *Conclusions:* Greater posterior hippocampus connectivity to the cerebellum was significantly related to longer reaction times. As the posterior hippocampus is broadly involved in self-referential processes (Guterstam et al., 2015), and the anterior cerebellum is broadly involved in processing sensorimotor information (Schmahmann, 2000), increased connectivity between these two structures is suggested to reflect a compensatory method to promote integration of internal and external cues. Thus, longer reaction times on ImPACT tasks, as we report here, could be related to the dysfunctional integration of signals between the posterior hippocampus and anterior cerebellum.

4.1 Introduction

Concussion leads to an array of cognitive, emotional, somatic, and sleep disruptions. Some specific symptoms include difficulties with working memory, sustained attention, balance, loud sounds and bright lights, and spatial navigation (McCrory et al., 2013; Saluja et al., 2015). Pediatric concussion is particularly challenging since the brain is undergoing active functional and morphometric changes. A concussion during this time of rapid growth may disrupt the many developmental processes taking place, especially in the subcortical regions (Wierenga et al., 2014) which are particularly susceptible to biomechanical forces (Cullen et al., 2016; DeRidder et al., 2006).

During adolescence, the brain shows both volumetric and functional changes in regions which are involved in regulating emotion, memory, and movement such as the hippocampus, amygdala, pallidum, caudate, and putamen (Blakemore & Choudhury, 2006; Daugherty et al., 2017; Uddin et al., 2010; Wierenga et al., 2014) Since these changes are involved in higher order cognitive processes and multi-sensory integration (Pendl et al., 2017), physical insult to the developing connections can lead to deficits in neurocognitive performance.

The hippocampus is one structure that is particularly vulnerable to biomechanical forces (DeRidder et al., 2006). It has a protracted development from childhood to adulthood with non-uniform volumetric and functional development between the anterior and posterior subdivisions (Blum et al., 2014; Giedd et al., 1996; Gogtay et al., 2006; Tang et al., 2020; Xiao et al., 2018).

Additionally, the hippocampus has a biochemical make-up that contributes to its vulnerability. The hippocampus has a high level of excitatory neurotransmitter receptors—as needed for memory formation (Bashir et al., 1993; DeRidder et al., 2006)—and exhibits elevated neuronal excitability following traumatic brain injury (Reeves et al., 1995). While the molecular structure of the hippocampus allows the hippocampus to display synaptic plasticity during development (Lasley & Gilbert, 2000) and adult neurogenesis (Deisseroth et al., 2004), excessive neuroexcitation which often occurs following concussion (Giza & Hovda, 2011) can lead to oxidative stress and neuronal death in the hippocampus (Cho et al., 2013; Hicks et al., 1993)

Studies on college athletes demonstrate that a wide-range of hippocampal abnormalities are observed post-concussion. College athletes exhibit a dose-response relationship between hippocampal volume and concussion history, where smaller hippocampal volume is associated with a greater number of concussions (Meier et al., 2021), and, similarly, with a greater number of years playing football (Singh et al., 2014). Athletes in impact-prone player positions also show lower

hippocampal volumes, specifically in the posterior subdivision (Parivash et al., 2019). From a functional viewpoint, college athletes display functional hyperconnectivity post-concussion between the hippocampus and a number of regions including the prefrontal cortex (Militana et al., 2016) middle and posterior cingulate cortex (Meier et al., 2017), and cerebellum (Cassoudesalle et al., 2021). An animal study has shown that even one concussion can lead to increased functional connectivity between the hippocampus and cerebellum (Kulkarni et al., 2019).

Hippocampal functional connectivity in pediatrics following concussion is much less studied. One study noted that children with concussion between ages 10-17 years did not perform statistically different from healthy controls in a navigational memory task but had increased activation of the left hippocampus, suggesting a compensatory overactivation of the hippocampus to sustain performance (Saluja et al., 2015). Further developmental studies on the impact of concussion on the developing hippocampus are needed.

While typically known for its role in memory (Daugherty et al., 2017), the hippocampus receives input from both cognitive and sensory parts of the brain. It is functionally connected to several regions of the frontal cortex and actively participates in memory recall, inhibitory control processes, and novelty detection (Poppenk et al., 2013). The functional and volumetric trajectories across development are dissociable between the anterior and posterior subdivisions as well (Dalton et al., 2019; Langnes et al., 2020). While there is functional overlap between the anterior and posterior subdivisions, the anterior hippocampus is more involved in global representations (Brunec et al., 2018a; Poppenk et al., 2013) such as map-like representations of spaces (Zeidman & Maguire, 2016), and memory of novel scenes (Poppenk et al., 2010); and the posterior hippocampus is known for fine-grain details (Brunec et al., 2018b; Poppenk et al., 2013) such as local details like landmarks to allow for spatial navigation (Woollett & Maguire, 2011). Disruption to normal

signaling of either division of hippocampus could result in many of the symptoms typical of concussion; however, it is not well studied in pediatric concussion populations.

To further develop our understanding of how concussion impacts the developing brain, we employed a region-to-region connectivity model in adolescents experiencing concussion. We compared whole-brain functional connectivity in adolescents experiencing concussion to adolescents without a history of concussion, and evaluated the relationship between functional connectivity and cognitive function in adolescents with concussion. To address the lack of research surrounding the hippocampus connectivity following pediatric concussion, the anterior and posterior subdivisions of the hippocampus were included in the analysis. In concordance with the literature identifying cognitive and somatosensory functions of the hippocampus, we hypothesized that whole-brain connectivity will reveal between the hippocampus and its functionally associated areas would be associated with neurocognitive performance scores. Secondly, we hypothesized that anterior and posterior divisions of the hippocampus will have separable connections displaying altered connectivity compared to healthy controls.

4.2 Methods

This was a prospective cohort study following children and adolescents with post-concussive injury. The study was approved by the Hamilton Integrated Research Ethics Board and all participants (including parents and guardians) gave informed consent and assent prior to participation.

4.2.1 Participants

34 adolescents with a current concussion diagnosis between the ages of 10-18 years were recruited from the longitudinal concussion study. The concussion had to have occurred within two months of recruitment and the adolescent had to be experiencing post-concussive symptoms. Adolescents were excluded if they had a diagnosis of moderate to severe brain injury requiring intensive care, developmental delay, or if they were asymptomatic by the time of testing. A small sample of healthy controls (n = 8) between ages 14-18 years old (mean = 15.3, SD = 1.5) who had no history of concussion were used to investigate differences in whole-brain connectivity between participants with and without concussion.

4.2.2 Procedure

All participants (N = 42) were scanned using resting state fMRI. Participants with concussion (n = 33) completed the Post-Concussive Symptom Scale (PCSS; (Lovell, Collins, Podell, Powell, & Maroon, 2000) and the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) following recruitment. The PCSS is a commonly-used concussion symptom inventory where participants were asked to rate the severity of their symptoms on an ordinal scale from 0 to 6 on 22 post-concussion symptoms. This scale was adapted for pediatric populations and has been reported to be a valid and reliable measure of post-concussion symptoms. Parents or guardians of participants with concussion also completed the parent-version of the PCSS. All symptom scores were collected at the time of recruitment.

ImPACT is a computerized test created to detect neurocognitive deficits in individuals with concussion. The test contains a series of tasks to obtain four composite scores: Verbal Memory,

Visual Memory, Visuomotor Speed, Reaction Time. Two additional scores (Impulse Control Cognitive Efficiency Index) are calculated to determine validity of the test performance. These scores are computed by the ImPACT software. ImPACT has normative data with age- and sex-matched controls to enable sideline measurement of concussion detection in athletes (Iverson et al., 2005). Each composite score is calculated using relevant aspects of a series of cognitive tests. Verbal Memory is based on memory performance from three tests (Word Memory, Symbol Match, Three Letters). Visual Memory combines correct answers on two tests (Design Memory, X's & O'x), Visual Motor Speed measures the total correctly selected items on two tests (X's & O's, Three Letters). Reaction Time averages correct response times on three tests (X's & O's, Color Match, Symbol Match). Lower Reaction Time scores corresponds to better performance. Impulse Controls sums commission errors across two tests (X's & O's, Color Match). Cognitive Efficiency Index describes the tradeoff between average correct scores on two tests (X's & O's, Symbol Match) compared to average speed of responses. ImPACT has shown to have good sensitivity to detecting performance abnormalities following concussion (Schatz & Sandel, 2013) with high validity (Iverson et al., 2005; Maerlender et al., 2010; Schatz & Sandel, 2013) and reliability scores (Schatz & Ferris, 2013).

For the purposes of this study, the four composite scores (Verbal Memory, Visual Memory, Visual Motor Speed, Reaction Time) were used to determine cognitive correlates of functional connectivity in participants with concussion. ImPACT was completed at a testing room as close to the injury as possible.

4.2.3 MRI parameters & pre-processing

Resting state functional imaging was performed in a 3-Tesla magnetic resonance imaging (MRI) scanner with a 32-channel radiofrequency receiver coil (General Electric Healthcare, Milwaukee, WI). The scanning procedure included a 3-plane localizer and ASSET calibration followed by a 3D T1-weighted anatomical image (TE = 4.25 ms, TR = 11.36 ms, flip angle = 12 o, image matrix = 256 x 256, slice thickness = 1 mm, FOV = 256 x 256 mm), and a 6-minute EPI resting state scan (TE = 35 ms, TR = 2000 ms, temporal points = 180, flip angle = 90o, image matrix = 64 x 64, slice thickness = 3 mm, FOV = 220 x 220 mm, 35 slices).

The default CONN Toolbox v20b (Whitfield-Gabrieli & Nieto-Castanon, 2012) pre-processing pipeline was conducted including: realignment and unwarping of EPI scans in SPM12 to correct for motion and fieldmap inhomogeneities (Andersson et al., 2001); segmentation of functional and structural images to skull-strip and normalize the images (Ashburner & Friston, 2005); transformation and registration of functional and anatomical images into MNI 152 space, smoothing of functional images using a spatial convolution with a Gaussian kernel of 8 full-width at half-max (FWHM), as recommended by(Mikl et al., 2008) to improve the signal-to-noise ratio and, thereby, signal sensitivity. Finally, denoising was conducted through the regression of motion and physiological artifacts (Behzadi et al., 2007; Friston et al., 1996); and temporal band-pass filtering [0.008-0.09 Hz] (Hallquist et al., 2013).

4.3.4 Functional connectivity analysis

Analyses were performed in CONN Toolbox v20b (Whitfield-Gabrieli & Nieto-Castanon, 2012). Whole-brain ROI-to-ROI correlation connectivity matrices were obtained by computing the

bivariate correlation coefficients between each pair of ROI timecourse series, and then performing a Fisher transformation on the correlation coefficients.

The ROIs were predefined using the Harvard-Oxford atlas, as distributed by FSL Software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). The two hippocampal ROIs (left/right) from the Harvard-Oxford atlas were replaced with four hippocampal partitions (left/right, anterior/posterior), as generated by (Fan et al., 2016) and shown in Figure 4.1. These four ROIs are used to evaluate the dissociative connectivity of the hippocampal divisions. A total of 134 ROIs (8911 connections) were used in this ROI-to-ROI analysis.

To investigate correlates of neurocognitive performance and functional connections in participants with concussion, the four ImPACT composite scores were used: Verbal Memory, Visual Memory, Visual Motor Speed, and Reaction Time. An outlier detection test (Grubb's test) was first conducted on all neurocognitive performance scores. ImPACT scores were correlated with whole-brain ROI-to-ROI analysis using non-parametric cluster-level inference analysis, threshold free cluster enhancement (TFCE) with a connection threshold of p-FWE < 0.05 (Smith & Nichols, 2007).

To explore differences between adolescents with a current concussion and adolescents with no concussion history in functional connectivity, participants with concussion (n = 34) were compared to a sample of healthy controls (n = 8) using a whole-brain ROI-to-ROI analysis was performed using parametric multivariate analysis with cluster-level inferences (Jafri et al., 2008) and a cluster threshold of p-FDR < .05 and a connection threshold of p-uncorrected < .05.

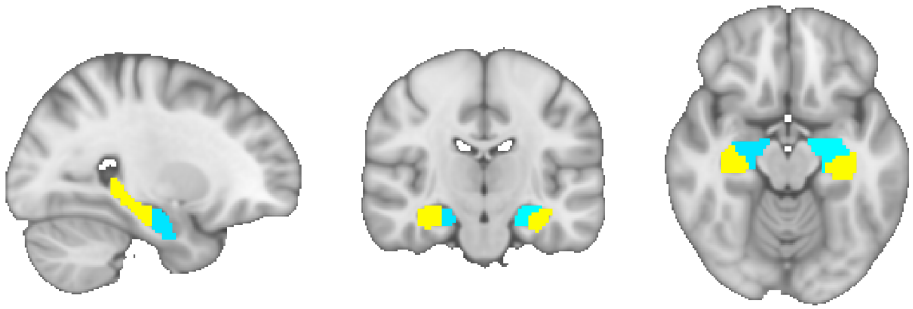


Figure 4.1. The anterior and posterior hippocampal subdivisions (Fan et al., 2016)

4.3 Results

4.3.1 Participants

An outlier detection test (Grubb's test) was performed on each ImPACT composite score, revealing one outlier score in Visual Memory, Reaction Time, Impulse Control and Cognitive Efficiency Index. Thus, this participant was removed from all analyses. Table 4.1 summarizes demographic information from the remaining participants (n = 33). Supplementary data reveal the results from the full sample without outlier removal (n = 34).

Table 4.1. Demographics of participants with concussion at recruitment

Demographic	
N	33
Sex N (%)	
Male	11 (33.3%)
Female	22 (66.6%)
Age in years mean (SD)	13.9 (2.4)
Mechanism of injury N (%)	
Sport / Recreational play	22 (33.3%)
Non-sport-related fall	7 (21.2%)
Motor vehicle accident	0
Assault	3 (9.1%)
Other	1 (3.0%)
Post-concussion symptom scale (max score 132) mean (SD)	
Participant rating	47.0 (22.1)
Parent rating	47.2 (28.2)
Days from injury to scan mean (SD)	52.2 (53.1)

4.3.2 Neurocognitive performance

Compared to normative data (Iverson et al., 2006), participants with concussion (n = 33) performed between the 15th to 42nd percentile ranks on average. Average scores for Verbal Memory (mean = 41.7th percentile, SE = 6.3) and Visual Memory (mean = 34.1th percentile, SE

= 5.2) were classified as "average". Average scores for Visual motor speed (mean = 21.2th percentile, SE = 3.5) and Reaction Time (mean = 15.3th percentile, SE = 2.5) were classified as "below average", as shown in Table 4.2 and Figure 4.2.

Table 4.2. ImPACT performance scores on adolescents with concussion (n = 33)

Composite score	Average Composite Score mean (SE)	Average Percentile Rank mean (SE)	Performance classification
Verbal memory	81.7 (2.1)	41.7 (6.3)	Average
Visual memory	69.9 (2.1)	34.1 (5.2)	Average
Visual motor speed	29.1 (1.0)	21.2 (3.5)	Below Average
Reaction time	0.72 (0.01)	15.3 (2.5)	Below Average

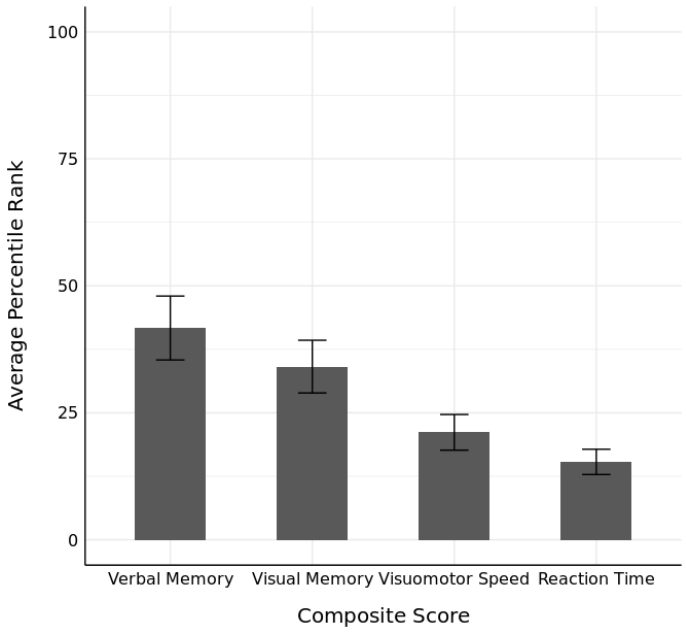


Figure 4.2. Average percentile rank for each ImPACT composite score (n = 33)

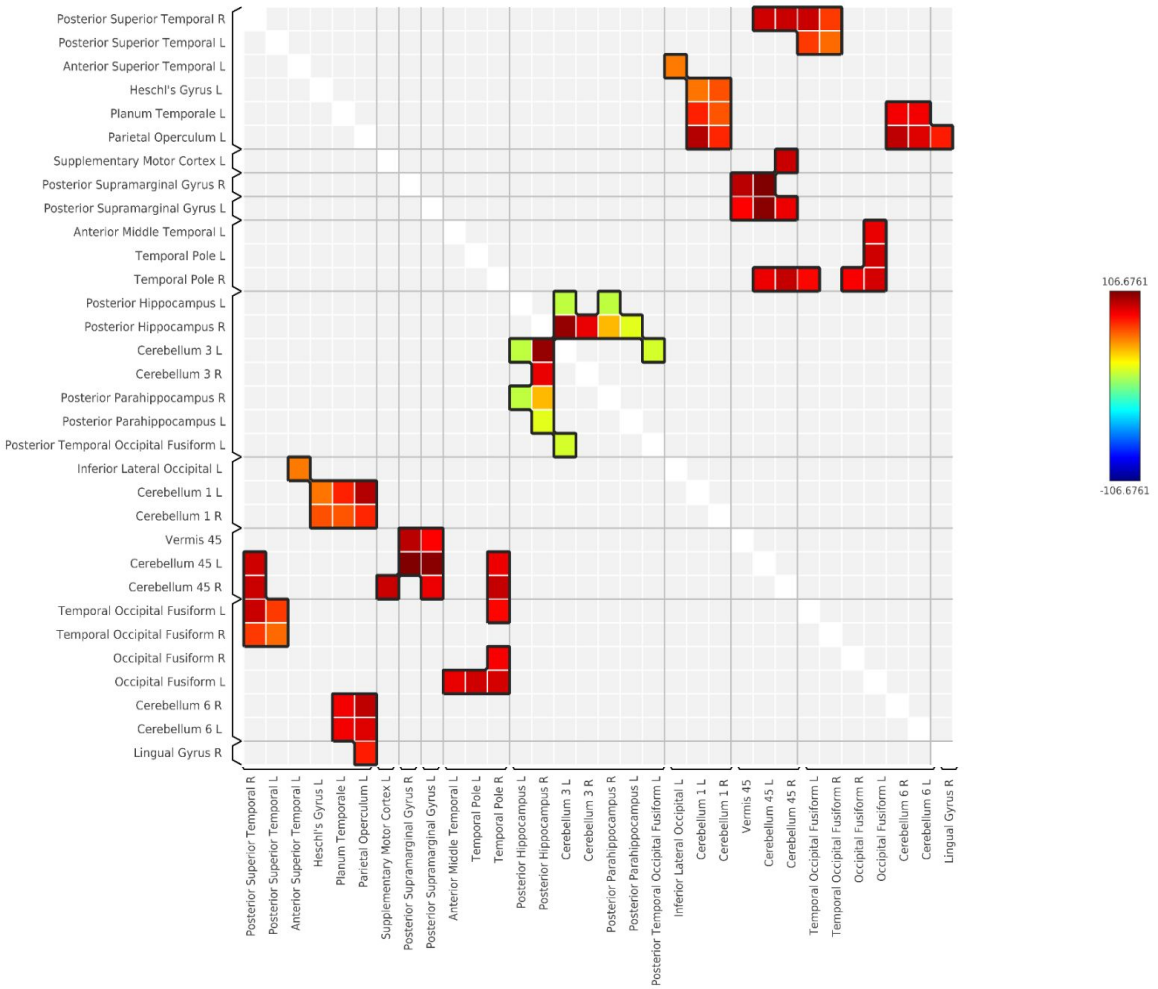
4.3.3 Connectivity correlates of neurocognitive performance

The whole-brain ROI-to-ROI analysis evaluating the relationship between each of the four ImPACT composite scores and connectivity in participants with concussion (n = 33) revealed that Reaction Time performance correlates with 38 connections, as shown in Table 4.3. The posterior hippocampus accounted for 6 of these connections, as displayed in Figure 4.3, such that longer response times was associated with higher connectivity between the posterior hippocampus to the cerebellum and posterior parahippocampus. The other three ImPACT composite scores did not yield significant connections.

Table 4.3. Connections significantly correlated with Reaction Time composite score in adolescents with concussion (n = 33)

Hub	Connection	Statistic T(31)	*p*-unc	*p*-FWE
Cluster 1 TFCE = 106.68			5.00E-05	0.002597
Supramarginal gyrus (posterior) L	Cerebellum 4-5 L	4.24	0.000187	0.10224
	Cerebellum 4-5 R	3.36	0.002084	0.188032
	Vermis 4-5	3.23	0.002923	0.188032
Supramarginal gyrus (posterior) R	Cerebellum 4-5 R	4.37	0.00013	0.10224
	Vermis 4-5	3.8	0.000635	0.134719
Supplementary motor cortex	Cerebellum 4-5 R	3.67	0.000903	0.156582
Cluster 2 TFCE = 102.73			6.20E-05	0.027
Posterior hippocampus L	Cerebellum 3 L	2.06	0.047582	0.34148
	Posterior parahippocampus R	2.01	0.053186	0.354746
Posterior hippocampus R	Cerebellum 3 L	5.87	2.00E-06	0.015818
	Cerebellum 3 R	5.26	1.00E-05	0.040743
	Posterior parahippocampus R	3.79	0.000644	0.134719
	Posterior parahippocampus L	2.69	0.01141	0.231157
Cerebellum 3 L	Temporal fusiform (posterior) L	2.43	0.020902	0.273459
Cluster 3 TFCE = 95.91			1.00E-04	0.038
Parietal operculum L	Cerebellum Crus 1 L	4.91	2.80E-05	0.04918
	Cerebellum Crus 1	3.6	0.000982	0.156582
Planum temporale L	Cerebellum Crus 1 L	3.69	0.000849	0.156582
	Cerebellum Crus 1 R	3.13	0.003819	0.188032
Heschl's gyrus L	Cerebellum Crus 1 R	3.19	0.003227	0.188032
	Cerebellum Crus 1 L	2.81	0.00854	0.216189
Superior temporal gyrus (anterior) L	Lateral occipital cortex L	2.73	0.010365	0.224182
Cluster 4 TFCE = 92.74			0.000117	0.043
Parietal operculum L	Cerebellum 6 R	4.17	0.000229	0.10224
	Cerebellum 6 L	3.77	0.00068	0.134719
	Lingual gyrus R	3.17	0.003454	0.188032
Planum temporale L	Cerebellum 6 L	3.54	0.00126	0.165464
	Cerebellum 6 R	3.52	0.001345	0.165464
Cluster 5 TFCE = 92.15			0.00012	0.044
Temporal pole L	Cerebellum 4-5 R	3.98	0.000386	0.131573
	Cerebellum 4-5 L	3.27	0.002605	0.188032

	Temporal occipital fusiform L	2.94	0.006148	0.203987
Cluster 6 TFCE = 90.8			0.000133	0.045
Superior temporal gyrus (posterior) L	Temporal occipital fusiform L	3.25	0.00276	0.188032
	Temporal occipital fusiform R	2.76	0.009643	0.222866
Superior temporal gyrus (posterior) R	Cerebellum 4-5 R	4.22	0.000195	0.10224
	Temporal occipital fusiform L	4.22	0.000196	0.10224
	Cerebellum 4-5 L	4.18	0.000221	0.10224
	Temporal occipital fusiform R	3.25	0.002796	0.188032
Cluster 7 TFCE = 90.46			0.000136	0.046
Temporal pole L	Occipital fusiform L	3.67	0.0009	0.156582
	Occipital fusiform	3.55	0.001263	0.165464
	Occipital fusiform R	3.08	0.004339	0.195863
Middle temporal gyrus (anterior) L	Occipital fusiform L	3.31	0.002376	0.188032



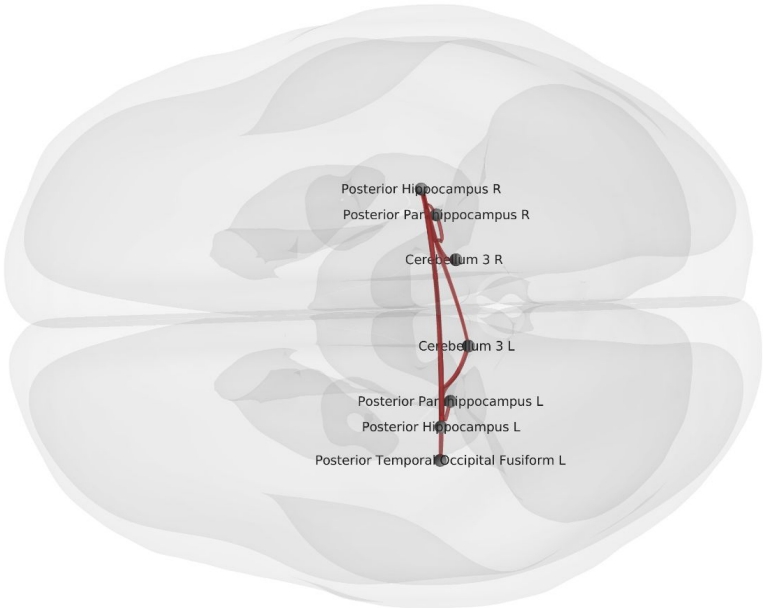


Figure 4.3. a. Connections with significant correlations with Reaction Time composite score in adolescents with concussion (n = 33). b. A depictions of the specific connections to the hippocampus (n = 33)

4.3.4 Connectivity differences compared to healthy controls

The whole-brain ROI-to-ROI analysis comparison between healthy controls and participants with concussion revealed several connections that were statistically different (Table 4.4 and Figure 4.4). In total, there were 37 connections where connectivity was significantly different between the two groups, of which 33 connections showed greater connectivity in participants with concussion. Both the anterior and posterior hippocampus subdivisions had greater connectivity to subcortical structures in participants with concussion, namely the putamen, pallidum, and insula (Table 4.5).

Table 4.4. Significant connections revealing differences in connectivity between adolescents with concussion and healthy controls (concussion > healthy controls) based on ROI-to-ROI connectivity

Hub	Connection	Statistic T(40)	*p*-unc	*p*-FDR
Cluster 1 F(2,39) = 10.47			0.00023	0.039315
Putamen R	Posterior hippocampus R	5.79	1.00E-06	0.000125
	Posterior hippocampus L	4.88	1.70E-05	0.001147
	Posterior parahippocampus R	3.07	0.003866	0.073462
	Posterior parahippocampus L	2.83	0.007298	0.11267
Putamen L	Posterior hippocampus R	3.01	0.004539	0.100612
	Posterior hippocampus L	3.42	0.001472	0.04896
	Posterior parahippocampus R	2.83	0.007184	0.119432
	Posterior parahippocampus L	2.45	0.018608	0.190373
Pallidum R	Posterior hippocampus R	3.72	0.000606	0.080635
	Posterior hippocampus L	2.71	0.009864	0.300633
	Posterior parahippocampus L	2.59	0.013237	0.300633
	Posterior parahippocampus R	2.58	0.013562	0.300633
Pallidum L	Posterior hippocampus R	3.00	0.004615	0.061384
	Posterior parahippocampus L	3.07	0.000652	0.02889
	Posterior parahippocampus R	3.45	0.001349	0.04371
	Posterior hippocampus L	3.25	0.002355	0.044742
Insula R	Cerebellar vermis 3	-2.86	0.006749	0.88952
Insula L	Cerebellar vermis 3	-3.32	0.001938	0.170254
SMA R	Cerebellar vermis 3	-2.15	0.037593	0.964295
Cluster 2 F(2,39) = 9.35			0.000481	0.041145
Putamen R	Amygdala R	3.75	0.000559	0.021352
	Anterior hippocampus L	3.7	0.000642	0.021352
	Amygdala L	3.11	0.003447	0.073462
Putamen L	Amygdala R	3.11	0.003431	0.091275
	Amygdala L	3.83	0.000442	0.029415
	Anterior hippocampus R	2.73	0.009304	0.128944
	Anterior hippocampus L	3.52	0.001108	0.04896
Pallidum R	Anterior hippocampus L	2.47	0.017718	0.322351
	Amygdala R	2.07	0.045315	0.502239
Pallidum L	Anterior hippocampus R	2.59	0.013233	0.109996
	Anterior hippocampus L	4.65	3.50E-05	0.004244
	Amygdala R	3.37	0.001694	0.04371

	Amygdala L	4.47	6.40E-05	0.004244
Insula R	Amygdala L	2.53	0.015286	0.88952
	Anterior hippocampus L	2.37	0.022913	0.88952
Insula L	Amygdala L	2.19	0.034406	0.543415
	Anterior parahippocampus L	-2.16	0.036562	0.543415
SMA L	Amygdala R	2.11	0.041269	0.884852

Table 4.5. Significant differences in functional connectivity comparing adolescents with concussion and healthy controls (concussion > healthy controls) specific to hippocampal subdivisions

Subdivision	Connections $p < .05$ FDR-corrected	
Posterior hippocampus		
Left	Putamen	L, R
	Pallidum	L, R
Right	Putamen	L, R
	Pallidum	L, R
Anterior hippocampus		
Left	Putamen	L, R
	Pallidum	L, R
	Insula	R
Right	Putamen	L
	Pallidum	L

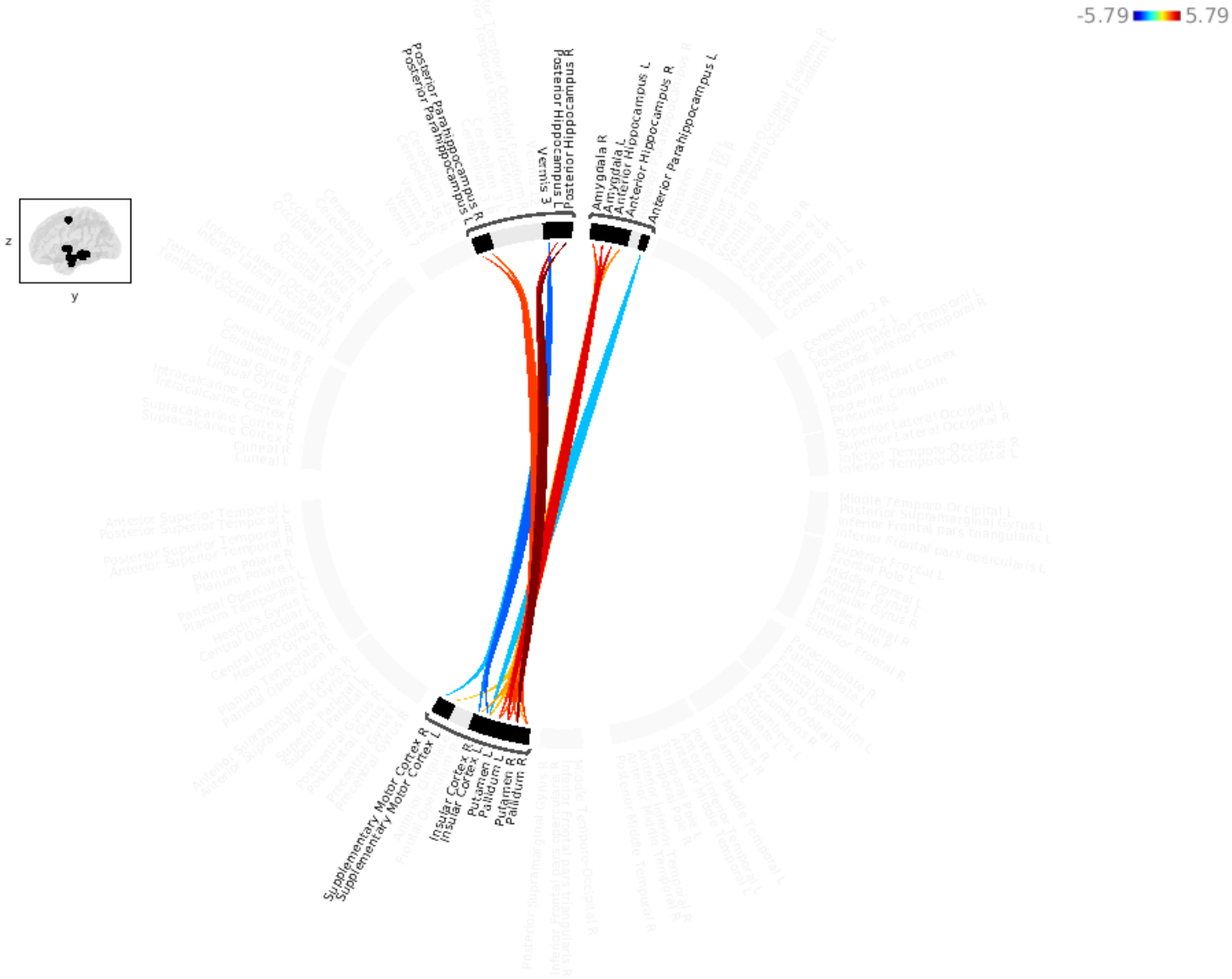


Figure 4.4. Whole-brain ROI-to-ROI analysis comparing adolescents with concussion (n = 34) to healthy controls (n = 8) (concussion > healthy controls).

4.4 Discussion

In this study, we investigated how concussion impacts the connectivity between regions across the whole brain. We hypothesized that concussion would impact the neurological processes of the hippocampus based on previous research demonstrating abnormalities in structure and function following traumatic brain injury (DeRidder et al., 2006; Militana et al., 2016; Singh et al., 2014).

4.4.1 Reaction time correlates

Given the hippocampal involvement in both motor and cognitive processes (Poppenk et al., 2013), we identified regions associated with performance within the group of participants with concussion. ImPACT, a concussion-sensitive battery of neurocognitive tasks, computes four composite scores of cognition including verbal and visual memory, visuomotor processing, and reaction time (Iverson et al., 2005; Schatz et al., 2006). Reaction Time was the only composite measure that revealed a significant correlation to resting state connectivity. This study showed that greater connectivity between the posterior hippocampus to the cerebellum and posterior parahippocampus was correlated with longer reaction times. In other words, participants with slower reaction times were more likely to have greater co-activation of the cerebellum and posterior parahippocampus to the posterior hippocampus during rest. Additionally, we found that the connectivity of the cerebellum was significantly correlated with slower reaction times, specifically in its connection to areas in the

temporal and parietal lobes, such as the supramarginal gyrus, supplementary motor cortex, and supervisor temporal gyrus.

These findings might suggest that, while concussion deficits may relate to functions of the hippocampus as previously hypothesized, the cerebellum is an additional area of interest in adolescents post-concussion.

The cerebellum, topographically differentiable by function with the anterior cerebellum (lobules I-V) primarily overseeing sensory processes (Arrigo et al., 2014; Schmahmann, 2000), is also known for its role in both emotion and cognition as well, particularly in the posterior axis (lobules VI-VII) (Arrigo et al., 2014; Stoodley & Schmahmann, 2010; Strata et al., 2011). Typically known for motor performance, researchers hypothesize that cerebellar fiber projections to the hippocampus support goal-directed spatial navigation (Bohne et al., 2019; Rochefort et al., 2013). The cerebellar-hippocampal interaction allows for the integration of two systems important for goal-directed navigation: the internal system encoding vestibular and self-referential processes that signal body orientation, and the external system encoding environmental cues that signal a subject's location in space (Rochefort et al., 2011).

As the posterior hippocampus is broadly involved in self-referential processes (Guterstam et al., 2015), and the anterior cerebellum is broadly involved in processing sensorimotor information (Schmahmann, 2000), increased connectivity between these two structures as shown in this study might reflect a compensatory mechanism to promote integration of internal and external cues. This may be further supported by the overall group performance on both reaction times and visuomotor speed scores which were below the average compared to a normative sample. Deficits in these behavioural domains may suggest aberrant processing of the underlying functional networks. Thus, longer reaction times and poor visuomotor speed on ImPACT tasks as reported in this study could

possibly be related to the dysfunctional integration of signals between the posterior hippocampus and anterior cerebellum.

4.4.2 Hyperconnectivity post-concussion

Additionally, this study revealed that adolescents with concussion are more likely to exhibit areas of hyperconnectivity in comparison to healthy controls. Here we reported that both the anterior and posterior hippocampal subdivisions had greater connectivity to the pallidum, putamen, and insula. The pallidum, putamen, and insula are regions involved in detecting saliency and reward (Seeley et al., 2007; Smith et al., 2011; F. Wang et al., 2020). The pallidum and putamen are also key areas of the basal ganglia. Evidence suggests that the interaction between the basal ganglia and hippocampus modulates cognitive and behavioural functions. One study suggests that the hippocampus is involved in creating and storing spatial maps while the basal ganglia is important for making decisions about how to behave in or navigate a given physical environment (Miyoshi et al., 2012), allowing for flexibility in behaviour (Atallah et al., 2004; Mizumori et al., 2009). The abnormal connectivity shown in the current study may underlie the deficits in neurocognitive performance as demonstrated by ImPACT composite scores.

While the functional connection between the hippocampus and basal ganglia is essential for navigational decision making, hyperconnectivity in the hippocampal-basal ganglia connection and their associated regions (e.g., parahippocampus, nucleus accumbens) has been linked to pain. Migraine studies revealed increased connectivity between the parahippocampus-putamen (Yuan et al., 2013) and hippocampus-cerebellum (Wei et al., 2020) during resting state in patients with migraines compared to healthy controls. Headaches, a common complaint in patients with

concussion, may also result from altered connectivity between hippocampus and basal ganglia regions.

As the hyperconnectivity hypothesis suggests, hyperconnectivity is a commonly-observed response in neuropathology (Hillary et al., 2014). It is reported in Alzheimer's disease (L. Wang et al., 2006), Autism Spectrum Disorder (Supekar et al., 2013), amnestic mild cognitive impairment (Cai et al., 2015), and moderate/severe traumatic brain injury (Bernier et al., 2017). The hyperconnectivity hypothesis suggests that this increase in functional connectivity displayed following injury may reflect an increased need for cross-regional input (Hillary et al., 2014). The increase in excitatory neurotransmitter release across the brain following concussion (Giza & Hovda, 2001) may contribute to hyperconnectivity exhibited in the current study. Upregulation of excitatory neurotransmitters can lead to abnormal function in connections involving the hippocampus in particular due to its high level of glutamate receptors (McDaid et al., 2021).

4.4.3 Limitations

This study is limited by its small and unequal sample size of healthy controls compared to participants with concussion. Age- and sex-matched healthy controls would improve the validity of the findings, particularly for an adolescent population. In addition, the time between injury and scanning is variable, thus some participants may have been further along in recovery than others. Symptom severity was captured using a self-report scale that is subject to each participant's ability to reflect on their experiences. The unique symptom profile of each participant may contribute to the variance in the population; however, only the overall score is presented as a general marker of symptom severity.

4.5 Conclusions

This study aims to explore functional connectivity of the hippocampus at rest of children and adolescents ages 10 to 18 years with a current concussion as it relates to neurocognitive performance and as it compares to healthy controls. Using a whole-brain ROI-to-ROI analysis, we found that greater posterior hippocampus connectivity to the cerebellum and posterior parahippocampus was significantly related to longer reaction times. In comparison to healthy controls, the participants with concussion had overall elevated connectivity. Most notably, the posterior and anterior hippocampus both had stronger connectivity to the putamen and pallidum compared to healthy controls. These findings suggest that the integration between hippocampus and motor-related regions may be susceptible to disruption following concussion, resulting in slower response times.

4.6 Supplementary Data

Table A. Connections significantly correlated with Reaction Time composite score in adolescents with concussion without outlier removal (n=34)

Hub	Connection	Statistic T(32)	*p*-unc	*p*-FDR
Cluster 1 F(2,31) = 17.55			8.00E-06	0.002597
Lateral occipital cortex (superior) R	Cerebellum 4-5 R	-3.9	0.00046	0.030569
	Cerebellum 4-5 L	-2.5	0.017617	0.249057
	Vermis 7	2.46	0.019368	0.249057
Lateral occipital cortex (superior) L	Vermis 7	2.7	0.011048	0.367337
	Cerebellum R	-2.11	0.042842	0.638839
Cluster 2 F(2,31) = 15.27			2.40E-05	0.003928
Cerebellum 10 R	Lateral occipital (inferior) R	-4.21	0.000193	0.012838
	Lateral occipital (inferior) L	-3.39	0.001859	0.061817
	Occipital pole R	-2.47	0.019167	0.182088
	Occipital pole L	-3.16	0.003431	0.077288
Cerebellum 10 L	Lateral occipital (inferior) R	-5.12	1.40E-05	0.00185
	Lateral occipital (inferior) L	-4.14	0.000235	0.015608
	Occipital pole R	-2.58	0.01482	0.216349
	Occipital pole L	-3.29	0.002467	0.082037
Brain stem	Lateral occipital (inferior) R	-3.37	0.001996	0.053087
	Lateral occipital (inferior) L	-2.43	0.020949	0.116878
	Occipital pole L	2.59	0.013237	0.300633
Temporal Fusiform (anterior) R	Lateral occipital (inferior) R	-3.09	0.004149	0.050167
Temporal Fusiform (posterior) R	Lateral occipital (inferior) L	-2.56	0.015387	0.18639
	Lateral occipital (inferior) R	-2.54	0.016068	0.18639
Temporal Fusiform (posterior) L	Lateral occipital (inferior) R	-2.63	0.012942	0.19709
Cluster 3 F(2,31) = 10.9			0.00026	0.02813
Posterior hippocampus R	Anterior hippocampus R	3.79	0.000626	0.016654
	Anterior hippocampus L	4.12	0.000247	0.01094
	Anterior parahippocampus L	2.8	0.008616	0.069047
Posterior parahippocampus R	Posterior hippocampus R	6.08	1.00E-06	0.000113
	Posterior hippocampus L	4.13	0.000242	0.008045
	Anterior hippocampus R	3.42	0.00171	0.020678

	Anterior hippocampus L	3.87	0.000507	0.01275
Posterior parahippocampus L	Posterior hippocampus R	3.9	0.000463	0.027237
	Posterior hippocampus L	3.55	0.001232	0.032776
	Posterior parahippocampus R	2.99	0.005284	0.087075
	Anterior hippocampus L	2.32	0.027085	0.200129
Anterior hippocampus R	Anterior hippocampus L	3.25	0.002738	0.044104
Anterior parahippocampus L	Anterior hippocampus L	2.07	0.046329	0.267905
Cerebellum 3 R	Posterior hippocampus R	-2.16	0.036562	0.543415
	Posterior hippocampus L	2.57	0.014857	0.295418
	Cerebellum 3 L	2.21	0.034032	0.47833
Cerebellum 3 L	Posterior hippocampus R	4.15	0.000226	0.030121
	Posterior hippocampus L	2.8	0.008625	0.26094
Cluster 4 F(2,31) = 9.97			0.000454	0.03444
Cerebellum 4-5 R	Posterior hippocampus R	2.68	0.011489	0.08042
	Posterior hippocampus L	4.25	0.000172	0.01609
	Posterior parahippocampus R	2.75	0.009839	0.0655
	Posterior parahippocampus L	2.82	0.008258	0.091526
	Anterior hippocampus R	2.17	0.037705	0.21003
	Anterior hippocampus L	3.16	0.003426	0.05696
	Anterior parahippocampus R	2.3	0.028408	0.208356
	Anterior parahippocampus L	2.42	0.021152	0.175829
	Cerebellum 3 R	3.08	0.004249	0.134211
Cerebellum 4-5 L	Posterior hippocampus R	3.1	0.004039	0.041324
	Posterior hippocampus L	3.01	0.005054	0.112032
	Posterior parahippocampus R	2.41	0.022042	0.119085
	Posterior parahippocampus L	2.86	0.007334	0.08868
	Anterior hippocampus R	3.06	0.004447	0.049287
	Anterior hippocampus L	3.64	0.000953	0.025356
	Anterior parahippocampus L	2.56	0.015265	0.145014
Cerebellum 3 L	Cerebellum 4-5 R	2.61	0.013734	0.26094
Cerebellum 3 L	Cerebellum 4-5 L	2.66	0.012166	0.26094
Vermis 4-5	Posterior hippocampus R	2.1	0.043306	0.205705
	Posterior hippocampus L	2.43	0.020978	0.232503
	Anterior hippocampus R	2.31	0.027581	0.185401
	Anterior hippocampus L	2.39	0.023159	0.225145
Cluster 5 F(2,31) = 9.51			0.000603	0.03444
Vermis 3	Posterior hippocampus R	3.34	0.002116	0.025584

	Posterior hippocampus L	2.63	0.013049	0.192839
	Posterior parahippocampus R	3.5	0.001395	0.02062
	Posterior parahippocampus L	2.9	0.006728	0.08868
	Anterior hippocampus R	4.48	9.00E-05	0.012008
	Anterior hippocampus L	4.75	4.10E-05	0.005517
	Anterior parahippocampus R	3.47	0.001517	0.049933
	Anterior parahippocampus L	3.31	0.002313	0.066025
Vermis 12	Posterior hippocampus R	3.36	0.002029	0.025584
	Posterior hippocampus L	3.03	0.004835	0.112032
	Posterior parahippocampus R	2.77	0.009343	0.0655
	Posterior parahippocampus L	2.69	0.011382	0.114043
	Anterior parahippocampus L	2.24	0.032243	0.204206
Cluster 6 F(2,31) = 9.41			0.00064	0.03444
Brain stem	Posterior hippocampus R	3.14	0.003635	0.056377
	Posterior parahippocampus R	3.82	0.000575	0.02322
	Posterior parahippocampus L	2.95	0.005892	0.058012
	Anterior hippocampus R	3.27	0.002545	0.056377
	Anterior hippocampus L	3.81	0.000594	0.02322
	Anterior parahippocampus R	3.04	0.004709	0.056377
	Anterior parahippocampus L	2.82	0.008092	0.063308
	Cerebellum 3 R	2.05	0.048131	0.200042
	Cerebellum 3 L	2.52	0.016896	0.112358
Cerebellum 10 R	Posterior hippocampus R	2.61	0.0138	0.167285
	Posterior parahippocampus R	2.21	0.034186	0.220274
	Posterior parahippocampus L	2.06	0.047646	0.233874
	Anterior hippocampus L	2.05	0.048823	0.233874
	Anterior parahippocampus R	2.6	0.013836	0.167285
	Anterior parahippocampus L	2.51	0.01716	0.175561
Cerebellum 10 L	Posterior hippocampus R	3.46	0.001558	0.069067
	Anterior hippocampus R	2.16	0.038063	0.361597
	Anterior hippocampus L	2.35	0.025003	0.278553
Temporal fusiform (posterior) R	Posterior parahippocampus R	2.31	0.027245	0.208152
	Anterior hippocampus R	3.15	0.003534	0.11751
	Anterior hippocampus L	2.57	0.01495	0.18639
	Anterior parahippocampus R	3.39	0.001877	0.083222
	Anterior parahippocampus L	2.61	0.013552	0.18639
Temporal fusiform (posterior) L	Anterior parahippocampus L	3.48	0.001451	0.09648

	Cerebellum 3 L	2.23	0.033016	0.286453
Temporal fusiform (anterior) R	Posterior parahippocampus L	2.05	0.048368	0.257318
	Anterior hippocampus L	3.33	0.00218	0.038844
	Anterior parahippocampus R	2.62	0.013263	0.103761
	Anterior parahippocampus L	3.5	0.001384	0.030668
	Cerebellum 3 L	2.17	0.037821	0.228643
Temporal fusiform (anterior) L	Anterior hippocampus L	2.34	0.025864	0.411813
Cluster 7 F(2,31) = 9.02			0.000817	0.03444
Temporal pole R	Posterior hippocampus R	2.79	0.008826	0.069047
	Posterior hippocampus L	2.35	0.025346	0.154028
	Posterior parahippocampus R	5.1	1.50E-05	0.000986
	Posterior parahippocampus L	3.75	0.0007	0.015521
	Anterior hippocampus R	3.02	0.004947	0.043862
	Anterior hippocampus L	2.19	0.036004	0.184173
	Anterior parahippocampus R	5.2	1.10E-05	0.000986
	Anterior parahippocampus L	3.28	0.002482	0.036681
	Cerebellum 3 R	3.07	0.004382	0.043477
	Cerebellum 3 L	3.05	0.004577	0.043477
Temporal pole L	Posterior hippocampus L	2.91	0.006445	0.085722
	Posterior parahippocampus R	2.68	0.01158	0.096255
	Posterior parahippocampus L	3.33	0.002171	0.082071
	Anterior hippocampus R	2.21	0.034342	0.207615
	Anterior hippocampus L	2.8	0.008546	0.093636
	Anterior parahippocampus R	2.77	0.009152	0.093636
	Anterior parahippocampus L	3.74	0.000723	0.082071
	Cerebellum 3 R	3.02	0.004997	0.085722
	Cerebellum 3 L	2.79	0.00882	0.093636
Middle temporal gyrus (anterior) R	Posterior hippocampus R	3.48	0.001472	0.063342
	Posterior hippocampus L	3.12	0.00381	0.063342
	Posterior parahippocampus R	3.16	0.003454	0.063342
	Posterior parahippocampus L	3.69	0.000819	0.054474
	Anterior hippocampus R	3.14	0.003659	0.063342
	Anterior hippocampus L	2.74	0.00988	0.131405
	Anterior parahippocampus R	4.05	0.000301	0.040095
	Anterior parahippocampus L	2.27	0.030077	0.249145
	Cerebellum 3 L	2.44	0.020248	0.226423
Inferior temporal gyrus (anterior) R	Anterior parahippocampus R	2.22	0.033648	0.405754
	Anterior parahippocampus L	2.76	0.009451	0.284638
Inferior temporal gyrus (anterior) L	Cerebellum 3 R	2.56	0.015548	0.476636

	Cerebellum 3 L	2.28	0.029382	0.651304
Cluster 8 F(2,31) = 8/96			0.000848	0.03444
Angular gyrus R	Middle frontal gyrus R	-3.15	0.003541	0.117734
	Frontal pole R	-3.04	0.004743	0.630826

Table B. Hippocampal subdivision connectivity associated with Reaction Time in adolescents with concussion with outlier removal (n=34)

Subdivision	Connections p < .05 FDR-corrected	
Posterior hippocampus		
Left	Posterior parahippocampus	L, R
	Temporal pole	L, R
	Anterior middle temporal	L
	Cerebellum 3	L, R
	Cerebellum 4-5	L, R
	Vermis 3, 4-5, 12	
Right	Posterior parahippocampus	L, R
	Anterior hippocampus	L, R
	Anterior parahippocampus	L
	Cerebellum 3	R
	Cerebellum 4-5	L, R
	Cerebellum 10	L, R
	Temporal pole	R
	Anterior middle temporal	R
	Vermis 3, 4-5, 12	
	Brain stem	
Anterior hippocampus		
Left	Posterior hippocampus	R
	Posterior parahippocampus	L, R

	Anterior hippocampus	R
	Anterior parahippocampus	L
	Temporal pole	L, R
	Anterior middle temporal	R
	Posterior temporal fusiform	R
	Anterior temporal fusiform	L, R
	Cerebellum 4-5	L, R
	Cerebellum 10	L, R
	Vermis 3, 4-5	
	Brain stem	
Right	Posterior hippocampus R	R
	Posterior parahippocampus	R
	Anterior hippocampus	L
	Temporal pole	L, R
	Anterior middle temporal	R
	Posterior temporal fusiform	R
	Cerebellum 4-5	L, R
	Cerebellum 10	L
	Vermis 3, 4-5	
	Brain stem	

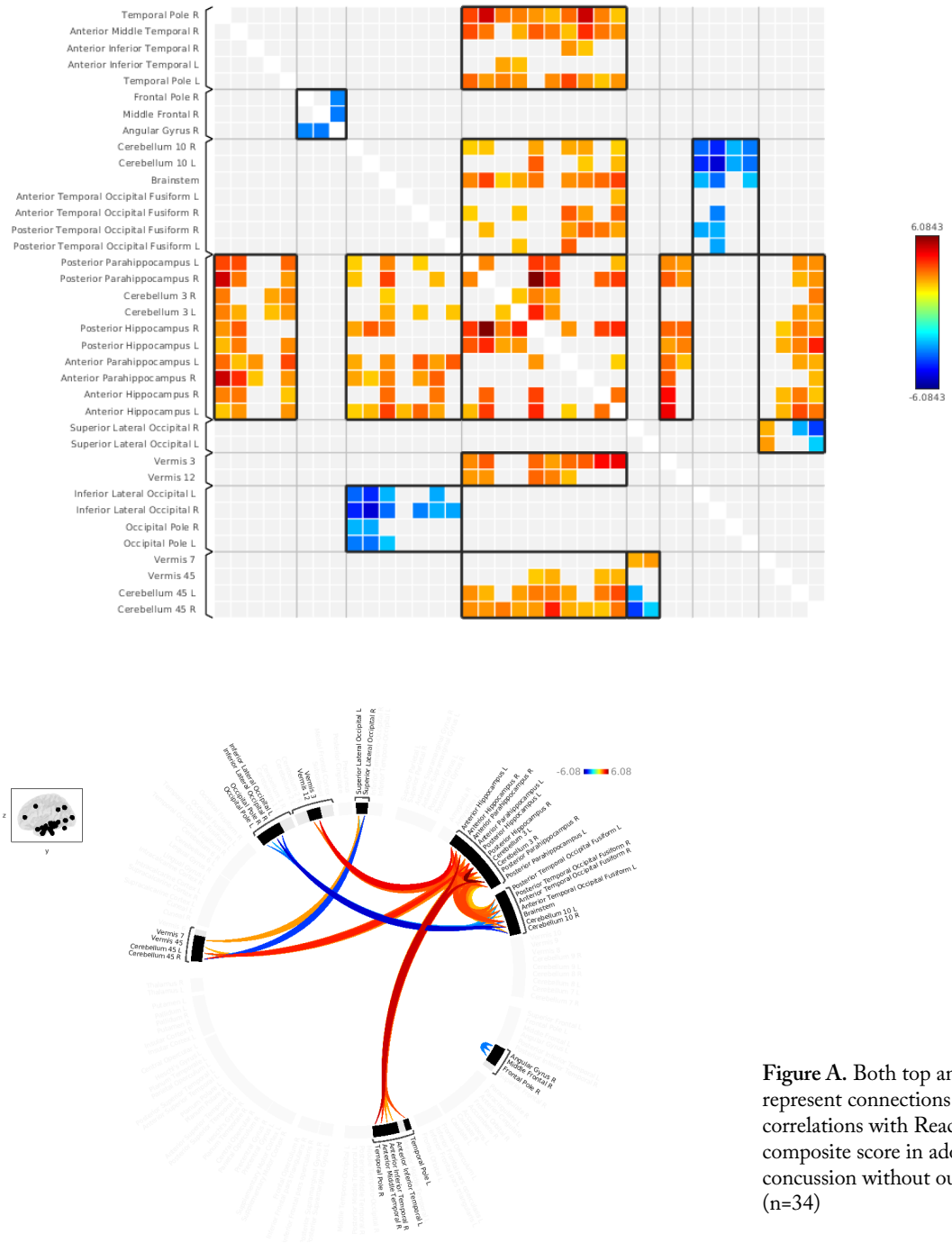


Figure A. Both top and bottom images represent connections with significant correlations with Reaction Time composite score in adolescents with concussion without outlier removal (n=34)

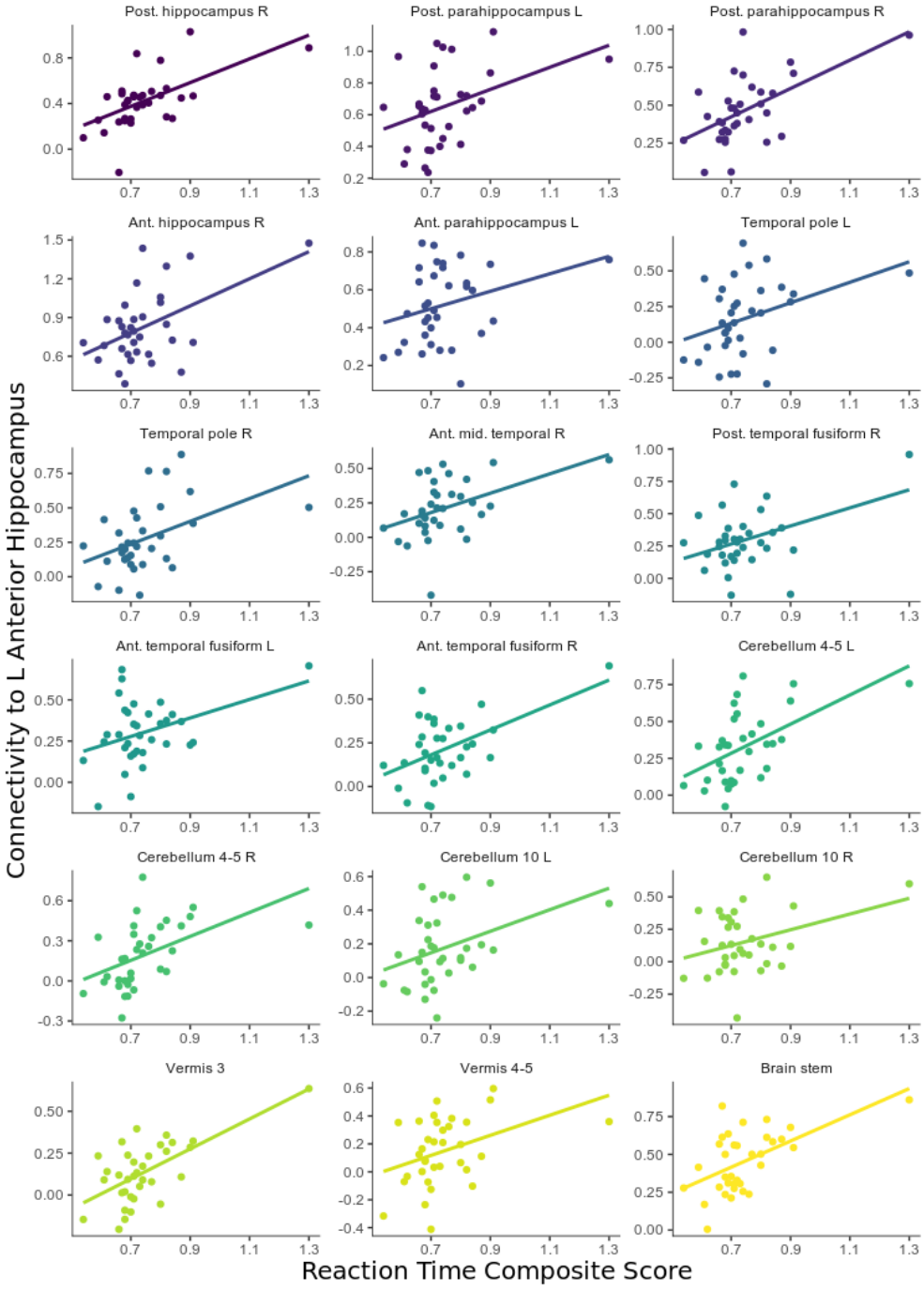


Figure B. Connectivity of the L Anterior Hippocampus in association with Reaction Time composite score (n = 34)

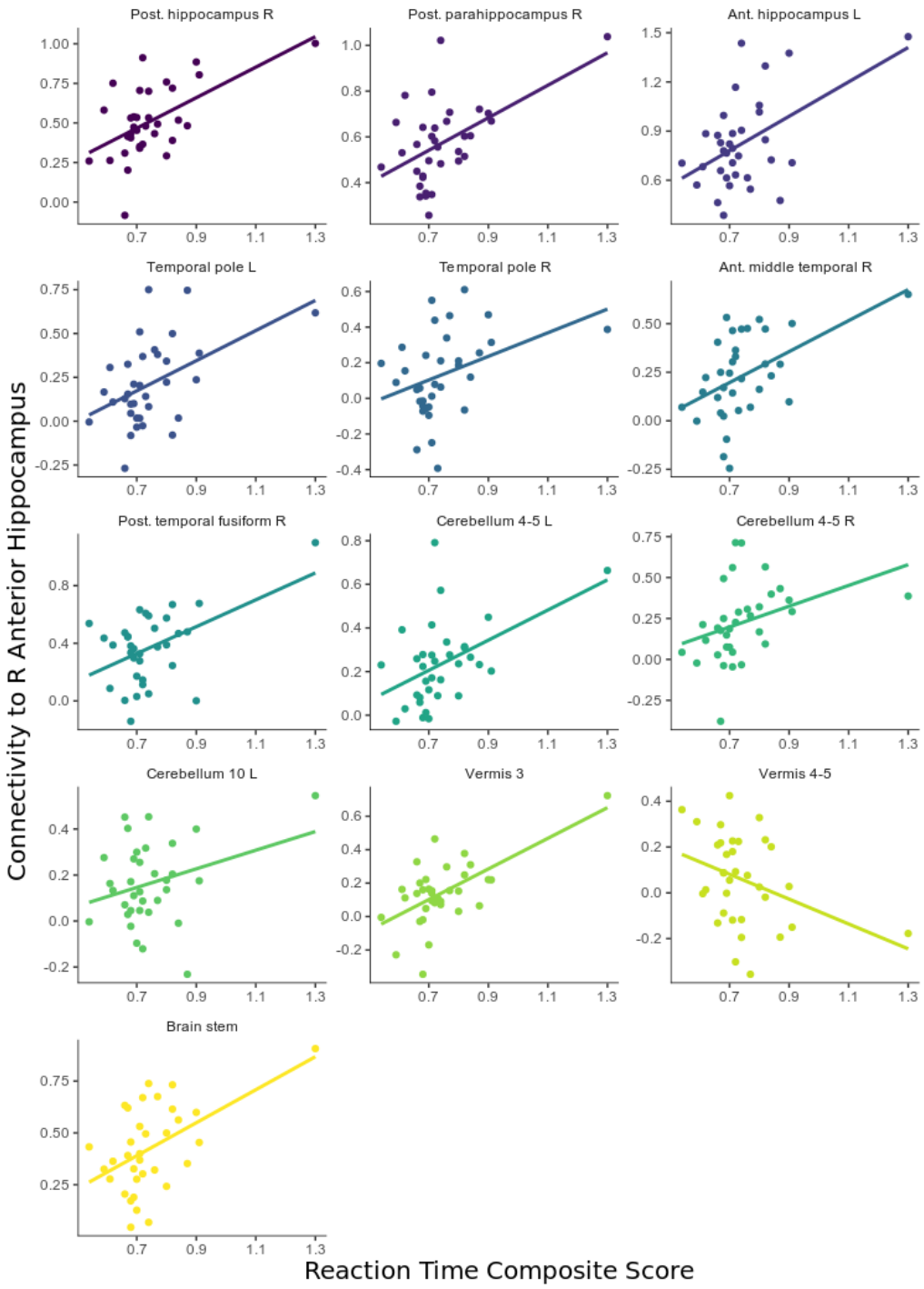


Figure C. Connectivity of the R Anterior Hippocampus in association with Reaction Time composite score (n = 34)

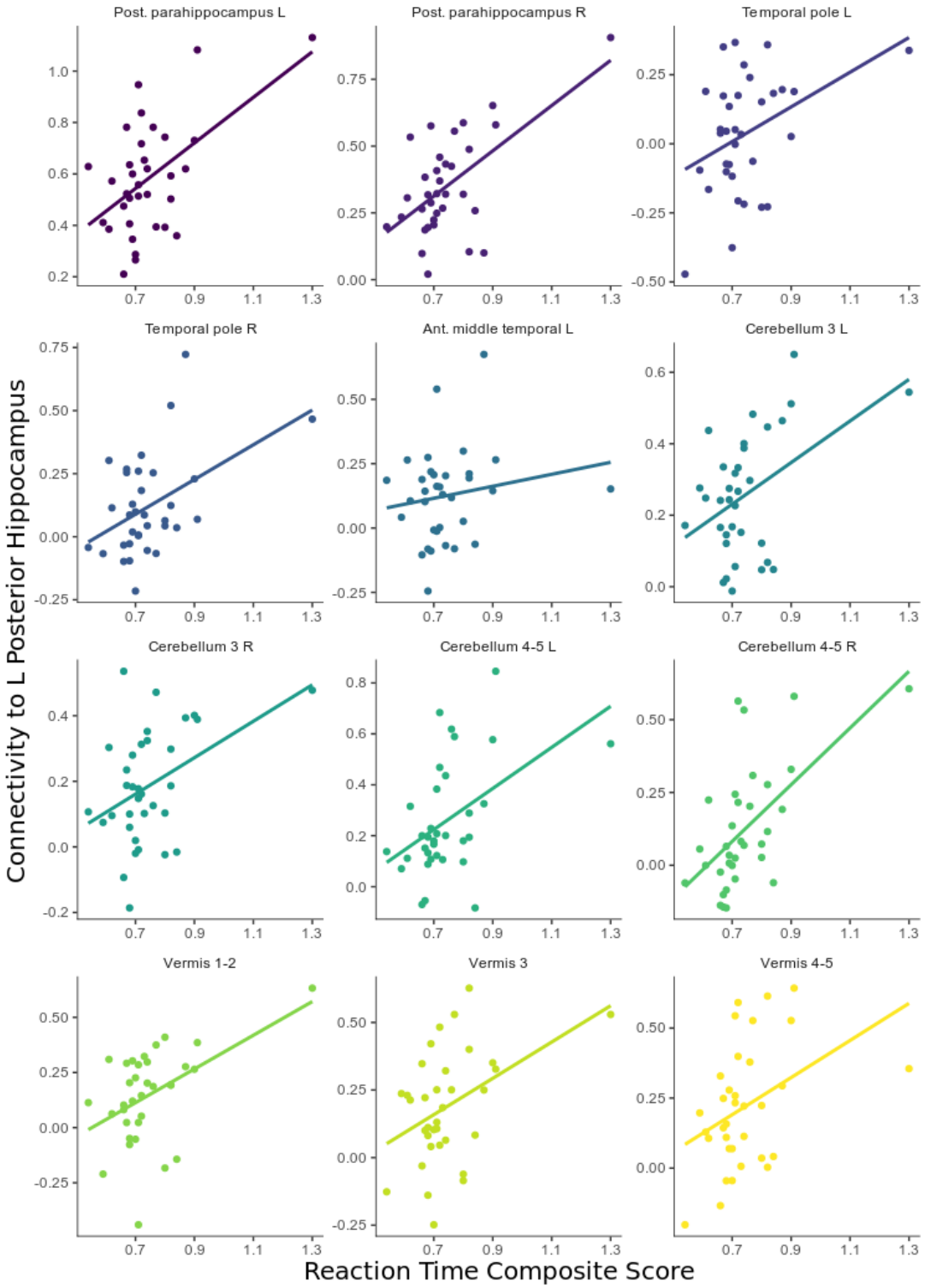


Figure D. Connectivity of the L Posterior Hippocampus in association with Reaction Time composite score (n = 34)

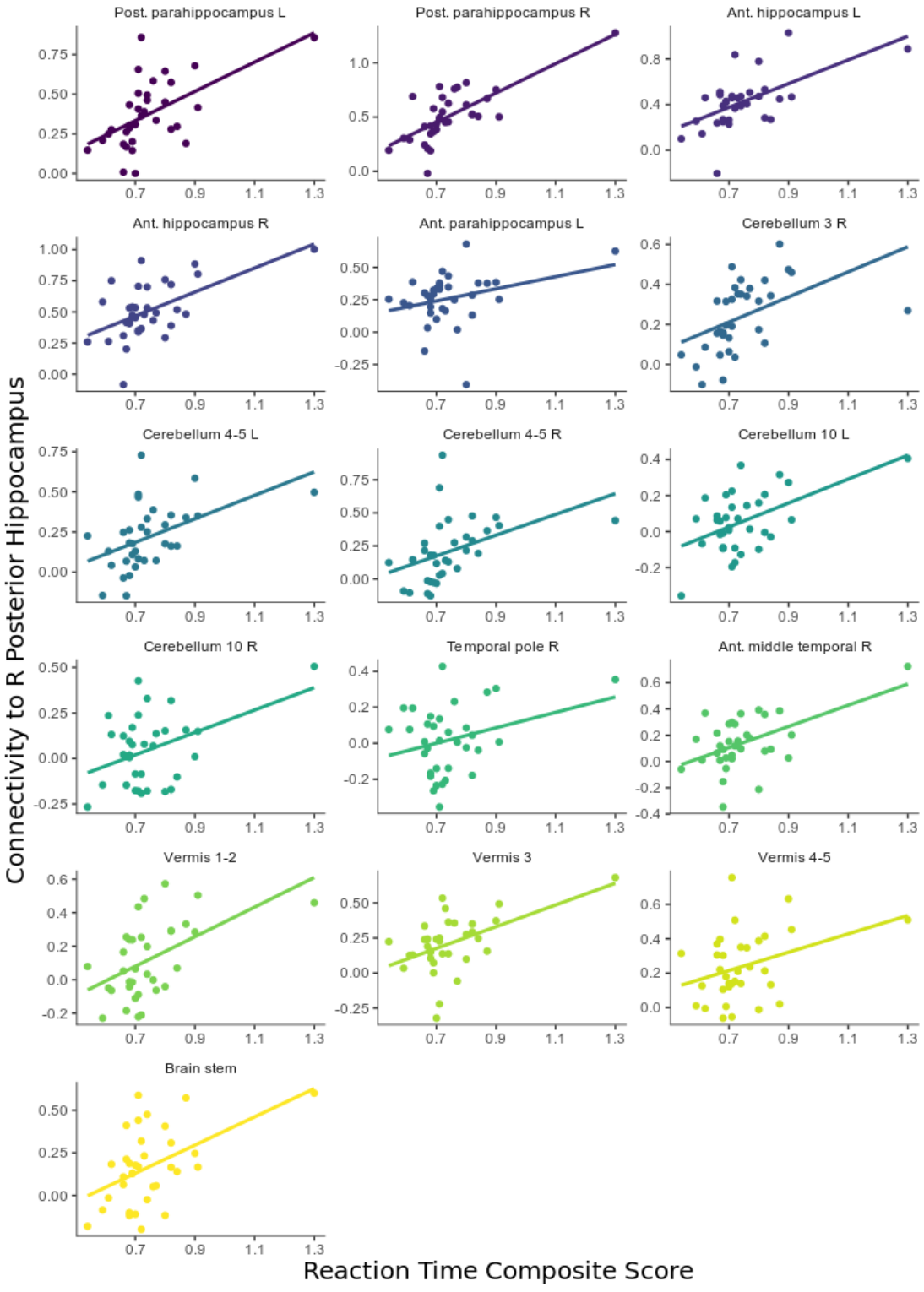


Figure E. Connectivity of the R Posterior Hippocampus in association with Reaction Time composite score (n = 34)

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Chapter 5

Dynamic network connectivity

Abstract

Introduction: Menon's triple network framework of neuropathology suggests that the default mode (DMN), salience (SN), and central executive (CEN) networks shed light on cognitive and emotional dysfunction of several neurological disorders (Menon, 2011; Menon & Uddin, 2010). Concussion, like other neuropathological disorders and conditions, may also lead to aberrant between-network connectivity in the DMN, SN and CEN (Jackson et al., 2019; Sours et al., 2013; van der Horn et al., 2016). Evidence suggests that concussion during childhood decreases the brain's ability to flexibly transition between network states (Muller & Virji-Babul, 2018); however, minimal research has specifically evaluated the dynamic connectivity of the DMN, SN and CEN in adolescents. *Methods:* Thirty-four adolescents with a concussion diagnosis underwent resting state fMRI within two months of injury. All adolescents with concussion were still symptomatic at the time of scanning. Thirty-four age-matched controls were obtained from the publicly available Autism Brain Imaging Data Exchange (ABIDE) (Di Martino et al., 2014) database from which healthy controls had no history of head trauma. Resting state analysis was conducted using CONN Toolbox 20b (Whitfield-Gabrieli & Nieto-Castanon, 2012) using a sliding window approach. Functional connectivity metrics were extracted from ROI-to-ROI and graph theory analyses.

Results: The sliding window ROI-to-ROI analysis revealed that the temporal average of functional connectivity was statistically different between groups. Participants with concussion had significantly greater connectivity between CEN-SN regions compared to controls, but significantly less connectivity within the DMN, between DMN-CEN, and between DMN-SN, relative to controls. The sliding window graph theory analysis revealed that the temporal average was statistically different between groups such that participants with concussion had significantly decreased global efficiency, cost, and degree compared to controls in the posterior cingulate cortex (PCC) of the DMN. The sliding window graph theory analysis also revealed that the temporal variability was different between groups such that participants with concussion had significantly decreased cost and degree compared to controls in the medial prefrontal cortex (mPFC) of the DMN. *Conclusion:* Following concussion, adolescents display aberrant dynamic connectivity between the default mode, salience and central executive networks, particularly in the engagement of the DMN. Dysfunction of the major nodes of the DMN (*i.e.*, PCC and mPFC) may be key to understanding deficits of the DMN, its functional dissociation from the SN and CEN, and the subsequent array of cognitive and emotional concussion symptoms in adolescents. Detecting abnormalities in functional connectivity during development may be informative of potential long-term deficits associated with concussion.

5.1 Introduction

Concussion is a biomechanical insult to the brain that can lead to a sequelae of neurobiological dysfunctions (McCrory et al., 2013). This includes abnormal neurochemical signaling that affects the activation of regions across the brain (Giza & Hovda, 2001). With diffuse abnormal neuronal

activity following concussion, brain regions that are typically activated together may lose the ability to function as a network. This may be particularly problematic for pediatric populations since the brain rapidly changes from childhood through early adulthood (Narvacan et al., 2017; Supekar et al., 2010). As each developmental advancement is a building block for another, a concussion during childhood and adolescence may interrupt network development and their behavioural functions.

Across development, brain networks undergo functional and morphological modulations at a rate that complements cognitive, emotional, and behavioural advances (Blakemore & Choudhury, 2006; Uddin et al., 2010). Magnetic resonance imaging (MRI) researchers are able to capture and characterize brain networks even in the absence of cognitive demand (Biswal et al., 1995; van den Heuvel & Hulshoff Pol, 2010). Networks measured in this manner are termed resting state networks.

While there are several resting state networks that subserve everyday functions, the default mode network, frontoparietal network, and salience network have been most commonly reported in the clinical literature (Menon, 2013). Although more commonly measured in adult populations, researchers have noted disrupted functioning in resting state networks following concussion, most notably in the default mode network (DMN) (Johnson et al., 2012; Zhou et al., 2012), lateral frontoparietal network (FNP; also known as the central executive network; task-positive network) (Ptak, 2012; Sours et al., 2013; Zanto & Gazzaley, 2013), and the salience network (SN) (Sours et al., 2013; Vasilevskaya et al., 2020). Although the majority of concussion research has involved adults, emerging evidence suggests disruptions in resting state networks children as well; however, the majority of the studies have focused on the DMN with little research on the FPN and almost none including the SN (Borich et al., 2015; Howell et al., 2013; Iyer et al., 2019).

Research suggests that these three networks work together to produce a number of cognitive tasks, including working memory, inhibitory control, and saliency detection (Bressler & Menon, 2010; Chen et al., 2013); the DMN, most prominent during rest and self-referential ideation (Buckner & Carroll, 2007; Raichle et al., 2001; Spreng et al., 2009), is suppressed during cognitively demanding tasks, whereas the FPN is activated (Chand & Dhamala, 2016; Dodds et al., 2011). The SN is proposed to function as a mediating network that facilitates the transition between the DMN and FPN by actively recruiting each network as appropriate (Chand & Dhamala, 2016; Corbetta & Shulman, 2002). The brain's ability to switch between cognitive states is associated with the interplay between these three networks (Chen et al., 2013).

In Menon's triple network of neurological dysfunction framework (Menon, 2011), the relationships between DMN, SN and FPN can shed light on how the brain functions in a number of neurological disorders and diseases including autism, schizophrenia, and mild cognitive impairment. Such neurological disorders, diseases, and injuries can lead to abnormal between-network connectivity, which is associated with cognitive and emotional dysfunction (Menon, 2011; Menon & Uddin, 2010). Concussion, like other neuropathological disorders and conditions, may also result in aberrant between-network connectivity in the DMN, SN and FPN (Jackson et al., 2019; Sours et al., 2013; van der Horn et al., 2016). An exploration on the effects of concussion on these three networks still remains, especially since the majority of this research is done in adults.

As these networks are not static, researchers have begun to evaluate not only the between-network relationships between the DMN, FPN and SN, but also their dynamic relationships. In fact, the brain is continuously modulating through transient states during rest (Ryali et al., 2016). Research on dynamic connectivity can measure how networks transition across the duration of a resting state scan, providing information about which networks are most dominant, how networks

are recruited or suppressed, and where neurological disorders and diseases may have the greatest effect on brain function (Menon, 2011). From the research to-date, evidence suggests that concussion during childhood decreases the brain's ability to flexibly engage and disengage from different networks as needed to transition between cognitive states (Muller & Virji-Babul, 2018). More studies are needed to study the dynamic relationship between the DMN, FPN and SN in concussion in children and adolescents.

To better understand Menon's triple network model as it pertains to concussion, we evaluated the dynamic functional connectivity of the default mode network, salience network, and frontoparietal network in children with concussion compared to age-matched controls using functional MRI. Using a sliding window model, we evaluated the changes in connectivity between the major nodes of our three networks of interest. To further explore the relationship between the DMN, SN and FPN, we used graph theory to assess the organization of all three networks, which can determine not only that any two regions are connected, but also how they are connected.

5.2 Methods

5.2.1 Procedures

This study was approved by the Hamilton Integrated Research Ethics Board. All participants gave their informed consent prior to enrolment in the study. On the day of assessment, participants were given the opportunity to try the mock scanner before scanning. In the MRI scanner, participants were instructed to lie awake and keep their eyes open. A fixation cross was presented on a screen

for participants to look at for the duration of the resting state scan. Participants were told to think of nothing in particular. Scanning took place as close to the injury as possible.

Post-concussion symptoms were measured using the Post-Concussion Symptom Scale (PCSS), a 22-question self-report survey of symptoms (Lovell et al., 2006). The PCSS is a reliable and valid measure of post-concussion symptoms.

5.2.2 Participants

Thirty-four children and adolescents between the ages of 10-18 years were recruited if they had a diagnosis of a concussion by a physician, as defined by a mechanical insult to the head or body leading to neurological dysfunctions. Participants had to be symptomatic at the time of recruitment. Participants were recruited within 2 months of injury. Exclusion criteria included: (1) multiple bodily injuries, (2) recovery of symptoms prior to testing, (3) injury occurred more than 8 weeks prior to recruitment, and (4) diagnosis of a severe developmental delay.

Thirty-four age-matched controls were obtained from the publicly available Autism Brain Imaging Data Exchange I (Di Martino et al., 2014) database. The scans were taken from the sample collected by the University of Michigan, from which healthy controls had no history of head trauma.

5.2.3 Image acquisition and preprocessing

Resting state data for participants with concussion were collected on a 3 Telsa GE magnetic resonance imaging (MRI) scanner at the Imaging Research Centre at McMaster University, which has a 32-channel radiofrequency receiver coil (General Electric Healthcare, Milwaukee, WI). Following three routine scans, a 3D T1-weighted structural scan (TE = 4.25 ms, TR = 11.36 ms,

flip angle = 12°, image matrix = 256 x 256, slice thickness = 1 mm, FOV = 256 mm, 152 slices) and a 6-minute whole-brain resting state fMRI scan (echo planar imaging, TE = 35 ms, TR = 2000 ms, temporal points = 180, flip angle = 90°, image matrix = 64 x 64, slice thickness = 3 mm, FOV = 220 mm, 35 slices) were collected.

Healthy control data were collected on a 3 Telsa GE scanner at the University of Michigan (General Electric Healthcare, Milwaukee, WI). A 3D T1-weighted structural scan (TE = 1.8 ms, TR = 8.9 ms, flip angle = 15°, image matrix = 256 x 160, slice thickness = 1.4 mm, FOV = 260 mm, 40 slices) and a resting state scan (echo planar imaging, TE = 30 ms, TR = 2000 ms, temporal points = 300, flip angle = 90o, image matrix = 64 x 64, slice thickness = 3 mm, FOV = 220 mm, 40 slices). To match the number of temporal points of the participants with concussion, only the first 180 temporal points were used, and the remaining temporal points were discarded.

Preprocessing was conducted in CONN Toolbox version 20b (www.nitrc.org/projects/conn, RRID:SCR_009550) using the default preprocessing pipeline (Nieto-Castanon, 2020). Functional realignment and unwarping were performed, involving the co-registering and resampling of images and estimation of motion per subject (Andersson et al., 2001). Outlier identification was conducted on the global BOLD signal and motion estimates. Framewise displacement was acquired and used as a first-level covariate to control for head motion. The structural image was skull-stripped. Then structural and functional images were registered to the MNI 152 template, segmented into grey matter, white matter, and cerebrospinal fluid (Ashburner & Friston, 2005). Functional images were smoothed with a spatial convolution (8 mm FWHM Gaussian kernel). Denoising was conducted by removing potential confounds from motion, signal noise, and physiological noise using linear regression. A temporal-pass filter [0.008-0.09 Hz] was

applied to minimize the effects of motion and noise and isolate resting state slow-frequency oscillations (Hallquist et al., 2013).

5.2.4 Resting state analysis

A sliding window approach was applied to two resting state analyses using CONN Toolbox. The duration of the resting state scan was segmented into 18 windows of 30 seconds blocks at 20-second onsets. In a sliding window model, the length of the timecourse series is split into a sequence of time blocks from which the temporal variability and temporal average connectivity can be measured. Each block of time (known as a "window"), is measured separately for each individual. To evaluate the dynamic relationship between the default mode, salience, and frontoparietal networks, regions-of-interest (ROIs) within each of those networks were selected. The ROIs, generated using independent component analysis on the Human Connectome Project (HPC) dataset of 497 subjects, were provided by CONN Toolbox v20b, shown in Figure 5.1. In total, 105 connections from 15 ROIs were measured (listed in Table 5.1).

Two connectivity analyses were then conducted on these regions: a region-to-region (ROI-to-ROI) analysis and a graph theory analysis, described below.

5.2.4.1 ROI-to-ROI analysis

To evaluate dynamic functional connectivity between the DMN, SN and FPN, a windowed ROI-to-ROI analysis was performed with a group contrast to compare participants with concussion and age-matched controls. Correlation coefficients were first derived for each pair of ROIs to create an ROI-to-ROI matrix for each window. A Fisher transformation was applied to each ROI-to-ROI

matrix to generate Z-scores of the correlation coefficients. The Z-scores represent the amount of temporal coherence between ROI pairs, which serves as a metric of functional connectivity strength per window.

Temporal variability and temporal average were derived from the standard deviation and the average Z-score across all windows, respectively. Temporal variability assesses the change in functional connectivity between each pair of ROIs over time. Temporal average assesses the strength of functional connectivity between each pair of ROIs averaged across all windows. The group contrast (concussion > controls) compares whether participants with concussion had statistically different variability in functional connectivity (temporal variability), and statistically different functional connectivity (temporal average) compared to controls.

Corrections for multiple comparisons were done using parametric multivariate statistics with a cluster threshold of p-FDR < .05 (multivariate pattern analysis (MVPA) omnibus test) and a connection threshold of p-uncorrected < .05 (Jafri et al., 2008).

5.2.4.2 Graph theory analysis

To characterize the organization and efficiency of network dynamics, a windowed graph theory analysis was performed using a group contrast (concussion vs. healthy controls). The ROI-to-ROI connectivity matrix is first computed for each subject at each window separately to provide the strength of connectivity between each pair of ROIs. The ROI-to-ROI matrix is then converted into an adjacency matrix by using the Z-score of the correlation coefficients. The correlation coefficients were evaluated with a two-sided analysis thresholded at p-FDR < .05.

Adjacency matrices provide topographical information about our networks of interest. In graph theory, the selected ROIs are represented as nodes and their respective connections as edges.

By evaluating these nodes and edges of a network, we can determine the global efficiency, local efficiency, cost, degree, average path length, betweenness centrality, and clustering coefficient of a network.

Degree and cost measure the number and proportion (respectively) of all connections a particular region has that have surpassed thresholding. Clustering coefficient represents the proportion of connections a given ROI has in a sub-graph. It evaluates how connected a particular region is to neighbouring ROIs of a cluster of nodes (or a subnetwork) as a metric of local inter-connectivity. Average path length refers to the number of edges needed to connect all other ROIs to one particular node using the shortest path. Average path length provides information about how "central" a particular node is to a network, where a node with a low average path length infers that the network relies on that node to transfer information. Betweenness centrality measures how many shortest-paths pass through a particular node. A node with high betweenness centrality is facilitates information passing. Global and local efficiency refer to how well information is transferred between nodes across an entire network (global efficiency) or across a subnetwork (local efficiency). These values are calculated using the average of the inverse of all shortest-path lengths to other nodes of a network or subnetwork (Bullmore & Sporns, 2009).

Table 5.1. Regions included in resting state analyses, as provided by CONN Toolbox v20b

Network	Region	Abbreviation	Centroid Coordinates		
			x	y	z
Default mode (DMN)	Medial prefrontal cortex	mPFC	1	5	3
	Lateral parietal L	LP-L	39	77	3
	Lateral parietal R	LP-R	7	67	9
	Posterior cingulate cortex	PCC	1	61	8
Salience (SN)	Anterior cingulate cortex	ACC	0	22	35
	Anterior insula L	AI-L	44	13	1
	Anterior insula R	AI-R	47	14	0
	Rostral prefrontal cortex L	rPFC-L	-32	45	27
	Rostral prefrontal cortex R	rPFC-R	32	46	27
	Supramarginal gyrus L	SMG-L	-60	-39	31
	Supramarginal gyrus R	SMG-R	62	-35	32
Frontoparietal (FPN)	Lateral prefrontal cortex L	LPFC-L	-43	33	28
	Lateral prefrontal cortex R	LPFC-R	41	38	30
	Posterior parietal cortex L	PPC-L	-46	-58	49
	Posterior parietal cortex R	PPC-R	52	-52	45

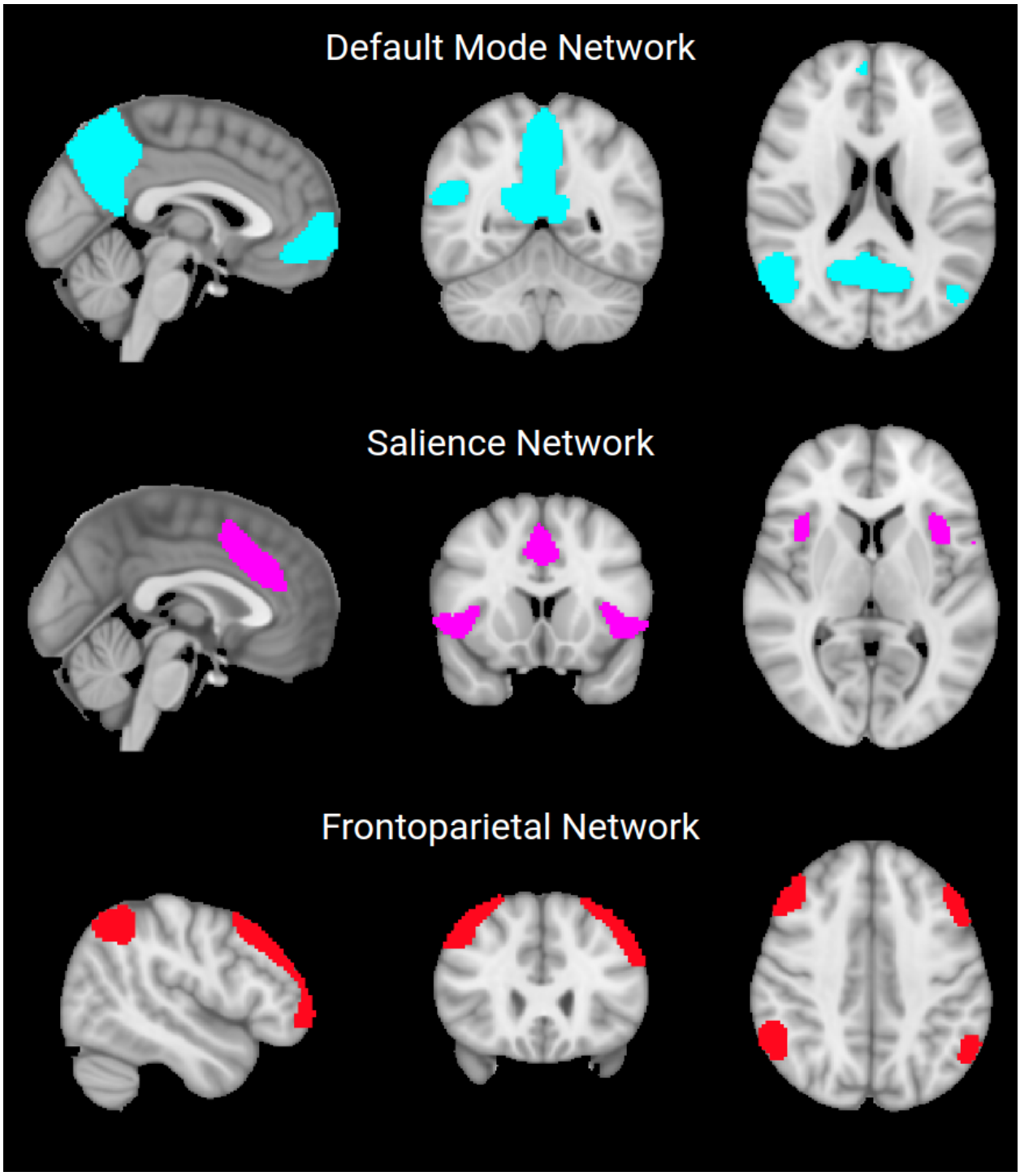

Figure 5.1. ROIs included in the DMN, SN and FPN, as provided by CONN Toolbox v20b.

5.3 Results

5.3.1 Participants

Demographics are shown in Table 5.2. Participants with concussion (22 females, 12 males) had a mean age of 13.8 ± 2.5 years. 55.9% of participants had a previous concussion (n = 19), and 14.5% reported having lost consciousness at the time of the current injury (n = 5). The median number of days from injury to scanning was 30.5 days. Age-matched controls (16 female, 18 male) had a mean age of 13.8 ± 2.7 years.

Table 5.2. Demographics of participants with concussion at recruitment

Demographic	
N	34
Sex N (%)	
Male	13 (35.3%)
Female	22 (64.7%)
Age in years mean ± SD	13.8 ± 2.5
PCSS at recruitment (max score 132) mean (SD)	47.4 ± 21.4
Loss of consciousness N (%)	
Yes	5 (14.7%)
No	22 (64.7%)
Unsure	7 (20.6%)
Participants with previous concussion(s) N (%)	
Yes	19 (55.9%)
No	15 (44.1%)
Time from injury to scan median days	30.5

5.3.2 ROI-to-ROI temporal analysis

In comparison between participants with and without concussion (concussion vs. controls), the sliding window ROI-to-ROI analysis revealed that the temporal average of functional connectivity was statistically different between groups. As shown in Figure 5.2, participants with concussion had significantly greater connectivity between FPN-SN regions compared to controls, but significantly less connectivity within DMN regions, and between DMN-FPN regions and between DMN-SN regions compared to controls.

Connections with statistically lower connectivity between DMN and SN regions included: posterior cingulate cortex to anterior cingulate cortex, posterior cingulate cortex to rostral prefrontal cortex, lateral parietal to supramarginal gyrus, and lateral parietal to anterior insula. Connections with statistically lower connectivity between DMN and FNP regions included: posterior cingulate cortex to posterior parietal cortex, posterior cingulate cortex to lateral prefrontal cortex, medial prefrontal cortex to posterior parietal cortex, medial prefrontal cortex to lateral prefrontal cortex, and lateral parietal cortex to posterior parietal cortex. Connections with statistically greater connectivity between FPN and SN regions included: posterior parietal to anterior insula, posterior parietal to rostral prefrontal cortex, lateral prefrontal cortex to anterior insula, and lateral prefrontal cortex to supramarginal gyrus. A full list of dynamic connectivity differences between groups is shown in Table 5.3. Temporal variability was not significantly different between groups.

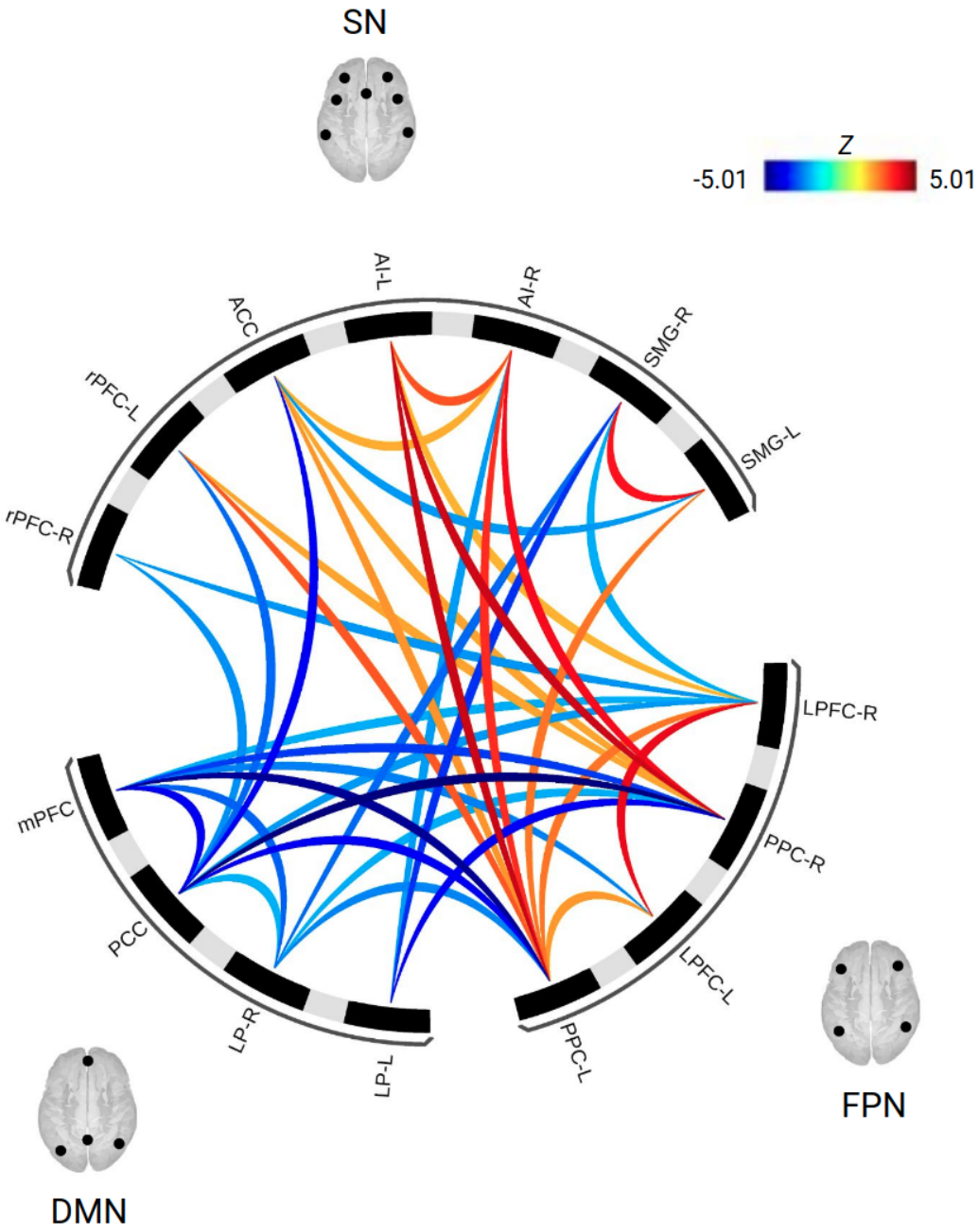

Figure 5.2. Significant connections from the ROI-to-ROI temporal average (concussion > controls) with a cluster threshold of *p*-FDR = 0.05 and connection threshold of *p*-unc. < 0.05.

Table 5.3. ROI-to-ROI temporal average between regions of the DMN, SN and FPN comparing adolescents with concussion to healthy controls (concussion > controls)

Node 1		Node 2		Statistic T(66)	*p*-unc	*p*-FDR
Network membership	Node	Network membership	Node			
Cluster 1 F(36, 64) = 11.59					0.000004	0.000022
FPN	Posterior parietal cortex L	SN	Anterior insula L	4.29	6.1E-05	0.000394
FPN	Posterior parietal cortex L	SN	Anterior insula R	3.38	0.001215	0.003949
FPN	Posterior parietal cortex L	SN	Rostral prefrontal cortex L	2.94	0.00451	0.011726
FPN	Posterior parietal cortex L	SN	Supramarginal gyrus L	2.64	0.01044	0.019389
FPN	Posterior parietal cortex R	SN	Anterior insula L	4.26	6.6E-05	0.000429
FPN	Posterior parietal cortex R	SN	Anterior insula R	3.84	0.000278	0.001206
FPN	Posterior parietal cortex R	SN	Rostral prefrontal cortex L	2.16	0.034533	0.074822
FPN	Lateral prefrontal cortex R	SN	Rostral prefrontal cortex R	-2.25	0.027603	0.091724
FPN	Lateral prefrontal cortex R	SN	Supramarginal gyrus R	-2.03	0.046132	0.091724
FPN	Lateral prefrontal cortex R	SN	Anterior insula L	2.00	0.04939	0.091724
Cluster 2 F(36, 64) = 6.29					0.000827	0.002275
DMN	Posterior cingulate cortex	FPN	Posterior parietal cortex R	-5.01	4E-06	5.7E-05
DMN	Medial prefrontal cortex	FPN	Posterior parietal cortex L	-4.72	1.3E-05	0.000166
DMN	Posterior cingulate cortex	FPN	Posterior parietal cortex L	-3.65	0.000514	0.002227
DMN	Lateral parietal cortex L	FPN	Posterior parietal cortex R	-3.65	0.000522	0.006791
DMN	Medial prefrontal cortex	FPN	Posterior parietal cortex R	-3.14	0.002521	0.010925
DMN	Medial prefrontal cortex	FPN	Lateral prefrontal cortex L	-2.48	0.015644	0.040675
DMN	Posterior cingulate cortex	FPN	Lateral prefrontal cortex R	-2.24	0.028431	0.061601
DMN	Lateral parietal cortex R	FPN	Posterior parietal cortex L	-2.43	0.017833	0.077276
DMN	Medial prefrontal cortex	FPN	Lateral prefrontal cortex R	-2.04	0.04533	0.098215

DMN	Lateral parietal cortex R	FPN	Posterior parietal cortex R	-2.02	0.047901	0.129406
Cluster 3 F(36,64) = 6.00					0.001137	0.002275
DM	Medial prefrontal cortex	DMN	Posterior cingulate cortex	-3.7	0.000446	0.002901
DN	Medial prefrontal cortex	DMN	Lateral parietal cortex R	-2.78	0.007165	0.023286
MN	Posterior cingulate cortex	DMN	Lateral parietal cortex R	-2.00	0.049772	0.092433
Cluster 4 F(36, 64) = 6.63					0.002404	0.003606
FPN	Lateral prefrontal cortex L	FPN	Lateral prefrontal cortex R	3.97	0.00018	0.002345
FPN	Posterior parietal cortex L	FPN	Lateral prefrontal cortex R	2.64	0.010353	0.019389
FPN	Posterior parietal cortex L	FPN	Lateral prefrontal cortex L	2.29	0.025354	0.036623
Cluster 5 F(36, 64) = 3.48					0.020765	0.024918
SN	Supramarginal gyrus R	SN	Supramarginal gyrus L	3.69	0.000461	0.005991
SN	Anterior insula L	SN	Anterior insula R	2.97	0.004101	0.01777
Cluster 6 F(36, 64) = 2.92					0.040455	0.024918
DMN	Posterior cingulate cortex	SN	Anterior cingulate cortex	-3.6	0.000601	0.002102
DMN	Lateral parietal L	SN	Supramarginal gyrus R	-3.21	0.002042	0.014292
DMN	Posterior cingulate cortex	SN	Rostral prefrontal cortex L	-2.7	0.008759	0.024525
DMN	Posterior cingulate cortex	SN	Rostral prefrontal cortex R	-2.31	0.024186	0.056434
DMN	Lateral parietal R	SN	Supramarginal gyrus R	-2.68	0.009298	0.065087
DMN	Lateral parietal L	SN	Anterior insula R	-2.18	0.032585	0.152062

5.3.3 Graph theory temporal analysis

When comparing participants with and without concussion (concussion > controls), the sliding windo graph theory analysis revealed that temporal average was statistically different between group such that participants with concussion had significantly decreased global efficiency (t(66) = -3.76, *p*-FDR = .005), cost (t(66) = -4.53, *p*-FDR = .0004), and degree (t(66) = -4.53, *p*-FDR = .0004) compared to controls in the PCC of the DMN.

When comparing participants with and without concussion (concussion > controls), the sliding window graph theory analysis revealed that the temporal variability was statistically different between groups such that participants with concussion had significantly decreased cost (t(66) = -3.08, *p*-FDR = .045878) and degree (t(66) = -3.08, *p*-FDR = .045878) compared to controls in the mPFC of the DMN. The global efficiency of the mPFC exhibited a trend towards a significant decrease (t(66) = -2.98, *p*-FDR = .059716) in adolescents with concussion, as shown in Table 5.4.

Table 5.4. Graph theory results comparing temporal average & temporal variability of the three networks between adolescents with concussion to healthy controls (concussion > controls)

Metric	Network membership	Node	Temporal average			Temporal variability		
			t(66)	*p*-unc	*p*-FDR	t(66)	*p*-unc	*p*-FDR
Global efficiency								
	DMN	PCC	-3.76	0.000366	.005487 *			
	SN	AI-L	2.62	0.011036	0.072082			
	DMN	mPFC	-2.51	0.014416	0.072082	-2.98	.003981	.059716
Cost								
	DMN	PCC	-4.53	0.000026	0.000383 *			
	DMN	mPFC	-2.58	0.012131	0.077715	-3.08	.003059	.045878 *
	SN	AI-L	2.46	0.016322	0.077715			
	DMN	LP-R	-2.37	0.020724	0.077715			
Average path length								
	DMN	PCC	2.98	0.004063	0.060949			
Degree								
	DMN	PCC	-4.53	0.000026	0.000383 *			
	DMN	mPFC	-2.58	0.012131	0.077715	-3.08	.003059	.045878 *
	SN	AI-L	2.46	0.016322	0.077715			
	DMN	LP-R	-2.37	0.020724	0.077715			

* *p*-FDR < .05

5.4 Discussion

Adolescence marks a period of cortical maturation, cognitive advancement, and emotional development. Concussion during adolescence can impact the underlying brain networks that subserve emotional, behavioural and cognitive performance. The current study investigated the effects of concussion on resting state network dynamisms of three large-scale networks (default mode, salience, and frontoparietal networks) on adolescents.

5.4.1 Reduced dynamic connectivity between intra-DMN nodes

Using a sliding window approach, we evaluated the fluctuations in network connectivity across a resting state scan in adolescents currently experiencing a concussion. In comparison to age-matched controls, we found that the default mode network (DMN) regions were significantly less functionally connected to other areas within the DMN. In particular, the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC) were regions of the DMN with markedly reduced dynamic connectivity. This reduced connectivity between the PCC and mPFC is associated with a less-developed DMN in healthy children and adolescents (Fair et al., 2008; Supekar et al., 2010). The cingulum, the fibre track that connects the mPFC and PCC, has a long-projected development and thus younger children show both functional and structural separation of the DMN nodes (Menon, 2013; Supekar et al., 2009).

As controls were matched in age, our results suggest that perhaps children and adolescents with slower DMN maturation trajectory may be more prone to the effects of concussion, or that concussion may impact the functional connectivity of the developing brain such that it resembles a

less mature state or delays DMN maturation. In support of the latter hypothesis, adults with traumatic brain injury (including mild, moderate and severe injuries) show lower functional integration of the DMN nodes (Bonnelle et al., 2011), which is associated with attentional deficits (Bonnelle et al., 2011; Kim et al., 2008). These findings suggest that a disconnected DMN following concussion may be a consequence of the injury.

5.4.2 Reduced inter-network connectivity between DMN and SN/FPN nodes.

In addition to the reduced connectivity within the DMN, children and adolescents with concussion also had lower connectivity between regions of the DMN and the salience network (SN) and frontoparietal network (FPN). Specifically, we found lower connectivity between the posterior cingulate cortex (PCC) of the DMN and anterior cingulate cortex (ACC) of the SN, as well as reduced connectivity between the lateral parietal of the DMN and the anterior insula of the SN. Dampened DMN and SN cross-communication following concussion may underlie the increases in cognitive and emotional issues often reported following injury. As shown in the adult literature, traumatic brain injury can impair the ability of the SN to reallocate resources from the DMN during a cognitive task, during which the DMN is typically down-regulated (Bonnelle et al., 2012; Sharp et al., 2014). Similarly, adults with concussion with lower connectivity between SN regions (specifically the anterior insula) to DMN regions were more likely to have higher levels of depression after injury (McCuddy et al., 2018). The functional disconnect between the SN and DMN might suggest that the SN is less able to communicate with the DMN.

Concussion during childhood and adolescence may have a similar effect of impairing the efficiency of the SN to flexibly transition between the DMN and FPN, as would be typically shown

under task load (Shaw et al., 2021), and in healthy individuals at rest (Corbetta & Shulman, 2002; Sridharan et al., 2008). Alterations between SN, DMN and FPN connectivity are also seen in other brain-related disorders during development (Uddin, 2015) and might also explain the higher incidence of mental health disorders in those with a history of concussion, especially post-concussion depression (Chrisman & Richardson, 2014; Kerr et al., 2012).

5.4.3 Increased inter-network connectivity between SN and FPN nodes

In fact, the results of the current study might provide evidence that, in addition to reduced DMN-SN/FPN connectivity, the SN has increased connectivity to the FPN. Heightened SN-FPN connectivity might suggest a tendency to recruit the FPN regions. This could imply a hypervigilant state even during rest. Research proposes that the anterior insula of SN is pivotal in redirecting attention either internally to the self, or externally to the environment (Corbetta & Shulman, 2002; Menon & Uddin, 2010), after which attention is sustained by the structures of DMN and FPN, respectively (Menon & Uddin, 2010). Increased SN-FPN connectivity following concussion might indicate a greater reliance on executive processing through the FPN to detect and process sensory stimuli from the external environment (Whitfield-Gabrieli et al., 2011). We interpret this dependence on external stimuli as compensation for the weakened connectivity between the SN-DMN, which is associated with poorer internal, self-referential processing in healthy individuals (Doll et al., 2015), and even in individuals post-concussion (Ju et al., 2021; Ryan et al., 2017).

5.4.4 Reduced PCC dynamic connectivity and mFPC variability.

The results from our sliding window graph theory approach revealed deficits in prominent nodes of the DMN. The PCC had significantly lower global efficiency, indicating reduced ability to transfer information between the PCC and connecting regions; and lower cost and degree, signifying fewer connections to the PCC compared to healthy controls. The PCC is central to the DMN as it is integrated with every region of the DMN, meaning that every DMN node shares information with the PCC (Fransson & Marrelec, 2008). Our findings are consistent with other lines of research in clinical populations with cognitive impairments (*e.g.,* Alzheimer's disease, schizophrenia) showing a particular sensitivity of the PCC to dysfunction (Çiftçi, 2011; Du et al., 2016; Yamashita et al., 2018).

We also found that another major node of the DMN, the mPFC, had lower temporal variability in children with concussion. This might indicate a deficit in the mPFC to flexibly connect and disconnect with other nodes of the network (i.e., a more rigid network connectivity pattern). This has been previously observed in Muller and Virji-Babul (2018), in which stronger rich-club nodal strength of the middle frontal gyrus was associated with dynamic inflexibility in switching between two brain states. Rich-club nodes are described as nodes with a high degree of connections and serve as intermediary connectors within a network (van den Heuvel et al., 2012; van den Heuvel & Hulshoff Pol, 2010). Altogether, dysfunction of the important nodes like the PCC and mPFC may be key to understanding deficits of the DMN, its functional dissociation from the salience and frontoparietal networks, and the subsequent array of cognitive and emotional concussion symptoms.

5.4.5 Limitations

As pre-injury resting state scans were not collected, we are unable to determine from this study whether the participants with concussion had network configurations that were more susceptible to the effects of concussion. One study on varsity athletes evaluated pre-injury resting state connectivity and found that athletes that received a concussion shortly after their pre-injury scan (within the same season) were significantly more likely to have had elevated DMN-SN connectivity than athletes without a concussion that same season (Churchill et al., 2021). These findings suggest that perhaps the post-injury findings could be related to pre-injury network states and propose that between-network connectivity could provide information about risk of injury. The number of past injuries an individual has sustained also may contribute to long-lasting changes in connectivity, as demonstrated by aberrant connectivity between regions of the SN and corpus callosum in athletes with a history of multiple concussions (Vasilevskaya et al., 2020). Future studies could evaluate a larger sample of children and adolescents to explore the functional connectivity changes in the DMN, SN and FPN associated with the number of past injuries an individual has sustained.

Our study was also limited by the range in concussion severity and time between injury to recruitment. As our study has a median of 30 days between concussion to imaging, our sample includes individuals in the acute, subacute, and chronic phases of concussion recovery. Nonetheless, our sample is reflective of the heterogeneity of children and adolescents seeking diagnosis or treatment for concussion in the emergency rooms and health care centres. We also acknowledge that our sample of healthy controls were retrieved from a different site which may lead to site-related effects that can confound our findings.

5.5 Conclusion

In summary, we evaluated the temporal connectivity of three large-scale networks, namely the default mode network, salience network, and frontoparietal network. These results indicate that concussion not only disrupts the within-network functional connectivity; it impacts the balance between the DMN-SN-FPN is functionally disrupted following concussion. More specifically, we observed decoupling of the connectivity between the DMN and the SN and FPN, and heightened connectivity between the SN and FPN. Within-DMN connectivity was significantly reduced in children with concussion, most critically between the mPFC and PCC. Additionally, we identified two dysfunctional nodes of the DMN. Crucially, the posterior cingulate cortex had significantly reduced global efficiency, cost and degree in adolescents with concussion, pinpointing a particularly vulnerable area of concussion. These results indicate an impairment of the PCC to function with associated brain areas. The medial prefrontal cortex had significantly lower temporal variability, suggesting lower integration of the mPFC in the functions of the DMN and reduced flexibility following concussion. Overall, the study highlights global deficits in the dynamic function of three important networks in cognitive and affective domains following concussion in adolescents.

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Chapter 6:

General discussion

6.1 Introduction

The goal of this thesis was to investigate the functional connectivity profile of selected resting state networks in children and adolescents with concussion. Measuring functional connectivity evaluates the strength of communication between different regions of the brain and provides insight into the functional nature of the resting state networks. The working analogy previously described in Chapter 1 was that of an orchestra wherein the communication between the different sections of the orchestra was important to the overall performance of the orchestra. The functional connectivity within and between the resting state networks is a beneficial measure of the neurological impact of concussion. In conjunction with behavioural and clinical measures, functional connectivity can shed light on the underlining differences between different clinical subgroups of a population. With fewer concussion studies involving children and adolescents compared to adults, health guidelines and protocols were not well catered towards younger age groups.

This thesis sought to elucidate the functional neural correlates of concussion outcomes in the developing brain including post-concussion symptom severity reports, age at the time of injury, and neurocognitive performance scores. This thesis focuses on networks related to cognitive and

emotional processes as concussion often leads to mood- and cognition-related deficits in children. The current chapter offers a summary of the findings and new contributions presented in each data chapter to the field of developmental functional connectivity and pediatric concussion. consideration for future extensions of the work presented in this thesis, a theoretical discussion of neurological dysfunction of brain networks post-concussion, and a reflection of the clinical applications of the research.

6.2 Summary of results

6.2.1 Chapter 3

Chapter 3 asks two questions: Do resting state networks correlate with concussion recovery? Is the age at the time of concussion an important factor in the recovery process? The Default Mode Network (DMN) and the Central Executive Network (CEN) were the main networks investigated. As opposed to the network regions presented in Chapters 4 and 5, the regions used to define the DMN and CEN in Chapter 3 were data-driven using independent component analysis. Functional connectivity was defined as the temporal correlation between each pair of voxels within each network.

This investigation revealed that two regions of the DMN are significantly correlated with clinical data: (1) a frontal cluster, and (2) a temporal cluster. The frontal cluster was specifically located in the right superior frontal gyrus and right medial prefrontal cortex. The functional connectivity of this cluster was significantly negatively associated with symptom ratings on the Post-Concussion Symptom Scale (PCSS). The relationship between right frontal connectivity and PCSS

scores showed that individuals with more severe post-concussion symptom ratings were more likely to have lower functional connectivity.

The temporal cluster was specifically located in the left temporo-occipital gyrus and the left inferior temporal gyrus. The functional connectivity of this cluster was similarly correlated with PCSS ratings but only for participants who had long recoveries of six months or longer (the "non-resolvers", as described in Chapter 3). For the non-resolvers, the functional connectivity of the temporal cluster was negatively associated with PCSS scores, meaning that the non-resolvers with more severe post-concussion symptom ratings were more likely to have lower functional connectivity. This trend mirrors that demonstrated in the frontal cluster, regardless of the length of time. The participants who recovered within six months of recruitment (the "resolvers", as described in Chapter 3) had a different association pattern. For the resolvers, the functional connectivity of the temporal cluster was positively associated with PCSS scores, suggesting that the resolvers with more severe symptom ratings had higher functional connectivity in this region.

The temporal cluster also revealed a significant effect of age. Most notably, the non-resolver group had significantly different functional connectivity values between younger and older adolescents. In fact, the younger adolescents from the non-resolver group were not statistically different from the older or younger adolescents in resolver group. This means that the older adolescents with longer recovery times had significantly lower connectivity in the temporal region at the time of recruitment. These results indicate that the connectivity of the temporal cluster is a marker for older adolescents with poor concussion outcomes.

Overall, this chapter demonstrates that reduced connectivity in the DMN is associated with greater concussion consequences, especially in terms of severity of symptoms and length of symptoms. A critical aspect of this study was its longitudinal design and, as such, the grouping

(resolver / non-resolver) is based on recovery status at six months, but the functional connectivity data is representative of the time at recruitment. Therefore, the results showing that the connectivity of the temporal cluster was significantly different between resolvers and non-resolvers suggests that it could provide prognostic value for pediatric concussion recovery and concussion symptom severity.

Additionally, the results demonstrating that older adolescents with prolonged recovery times have lower connectivity in the temporal cluster compared to their younger counterparts suggests that older and younger adolescents have different neurological responses to concussion. From a health care perspective, consideration for the age at the time of injury may be insightful for personalized clinical care. This demonstrates a need to further elucidate how concussion impacts individuals at different developmental ages. A further discussion related to the significance of the temporal and frontal regions identified in this study is described below.

6.2.2 Chapter 4

Chapter 4 asks: *Does hippocampal functional connectivity relate to neurocognitive function following concussion?* In this chapter, a whole-brain ROI-to-ROI analysis was employed as opposed to seed-based connectivity analysis where only the hippocampus connectivity would be measured. This method was employed as a conservative approach that would reveal connectivity patterns between all brain regions in addition to the hippocampal connections. This provides a more comprehensive view of dysfunction and compensation following pediatric concussion. Functional connectivity was defined as the temporal correlation between each pair of regions across the whole brain.

The hippocampal connectivity was of particular interest for a few reasons. The functions of the hippocampus are widespread across memory and attention among other cognitive functions (Daugherty et al., 2017; Poppenk et al., 2013) and sensory integration for neurocognitive activities like spatial navigation and spatial memory (Bates & Wolbers, 2014; T. Li et al., 2020; Sang et al., 2012). The hippocampus is also a region of high cell-turnover with sensitivity to concussion (Cassoudesalle et al., 2021; Meier et al., 2021; Saluja et al., 2015).

The results revealed that Reaction Time scores, as calculated by ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) were significantly correlated with functional connectivity between the hippocampus and cerebellum. As higher reaction times are associated with poorer functioning, increased connectivity between the hippocampus to the cerebellum (lobule III) was associated with poorer response times. Thus, within the sample of adolescents with concussion, slower correct motor responses are related to overcommunication between the posterior hippocampus to the cerebellum.

The exploratory analyses comparing adolescents with concussion (n = 34) to a small sample of healthy controls (n = 8) similarly demonstrated that hyperconnectivity between the hippocampus to sensory-related regions (*e.g.*, the basal ganglia) is associated with dysfunction. In particular, the adolescents with concussion exhibited 33 connections with increased connectivity that included both the anterior and posterior hippocampal subregions to the putamen, pallidum, and insula. These regions are also associated with movement (Cotterill, 2001).

Overall, these results suggest hyperconnectivity of the hippocampus is maladaptive post-concussion. Increased connectivity may be indicative of a compensatory mechanism to upregulate multisensory processing pathways. Additionally, it suggests dysfunction in the ability to integrate the information from internal vestibular state and external environmental cues necessary for goal-

directed behaviours. As hippocampus-cerebellum connectivity is involved in goal-directed spatial navigation (Rochefort et al., 2011), and hippocampus-basal ganglia connectivity is involved in spatial decision-making (Miyoshi et al., 2012), concussion during adolescence may impede an individual's ability to make goal-oriented decisions in a physical environment. Making goal-oriented decisions in a given environment would be pertinent, for instance, in the event that a young soccer player is aiming to guide the ball down the field and is navigating several other players moving in multiple directions. To successfully score (or setup a tactful play), the young player must be adept at moving within the quickly-changing environment and adapting his or her behaviours to maintain the goal of scoring.

6.2.3 Chapter 5

Chapter 5 asks one central question: *How do the DMN, SN, and CEN interact dynamically during rest in adolescents with concussion?* The question was addressed using a sliding window analysis on ROI-to-ROI connectivity and graph theory metrics. A sliding window approach provides insight into the relationships between the nodes of the three networks as they change over the course of the scan. Adolescents with concussion were compared to a cohort of healthy controls from the ABIDE database (di Martino et al., 2013).

Functional connectivity was defined as the temporal correlation between each pair of regions in all three networks (ROI-to-ROI analysis). It was additionally defined using properties of the nodes and edges represented by each network (graph theory analysis). These metrics offer insight into the role each region plays within a network. The sliding window approach provided

information about the temporal variability and temporal average connectivity (i.e., dynamic properties) for each analysis to each analysis.

The ROI-to-ROI analysis revealed that adolescents with concussion had reduced within-DMN connectivity, reduced DMN-CEN connectivity, and reduced DMN-SN connectivity over time. The graph theory metrics also revealed statistically different DMN connectivity in adolescents with concussion. The two major nodes of the DMN, the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC), demonstrated significantly reduced temporal variability and efficiency, respectively.

Overall, the findings in this chapter suggest abnormalities in the balance between the DMN, CEN and SN. The results could be interpreted as aberrant functioning of the DMN and compensation within the SN and CEN. Poor within-network communication as shown in the ROI-to-ROI analysis could be a result of specific deficits in the mPFC and PCC. The connection between these two regions is the cingulum (Supekar et al., 2009), which undergoes a slow protracted development across childhood and may be an area of susceptibility for pediatric concussion. Reduced connectivity in the mPFC was also discussed in Chapter 3 in association with poorer concussion symptomatology.

6.3 Synthesis of findings

Both Chapters 3 and 5 revealed that the medial prefrontal cortex and temporal lobe were areas of susceptibility. As major nodes of the DMN, they are involved in self-other processes and theory of mind (W. Li et al., 2014). Traumatic brain injury has been shown to impair theory of mind functions (Calvillo & Irimia, 2020; Ryan et al., 2021). Although theory of mind was not assessed

in this thesis, the impact of concussion on the nodes subserving the functions of the DMN shown in Chapters 3 and 5 might suggest that social cognition in children with concussion may hindered. Given that the severity of concussion symptoms was related to hypoconnectivity of the mPFC of the DMN (Chapter 3), it would be interesting to evaluate whether social cognition is also related to connectivity of the mPFC. This might provide further insight into the behavioural issues that children with concussion might present with.

Chapter 3 also revealed that age is a clinically important factor in the recovery process following concussion. This aligns with previous research showing a particularly vulnerable period in older adolescents to the effects of concussion. This includes longer recovery periods, higher prevalence rates of depression, lower neurocognitive scores (Chrisman & Richardson, 2014; Howell et al., 2013). Chapter 3 identifies a neurobiological identifier that may contribute to the clinical presentation of older adolescents, particularly those that have longer recovery tracks, namely the inferior temporal / temporo-occipital region of the DMN.

While Chapter 3 divides participants' ages through a median split, perhaps a future approach could divide participants by pubertal status. Puberty is a developmental marker for brain maturation (Sisk & Zehr, 2005). With physiological changes impacting hormonal balance, a host of developmental processes occur in the brain including synaptogenesis in the prefrontal cortex, white matter density increases in speech-related regions and the corpus callosum (Blakemore & Choudhury, 2006). Puberty status also impacts the functional connectivity of the resting state networks evaluated in this thesis (van Duijvenvoorde et al., 2019). Pubertal development is a stronger and more personalized indicator of brain maturity than age, even though age and puberty status are expected to be correlated.

Chapter 2 found interesting areas of hyperconnectivity involving the hippocampus and cerebellum. Because of the hippocampus and cerebellum involvement in spatial memory and navigation, future fMRI projects could include tasks related to spatial navigation and body rotation tasks both in the scanner (as a task-related study) or out of the scanner (as a behavioural covariate of resting state functional connectivity).

Multisensory integration and behavioural decision-making are additional domains of interest given the findings from Chapter 2. While challenging to create a life-like navigation activity in the MRI, virtual-reality tools are becoming increasingly popular in determining motor judgements in concussion (Santos et al., 2020; Slobounov et al., 2006; Teel et al., 2016) and could test for sensory integration deficits (Lubetzky et al., 2018).

Puberty status would also be an interesting element in the investigation of hippocampus connectivity in a future study. Since puberty alters the subcortical-cortical connectivity levels (Menon, 2013; van Duijvenvoorde et al., 2019), dividing participants into similar developmental stages might allow for greater accuracy in evaluating the effect of concussion on hippocampal connectivity. Hippocampus dysfunction and especially the hyperconnectivity between the posterior hippocampus and anterior cerebellum exhibited in this thesis is important to note in children and adolescents has they navigate sport activities and navigational skills like driving.

6.4 Main contributions

6.4.1 Hypoconnectivity of the DMN

This thesis was heavily influenced by the recent work from Vinod Menon, Lucina Uddin, and Michael Fox among several other network researchers. It has, therefore, focused on networks involved in cognition and emotion. It has come to light, however, that the dysfunction presented by this population are related to sensory and motor integration. While not directly evaluated in the current work, the connectivity profiles of children and adolescents with concussion in this thesis suggest disruption to sensorimotor and self-referential processes.

Our cumulative evidence suggests that it is dysfunction of the DMN that may be particularly leading to a host of symptoms. As demonstrated in Chapter 3, lower functional connectivity of the *frontal* cluster of the DMN was associated with greater symptomatology. This trend was supported by both early recovery participants (recovery < 6 months) and late recovery participants (recovery ≥ 6 months). The late recovery participants additionally showed the same trend in the *temporal* cluster of the DMN where lower functional connectivity was associated with worse symptoms.

The results showing low connectivity in the DMN in Chapter 3 were corroborated by the results of Chapter 5. In comparing the dynamic functional connectivity of the participants with no concussion history to participants with a current concussion, the DMN demonstrated poor integration by two metrics of network connectivity. The ROI-to-ROI analysis revealed not only that the DMN had reduced intra-network connectivity, but also that the DMN was statistically less connected to the SN and CEN. This means that across the resting state scan, the nodes of the

DMN had less temporal synchrony with one another, perhaps signifying that the DMN was not behaving like one coherent network. It also means that the nodes of the DMN were less likely to be integrated with the SN and CEN. The graph theory metrics pinpointed the PCC and mPFC as the two regions with significantly lower network integration. Both of these nodes belong to the DMN, which is further evidence that the DMN function is particularly impacted following concussion.

These findings are in line with Hillary's theory of neurodysfunction (Hillary & Grafman, 2017) which states that areas of dysfunction are targeted at major nodes of networks. The protracted development of the DMN structure (including both grey and white matter) may produce a vulnerability to concussion impact on the many functions of the DMN in pediatric populations. However, rather than exhibiting hyperconnectivity (increased connectivity) as hypothesized by Hillary, the nodes of the DMN demonstrate hypoconnectivity (reduced connectivity). So, while the hyperconnectivity was not exhibited in the DMN in Chapters 3 and 5, the regions expressing dysfunction are indeed those with the highest degree of connectivity, in line with Hillary and Grafman's theory.

Hypoconnectivity of the DMN can impede an array of behaviours supported by the DMN. Although the DMN was previously known as a task-negative network, the name is misleading as the DMN is actively involved in several cognitive tasks. With reduced communication between the DMN structures, processes like autobiographical memory, visual memory, and theory of mind activities (Doll et al., 2015; Greicius et al., 2003; Raichle, 2015) may show reduced performance. In Chapter 4, both visual and verbal memory were considered "average" as scored by ImPACT. An interpretation of why this might be the case is described below.

What the collective results do show, however, is that visuomotor speed and reaction time have "below average" performance (Chapter 4). Could the DMN hypoconnectivity affect these processes too? In fact, the DMN is involved in sensory and perceptual information. It is involved in integrating emotions and bodily sensations into autobiographical memories (Lindquist & Barrett, 2012), as facilitated through the PCC and its connection to the hippocampus (Raichle, 2015). In short, DMN allows perceptions of the environment to be meaningful to the individual (Lindquist et al., 2012). Previous research has determined that it is the ventral mPFC that is particularly important for receiving sensory information and communicating that sensory information to other areas of the brain (Raichle, 2015). Lack of information transfer within the DMN with specific dysfunction in the mPFC and PCC could mean impairment in sensory, perceptual and visceromotor responses.

In summary, hypoconnectivity of the DMN (Chapter 3 and 5) following concussion may impact cognitive, emotional, and motor domains that are typically seen in post-concussion symptomatology. Reduced temporal variability of the mPFC (Chapter 5) might mean poor processing of sensory and perceptual information from the environment. Reduced temporal connectivity of the PCC (Chapter 5) might mean poor communication about sensory information to the hippocampus. The implications of this lack of connectivity between the DMN and hippocampus is discussed in the following section.

6.4.2 Hyperconnectivity of alternative pathways

Brain imaging results from concussion studies often cite changes in brain physiology as "compensatory". Compensatory mechanisms allow for the individual to sustain behavioural

performance in the event of injury. Children and adolescents have on-going developmental processes that might inhibit or reduce the flexibility of the brain networks to compensate following concussion.

This thesis suggests that children and adolescents do present with compensatory mechanisms. In particular, the results from this thesis suggest that hypoconnectivity of the DMN could drive a need for increased communication to supplement processes that would be typically done by the DMN. As shown in this thesis, the increased connectivity between the nodes of the SN-CEN (Chapter 5) and the increased connectivity between the hippocampus-putamen and hippocampus-pallidum (Chapter 4) could be interpreted as a reliance on alternative pathways to maintain normal behaviour. These compensatory pathways could support complex processes like verbal and visual memory, but at the expense of lower-level functioning like motor speed.

With poor DMN integration, the increased dynamic functional connectivity of the SN and CEN could suggest a reliance on the CEN to process incoming sensory information to make judgements about the environment and the self within the environment. Reliance on cognitive pathways to monitor the self could reduce cognitive capacity for other attention-demanding tasks and result in difficulty concentrating among other cognitive complaints following concussion. This is additionally supported by the hippocampal hyperconnectivity to the basal ganglia which could improve perceptual, motor and emotional processing power to encode details about an event in a given environment (*i.e.*, autobiographical memory aspects). These interpretations should be taken with caution since the results were based on the comparison between participants with concussion and healthy controls. Without pre-injury data, the interpretation about the post-concussion state could actually represent differences between individuals prone to concussion and those who are not.

Another interpretation of the results could be found in the hyperconnectivity hypothesis (Hillary & Grafman, 2017). This posits that prolonged hyperconnectivity is detrimental. From this point of view, hyperconnectivity in emotion-related pathways (*e.g.*, saliency and reward structures like the putamen, hippocampus, amygdala) as shown in both Chapters 4 and 5 could lead to secondary pathological impact to less-developed nodes of a network. The secondary pathological impact could present as failure to function as a result of the metabolic overdrive of hyperconnected areas. This is similarly what is demonstrated by dysfunction in the mPFC and PCC of the DMN, which have a slow developmental trajectory. It also suits the reserve theory (Stern, 2002) which theorizes that an individual with a lower reserve (or lower development) might be more vulnerable to pathology.

Taken together, the findings of this thesis are aligned with the triple network framework that suggests dysfunctional properties of neurocognitive networks in pathological conditions. The hyperconnectivity hypothesis sheds light on the hyperconnectivity seen between executive function networks and the sensory-related networks. Whether the hypoconnectivity of the DMN precedes or leads to the hyperconnectivity of the hippocampus remains unknown. Nevertheless, traumatic brain injury during childhood is best understood from a holistic or "constructionist" standpoint which states that cognitive, emotional, and perceptual domains are facilitated by multiple networks rather than a single brain structure or brain network (Lindquist & Barrett, 2012). As demonstrated across Chapters 3-5, the pediatric concussion is transregional injury affecting a widespread number of functions as the developing brain works to preserve behaviour.

6.3 Clinical reflection

The work presented here was motivated by the clinical presentation of children with concussion and the outstanding questions related to diagnosis, prognosis and recovery patterns. The behavioural, emotional and cognitive consequences of concussion and the long-term implications on a child's life illustrates the need to further investigate the neurobiology underlying the observable deficits. Because childhood development and concussion are both heterogeneous processes, pediatric brain injury requires more research to provide evidence-based personalized care.

This thesis demonstrates two post-concussion abnormalities in the brain in adolescents: (1) poor communication of the network subserving self-referential processes, and (2) compensatory recruitment of alternative networks to support behaviour.

What this means clinically is that a child with a concussion may have a decreased sense of self-awareness. That could include all the functions that rely on structures of the Default Mode Network such as memories about the self, body awareness, managing emotions, or navigating a physical environment. The severity of symptoms has a linear relationship to the physiology of the Default Mode Network. Thus, the individual differences seen in symptom reporting between adolescents with concussion relate to the reduction in the prefrontal cortex's ability to communicate with other brain areas of the Default Mode Network (Chapters 3 and 5).

The implications of poor Default Mode Network functionality might include an increase in cross-communication between other regions of the brain. This includes enhanced signalling between cognitive-, motor- and emotion-related regions such as the hippocampus and the basal ganglia, or the anterior insula (from the Salience Network) and the lateral prefrontal cortex (from the Central Executive Network).

To compensate for poor Default Mode Network functionality, the brain might strengthen alternate neural pathways to improve self-awareness, but might, in the process, lead to a decrease in mental capacity to complete other cognitive tasks while in school. This could be important for a student athlete experiencing poor self-awareness after a concussion, but also needs to focus in class and on the field.

6.4 Final conclusion

Overall, the work from this thesis contributes to further awareness of how several concussion symptoms are related through brain networks. Chapter 3 demonstrated lower prefrontal cortex connectivity correlates with worse symptomatology. Chapter 4 revealed that slower reaction times corresponds with higher connectivity between hippocampus-cerebellar regions. Chapter 5 showed abnormal functional connectivity between neurocognitive networks. As evidenced by the work presented in this thesis, there are a number of interacting processes that influence clinical presentation of the injury and the length of recovery.

While only a few select influences were examined (*e.g.*, age, symptom severity, etc.), the results shed light on the importance of evaluating adolescents. With many developmental processes in the brain during childhood, pediatric concussion is analogous to a youth orchestra that is trying to perform with missing players. As each youth orchestra might manage the mishap of missing musicians in a slightly different manner, continued investigation into the characteristics of different orchestras becomes increasingly more important, much like investigating the functional neurology of any subset of the population.

Clinical research, especially on a vulnerable population like children with concussion, should have the goal of furthering health care. Given that adult-centered research leads to adult-centered applications, building the body of pediatric-focused research enhances the possibility of future pediatric clinical care. In that light, insight into the underlying neurological processes following childhood concussion is and will be invaluable to researchers, clinicians, and future athletes alike.

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