EXAMINING RESTING-STATE FUNCTIONAL AND STRUCTURAL CONNECTIVITY OF THE ATTENTION NETWORKS AFTER EARLY BRAIN INSULTS

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March 2022

Aston University

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Ling Lynette Looi, Doctor of Philosophy, 2022

Thesis Abstract

Brain insults that occur early in life often lead to cognitive impairments, and sustained attention is highly vulnerable to the initial event as well as to the altered structural and functional brain development that follows. Sustained attention impairments are associated with neural changes in specific brain networks – default mode network (DMN) and central executive network (CEN) – that are crucial for proper attention functioning in healthy populations. Prior studies have, however, typically focused on adult cohorts, which is not applicable to understanding structural and functional changes in the developing brain. There are relatively few studies that have examined these networks in children with an early life injury with advanced quantitative neuroimaging techniques (structural magnetic resonance imaging (MRI) and functional MRI). Thus, the current thesis used these methods to investigate DMN and CEN changes following an early life brain insult in children with traumatic brain injury (TBI), epilepsy, or heterogeneous brain insults with the aim to identify shared neural changes in heterogeneous patient cohorts that underpin common attention impairments.

The current thesis has reported reduced functional connectivity in the DMN regions (posterior cingulate cortex and medial prefrontal cortex) in children with TBI, and in the left parietal lobe in children with focal epilepsy as compared to controls at 2-years post-injury. Children with epilepsy however showed no differences in the structural covariance network when compared to controls. Children with heterogeneous brain insults also showed no significant functional and structural connectivity changes when imaging data were acquired in the acute post-insult period.

This thesis is however limited by the lack of behavioural measures, and future studies should integrate neuropsychology and neuroimaging to better understand the relationships between the brain connectivity changes and attention deficits, therefore allowing the identification of children who would benefit most from early interventions that could improve their long-term neurocognitive outcomes.

Keywords: ‘Early Brain Injury’, ‘Epilepsy’, ‘Traumatic Brain Injury’, ‘Resting-state Functional Connectivity’, ‘Sustained Attention’, ‘Structural Covariance Network’, ‘MRI’

To my parents,

This thesis is dedicated to you.

I hope that I have made you as proud as I am to call you my mum and dad.

Acknowledgments

I am thankful for all the participants and their families who have contributed their effort and time to the studies whose data was used in the current thesis.

I am very fortunate to be supervised by Professor Amanda Wood, Dr Elaine Foley and Dr Laura Shapiro. Amanda, thank you for believing in me, and for your unwavering support throughout. You have taught me to always engage in rigorous research, and more importantly, that taking breaks are vital to going further! Elaine, thank you for being so generous with your time and having the patience to answer all my questions, and letting me know that there is no such thing as a silly question. Laura, thank you for always being so ready to provide help when I needed, and for all the encouragements you have given me.

I am very grateful for the wonderful people I have met during my PhD journey – the PROBIt research team, and everyone in office SW419. Thank you to my wonderful colleagues, Nikki Ngombe, Daniel Griffiths-King and Sarah Wong for having shared my tears and joys, and the much appreciated motivational speeches and/or pet pictures. Special thanks to Rochelle Hamilton for always having my back, and being the best office neighbour (lady to my left).

I am also grateful for my childhood friends who have supported me through periods of self-doubts – Patricia Phua and Nur Aqilah Azmi, and a huge thank you to Stefanie Tan, who has checked up on me periodically, and for always cheering me on.

Words cannot express my gratitude to my family – my mum, Toh Siew Luan, and dad, Looi Hong Chye, – who worked hard to raise me with unconditional love, and for always having my back even when others doubted me. Mum, thank you for always ensuring that I am well fed, and for being so selfless. Regardless of the time, you have never hesitated to answer my calls when I needed you, and I cannot be more thankful. Dad, thank you for the ever-timely reminders on why I am doing what I am doing when times get hard. Thank you for all your trust in me (even when you do not understand what I am doing). I am also thankful to Kelvin Ho – Kor, thank you for being so patient with my pessimism during my write-up year, and for the constant reminders that a life outside my PhD exists.

My final gratitude goes to a special person - Matthew Strachan, I would forever be grateful for your kindness and patience. You have been so tolerant with my sudden outbursts, my crazy sleep schedules and my irrational anger, and have responded only with kindness and understanding. Without you, this thesis would not be finished.

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List of Abbreviations

ABI	Acquired Brain Injury
ADHD	Attention Deficit Hyperactivity Disorder
AEDs	Antiepileptic Drugs
BOLD`	Blood-Oxygen-Level Dependent
CAE	Childhood Absence Epilepsy
CEN	Central Executive Network
CPT	Continuous Performance Task
DK	Desikan-Killiany
DMN	Default Mode Network
FLE	Frontal Lobe Epilepsy
fMRI	Functional Magnetic Resonance Imaging
FDR	False Discovery Rate
FWE	Family Wise Error
ICA	Independent Component Analysis
IQ	Intelligence Quotient
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NBS	Network Based Statistics
PCC	Posterior Cingulate Cortex
ROI	Region of Interest
ROIs	Regions of Interest
SCN	Structural Covariance Network
SCNs	Structural Covariance Networks
SPM	Statistical Parametric Mapping
TBI	Traumatic Brain Injury
TEA-Ch	The Test of Everyday Attention for Children
TLE	Temporal Lobe Epilepsy
VBM	Voxel-Based Morphometry

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Chapter One: General Introduction

1.1 Introduction

Attention impairments in children are common after brain injury, and there is enormous potential for quantitative neuroimaging techniques, specifically functional and structural magnetic resonance imaging (MRI), to improve early identification of affected children by examining relevant neural networks. The current thesis represents an important step towards examining the use of these methods in paediatric cohorts. Attention is important to our daily life, as it allows us to ignore irrelevant distractors and focus on relevant information. It plays a vital role in both explicit and implicit learning, and consequently in academic achievement (Posner & Rothbart, 2014; Rabine & Coie, 2000). Importantly, attention is not a single process but instead one made up of several types of cognitive processes, which are supported by their own distinct sets of brain regions (Luo & Maunsell, 2019; Raz, 2004). There is ample evidence, particularly in the adult brain injury population, that functional and structural alterations to these brain regions are associated with attention impairments (Bonnelle et al., 2011; Sharp et al., 2011). Less is known about the effects of brain injury on the regions associated with attention problems in children with brain injuries, despite this population's susceptibility to attentional impairments (Bloom et al., 2001; Konigs et al., 2015). Furthermore, the continuous development of connections between regions in the brain across childhood potentially increases the susceptibility of children's brains to insults; this may depend in part on whether the injury is focal or generalised in nature (Harris, de Rooij, & Kuhl, 2019). Cortical networks are therefore important to our understanding of the attentional consequences of early-life brain changes. Advances in neuroimaging techniques such as functional MRI (fMRI) allow us to examine injury- or disease-related changes in the brain and can reveal relationships between specific cognitive impairments and the neural substrate underpinning them (Scheibel, 2017; Yin, Li, Zhao, & Feng, 2013). Advances in quantitative brain imaging techniques allow us to move beyond simple lesion-based approaches and instead examine the complex neural networks underlying attention in diseased and healthy development. Identifying these networks could help us identify children at risk of poor attentional outcomes.

The current chapter provides an overview of acquired brain injury (ABI) and its consequences. It then discusses the disparity between the brains of children and adults, and the impacts this disparity has on their respective responses to brain injury. The chapter proceeds to discuss attention impairments after a brain injury and present several prominent attention models and relevant attention studies, explaining the neuronal substrates underlying the different attention components. Next, the chapter focuses on the impacts of brain injuries on sustained attention, and their influence on a child's life. The use of neuroimaging techniques – including fMRI and structural covariance network (SCN) analysis – to examine changes in the brain that may underpin impairments in cognitive skills after a brain injury is then discussed. A review of recent studies that use these techniques to examine sustained attention in healthy

and patient populations, including brain injury patients, will provide the rationale for the aims of this thesis and lead into an overview of the subsequent experimental chapters.

1.2 Acquired Brain Injury

ABI is an umbrella term that includes any neurological damage sustained after birth that is not congenital or degenerative. There are two subtypes of acquired brain injury. The first subtype, known as traumatic brain injury (TBI), is caused either by external open or closed trauma to the head; closed-head injuries refer to injuries that do not penetrate the brain. The second type of acquired brain injury results from a medical condition or disease processes within the body, and does not involved any external mechanism (for example, stroke – Barker, Gibson & Robinson, 2018). According to Kraus, Fife, Cox, Ramstein, and Conroy (1986), common causes of TBI include falls, recreational activities and motor accidents; common causes of non-traumatic brain injury include brain tumours, encephalitis, stroke and neurological disorders (Kamalakannan, Gudlavalleti, Murthy Gudlavalleti, Goenka, & Kuper, 2015). ABI does not refer to a single negative developmental process, but rather a situation in which a person, previously intact from a neurological perspective, subsequently acquired some form of brain pathology that may lead to the physical, neurocognitive and psychological impairments to be discussed below (Teasell et al., 2007).

1.2.1 Consequences of ABI

Approximately 350,000 people in the UK sustain ABI yearly (Tennant & Headway, 2015), and survivors of ABI often suffer from physical, cognitive and psychosocial problems post-injury (Menon & Bryant, 2019). ABI is a major health issue in children because of its persistent impact on a child's cognitive skills, academic performance and health (Youngblut et al., 2000). TBI is one of the leading causes of hospitalisation among children in the United Kingdom (Trefan et al., 2016). At least 35,000 children are admitted due to traumatic brain injury each year (Fernandez, 2018). It is also estimated that non-traumatic brain injuries affect 82.3 children per 100,000 each year (Chan, Pole, Keightley, Mann & Colantonio, 2016). Moreover, ABI is the leading cause of death and disability, particularly in childhood (Forsyth & Kirkham, 2012). It is also one of the main causes of permanent disability in school age children and is often accompanied by cognitive, behavioural and affective impairments (Garcia, Hungerford, & Bagner, 2015; Li & Liu, 2013). Among these impairments, cognitive impairments are thought to have the largest impact on the patient, their family and society, as they can interfere with daily life, work, socialising, hobbies and active community engagement (Barman, Chatterjee, & Bhide, 2016). As a result of cognitive and behavioural impairments following brain injury, individuals with ABI are prone to facing difficulties reintegrating into school and/or work, ultimately affecting their ability to attain financial independence, as well as difficulties with social integration, consequently impacting their quality of life (Odumuyiwa et al., 2019). This is in line

with the findings of Hewer and Tennant (2005), who have suggested that cognitive and behavioural problems are expected to pose the greatest challenges for reintegration into school, work and social life. Moreover, the societal and economic cost of ABI can be substantial (Patil et al., 2017; Ghajar, 2000), as those affected will require a range of services to aid their recovery. The process of rehabilitation may include but is not limited to social care, primary health care, and mental health services (Holloway, 2014). Cognitive impairment from early brain injury has therefore shown to be a significant factor in the personal, societal and economic costs of brain injury, and as such early identification and intervention is likely to help reduce some of these costs.

1.2.2 Cognitive Outcomes following ABI

Acquired brain injuries, including TBI and non-traumatic brain injuries such as epilepsy and brain tumours, share a common characteristic: they are often associated with impairments in cognitive functions such as attention, memory and executive functions (Westerveld, 2010; Ris & Abbey, 2010; Yeates, Ris, Taylor, & Pennington, 2009). The presence of cognitive impairments in ABI (i.e., stroke and TBI) is also supported by systematic reviews and/or meta-analyses of cognitive rehabilitations/interventions for children with ABI that included participants who had sustained an ABI and demonstrated deficits across different domains, including attention, memory, executive function, learning and problem solving (Laatsch et al., 2007; Slomine & Locascio, 2009; Virk, Williams, Brunsdon, Suh, & Morrow, 2015). More specifically, over 60% of the TBI adult patients showed memory impairments, and more than 50% reported concentration difficulties (Ponsford et al., 2014). In addition to those functions, language and executive functioning impairments were also seen in children with TBI (Garcia et al., 2015). On the other hand, 20–80% of adult stroke patients demonstrated cognitive impairments using the Mini-Mental State Exam that tests for several functions including attention, memory, language, visual-spatial skills and orientation (Sun, Tan, & Yu, 2014). These findings align with long-term cognitive outcomes for paediatric stroke patients, who showed poorer attention, memory, language and sensorimotor functions compared to healthy children (Kolk, Ennok, Laugesaar, Kaldoja, & Talvik, 2011).

Importantly, these cognitive deficits can be long-lasting, and affected children have been shown to exhibit impairments years after the injury (Beauchamp & Anderson, 2013). This is evidenced across several cognitive skills in TBI patients, including executive function (Beauchamp et al., 2011), memory (Catroppa & Anderson 2007), language (Liegeois et al., 2013) and attention (Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2007); deficits in these cognitive skills were observed years following the injury. For example, children with early brain injury suffered from long-term impairments to fluid reasoning, inhibitory control and processing speed into young adulthood, and those with deficits in fluid reasoning and processing speed were at a higher risk of poor adaptive functioning into adulthood (Treble-Barna et al., 2017).

Similar long-term cognitive impairments (i.e., attention, language, memory and intelligence quotient (IQ) deficits) are also reported in patients with non-traumatic disorders such as brain tumour (Macedoni-Luksic, Jereb, & Todorovski, 2003), paediatric stroke (Kolk, Ennok, Laugesaar, Kaldoja, & Talvik, 2011) and paediatric epilepsy (Baumer, Cardon, & Porter, 2018).

A consistent finding across studies is the influence of age and injury severity on cognitive outcome from brain injury; the poorest cognitive recovery is presented in younger patients with severe injuries (Beauchamp & Anderson, 2013). This is evidenced by studies that have shown that cognitive outcomes in children with severe injury are poorer than in those with mild/moderate injuries (Babikian & Asarnow, 2009; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2008; Yeates et al., 2004). Whilst Anderson et al. (1997) also illustrated the association between severe injuries and poorer language, memory and IQ outcomes, the study reported that age had a larger effect on cognitive outcome; younger age at the time of injury was notably associated with poorer memory outcome. This is because memory is an immature cognitive skill in young children, as it develops through the early childhood period (Anderson et al., 1997) alongside ongoing neural development in the brain regions supporting memory and other cognitive skills (Dennis et al., 2014). Therefore, brain injury at a particularly young age can affect both ongoing neural and behavioural development and lead to skill deficits, later emergence of deficits, skill declination and even arrested development of cognitive skills (Dennis et al., 2014). Thus, developing skills (such as memory) may be particularly susceptible to early brain injury. Compared to pathology, age has also been reported as more important for the long-term cognitive outcome in paediatric stroke; the study found the worst outcomes in terms of cognitive flexibility, processing speed and verbal learning in cases of early childhood stroke (< 6 years) as compared to late childhood stroke (>6 and <16 years) (Abgottspon et al., 2021). The influence of age on cognitive outcomes suggests that the developing brain may respond to brain injuries differently from the mature brain, which may explain the poorer outcomes in children. This is discussed in the following section.

1.3 The Developing Brain

Early developmental theories have proposed stage-like characteristics of cognitive development. One example is Piaget's theory of cognitive development, which suggests that the development of cognitive functions is a continuous reorganisation of mental processes due to environmental interaction and biological maturation (Ghazi & Ullah, 2015). The theory suggests that concepts are constructed from more basic perceptual and cognitive precursors, and that children should only be taught certain functions based on the stage of cognitive development they have reached: sensorimotor (birth to 2 years), preoperational (2 to 7 years), concrete operational (7 to 11 years) or formal operational (12 to 16 years). On the other hand, the information-processing approach to cognitive development emphasises the long-term continuity nature of development from infancy, as demonstrated by the progression of attention,

processing speed, memory and representational competence (Johnson, 2003; Rose, Feldman, Jankowski, & Van Rossem, 2012).

In addition to the behavioural concepts, studies have proposed the concept of critical periods in the development of the brain, which are discussed in greater details in the next section. Obtaining the expected experience during these critical windows is necessary for appropriate neural circuit wiring and consequently proper development of higher-order functions (Reh et al., 2020). This is evidenced in Larsen and Luna (2018)'s study that proposed a model in which the critical period of adolescent neurocognitive development is strongly influenced by experience, and adverse experiences can lead to an abnormal developmental trajectory of the brain and of higher-order cognition. As a result of the developing nature of children's brains, a different response to brain injury has been proposed for children compared to adults (Araki, Yokota, & Morita, 2016; Figaji, 2017). For example, it has been suggested that while adults present an initial pattern of deficit followed by recovery, this pattern is not necessarily found in children due to their developing brains (McKinlay, Dalrymple-Alford, Horwood, & Fergusson, 2002). As a result, early brain insult can interrupt the development of new skills, and cognitive deficits are likely to later emerge (Taylor & Alden, 1997).

Moreover, longitudinal studies have shown that 'emerging' skills (i.e., skills that are not functional or in the initial phase of being acquired (Dennis, 1987)) at the time of injury are most affected (Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2007) and may develop abnormally in the long term, indicating the importance of examining long-term neural and cognitive changes, which is the key interest of this thesis. However, other studies have found that older patients who sustain brain injury (> 40 years) are at a higher risk of cognitive decline following the injury as compared to younger patients (16–39 years), who showed the most robust cognitive recovery (Marquez de la Plata et al., 2008). In contrast, the youngest patient group (16–26 years) showed the most improvement in the long term, suggesting that age at the time of brain injury has a strong influence on the functional recovery. This is potentially because the developing brain in children and adolescents is associated with greater plasticity (further discussed below), which differentiates the developing brain's response to external factors from the adult brain's response (Araki et al., 2016). Thus, brain plasticity plays an important role in brain injuries, and will be discussed next.

1.3.1 Brain Plasticity

Brain plasticity refers to the ability of the nervous system to adapt to intrinsic or extrinsic stimuli by reorganising its functions, structure or connections (Mateos-Aparicio & Rodriguez-Moreno, 2019). Plasticity has been suggested to play an important role in the normal development of cognitive and behavioural skills throughout childhood (Fandakova & Hartley, 2020). Moreover, Galvan (2010) has suggested that the link between learning/development and plasticity can be better understood with experience-expectant and experience-dependent processes. These

processes are especially important during the sensitive, or critical, period in development (Greenough, Black, & Wallace, 2002), when the functional maturation of the brain is highly dependent on the relevant experience and environmental stimuli (Cioni, Inguaggiato & Sgandurra, 2016), discussed below, and have been theorised to support the development of various cognitive skills such as higher-order language skills (Kuhl, 2010).

Experience-dependent processes refer to brain changes that occur as a result of environmental input or experiences that can vary across individuals; in contrast, experience-expectant processes suggest that the brain awaits specific environmental input or experiences to occur within a specific time frame during normal development (Galvan, 2010). For example, appropriate visual experiences during the sensitive period of development have been demonstrated to be critical to the normal development of visual processing in kittens (Hubel & Wiesel, 1970). Deprivation of this experience via monocular deprivation during this sensitive period can result in atypical vision processing (i.e., shift in ocular dominance to the eye that has not been deprived) along with lasting brain changes (Hubel & Wiesel, 1970). The importance of relevant experience during sensitive period has also been demonstrated in the Bucharest Early Intervention Project (BEIP), which found that children who were institutionalised showed stunted and delayed physical and cognitive growth along with different brain activity patterns compared to children who were never institutionalised. This is because the institutionalised children were deprived of relevant experiences during the sensitive period of their development that would otherwise have stimulated healthy normal growth. Taken together, these findings suggest that normal cognitive and physical developments in children are highly reliant on the presence of relevant experiences during the sensitive period of development. Conversely, adverse childhood experiences during these periods, such as brain injury, can severely impact the typical development of the brain and cognitive skills. This is evidenced in Crowe, Catroppa, Babl and Anderson (2012)'s study, which found that children who sustained a brain injury during middle childhood (7–9 years) demonstrated the poorest cognitive outcomes (in terms of verbal IQ, non-verbal IQ, processing speed and overall IQ) as compared to younger (infant and preschool-aged) and older (late childhood) children. Crowe et al. (2012) suggested that the middle childhood period likely coincides with a critical developmental period for the brain and cognitive skills. As a result, brain injury during this period can result in impairments in these skills and consequently in cognitive performance. Thus, it is reasonable to suggest that the timing of a childhood brain injury plays a crucial role in the injury outcome. This theory is, however, in contrast to an early notion (known as the Kennard Principle) that brain injury causes less impairment in children than in adults because the developing brain allows for more reorganisation and recovery after injury (Kolb, 2014), a topic which is discussed in the following section. These studies highlight the multifaceted nature of plasticity. To better understand the influence plasticity can have on brain injuries, the following section will further discuss the neural response to early brain injuries in children.

1.3.2. Neural Response to Early Brain Injuries

The developing brain in children is typically assumed to have greater plasticity than the adult brain because of the processes underpinning plasticity, which include neurogenesis (formation of new neurons), apoptosis (programmed cell death) and activity-dependent synaptic plasticity (changes in neuronal connectivity as a result of synaptic transmission) (Johnston, Nishimura, Harum, Pekar, & Blue, 2001). Animal studies have demonstrated an overproduction of neurons in babies, and this overproduction could be adaptive for the brain by supplying available neurons that can be used to repair injury in the immature brain (Rakic, 2000). Similarly, the developing human brain undergoes an early burst of synaptogenesis during postnatal life, followed by later, experience-dependent pruning of excessive synapses (Huttenlocher & Dabholkar, 1997). This may contribute to greater plasticity in children by providing an excess of synapses to be selected based on childhood experiences. The implication of enhanced plasticity in children is a greater capacity for the brain to respond to changes caused by brain injuries, and consequently better functional outcomes in children compared to adults (Kirkwood & Yeates, 2012; Li & Liu, 2013).

Other data suggest that the developing brain is more easily reorganised following an injury. This is thought to be due to a large number of unspecified synapse connections that are functionally less committed than the synapses of an adult brain (Katušić, 2011). Also known as the Kennard principle, this theory suggests that the developing brain has a greater capacity for reorganisation and thus recovery after a brain injury (Kolb, 2014). This is evidenced by the visual cortex in the developing brain; its development of neural organisation is dependent on visual experience, and if the experience is warped – where one eye receives more stimulation than the other – fewer synaptic connections would be pruned in the experienced eye, and more pruning would with the inexperienced eye (National Research Council, 2000). This suggests that the developing brain is characterised by functionally unconfirmed synapse connections, and as a result the young brain may respond more flexibly to experiences or injury and can undergo greater reorganisation.

Plasticity, therefore, can be conceptualised as a double-edged sword that can help with neural adaption but also lead to vulnerability. Adaptive plasticity refers to alterations in the synaptic function or reorganisation of neural pathways associated with, for example, the acquiring of a new motor skill or language, or recovery post-injury (Johnston, 2004). An example is amblyopia in children, where the selection of visual input from one eye results in the loss of synaptic connections associated with the other eye, and correction (patching the eye) done within the period of maximal visual plasticity has been shown to improve vision (Vaegan & Taylor, 1979). Similar neuronal plasticity adaptation is also observed in other domains, including the central auditory system, where studies have suggested that the implantation of a cochlear implant during the window of maximal plasticity would allow normal P1 latencies (i.e., cortical evoked responses) to auditory stimulants after a period of electrical stimulation (Sharma,

Dorman, & Spahr, 2002). Adaptive plasticity is also evidenced in a study by Caeyenberghs, Wenderoth, Smits-Engelsman, Sunaert, and Swinnen (2009), which found comparable task performance between paediatric patients with brain injuries and healthy children, along with an increase in functional activity (in the medial and anterior parietal regions, and posterior cerebellum) in patients. The increase in activity was suggested to reflect compensatory neural recruitment to increase the recruitment of neural resources for attentional deployment and sensory processing in order to compensate for deficits. Thus, there is a range of data indicating that different cortical regions and their associated primary functions exhibit reorganisation of neural pathways, and that this produces better functional outcomes for brain injuries sustained in childhood as compared to the same injuries sustained in adulthood (Aram & Ekelman, 1986).

Previous studies have supported the notion that children are better protected against damage to the brain (Berger, Pitts, Lovely, Edwards, & Bartkowski, 1985; Marquez de la Plata et al., 2008). Importantly, Marquez de la Plata et al. (2008) examined the influence of age on long-term functional recovery from traumatic brain injury and reported that the oldest age group (> 40 years) suffered greater disability than the intermediate (27–39 years) and youngest (16–26 years) groups, despite the oldest age group having less severe injuries. Findings from the study suggested that whilst all age groups demonstrated early improvements in functioning, younger patients showed continued improvement whilst older patients were more likely to show declining ability, suggesting the potential for greater functional improvement in younger patients compared to older patients. Greater plasticity and compensatory ability in children was also found in a study by Gleissner, Sassen, Schramm, Elger, and Helmstaedter (2005), which compared paediatric and adult patients who were matched according to their pathology and onset of seizure (i.e., age). They found that children with epilepsy showed greater functional recovery (in visual memory, verbal learning and attentional skills) than adults with epilepsy after temporal lobe resection (which entails removing parts of the brain involved in these functional skills). As the paediatric and adult groups were matched based on important clinical and aetiological variables, Gleissner et al. (2005) suggested that the difference in findings between groups was likely because of the age difference, and specifically the developing nature of a child's brain. Importantly, the study showed that the skills of children with epilepsy, unlike those of adults, were recovered to pre-surgery levels, suggesting greater plasticity and better neural compensation in children. The current literature has therefore illustrated that enhanced plasticity in children can lead to adaptation to experiences faced.

Conversely, there is a range of studies that show increased plasticity in fact places children in a vulnerable position, causing *maladaptive* recovery from early brain injury (Giza & Prins, 2006). This vulnerability is described by the 'early vulnerability' theory, which suggests that the developing brain is susceptible to brain damage and its associated cognitive deficits (Crowe et al., 2012). Due to the lack of functional specialisation in the developing brain, non-suitable neuronal connections and abnormal changes in neuronal networks may occur as the

brain attempts to recover impaired functions (Giza, Prins, Hovda, Herschman, & Feldman, 2002; Li et al., 2014). Thus, healthy tissue that is specialised for other functions will abandon the specialisation in an attempt to recover the impacted function, resulting in the 'crowding' of cognitive functions for that tissue, also known as the 'crowding effect' (Sheppard & Lippe, 2012). The crowding effect is observed in a refractory epilepsy population, in which left hemisphere damage early in life led to normal language development but impaired development of non-verbal skills. This occurred as a result of brain plasticity, which redirected tissues dedicated to non-verbal skills to the emerging language functions (Satz, Strauss, Hunter, & Wada, 1994). As a result of the crowding effect, the reorganisation of the brain network may impact normal development, and in particular the development of later-developing skills (Katusic, 2011) such as attention, processing speed and executive function (Aaro Jonsson, Smedler, Leis Ljungmark, & Emanuelson, 2009; Lehnung et al., 2003; Muscara, Catroppa, & Anderson, 2008). This process represents a vulnerability of the developing brain, wherein brain injuries can affect both developed and developing cognitive skills, and as a result potentially lead to dysfunction across several cognitive functions.

The importance of sensitive or critical periods for normal cognitive development, as discussed earlier, suggests that injury during these periods leaves patients particularly vulnerable to impairments. This is evidenced by Anderson et al. (2010)'s study, which illustrated that the skills emerging at the time of injury are more vulnerable to dysfunction as compared to previously 'established' skills. This vulnerability is due to the fact that brain injury affects the development of immature or developing skills and can lead to cognitive deficits during later developmental periods (Donders & Warchausky, 2007). Whilst no significant difference in overall cognitive ability was demonstrated between children with early and late onset of brain injury in a study by Donders and Warchausky (2007) study, poorer outcomes, for example in higher-level cognitive skills, were found in the former group. The delayed onset of cognitive dysfunction is presented in a patient with early brain injury to the frontal lobe, alongside abnormal neural patterns in the frontal regions (Eslinger, Grattan, Damasio, & Damasio, 1992). The study also suggested that the higher-level cognitive deficits found were a result of changes in brain development during the developing period. As higher-level cognitive skills develop at a later stage in childhood/adolescence, early brain injury likely leaves children vulnerable to delayed-onset cognitive dysfunctions that may present themselves at a later stage because of early, disruptive neural changes in the brain.

The existing literature has thus illustrated the plasticity-driven neural changes following a brain injury, which can explain the commonly reported cognitive outcomes in these patients – for example, attention – and is discussed in greater detail in the next section.

1.4 Attention Outcomes Following ABI

Attention deficits are among the most commonly reported cognitive concerns in children following a brain injury (Allen et al., 2010; Bloom et al., 2001; Konigs et al., 2015; Yeates et al., 2005) and will thus be further elaborated on in this section. Attention deficits have been consistently reported across different types of brain injuries; an estimated 15% to 20% of TBI patients report attention problems (Wu et al., 2018), and a significant proportion (46% to 92%) of stroke patients report attention deficits (Barker-Collo et al., 2009). The literature suggests that the susceptibility to attention deficits presents across the different types of brain injuries: traumatic, including mild injury, and non-traumatic brain injury (i.e., stroke). For example, Catroppa, Anderson, Morse, Haritou and Rosenfield (2008) found that children with brain injury performed attention tasks more slowly and less accurately, even five years after their injury. The persistence of attention deficits is also reported in paediatric stroke patients (Steinlin, Roellin, & Schroth, 2004) and paediatric brain tumour patients (Briere, Scott, McNall-Knapp, & Adams, 2008; Shabason et al., 2019). Importantly, studies have illustrated that whilst other cognitive deficits stabilised over time, the deficits in attention only worsened (Briere et al., 2008). This suggests that attention is not only the most susceptible to brain injury among the cognitive processes, but may also have the poorest outcome.

The vulnerability of the cortical (including frontal, prefrontal and parietal) and subcortical brain structures (including the limbic system, thalamus, hypothalamus, reticular formation, and basal ganglia) that support general attention processes to brain injury could potentially explain the prevalence of attention deficits (Park, Allen, Barney, Ringdahl, & Mayfield, 2009). Damage to these brain structures and the neuronal pathways between them would lead to deficits in the associated attention processes. For example, Halterman et al. (2006) suggested that some brain regions are more vulnerable to brain injuries than others; their findings supported deficits in the orienting and executive components of visuospatial attention, and they found that the associated brain regions (parietal and prefrontal regions) are most vulnerable to neural damage from brain injury. The vulnerability of the brain regions supporting attention to brain injury, and the resulting susceptibility to attention deficits, is discussed in greater detail in section *1.7*.

1.4.1 Impact of Attention Deficits

Attention is fundamentally important for performing other cognitive tasks. Thus, attention problems can lead to problems in other cognitive domains, including executive function (i.e., response inhibition, working memory, and shifting) and IQ (Friedman et al., 2007). The association between early attention problems and poor long-term academic outcomes has also been well-established, and is particularly evident in reading and maths achievement (McKay et al., 2019; Rabiner, Carrig, & Dodge, 2016; Rabiner & Coie, 2000; Taylor et al., 2002). It has been suggested that attention deficits might prevent children with TBI from engaging in classroom activities, contributing to their lower academic performance (Treble-Barna et al.,

2017). As a result of poorer reading achievement and grades due to early attention difficulties, the rate of high school graduation in these children is reduced by 40 percent (Rabiner, Godwin, & Dodge, 2016), suggesting an association between attention impairments and dropping out of high school. This in turn burdens both the economy and society due to several factors including lower salary, higher risk of unemployment, and welfare reliance (Fitzpatrick, Archambault, Janosz, & Pagani, 2015). Taken together, the current literature has shown that early attention problem have a significant impact on the child's life, likely leading to long-term problems persisting into adulthood. This constitutes an important research area.

Attention is, however, recognised to be not be a single process but rather a complex process consisting of a group of attention sub-processes or components (Sohlberg & Mateer, 1987). Therefore, to better understand the impact of brain injury on attention, it is important to understand the components of attention, which will be further discussed in the following section via prominent attention models.

1.5 Attention

The following section will discuss prominent attention models, particularly those relevant to patient and paediatric cohorts.

1.5.1 Attention Models

Attention was originally divided into two broad subtypes: selective and sustained attention (Halperin, 1991). Sustained attention, also known as vigilance, denotes the ability to preserve a consistent behavioural reaction towards a repeated task over a long period of time, while selective attention refers to the ability to preserve a reaction when faced with distractions (Sohlberg & Mateer, 1987). However, there have been a number of debates surrounding the cognitive construct of selective attention, in terms of further separating selective attention into divided attention (in which attention is directed simultaneously at multiple stimuli) and focused attention (in which attention is directed to one stimulus while ignoring any other stimuli) (Nebel et al., 2005).

Prominent models have conceptualised attention at the levels of both cognitive processing and neuronal activity. One of the earliest attention models by Posner and Petersen (1990) was generated based on three assumptions: that attention is anatomically differentiated from other perceptual and processing systems, that the attention system is composed of several domains, and that each attention domain is associated with specific networks of anatomical brain structures and pathways. Based on these assumptions, a model was proposed including spatial orientation to sensory stimuli, top-down control of attended stimuli and sustaining attention towards the attended stimuli. In agreement with the assumption of Posner and Petersen (1990), Mirsky, Anthony, Duncan, Ahearn and Kellam (1991) proposed their own four-

factor model in which each attention domain is supported by distinct anatomical structures. The four factors include focus (the capacity for selective attention), sustain (maintaining attention over time), shift (shifting attentional focus) and encode (mental manipulation of information). Based on the model of Mirsky et al. (1991), several other attention models (characterised by sustained attention, selective attention and attentional control) were proposed later on (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996; Manly et al., 2001).

The validation of these models has relied on studies of patient groups. For example, the model of Mirsky et al. (1991) was evaluated in cohorts of neuropsychiatric patients (Kremen, Seidman, Faraone, Pepple, & Tsuang, 1992). The four factors (perceptual motor speed, mental control, flexibility and vigilance) found in Kremen et al. (1992)'s study closely replicated Mirsky et al. (1991)'s model, which suggests a typical organisation of attention types both in neuropsychiatric patients and in healthy participants. However, using confirmatory factor analysis (CFA), Strauss, Thompson, Adams, Redline and Burant (2000) – whose study included adults with sleep disorders who completed neuropsychological tests meant to tap into Mirsky et al. (1991)'s four factors of attention – found that the four-factor model was not appropriate. Strauss et al. (2000), however, suggested that the four attention factors might simply not be clearly validated by the measures used to measure them, suggesting that variance in methods likely influences testing for relations. Robertson et al. (1996) instead proposed a three-factor attention model (selective, sustain and attentional switching); these components were used as a basis for developing a new measure that would capture associated skills appropriately. The authors' Test of Everyday Attention (TEA) included eight subtests that evaluated the three factors. The use of several tests for each factor was intended to eliminate the problem of method variance, as suggested by Strauss et al. (2000). Using factor analysis with the TEA subtests and other established attention tests (Winconsin Card Sorting Test, Stroop, Digit Span, Trail Making and the Paced Auditory Serial Addition Test), Robertson et al. (1996) in fact extracted four factors quite similar to Mirsky et al. (2001)'s model (visual selective, attentional switching, sustain and auditory-verbal working memory). The uncertainty regarding whether attention is best broken down into three or four factors may have resulted from differences in the measures used to assess attention as well as the differences in the demographics of participants; Strauss et al. (2000) suggested that the attention factor measured may differ across neuropsychiatric and brain injury populations as a result of affected brain structures and compensatory changes. Thus, the models and measures of attention developed in adult populations may require revision in the developmental context.

There has also been inconsistency regarding the optimal account of attention skills within paediatric studies. Similar to the adult population, Mirsky et al. (1991) tested their attention model with 435 healthy children with an average age of 8 years using similar subtests that were used with the adults. The study found the same attention elements (focus, shift, sustained and encode) in the children cohort as the adult cohort. Despite using the same

subtests as Mirsky et al. (1991), Kelly (2000) instead found support for a three-factor model in which focus and encode were collapsed into one component referred to as the speed of response. Kelly (2000)'s model is, however, consistent with Mirsky et al. (1991)'s actual prediction that the encode tests (Arithmetic and Digit Span from the Wechsler Intelligence Scale for Children (WISC-R)) were originally included as measures of focused attention. The disparity in findings may be due to the age difference in the participants of the two studies; Kelly (2000)'s study included children between the ages of 7–13 years, while the children in Mirsky et al. (1991)'s study were 8 years old on average. Whilst the speed of response factor (comprising the focus and encode factors) demonstrates significant development across the age group of 7–13 years, the developmental profiles of the attention tests were not considered in Mirsky et al. (1991)'s study.

Manly et al. (2001) then developed the Test of Everyday Attention for Children (TEA-Ch) based on Robertson et al. (1996)'s original TEA. Using confirmatory factor analysis (CFA), the authors tested TEA-Ch with typically developing children between 6 and 16 years of age and found that a three-factor model was appropriate (selective, sustain and attentional control). Studies have shown that subtests from TEA-Ch are age-sensitive and, as with the three-factor model, are found to be appropriate for both younger and older children (Chan, Wang, Ye, Leung, & Mok, 2008; Manly et al., 2001). One of the reasons that encode may not be a domain in children's attention model is that since different domains of attention have distinctive underlying neuroanatomical structures, the cortical structures underlying encode may only be developed fully later in life and thus cannot be appropriately measured in children. This notion was further supported by other studies that have supported the three-factor model as the best fit for children (Burgess, Veitch, de Lacy Costello, & Shallice, 2000). Accordingly, this thesis evaluated attention and its neural networks in children based on Manly et al. (2001)'s attention model.

1.5.2 Brain Regions Associated with Attention

This section will discuss the brain regions associated with the different components of attention based on Manly et al. (2001)'s model: selective, sustain and attentional control. Some brain regions are known to support multiple components of attention. For example, tasks involving sustained and selective attention activate similar parietal and frontal brain regions (Asplund & Chee, 2013; Corbetta & Shulman, 2002). Moreover, some attention components may tap into another common attention subtype, such as sustained attention and attentional control; therefore, we may identify brain regions underpinning attentional control when examining neural substrates supporting sustained attention (Malinowski, 2013). Despite the overlaps in neural regions underpinning some attention subtypes, there are also distinct brain regions associated with specific attention subtypes (Luo & Maunsell, 2019; Mirsky et al., 1991; Posner & Petersen, 1990).

1.5.2.1 Selective Attention

Selective attention is the ability to focus on target stimuli while ignoring other distractor stimuli, and is proposed to be an important skill for learning and academic achievement (Astheimer & Sanders, 2012). Early studies have identified that several brain regions, including the precuneus, superior parietal lobule, lingual gyrus, fusiform gyrus, parahippocampal areas, thalamus, and frontal gyrus are activated during selective attention tasks in both healthy adults and children (Booth et al., 2003). The study did, however, find that compared to adults, children showed greater activation in the left thalamus and right anterior cingulate; this could reflect developmental differences. Booth et al. (2003) suggested that as the developmental difference was small, the observed difference may reflect earlier maturation of the brain regions underpinning selective attention as the longer maturation of the fronto-striatal network, which is consistent with the prolonged developmental nature of the response inhibition. The developmental differences may, however, indicate that the selective attention ability of children is not maturely developed at the ages 9–12 years. This is supported by later studies showing that selective attention continued to develop into early adulthood (Cowan, Fristoe, Elliott, Brunner, & Saults, 2006). Plude, Enns and Brodeur (1994) suggested that children's poorer selective attention is a result of their poorer ability to ignored unattended stimuli, as this ability continues to develop into adulthood. This was observed in Booth et al. (2003)'s study, which demonstrated extensive developmental differences in response inhibition between children and adults. Thus, whilst brain regions underpinning selective attention may be developed in childhood, selective attention ability may still be immature because of its dependence on response inhibition, which is not fully developed until adulthood.

1.5.2.2 Sustained Attention

Sustained attention is the ability to maintain attentional focus over a prolonged period when presented with a task (Posner & Rothbart, 1992). Earlier studies have found that the prefrontal and superior parietal cortex, predominantly in the right hemisphere, consistently underpin sustained attention; an increase in regional brain activity in these areas was reported during attention tasks in healthy adults (Cohen, Eckhardt, & Schagat, 1998; Pardo, Fox, & Raichle, 1991). Whilst similar brain regions are activated in children and adults during a sustained attention task, studies have found increased activation in the right inferior frontal, superior temporo-parietal and cerebellar cortices, and reduced activation in the posterior cingulate, insular and posterior cerebellar cortices with increasing age (Smith, Halari, Giampetro, Brammer, & Rubia, 2011). The increased activation in the brain regions found in conjunction with increasing age suggests the continued development of these brain regions through childhood into mid-adulthood; the continued maturation of sustained attention abilities throughout adolescence is suggested to be associated with the still-maturing frontal cortices (Thillay et al., 2015). Meanwhile, the increased activation of the posterior cingulate, insular and

posterior cerebellar cortices in younger participants during sustained attention tasks may reflect a compensatory and less mature attentional system in children, who may require more effort to perform comparably to older participants; Smith et al. (2011)'s study found a lack of significant differences in accuracy between children and adolescents. Taken together, the existing studies suggest that sustained attention develops throughout childhood into adulthood, as the brain regions underpinning it, particularly the frontal cortices, do not fully mature until adulthood.

1.5.2.3 Attentional Control

Lastly, attentional control is the ability to choose what to devote attention to and what to ignore (Eysenck, Derakshan, Santos, & Calvo, 2007). Attentional control is measured by approximating changes in the blood-oxygen-level-dependent (BOLD) signal caused by the cue independent of the signal changes caused by the target (Hopfinger, Buonocore, & Mangun, 2000). By measuring the fMRI signals obtained in the spatial attention task, in which participants were cued to covertly direct attention to one of four stimuli displayed in the right or left visual field and to detect the occurrences of a target stimulus, a study found activations in the frontal and parietal cortex (including the right intraparietal sulcus, the left frontal eye field and the left posterior parietal cortex) in healthy adults (Szczepanski, Konen, & Kastner, 2010). Using event-related fMRI while participants performed a revised version of the Attention Network Task (a combination of the cued reaction time task and the flanker task), Konrad et al. (2005)'s study found that children showed less activation in the right inferior frontal gyrus and left superior parietal cortex, and greater activation in the left superior frontal gyrus and the right superior temporal gyrus, compared to adults. This may reflect immature neural systems in the fronto-parietal networks, which are known for their protracted development (Casey, Tottenham, Liston, & Durston, 2005). The immaturity may in turn explain the poorer attention abilities in children as compared to adults (Gaspelin, Margett-Jordan, & Ruthruff, 2015).

Early neuroimaging studies have focused largely on the activation of specific brain regions that are associated with specific cognitive skills, providing valuable information on the nodes of task-relevant networks (Parks & Madden, 2013). Findings from more recent studies, however, have demonstrated that a distributed network, specifically the frontal and parietal regions, is active concurrently when carrying out specific attention-demanding tasks (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). This suggests that instead of focusing on the activation and deactivation of brain areas during task conditions, it is more appropriate to utilise a network approach to understand the neural basis of specific attention skills.

1.5.3 Neural Networks of Attention Skills

There is considerable evidence that cognitive skills are not simply reliant on specific brain areas, and that the links or connectivity pattern between brain regions can provide us with important information on the neural substrates underpinning cognitive skills (Menon, 2010). Accordingly, the performance of attention tasks is heavily reliant on coordination between brain regions, such as the frontal and parietal regions. Disruptions in this network have been linked to attention problems (Parks & Madden, 2013). For example, the functioning of the attentional control system is reliant on a widespread network involving the dorsal posterior parietal and the frontal eye field (Corbetta & Shulman, 2002). One study has found increased activation in widespread fronto-parietal brain areas, particularly in the inferior parietal lobule, in problematic smartphone users compared to control participants, and the increased activation was found to be associated with attentional control impairments (Choi et al., 2021). Similarly, studies have demonstrated that selective attention is also underpinned by intrinsic connectivity networks; Rohr et al. (2017)'s study suggested that greater connectivity within the dorsal attention network (intraparietal sulcus and the frontal eye fields) is associated with better selective attention performance in healthy children. Lastly, studies have identified correlated activation in several brain regions that constitute the default mode network (DMN), including the posterior cingulate cortex, precuneus, lateral temporal cortex and medial prefrontal cortex, during the performance of sustained attention tasks in healthy adults (Danckert & Merrifield, 2018). Moreover, when the sustained attention tasks were performed, these regions were found to be anti-correlated with brain regions commonly associated with the central executive network (CEN), such as the rostral middle frontal gyrus, which suggests that as with the other attention elements, sustained attention is also underpinned by a network of correlating brain regions. Overall, the literature has illustrated that the proper functioning of all three types of attention relies on the cooperation between/within neural networks as opposed to specific, isolated brain regions.

1.6 Sustained Attention in ABI

Despite brain injury affecting all aspects of attention (selective, sustained and attentional control), sustained attention (measured with reaction time and accuracy parameters of the continuous performance task or auditory tasks) has been identified in a review as being the most vulnerable to brain injury and is thus the interest of the present thesis (Ginstfeldt & Emanuelson, 2010). Sustained attention deficit can severely impact a child's daily functioning and academic achievements (Mahalick et al., 1998); it is also linked to sleep disturbance (Bloomfield, Espie, & Evans, 2010). Importantly, while other aspects of attention recovered over time, sustained attention remained impaired (Kwok, Lee, Leung, & Poon, 2008) even one year after the injury (Ginstfeldt & Emanuelson, 2010; Robin, Max, Stierwalt, Guenzer, & Lindgren, 1999). Using the continuous performance test (CPT), Vriezen and Pigott (2000) found that moderate and severe TBI patients continued to demonstrate poorer performance (worse

accuracy) two years after the injury. The persistence of sustained attention deficits is also found in survivors of non-traumatic brain injuries, such as strokes (Suppiej et al., 2016) and tumours (Reddick et al., 2003; Reeves et al., 2006). Using the accuracy parameter of the Bell's test, Suppiej et al. (2016) found that children with a history of perinatal arterial ischemic stroke demonstrated long-term sustained attention impairments (i.e., lower accuracy), and sustained attention has also been found to be the most affected cognitive function in these patients.

As sustained attention underpins other attention processes such as selective and divided attention, as well as general cognitive skills (Sarter, Givens & Bruno, 2001), impairments to sustained attention can result in deficits in the other attention processes, as well as in executive control (Dockree et al., 2004). Moreover, sustained attention deficits have been linked to lower IQ and academic achievement (Reddick et al., 2003), particularly reading and math performance (Reeves et al., 2006). The poorer performance could be due to the fact that impairments in sustained attention are likely to affect a child's ability to gain and incorporate new skills and knowledge, which in turn affects their academic performance (Betts, McKay, Maruff, & Anderson, 2006). This is in line with early papers that illustrated correlations between deficits in sustained attention and challenges in learning, highlighting the importance of sustained attention to the skills that support academic achievement (Ricks & Mirsky, 1974).

In short, the current literature has illustrated not only the devastating impacts of attention deficits on a child's academic performance, but also, and more importantly, the vulnerability of sustained attention to different types of brain injuries, suggesting a potential common underlying neural dysfunction across disorders/injuries. Advancements in neuroimaging methods have made it possible to study the brain after an injury, and existing studies suggest that brain structures associated with sustained attention are particularly vulnerable to neural disruptions as a result of brain injury. Thus, the vulnerability of sustained attention to brain injury is unsurprising (Bigler, 2001). Specifically, consistent alterations in the DMN and CEN are found in adult brain injury patients, as these networks intersect at the prefrontal midline regions, which are susceptible to brain injury (van der Horn et al., 2017). These networks play important roles, particularly in performing sustained attention tasks. This can explain the vulnerability of sustained attention to brain injury. Moreover, other studies have suggested that brain injury interrupts the fronto-parietal network, impairing endogenous control during attention tasks and consequently leading to an increase in lapses of attention and impairing sustained attention performance (Dockree et al., 2004).

Despite the vulnerability of sustained attention to early brain injury, very few studies have actually examined the associative neural networks in these patients. This represents a gap in the literature. To bridge the gap, the current thesis includes several experimental studies that examine the neural substrate of sustained attention following a brain insult using existing non-invasive neuroimaging methods. These methods are based on existing studies that will be discussed in the next few sections.

1.6.1 Measures of Sustained Attention in Clinical Practice

Sustained attention has been operationalized differently in different studies, and this thesis has defined and operationalized it as an individual's readiness to detect unpredictable relevant signals/targets over a prolonged period of time (Sarter et al., 2001). Due to the large variation of the operationalization of sustained attention in the current literature, there is inconsistency in the measures or tests used to examine it. One of the most common tasks used in clinical settings to assess sustained attention is the continuous performance task (CPT; Riccio, Reynolds, Lowe & Moore, 2002). CPT typically involves presenting participants with a series of stimuli (i.e., numbers, letters) over a prolonged period of time, and participants are required to respond to target stimulus and to not respond to a non-target stimuli. Studies have however suggested that the usefulness of CPT is limited by its reduced sensitivity, specificity and ecological validity due to the lack of external stimuli (Berger, Slobodin & Cassuto, 2017). Moreover, many variants of the CPT exist (as illustrated in later chapters when discussing about previous works), and whilst these variants may share the core constructs of sustained attention, there are also many differences (i.e., test duration, test design, stimulus type (auditory or visual) and outcome variables) between them (Fuermaier et al., 2022). Due to these differences, studies have questioned if the different versions of CPT share the same sustained attention construct, and have highlighted that some of the CPT measures may instead involve other non-attention cognitive skills rather than providing a pure sustained attention measure (Shalev, Ben-Simon, Mevorach, Cohen & Tsal, 2011). Shalev and colleagues (2011) have instead proposed the use of conjunctive continuous performance task (CCPT) as it was found to provide a pure sustained attention measurement while being insensitive to the other attention domains (i.e., selective and orienting attention). Despite being an effective measurement of sustained attention, the CCPT has however not been validated in the paediatric and/or patient populations. Using adult measures with children population can be an issue due to the differences in terms of development, ability to understand instructions and age relevant behaviours between the populations (Mitchell et al., 2021). Instead measures/assessments that consider the younger subjects' abilities and development would be a more appropriate choice to measure attention in children (Prieler, Wood & Thomson, 2018). For example, the Test of Everyday Attention for Children (TEA-Ch), which uses nine game-like subtests to assess sustained, selective and attentional control, could be a more appropriate measure of sustained attention in the children population (Manly et al., 2001). TEA-Ch has been adapted from the test of Everyday Attention (TEA; Robertson et al., 1996), originally designed to assess a range of attention domains in adults. TEA-Ch is potentially a more appropriate measure , as it is normed for children ages 6-16 years, and is well established with the children population (Heaton et al., 2001), and also in paediatric patients (Shortman et al., 2014). In addition, as compared to other attention measures like CPT, TEA-Ch may also have better ecological validity as the subtests are more aligned to the real world attentional demands (Anderson, Fenwick, Manly & Robertson, 1998).

Importantly, the use of game-like subtests in TEA-Ch may also aid in increasing participants' engagement when performing the tasks, which can be a challenge especially when assessing children (Heaton et al., 2001).

These tests can, however, be limited in their usefulness as clinical research tools, as many were originally intended for measuring severe cognitive difficulties originating from a TBI or stroke (Horowitz, Suls, & Trevino, 2018). As a result, the tests may lack sensitivity to subtle impairments in other clinical populations with less severe deficits (Nelson & Suls, 2013). More importantly, there are challenges in carrying out these standardised tests with a paediatric patient population as opposed to adults or even typically developing children, as the paediatric patients may find the tests to be difficult or boring (Conniff, 2008). These factors can affect the reliability of the test scores and consequently influence the interpretation of the findings. Moreover, studies have also suggested that the interpretation of test results in paediatric patients appears to be more challenging than in adults because of the need to consider that the child may be trying to recover previously developed skills in addition to developing new, age-appropriate skills (Heilbronner et al., 2010). Given these complicating factors, the use of neuroimaging techniques to assess attention may be more suitable for the paediatric patient population; these techniques will be discussed in the following sections.

1.7 Neuroimaging

The development of non-invasive neuroimaging techniques has allowed researchers to deepen our understanding of how paediatric brains develop and how vulnerable or resilient they are to diseases and environmental harms. Techniques such as magnetic resonance imaging (MRI), magnetoencephalography (MEG), positron emission tomography (PET) and the electroencephalogram (EEG), which allow the study of brain functioning in healthy participants, are increasingly being used in paediatric participants (Morita, Asada, & Naito, 2016).

The EEG imaging technique involves placing tens to hundreds of electrodes on the participant's scalp to measure electrical activities within the brain (Gui, Chuansheng, Zhong-Lin, & Qi, 2010). The electrical activity manifests as electrical potentials resulting from the flow of current in and around the brain cells (neurons) as they are activated (Biasiucci, Franceschiello, & Murray, 2019). Despite the cost-effectiveness and ease of use of EEG, the MEG is recommended for greater spatial resolution compared to EEG (Singh et al., 2014). With MEG, sensors are placed on the participant's scalp to measure changes in the magnetic fields produced by the electrical activity of neurons, providing sharp resolution of neural activity (Singh et al., 2014). PET, another functional imaging technique, uses a radioactive isotope (radiotracers) to measure metabolic activity in the brain, but may be at a disadvantage compared to the other imaging techniques due to its poorer spatiotemporal resolution, exposure of the participant to ionising radiation, and the involvement of an intravenous injection, which makes PET slightly invasive (Walker & Bilgel, 2021).

Despite the usefulness of other neuroimaging techniques, MRI holds the advantage of being a versatile imaging modality; it allows researchers to examine both functional and structural aspects of the brain (Lenroot & Giedd, 2006; Morita et al., 2016). In clinical centres treating children with ABI, the standard MRI is routinely used, and many centres have adopted advances in functional imaging (Lee & Newberg, 2005; Orringer, Vago, & Golby, 2012). Structural MRI (inclusive of T1-weighted MRI and diffusion tensor imaging (DTI)) is a non-invasive technique that examines the anatomy and pathology of the brain, while functional MRI (also non-invasive) examines brain activity. While both techniques use structural MRI, T1-weighted MRI and DTI are vastly different in terms of the structural measurements derived from them. T1-weighted MRI uses differences in T1 relaxation time between the different tissues (grey matter, white matter and cerebrospinal fluid) to generate high-resolution anatomical images that tissues measurements (commonly cortical thickness and grey matter volume) are derived from (Symms, Jager, Schmierer & Yousry, 2004), discussed further below; DTI is a variant of MRI based on the tissue water diffusion rate (O'Donnell & Westin, 2011) and is mainly used to estimate white matter connectivity patterns from white matter tractography derived from DTI (Alexander, Lee, Lazar & Field, 2007). Importantly, due to their simpler implementation (i.e., not requiring that electrodes be placed on participants, which can be a problem particularly for participants with behavioural or sensory issues (Paasch, Hoosier, Accardo, Ewen, & Slifer, 2012)), their use is well-established in the paediatric population for examining the development of the brain as well as neural changes in patients (Morita et al., 2016; White et al., 2018). MRI has also been shown to effectively capture functional and structural changes in the brain sustained after a brain injury. This capability is further addressed in the following sections and utilised in this thesis (Lee & Newberg, 2005).

1.7.1 Functional MRI

Functional MRI (FMRI) measures the BOLD signal in the brain; the signal depends on the level of oxyhaemoglobin and deoxyhaemoglobin and reflects neuronal activity. Task-based fMRI is widely used to examine brain regions that are functionally involved in carrying out a cognitive or behavioural task (Logothetis, 2008); task-based evoked neural response leads to altered metabolism, which in turn, results in an observable change in the oxygenation level of the brain tissue, which fMRI can detect (Chen & Glover, 2015). Resting-state fMRI studies functional networks without requiring participants to complete tasks by measuring the spontaneous, low-frequency fluctuations in the BOLD signal (Fransson, 2005). Spontaneous BOLD fluctuations are fluctuations in the neuronal activity that are correlated between functionally related brain regions (Fox & Raichle, 2007) or within distinct functional networks, including the DMN (Rasero et al., 2018).

1.7.1.1 Resting-state functional MRI

Compared to traditional task-based fMRI, resting-state fMRI is particularly advantageous for examining the spontaneous fluctuations in the BOLD signal, in both patient and paediatric populations. This is because it can overcome the limitations of task-based fMRI use with patients who are cognitively impaired and/or are unable to perform the tasks (Kumar et al., 2020) and allow the studying of these populations that may have been excluded previously from task-based fMRI (Shimony et al., 2009).

Moreover, recent studies have established the use of resting-state fMRI to identify several functional networks (such as the attention networks and fronto-parietal network) during rest that were similarly activated during task-based fMRI (Rasero et al., 2018). For example, studies have shown that the language network obtained from resting-state fMRI overlaps significantly with that obtained from task-based fMRI in both healthy and patient (brain tumour/epilepsy) populations (Branco et al., 2016; Tie et al., 2014). Similar overlap is also observed in attention networks during the resting-state and while completing attention tasks (Harrewijn et al., 2020). Resting-state fMRI can therefore be useful in identifying alterations in activation patterns in networks underpinning specific cognitive skills in patients with neurological diseases. This can help in identifying patients who may suffer from those specific cognitive impairments.

Despite its effectiveness and widespread use as a research tool, fMRI is still not widely used clinically, and the fMRI abnormalities found in research have not been translated into an ability to obtain useful prognostic knowledge in patients. This is primarily because of the inconsistencies in findings across studies, which should be urgently addressed (Fox & Greicius, 2010).

1.7.1.2 Analysis Methods for fMRI

Conventional fMRI analysis focuses on detecting activated brain regions and identifying specific brain regions that are functionally associated with behavioural or cognitive processes (Kriegeskorte & Bandettini, 2007). The change in oxygenation, as measured by BOLD, is often used to characterise the activation maps of the brain, and, in turn, characterise neuronal activity (Glover, 2011). Region of interest (ROI) analyses are then used to perform functional analysis to examine the particular brain regions that were activated (Poldrack, 2007). These analysis methods, however, only focus on the functional activity of specific brain regions, and do not examine how the different brain regions interact functionally as a network—something that functional connectivity analyses permit (Bullmore & Sporns, 2012). This is especially important when studying individuals with brain injuries. Brain injuries can be divided into focal (contained to a specific region of the brain) and diffuse/generalised injuries (occurring over a widespread area), and diffuse traumatic brain injury, for example, is known to disrupt the white matter tracts connecting distant brain regions, leading to alterations to several large-scale brain networks

(Hayes, Bigler, & Verfaellie, 2016). Moreover, despite differences in brain recruitment found in paediatric patients with either focal or diffuse acquired brain injuries, more important is the fact that both injury types have demonstrated network alterations (Strazzer et al., 2015). This suggests that even focal injury can lead to widespread disruptions, and underscores the relevance of transitioning from a conventional ROI analysis to the more suitable functional connectivity methods.

One of the earliest functional connectivity analysis methods to emerge was seed-based correlational analysis (Biswal, Yetkin, Haughton, & Hyde, 1995). Seed-based functional connectivity analyses are dependent on a priori selection of ROI and measure the correlation between activity (i.e., time series of the BOLD response) in the ROI and the rest of the brain (Lv et al., 2018). The correlation of activation between the different brain regions suggests that they are part of the same network underpinning the same functional processes, and thus can be regarded as functionally connected. Greater correlations would therefore suggest stronger functional connectivity between the brain regions. Though seed-based analyses are simple and the findings are straightforward to interpret, the dependence on a priori selection of regions leaves room for bias, and the method may not provide a complete picture of the brain networks that are involved in specific cognitive tasks (Lv et al., 2018).

Exploratory data-driven analyses methods, which do not require a priori information, can overcome the potential bias associated with the seed selection in seed-based analysis that can result in extensive variability in the findings and their interpretations if irrelevant seeds are selected (Cole, Smith, & Beckmann, 2010). The method most commonly used in resting-state fMRI studies is independent component analysis (ICA) (Jutten & Herault, 1991), which divides fMRI data into spatially or temporally independent networks based on the time series BOLD signals. An advantage of the ICA approach is that the ICA algorithm can automatically separate resting BOLD fluctuations from noise signals such as head motion or scanner-induced artefacts (Damoiseaux et al., 2006), an issue faced in seed-based analyses as noise can influence the connectivity measurements (Cole et al., 2010). ICA identifies independent functional networks that present functionally connected brain regions as they covary together; these are derived by maximising statistical independence between estimated functional components (Park, Kim & Park, 2014). Compared to seed-based analyses, the interpretation of connectivity is less straightforward (Sheffield & Barch, 2016). Moreover, ICA presents the networks as individual components, which does not permit a measurement of connectivity (i.e., the connectivity strength) between modules within the component, or communication between components (i.e., different brain networks). The interpretation of ICA findings can thus be limited (Lv et al., 2018; Park, Kim, & Park, 2014). This is particularly relevant to brain injury research because it is well-established that brain injury does not cause merely isolated disruption, and the cognitive impairments observed are known to be underpinned by disruptions both between and within different neural networks (Han, Chapman, & Krawczyk, 2016). Instead, studies have suggested

that whilst ICA can identify the neural networks, seed-based analyses are useful in providing information for specific ROI (Gandhi, 2016), and combining both methods could overcome the challenges discussed, as the seeds for seed-based analysis can be derived from the ICA, which may be more sensitive, whilst providing a complete picture of the functional networks (Kelly et al., 2010).

Another analysis method commonly used in fMRI studies is graph theory, which establishes mathematical models of the brain as a network including nodes (regions) and edges (connectivity between the nodes). Graph theory describes the interaction between nodes (Soares et al., 2016), revealing highly connected or centralised hubs, small-worldness, and modular organisation. Unlike seed-based analyses, which only focus on the functional connectivity between two ROIs, graph theory accounts for all potential seeds and considers the functional connectivity between all brain regions, consequently modelling the whole-brain network as a graph, also known as the functional connectome. This allows researchers to study the large-scale organisation of the brain networks. However, the increased multiple comparisons in connectome analysis, as compared to seed-based analysis, may be more sensitive to a small sample size and its accompanying lack of power (Wen & Hsieh, 2016), which can lead to biased inference and inflate the false positive and false negative rates (Columb & Atkinson, 2016; Gerlovina, van der Laan, & Hubbard, 2017). This is evidenced in Hong et al. (2013)'s study, which only found decreased functional connectivity in internet-addicted individuals (n = 12) when using graph-based network measures. It did, however, find both increased and decreased connectivity upon re-analysis using seed-based analysis, which involves fewer multiple comparisons than a whole-brain approach (Hong et al., 2015). This suggests that seed-based analysis may be a more appropriate approach for studies with small sample sizes.

These analysis methods are generally considered to be complementary to one another. Combining the different methods – for example, ICA and seed-based analyses (Kelly et al., 2010), as earlier discussed – could potentially result in a more well-rounded, data-driven representation of the resting network in the brain (Lv et al., 2018). Importantly, no single analysis method is considered to be the criterion standard method. Each method has its own advantages and limitations, and it is more important to choose an appropriate method for the specific research question. The present thesis therefore uses different analysis methods that are relevant to answering the different questions posed in the experimental chapters. The following sections discuss previous neuroimaging studies in relation to sustained attention.

1.7.1.3 Functional Neural Substrates of Sustained Attention in Healthy Adults

Using different neuroimaging methods (such as fMRI and PET), the existing literature suggests a mostly right-lateralised network in the fronto-parietal cortices underlying sustained attention based on studies of healthy adults across different sensory modalities (Cabeza & Nyberg, 2000; Cohen, Semple, Gross & Holcomb, 1988) and different behavioural methods (Cabeza & Nyberg, 2000; Ogg et al., 2008). It has been suggested that the simpler paradigms used in studies may account for the more strongly lateralised right hemisphere activation (Sturm et al., 1999), and indeed when cognitive complexity was increased, bilateral activation was observed (Ogg et al., 2008).

Similar to functional MRI, PET relies on the rationale that neuronal activity is proportionate to regional cerebral blood flow or level of metabolic activity (Lassen, Ingvar, & Skinhoj, 1978). Using PET while carrying out an auditory discrimination task, a significant association was found between sustained attention and the dorsolateral prefrontal cortex (PFC), parietal cortex, and left-sided subcortical structures (Paus et al., 1997). Using an auditory simple reaction time task, another PET study demonstrated that reaction time increased along with reduced activity in the right dorso- and ventrolateral PFC, inferior parietal cortex, anterior frontal gyrus and left thalamus, suggesting that better sustained attention performance is reliant on greater neural activity in these regions (Sturm et al. 2004). Despite reporting an increase in cerebral blood flow in the bilateral frontal gyri, parietal cortex, fusiform gyrus and right frontal superior gyrus, when participants performed a rapid visual information-processing task (a sustained attention test that also requires working memory), the results suggested that the left fronto-parietal network underpinned working memory. Additionally, and consistent with previous studies, sustained attention is suggested to be supported by the right fronto-parietal network sustained attention (Coull, Frith, Frackowiak, & Grasby, 1996). The general consensus of PET studies is therefore that the right hemisphere of the brain, particularly the frontal and parietal regions, plays an important role in sustained attention (Pardo et al., 1991).

Similar to PET studies, fMRI studies have also suggested the importance of the frontal and parietal regions in sustained attention. One study reported that the performance of sustained attention tasks (rapid visual information processing task) activated a network of frontal, parietal, occipital, thalamic and cerebellar regions (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003). Along with the activated brain regions, however, the study reported deactivations in the anterior and posterior cingulate, insula and the temporal and parahippocampal gyri when performing the task. The study found a correlation between better attention performance (i.e., number of hits and faster reaction time to hits) and increased activation in the fronto-parietal regions along with greater deactivation in the left temporo-limbic and cingulate regions. Importantly, the study by Lawrence et al. (2003) study suggested that the neuronal network underpinning sustained attention comprises a task-positive network (brain regions that are active when performing a task) and a task-negative network (brain regions that

are not active when performing a task). The performance of attention tasks is reliant not only on activation in the frontal-parietal brain regions, but also on both proper activation in the task-positive network and deactivation in the task-negative network.

The nature of a task-positive and task-negative network underpinning sustained attention is also evidenced by other task-based fMRI studies (Ogg et al., 2008). Ogg et al. (2008)'s study showed activations in an extensive neural network including the frontal, cingulate, parietal, temporal and occipital cortices, the cerebellum and the basal ganglia, along with deactivations in the posterior cingulate, precuneus, medial frontal and lateral parietal regions when performing the continuous performance test (CPT). The study has also reported that better CPT performance (i.e., faster reaction time) was largely associated with the regions that were found activated or deactivated. The brain regions forming the task-negative network in Ogg et al. (2008)'s study corresponded widely to the regions forming the DMN, a finding consistent with the general consensus of the current literature (Gusnard & Raichle, 2001; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Meanwhile, the task-positive network underlying sustained attention has repeatedly been identified as the fronto-parietal network, commonly known as the central executive network (CEN) (Dosenbach et al., 2006; Yarkoni et al., 2005).

The task positive network (the CEN) comprises the lateral prefrontal cortex and posterior parietal cortex, and the core regions of the task-negative network (the DMN) include the prefrontal cortex, posterior cingulate cortex/precuneus, and parietal cortex. Using MNI coordinates provided by the CONN toolbox, obtained from the ICA of 497 participants from the Human Connectome Project (Whitfield-Gabrieli & Nieto-Castanon, 2012), the DMN and CEN are presented in Figure 1.1 and Figure 1.2 using BrainNet Viewer, Version 1.63 (Xia, Wang, & He, 2013). According to previous studies, the DMN is suppressed during tasks but shows greater activity in the resting state and in the performance of internal tasks, such as retrieving an autobiographical memory, imagining the future or forming perspectives of others (Buckner, Andrews-Hanna, & Schacter, 2008). The CEN, meanwhile, is activated during goal-directed tasks (D'Esposito, 2007). It has been suggested that the DMN regions are deactivated during sustained attention tasks to meet the need for focusing attention on the demands of the task, instead of distributing the attention to introspective processes during the resting state (Coull et al., 1996; Gusnard & Raichle, 2001). Studies have suggested that the DMN and CEN share an anti-relationship in which the two networks are negatively correlated (Fox et al., 2005), and this anti-correlation is crucial for proper cognitive functioning (Hampson, Driesen, Roth, Gore & Constable, 2010). This is because the anti-correlation relationship between the DMN and CEN requires both networks to cooperate to divert attentional resources away from self-referential processes and towards the demands of cognitive tasks (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). The importance of the anti-correlation between both networks is observed in a study by Sonuga-Barke and Castellanos (2007) that suggested the interference of task-

unrelated brain activity in the DMN is due to the intrusion of task-negative thoughts (i.e., introspective thought) affecting the integrity of task-related functional networks, which in turn affects sustained attention performance. The current literature has therefore highlighted the important roles played by the DMN and CEN, as well as their interaction in proper brain function, specifically in relation to sustained attention in healthy adults. The next section focuses on the healthy paediatric population (Hampson et al., 2010; Kelly et al., 2008; Spreng, Stevens, Chamberlain, Gilmore & Schacter, 2010).

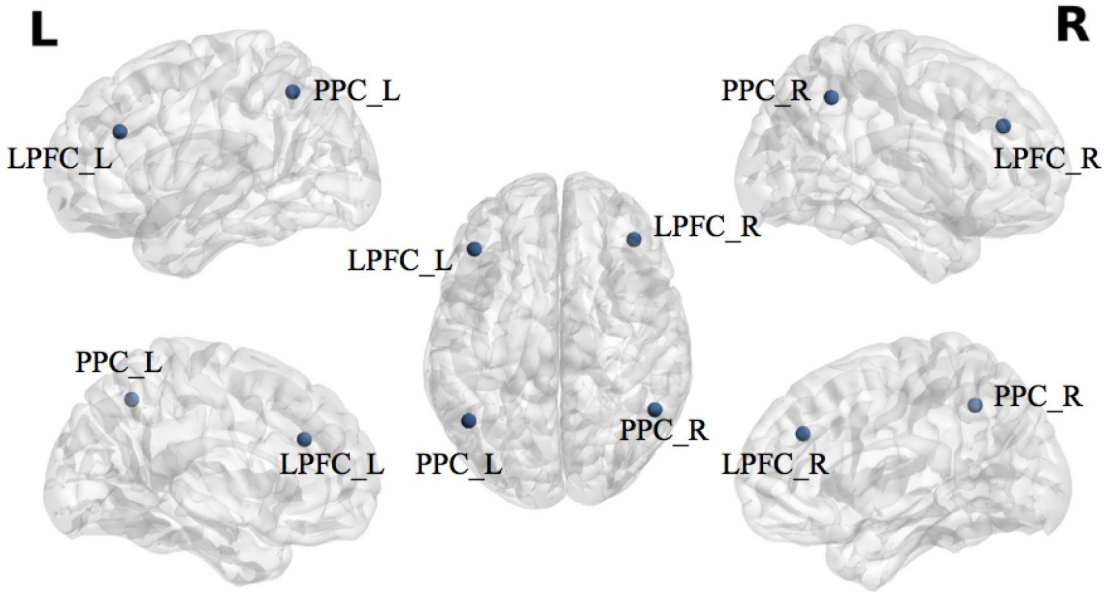

Figure 1.1. *Regions of interests (ROIs) corresponding to the central executive network (CEN) obtained from the CONN toolbox displayed on a template brain generated using the BrainNet Viewer toolbox. LPFC = lateral prefrontal cortex, PPC = posterior parietal cortex.*

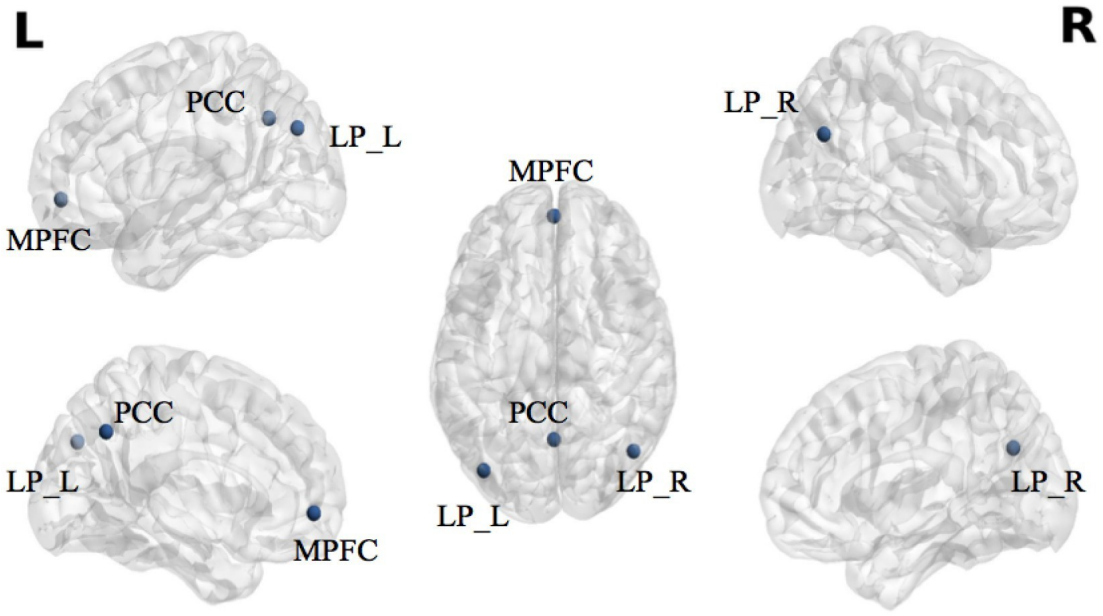

Figure 1.2. *ROIs corresponding to the default mode network (DMN) obtained from the CONN toolbox displayed on a template brain generated using the BrainNet Viewer toolbox.*
MPFC = medial prefrontal cortex, PCC = posterior cingulate cortex, LP = lateral parietal cortex.

1.7.1.4 Functional Neural Substrates of Sustained Attention in Healthy Children

Given the differences in the maturation rates of different brain regions, such as the slower maturation of the prefrontal cortex (Arain et al., 2013), which is pertinent to the performance of attention tasks, there may be disparities between the underlying neural mechanisms of sustained attention in children and adults. Despite sustained attention having been extensively studied in functional and structural imaging studies in healthy adults, studies in typically developing children are far more scarce, and most attention studies involving children are conducted on clinical samples.

Similar to healthy adults, studies have found that sustained attention in healthy children is reliant on the DMN and CEN (Bauer et al., 2020). More specifically, the study by Bauer et al. (2020) suggested that greater sustained attention performance (i.e., better accuracy measured using the Go-Accuracy accuracy parameter of the sustained attention to response task) was associated with greater resting-state anti-correlation between the DMN and the right dorsolateral prefrontal portion of the CEN in sixth graders. However, studies have suggested that the relationship between the DMN and the CEN changes from a positive correlation in healthy children to anti-correlation in adults, with typically developing adolescents exhibiting an intermediate level of anti-correlation (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Sherman et al., 2014). These studies suggest that the DMN and CEN relationship matures through development from a positive correlation to an anti-correlation. This maturation of anti-correlation is associated with better cognitive control, supporting the poorer sustained attention performance in children, as discussed earlier.

A developmental fMRI study of sustained attention including children and adults between 10 and 43 years of age also found that the right fronto-temporal-parietal network underpins attention across both age groups (Smith, Halari, Giampetro, Brammer, & Rubia, 2011). Smith et al. (2011) reported that with increasing development from adolescence to adulthood came greater activation in the right inferior frontal, superior temporo-parietal and cerebellar cortices, which are typical regions associated with sustained attention; they also demonstrated reduced activation in the posterior cingulate, insula and posterior cerebellar cortices. Besides the increased activation with age in these brain areas known to be important for sustained attention, Smith et al. (2011)'s study has also demonstrated faster reaction time to target trials in adults than adolescence, reflecting that performance in the sustained attention task (measured by CPT) also improved with age. In addition to emphasising the relevance of the fronto-temporal-parietal regions underlying sustained attention, the study also suggests the immature (i.e., still developing) brain in children, highlighting the disparity in brain regions supporting sustained attention across age groups. The developmental maturation of the brain is supported by a study by Rubia, Hyde, Halari, Giampietro, and Smith (2010), which found a progressive increase in activation in the fronto-temporo-parietal regions involved in sustained attention throughout adolescence. The disparities in the underlying neural mechanisms of sustained attention

between children and adults are also discussed in other studies (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006). A study by Bunge et al. (2002) study observed that effective suppression of distractors in children was associated with prefrontal activation in the opposite hemisphere compared to adults. Furthermore, while the prefrontal regions of adults are activated during response inhibition, the posterior regions are activated in children during the same process, and while the right ventrolateral prefrontal cortex was activated in adults, it was not activated in children, showcasing the immaturity of prefrontal cortex activation in children. This could be the underlying culprit behind poorer sustained attention in younger children as compared to older children and adults, as the frontal cortex develops throughout childhood and is vital to sustained attention (Fan et al., 2005). Despite the differences between healthy adults and typically developing children, the current literature has also highlighted the important roles the brain regions in the DMN and CEN play in sustained attention functioning in both populations. Given the importance of both the DMN and CEN in carrying out sustained attention tasks, it will be useful to examine both networks when attempting to study the neural changes underlying sustained attention impairments in patients.

1.7.1.5 Perturbations of Developing Sustained Attention Networks

Given the selective role of the DMN and CEN in sustained attention, neural disruptions in these networks as a result of disorders or injuries are a likely cause of poor sustained attention performance, and are further discussed in this section (Bonnelle et al., 2011; Fan et al., 2018).

Studies of children diagnosed with attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), who share common problems in sustained attention, have provided convergent evidence of the role that abnormal brain development in these regions plays in the later development of associated sustained attention skills (Norman et al., 2017). Though the study found disorder-specific neural alterations, it also illustrated alterations that are shared between both disorders; Norman et al. (2017) found that commonalities include under-activation in the inferior frontal gyrus and over-activation in the posterior DMN compared to controls. Importantly, the study highlighted that across both disorders, sustained attention performance (i.e., reaction time of a variant of psychomotor/vigilance and delay tasks) is largely associated with activation abnormalities in regions associated with the task-positive and task-negative networks. Their findings suggest that insufficient switching from the DMN to CEN underlies sustained attention impairments (e.g., poorer response time) in these patient populations, emphasising the importance of the anti-correlated relationship between both networks discussed earlier (Carlisi et al., 2017; Christakou et al., 2013). The under-activation in the CEN regions (specifically the dorsolateral prefrontal cortex) and increased activation in the DMN regions (i.e., precuneus) have also been found in patients with autism spectrum disorder and patients with ADHD (Christakou et al., 2013). These shared neural deficits, together with

shared abnormalities in switching off the DMN, are suggested to underlie the frequently reported sustained attention impairments in these patients.

The studies by both Norman et al. (2017) and Christakou et al. (2013) crucially highlighted that despite disorder-specific functional abnormalities, these patients shared abnormalities in terms of under-activation in the CEN regions and over-activation in the DMN, abnormalities which likely underpin sustained attention impairments in these patients. This is further evidenced by Fan et al. (2018)'s study, which suggested that despite the disorder-specific functional connectivity changes in schizophrenia and obsessive-compulsive disorder patients between 16 and 35 years old, the functional connectivity between the left medial prefrontal cortex and right parietal cortex in the DMN and the task positive network (fronto-parietal network) was correlated with sustained attention performance (derived from the mean reaction time from the sustained attention to response task) in both patient groups. This study reiterates the importance of maintaining the anti-correlated relationship between the two networks for normal sustained attention functioning. As discussed in the earlier section, reduced anti-correlation between the networks can lead to the intrusion of the DMN upon the task-positive network, preventing the reallocation of attentional resources to the task and instead leading to an increase in mind-wandering, thus resulting in poorer sustained attention performance.

Similar to previous studies (Christakou et al., 2013; Norman et al., 2017), the study by Fan et al. (2018) also reported disorder-specific functional connectivity changes associated with sustained attention. The study suggested that this may reflect differences in resting-state dysfunction baselines between different disorders. Therefore, despite sustained attention impairments being shared across the different disorders, the findings regarding one disorder are not directly translatable to a different disorder. Thus, in order to obtain a better understanding of attention and its underlying neural networks, it is necessary to explore different disorders separately. However, the current literature has demonstrated that the abnormalities in the functional connectivity within and between the DMN and CEN constitute good markers of abnormal sustained attention performance across disorders in which a primary cognitive impairment occurs within the attention domain.

1.7.1.6 Sustained Attention Networks in Adult Brain Injury Population

Previous brain injury studies in adults have provided evidence of DMN abnormalities that may underlie cognitive impairments (Arciniega et al., 2021; Bonnelle et al., 2011; Esposito et al., 2012; Hillary et al., 2011; Sours et al., 2013; Tsai et al., 2014; Zhou et al., 2012). Zhou et al. (2012) found a correlation between abnormalities in the functional connectivity of the DMN regions (i.e., reduced connectivity in the posterior cingulate cortex and parietal regions) in adults with TBI and cognitive impairments (including attention). Other studies on non-traumatic brain injury have also reported disruptions to the DMN after brain injury and suggested that these

disruptions may be associated with commonly reported cognitive impairments, including attention, in patients with absence epilepsy (Luo et al., 2011), generalised epilepsy (Gauffin et al., 2013) and temporal lobe epilepsy (Gao et al., 2018). Disruptions in the DMN are well-established in both the traumatic and non-traumatic brain injury populations; however, few studies have directly examined the association between these disruptions and sustained attention impairments.

Bonnelle et al. (2011)'s study is among the few traumatic brain injury studies to have directly drawn an association between the impacts of abnormalities within the DMN and poor sustained attention performance. Using a simple choice reaction time task, sustained attention was assessed by measuring subjects' response time to the target cues (i.e., left or right arrows). The study reported that TBI patients exhibited insufficient deactivation of the DMN, particularly within the precuneus and posterior cingulate cortex, when carrying out cognitive tasks. It further suggested that the abnormalities in functional connectivity within the DMN may reflect a neurological marker of attention impairments. According to the authors, the findings support the notion that functional connectivity alterations within the DMN are central to the development of impairments in attention following brain injury. This underscores the importance of examining DMN changes that underpin attentional impairments and learning how these neural changes can help us identify brain injury patients who will go on to show impairments. Using a similar choice reaction task, Sharp et al. (2011) concur that alterations in the DMN following a brain injury influence sustained attention performance, the increased activation in the DMN during tasks is thought to reflect a compensatory response to brain injury that was similarly interpreted by other studies (Caeyenberghs et al., 2009; Kim et al., 2009; Palacios et al., 2013). Given that the study found an association between the increase in functional connectivity, particularly in the frontal regions of the DMN, and better cognitive outcome, Palacios et al. (2013) suggested that functional brain reorganisation occurs in order to compensate for the loss of structural connectivity between the DMN regions and to improve cognitive performance. The study by Bonnelle et al. (2011), however, suggested otherwise, interpreting the increased activation within the DMN as a failure to maintain goal-directed attentional focus, consistent with other studies as discussed earlier (Fan et al., 2018; Sonuga-Barke & Castellanos, 2007). Their study instead found an association between increased activity in the DMN regions – PCC and precuneus – and slower reaction times, in line with a previous study that found an association between the failure to suppress the same DMN regions and slower reaction times in healthy adults (Weissman, Roberts, Visscher & Woldorff, 2006). The findings from Bonnelle et al. (2011) therefore propose the increase in activity in these DMN regions to be a deviation from sustained, goal-directed behaviour, indicating that the DMN function is predictive of sustained attention impairments after a brain injury.

The current literature has therefore illustrated that the inability to sufficiently suppress the DMN regions likely directs attentional resources away from the task, resulting in poorer

sustained attention performance. This inability to suppress the DMN can be explained by the default mode interference hypothesis, which suggests that the failure of the task-positive network (i.e., CEN) to sufficiently deactivate the DMN during a goal-oriented task can result in lapses in attention, consequently affecting task performance (Sonuga-Barke & Castellanos, 2007; Weissman et al., 2006). It is therefore likely that, alongside an increased in activity in the DMN regions, there are also alterations in the CEN regions contributing to poor attention performance. Although fewer studies have examined the CEN in the brain injury population, some have reported alterations in these patients (Arciniega et al., 2021; Ham et al., 2014; Han, Chapman, & Krawczyk, 2016; Li et al., 2020). These studies have demonstrated reduced connectivity within the CEN, specifically between the dorsolateral prefrontal cortex and the posterior parietal cortex (Arciniega et al., 2021). Moreover, Li et al. (2020) suggested that reduced connectivity within the CEN, particularly in the superior frontal gyrus and superior parietal lobe, contributes to the cognitive impairments in brain injury patients. Ham et al. (2014) further suggested that the activity in the fronto-parietal network contributes to the performance of top-down attention in adults with a brain injury. No known study has directly examined the relationship between the CEN and sustained attention following a brain injury. However, given the importance of the neural connectivity within the CEN and between the CEN and DMN, it is likely that the alterations found in brain injury patients are associated with sustained attention deficits.

As discussed earlier, disruptions in the anti-correlated relationship between the DMN and CEN are reported to be associated with sustained attention impairments in individuals with neurological disorders (Fan et al., 2018). Abnormalities between the DMN and CEN are also commonly found across different types of brain insults, including TBI (Li et al., 2020; Palacios et al., 2013; Sours et al., 2013; Sours, Zhuo, Roys, Shanuganathan & Gullapalli, 2015; Sours, Kinnison, Padmala, Gullapalli, & Pessoa, 2018), tumours (i.e., gliomas) (de Dreu, Schouwenaars, Rutten, Ramsey, & Jansma, 2020), epilepsy (McGill et al., 2012, Vollmar et al., 2011; Zhang et al., 2017), and hippocampal sclerosis (Stretton et al., 2013). During a cognitively demanding 2-back task, Sours et al. (2018)'s study reported that brain injury patients demonstrated reduced segregation between the DMN and the task-positive network, suggesting a reduced anti-correlation relationship (i.e., reduced functional connectivity) between the two networks, which could underpin the poorer task performance in those patients. This is further evidenced by Stretton et al. (2013), whose study reported disruptions in the segregation of the task-positive and task-negative networks in patients with temporal lobe epilepsy, which is associated with deficits in working memory. Other studies have also demonstrated an increase in functional connectivity between the DMN and CEN during rest following a brain injury (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Sours et al., 2013; Sours et al., 2015). These findings further support the importance of the anti-correlated relationship between the task-negative regions (DMN) and the task-positive regions (CEN). Additionally, the altered network

communication following brain injury may be a contributing factor to the frequently reported sustained attention impairments.

Few studies, however, have explicitly examined the relationship between the DMN and CEN, and sustained attention. One study found a positive correlation between the connectivity between these two networks and attention scores which are derived from the Montreal Cognitive Assessment (Li et al., 2020). In line with the current literature, the findings of Li et al. (2020) indicate the importance of the relationship between the DMN and CEN to attention outcomes, and suggest that alterations between coordination of the task-positive and task-negative networks can lead to cognitive impairments (Fan et al., 2018; Kelly et al., 2008). Therefore, despite the lack of studies explicitly focusing on the relationship between the CEN and sustained attention, it is likely that disruptions to the CEN along with the DMN would influence sustained attention outcomes.

1.7.1.7 Neural Alterations in Sustained Attention Networks in Paediatric Brain Injury

Disruption within the DMN has also been reported following paediatric brain injuries, including TBI (Kramer et al., 2008), brain tumours (Anandarajah et al., 2020), concussions (Iyer, Zalesky, Barlow, & Cocchi, 2019) and acquired brain injuries (Strazzer et al., 2015). Along with a decreased deactivation in the anterior cingulate cortex, Strazzer et al. (2015)'s study reported that the increased activation of the frontal regions in children with acquired brain injuries is correlated with worse cognitive performance, including attention as assessed using Conners' CPT. Similarly, Kramer et al. (2008) found that during a computational performance task that measured sustained attention, children with TBI exhibited over-activation of the attention network, particularly in the parietal and frontal regions. As the brain injury and control (orthopaedic injuries) groups did not differ significantly in their attention performance, the findings may suggest that children with brain injuries may require more neural resources to attain a similar level of performance as children without brain insults. Over-activation during the task is, however, in line with studies that included other disorders. These studies suggested an association between the over-activation and poor attention performance (Christakou et al., 2013; Norman et al., 2017). The over-activation was suggested to reflect the decrease in attentional capacity in children with brain injuries, contributing to the difficulty of the task; thus, patients were forced to allocate more cognitive resources compared to the healthy controls in order to perform the same task (McAllister et al., 2001). Alternatively, McAllister et al. (2001) have suggested that subtle deficits in frontal executive functions may have affected the ability of children with brain injuries to efficiently allocate cognitive resources to the task's demands, resulting in over-allocation of resources without significant improvement in performance.

Only one known study has examined the relationship between the neural networks (DMN and CEN) underlying sustained attention in children with a brain injury, highlighting the

presence of a research gap (Li et al., 2015). The study reported an increase in functional connectivity between the CEN and DMN in children with childhood absence epilepsy (CAE), reflecting abnormal cooperation between the two networks that may underpin attention impairments in these patients. The findings are consistent with studies on adult brain injury and other neurological disorders characterised by sustained attention impairments, as discussed earlier. Whilst the findings of Li et al. (2015) regarding children with CAE are not representative of all brain injuries, they do support the importance of the cooperation between the DMN and CEN for normal cognitive functioning. The importance of cooperation between networks is also evidenced by Anandarajah et al. (2020)'s study, which reported a segregation between the DMN and dorsal attention network (DAN) in paediatric brain tumour survivors and suggested that the segregation between the DMN and DAN could explain the large variance in cognitive impairments. The DAN is a task-positive network like the CEN and has an anti-correlated relationship with the DMN in cognitively normal individuals (Chand, Hajjar & Qiu, 2018).

The current literature has demonstrated the importance of the functional connectivity within and between the DMN and CEN to sustained attention performance. Whilst studies have illustrated the changes to these networks in broader psychiatric and developmental disorders, fewer studies have examined them in the brain injury population, in particular paediatric brain injury. Given the importance of sustained attention, it is vital to examine these neural changes that could underlie attentional impairments and aid in identifying children who are likely to struggle and require early interventions.

1.7.2 Relationship between Structural and Functional Connectivity

The current literature has demonstrated a consensus that functional connectivity may reflect structural (anatomical) connectivity patterns (James et al., 2015; Vincent et al., 2007). Studies have suggested that functionally defined connectivity networks are underpinned by corresponding anatomical connectivity (Matsui et al., 2011). This suggests that anatomical connectivity between brain regions provides the structural basis for functional interactions between these regions. For example, a study by Vuksanovic, Staff, Ahearn, Murray and Wischik (2019) found convergence between cortical thickness and functional connectivity networks in the frontal, temporal, parietal and occipital lobes of the cortical surface. This finding is in line with that of Park et al. (2017), which explained that the inter-regional correlation map derived from cortical thickness reflects the underlying resting-state functional connectivity within the medial frontal cortex (MFC) regions, as well as across the whole-brain with the MFC used as seed regions. The relationship between two imaging modalities can be explained by the nature of fMRI—since it is reliant on the BOLD signal as a correlate of neuronal activity, it is affected by cortical morphology changes that impact the haemodynamic properties of the brain (Pur, Eagleson, de Ribaupierre, Mella & de Ribaupierre, 2019).

Another study suggested that the functional connectivity changes found were linked to the structural cortical thickness changes, which were hypothesised to be related to the cognitive skills required for better chess performance (Ouellette, Hsu, Stefancin, & Duong, 2020). This relationship is also found in the patient population (neurodegenerative disorders, brain injury), where studies found overlapping alterations in functional and anatomical connectivity; these measures correlate with cognitive measures (Urban et al., 2017; Whitwell et al., 2011). The structural and functional relationship is also found in patients with minimal hepatic encephalopathy; Garcia-Garcia et al. (2017)'s study suggested that the reduction in grey matter volume potentially contributed to the alterations in resting-state fMRI in the brain regions of the DMN, frontal-parietal and salience, which were associated with the progression of cognitive impairment. Similarly, the relationship between cortical thickness and functional activation has been demonstrated in early blindness patients (Anurova, Renier, De Volder, Carlson, & Rauschecker, 2015). Correlations found between both functional and structural measures when carrying out attention-demanding auditory tasks differed between early blind participants and controls. The deprivation of early sensory input and the effects of plasticity are suggested to shape the brain differently and explain these differences, suggesting a similar convergence of functional and structural changes in non-typically developing populations. Similar findings have also been illustrated in children who have sustained brain injuries; Iyer et al. (2019) demonstrated convergence between functional and structural alterations, specifically in the DMN regions, in children with concussion. The study suggested that the structural and functional alterations in the posterior cingulate cortex and medial prefrontal cortex are linked to an increase in sleep disturbances, which in turn affect the maintenance of cognitive performance. There is a general consensus in the current studies some overlapping exists between the functional and structural networks, and that both play an important role in cognitive processes.

Other studies have, however, found the correlation between functional connectivity and cortical thickness changes to be weaker in high-functioning individuals with autism (Pereira et al., 2018). The study suggested that the lack of close correlation could reflect the fact that changes in cortical thickness are not sufficiently severe to be visible on routine MRI and do not directly impact functional connectivity in patients. Similarly, another study found that cortical thickness changes in one brain area do not necessarily lead to functional changes in the same region (Haier, Karama, Leyba, & Jung, 2009). Haier et al. (2009) have, however, suggested that changes involving specific anatomical regions may not necessitate functional changes, and instead suggested that the lack of overlap could be a consequence of the MRI methods used. The inconsistency in findings may also be due to differences in analysis methods: some studies examined regional changes, while others focused on changes in connectivity between regions. Therefore, in addition to examining regional cortical thickness changes, it would be useful to examine the structural correlations between brain regions, also known as the structural

covariance network (SCN), which has derived similar neurocognitive networks as functional imaging (DuPre & Spreng, 2017). Furthermore, given that MRI is more readily available as it is normally acquired as part of clinical scans (Bernhardt, Bernasconi, Hong, Dery, & Bernasconi, 2016), it will be useful to jointly examine structural and functional changes following a brain injury. The following sections discuss the use of structural MRI.

1.7.3 Structural MRI

Unlike fMRI, structural MRI provides structural measurements including grey and white matter volume and cerebrospinal fluid. Structural MRI measures brain morphometry, capturing the grey and white matter atrophy that correspond to the loss of neurons and synapses, respectively, as well as loss of structural integrity of white matter tracts, which can reflect damage to the brain as a result of disease (Vemuri & Jack, 2010). It allows the study of structural changes in different brain regions due to disease; importantly, determining neuronal loss may provide a prognosis of the disease and its cognitive consequences (Vemuri & Jack, 2010). For example, studies have demonstrated a relationship between brain volumes (grey matter volume and cortical thickness) and cognitive functions in healthy adults (Newman, Trivedi, Bendlin, Ries, & Johnson, 2007; Ruscheweyh et al., 2013) as well as patients (Velayudhan et al., 2013).

Common approaches for assessing structural changes in the brain include ROI-based analysis, voxel-based morphometry (VBM) and surface-based analysis. ROI-based analysis methods parcel the brain into ROIs via warping an anatomical atlas so as to compare tissue volumes between groups (Ortiz, Gorriz, Ramirez, Martinez-Murcia, & Alzheimer's Disease Neuroimaging Initiative, 2014). This method is sensitive enough to detect moderate to severe grey matter changes (Seyedi et al., 2020); it is, however, restricted by the limited number of brain regions that can be examined. Additionally, the findings are heavily dependent on the ROIs chosen, which can pose an issue because of the high variability in the individual brain regions, especially in a diseased population (Chen, Jiao, & Herskovits, 2011; Seyedi et al., 2020). VBM instead performs statistical tests on T1-weighted MRI to identify grey-matter volumetric differences in the brain anatomy between groups, and is reported to be more sensitive to small structural changes in comparison to ROI-based methods (Seyedi et al., 2020). Compared to VBM, surface-based analysis allows for the measurement of cortical topography via cortical thickness measures (Chen, Jiao, & Herskovits, 2011), and is indicated to be more sensitive than VBM in detecting small grey matter changes across a large cortical area (Duncan, Firbank, O'Brien, & Burn, 2013). Thus, the current thesis uses surface-based analysis (i.e., cortical thickness measures) to examine structural changes in the brain regions underpinning sustained attention impairments after an early brain injury; this is discussed in the following sections in relation to existing studies.

1.7.3.1 Structural Neural Substrates of Sustained Attention in Healthy Population

Despite the abundance of fMRI studies on sustained attention, few structural studies have examined the structural morphometry of specific attention skills, and in particular sustained attention.

In healthy adults, Westlye, Grydeland, Walhovd and Fjell (2011) found correlations between cortical thickness and the attention components (i.e., executive control, alerting and orienting) measured by attention network tests. Westlye et al. (2011) found that greater cortical thickness is correlated with better executive control and altering skills in fronto-parietal regions, including the anterior cingulate, lateral prefrontal and right inferior frontal, as well as with parietal regions for better alerting performance. The relationship between greater cortical thickness in the frontal and parietal regions and better attention (measured using the Child Behaviour Checlist Attention Problems scores) is also found in healthy children (Ducharme et al., 2012). Ducharme et al. (2012) found that thinner cortices in the frontal regions (i.e., inferior frontal cortex, ventromedial prefrontal cortex, dorsolateral prefrontal cortex and orbito-frontal cortex) are associated with greater inattention in younger children (6–10 years old), who are known to have poorer attention than older children (>10 years old), suggesting that greater cortical thickness is associated with fewer attention problems, consistent with Westlye et al. (2011)'s study. The study also found that the relationship between reduced cortical thickness and attention problems reduced with age and suggested that this reflects the association between cortical maturation in the frontal regions, which have been established to develop the slowest, and attention during healthy development.

The current studies have consistently demonstrated that in both healthy adults and typically developing children, greater cortical thickness, especially in the frontal and parietal regions, is associated with stronger cognitive skills. Despite the lack of studies directly examining the cortical substrates underlying sustained attention in healthy adults/children, the importance of the frontal and parietal brain regions reported in structural MRI studies is consistent with fMRI studies, as discussed earlier, and again highlights the close association between the two modalities.

1.7.3.2 Structural Neural Substrates of Sustained Attention in Patient Population

Given the association between structural morphometry and cognitive skills, alterations in structural morphometry could lead to cognitive dysfunction. This relationship is well-supported in patient populations. For example, patients with minimal hepatic encephalopathy exhibit reduced grey matter volume in various brain regions, including DMN-related regions (such as the precuneus, isthmus cingulate cortex and supramarginal gyrus). Given the importance of the DMN in attention-demanding tasks, the study suggested that the decreased cortical complexity in these regions is likely related to the frequently reported attention deficits in these patients (Chen, Zhang, Zou, Huang, & Chen, 2020). Similarly, studies have reported an association

between the structural changes in the frontal lobe and poorer cognitive outcomes (i.e., inattention based on the persistence/remission of the *DSM-IV* criteria) in both children and adults with attention deficit/hyperactivity disorder (ADHD) (Makris et al., 2007; Shaw et al., 2006). Makris et al. (2007) reported cortical thinning in regions related to the DMN and the CEN, including the inferior parietal lobe, dorsolateral prefrontal cortex and anterior cingulate cortices, in adults with ADHD. Since these cortical networks are known to support cognitive skills including executive function and attention, which are commonly impacted in ADHD patients, it is likely that the cortical thinning in these regions can explain the impairments.

Structural studies, similar to fMRI studies, have reported an association between the frontal and parietal regions and sustained attention performance in populations with known attention impairments, such as adults diagnosed with schizophrenia (Salgado-Pineda et al., 2003). Using a variation of the CPT (i.e., Identical Pairs Version), Salgado-Pineda et al. (2003)'s study reported that adults with schizophrenia showed significantly more omission and commission errors, alongside significant impairments in the d' score (a measure of discriminability), where the latter is correlated with decrease in the grey matter density in the mentioned brain regions. This finding is in line with a study that included adult patients diagnosed with major depressive disorder and found an increase in the grey matter volume in the DMN-related regions, posterior cingulate cortex, frontal gyrus and lingual gyrus, alongside a decrease in volume in the medial/superior frontal gyrus and lingual gyrus; these are important regions in cognitive performance (Yang et al., 2015). More specifically, the study found an association between an increase in the grey matter volume in the inferior frontal gyrus and sustained attention performance as measured by the Rapid Visual Information Processing task (from the Cambridge Neuropsychological Test Automated Battery) total correct rejection index. Yang et al. (2015) have further suggested that sustained attention impairments are likely to be associated with structural alteration of many brain regions as opposed to a specific brain region, suggesting the importance of not only relying on regional measures, but also incorporating network measurements to examine structural connectivity, such as the structural covariance network, which is discussed next. Regardless, there is a general consensus across the current studies illustrating the vulnerability of the frontal and parietal regions across different patient populations, a vulnerability which could underpin the sustained attention impairments observed in these patients.

1.7.3.3 Structural Covariance Network

Recent studies have, however, increasingly demonstrated that the regional brain anatomical measurements between pairs of brain regions are highly correlated (Gilmore, Knickmeyer, & Gao, 2018). This correlation is also known as a structural covariance network (SCN). A SCN reflects shared variation in grey matter morphology, which is assessed using measures such as regional volume and cortical thickness (Mechelli, Friston, Frackowiak, & Price, 2005).

In a healthy population, the establishment of a SCN is reliant on similarities in function, structural homology and location among the contributing brain regions (Alexander-Bloch, Giedd, & Bullmore, 2013). Though a SCN is not a direct representation of functioning connectivity, it does provide insights into the properties of healthy and atypical brains, and to some degree correlates with functional connectivity (Liao et al., 2013). This is evidenced by the developing brain; the networks derived from a SCN study reflected established functional networks including the primary sensory, language and executive networks (Zielinski, Gennatas, Zhou, & Seeley, 2010). Moreover, structural covariance networks (SCNs) are replicable at both the population and the individual level, and are suggested to be useful in revealing disease-related changes (Alexander-Bloch et al., 2013).

Studies have also suggested the potential usefulness of examining SCN changes in order to predict cognitive outcomes in patients (Chen et al., 2021). Existing studies have demonstrated altered SCNs in patient populations, including dementia (Nigro et al., 2021), Alzheimer's disease (Spreng & Turner, 2019; Dicks et al., 2018), major depressive disorder (Ge et al., 2021), obsessive-compulsive disorder (Yun et al., 2020) and children with autism or ADHD (Bethlehem, Romero-Garcia, Mak, Bullmore, & Baron-Cohen, 2017). Nigro et al. (2021) demonstrated a correlation between SCN alterations (derived from cortical thickness) in the fronto-parietal regions and performance of the mini-mental state examination (MMSE), and suggested that these network alterations might contribute to cognitive impairments. Similar findings have been reported in Alzheimer's patients with mild cognitive impairment (Dicks et al., 2018). Dicks et al. (2018) reported an association between the number of disruptions in grey matter connectivity (i.e., precuneus, medial frontal and temporal cortex) and a decline in MMSE performance, along with attention, memory and executive function. The study suggests that SCNs can provide information about patients likely to exhibit later impairments in specific cognitive skills, aiding in identifying patients with poor cognitive outcomes. Similar to other functional and structural studies, Spreng and Turner (2019) have also illustrated the importance of the DMN in normal cognitive functioning in Alzheimer's patients; the study reported an association between reduced SCNs between the DMN regions and poorer cognitive performances.

Despite the absence of studies examining SCNs and sustained attention specifically, the current studies have illustrated the importance of the DMN and fronto-parietal regions in proper cognitive functioning, including attention.

1.7.3.4 Structural Neural Substrates of Sustained Attention in Adult Brain Injury Population.

Regional structural changes, measured by cortical thickness and grey matter volume, are commonly reported in traumatic brain injury (Mitko et al., 2019; Newsome et al., 2018), neurodegenerative diseases (Ozzoude et al., 2020), stroke (Chen et al., 2021), epilepsy

(Galovic et al., 2019) and in patients with lesions (Zhuang et al., 2017). In line with healthy studies suggesting that greater cortical thickness typically correlates with better cognitive performance, these studies have commonly reported cortical thinning in patients known to exhibit cognitive impairments.

Few studies have examined the relationship between structural morphometry changes and sustained attention in brain injury patients. A VBM study found diffuse cortical changes following a traumatic brain injury and reported a correlation between reduced grey matter volume in several brain regions (including the right frontal, temporal and parietal lobes, and the left cingulate and frontal lobe) and lower scores on tests of attention as measured by the Conners' continuous performance test (CPT) d' variable – the ability to discriminate targets from non-targets (Gale, Baxter, Roundy, & Johnson, 2005). The study also highlighted that despite the differences in injury severity across patients, patients shared structural changes in brain regions commonly associated with attention poorer attention, underscoring the possibility that sustained attention deficits are underpinned by disruptions in the same brain regions. Similar findings have been reported in other studies, such as that of Mitko et al. (2019), which reported that thicker cortices in the visual, somatomotor, frontal and parietal cortices were associated with better sustained attention performance in veterans with mild traumatic injury. Importantly, the authors reported that these regions/networks were correlated with both of the two attention measures used – a variation of the CPT (i.e., a gradual onset version) and the Test of Variables of Attention – which suggested that the cortical thickness of these areas may reflect better sustained attention, beyond the specifics of a single attention measure. The importance of frontal and parietal regions in sustained attention is also found in patients with right-hemisphere lesions in the posterior parietal cortex, who demonstrated sustained attention impairments (Corbetta & Shulman, 2011; DeGutis & Van Vleet, 2010). These studies have also emphasised the importance of the right parietal cortex in maintaining vigilance, which has also been illustrated in studies of healthy individuals, as discussed earlier. Similarly, patients with right frontal lesions also exhibited poorer and slower performance during sustained attention tasks as measured using the Sustained Attention to Response task commission errors and post-error slowing parameters (Molenberghs et al., 2009). These lesion studies emphasise that proper functioning the frontal-parietal regions is necessary for optimal maintenance of attention (He et al., 2007). More importantly, these structural studies, consistent with fMRI studies, have highlighted that the different disorders likely share similar neural disruptions, particularly involving brain regions related to the DMN and the task-positive network, which contributed to their shared sustained attention deficits.

As previously discussed, brain injuries are considered to be disorders of brain connectivity, disrupting not only brain regions but also the connections between regions. Thus, it is important to also examine structural connectivity changes after a brain injury (Hayes, Bigler, & Verfaellie, 2016). However, few SCN studies have examined brain injury populations. One study

has, however, demonstrated disrupted SCNs (i.e., grey matter volume) within the DMN and CEN in mild TBI patients (Song et al., 2021). The study reported reduced structural covariance in the executive control network, also known as the CEN, in patients with an acute stage of brain injury, along with increased structural covariance in the DMN in patients with chronic-stage brain injury, as compared with healthy controls. As these networks are important for normal cognitive functioning – for example, the failure to deactivate the DMN regions during the performance of a task is associated with cognitive deficits (Sours et al., 2013) – it is reasonable to infer that altered structural covariance within these regions may be associated with impaired cognitive functions in brain injury patients. Whilst SCN alterations are also reported in focal epilepsy, one study found reduced structural covariance (i.e., grey matter volume) between DMN regions (including the posterior cingulate cortex and medial prefrontal cortex) in patients with focal epilepsy (Shu, Xiao, Long, & Zhang, 2020). The difference between the findings of Shu et al. (2020) and Song et al. (2021) is likely because the pathologies of TBI and epilepsy are different and affect the neural networks differently. Therefore, in order to better understand attention and its underlying neural networks, it is important to explore the different forms of brain injuries on their own. However, despite only having a few SCN studies, findings from the current literature have illustrated structural covariance disruptions in similar brain regions/networks to the ones affected by functional connectivity alterations uncovered in fMRI studies.

1.7.3.5 Structural Neural Substrates of Sustained Attention in Paediatric Brain Injury Population

Similar to the adult brain injury literature, studies have also demonstrated that structural morphometry alterations are widely found in children following a brain injury (Bigler et al., 2018; Hanten et al., 2011; Iyer, Zalesky, Barlow, & Cocchi, 2019; Krawczyk et al., 2010; Merkley et al., 2008; Ryan et al., 2021; Wilde et al., 2005; Wilde et al., 2011; Wilde et al., 2012).

The importance of the frontal-parietal regions to cognitive tasks is discussed in Wilde et al. (2011)'s study, which demonstrated an association between greater cortical thickness of the frontal and parietal lobes and reduced accuracy of the Sternberg Item Recognition Task (often used to measure working memory) as well as longer reaction time in children with orthopaedic injury. The relationship was, however, found to be less robust in children with a brain injury, which Wilde et al. (2011) attributed to disrupted fronto-parietal functioning in attention and working memory. Similarly, Krawczyk et al. (2010) illustrated that adolescents with brain injuries failed to exhibit the robust cortical-task performance (i.e., accuracy parameter of a picture analogy experiment) correlations, specifically in the frontal and temporal regions, that were normally found in typically developing youths. The weaker correlations were suggested to be a consequence of altered plasticity due to the brain injury, which could have affected the cortical maturation that would otherwise be found in normal development. Regardless, the current

literature has demonstrated the relationship between structural disruptions (i.e., cortical thickness) and cognitive performance.

Whilst many studies have examined regional structural alterations following a paediatric brain injury, only two known studies have examined SCNs in children with brain injuries. One study, by King et al. (2020), investigated the divergence between the structural brain networks in paediatric traumatic brain injury patients and those in typically developing children across the entire brain and in the CEN. Comparing the SCN derived from paediatric brain injury patients to the typical SCN estimated from healthy children, the study found that the magnitude of deviation from the typical reference network corresponded to the level of executive function skills (i.e., set shifting, inhibition and working memory) measured using subtests from several battery including The Everyday Attention of Children, Delis-Kaplan Executive Function System and Wechsler Intelligence Scale for Children. Greater deviation due to injury could explain worse executive function in the patient group. Crucially, this study demonstrated that SCNs are sensitive to changes in the developing brain, particularly the effects of a paediatric brain injury. Support for this is also provided in a study by Tuerk, Degeilh, Catroppa, Anderson, and Beauchamp (2021). They found that compared to healthy children, children with traumatic brain injuries showed reduced structural covariance within the DMN and CEN approximately 12–24 months after the injury (Tuerk et al., 2021). Given the roles the DMN- and CEN-related brain regions play in cognitive functioning, the study suggested that disruptions to these networks likely relate to the cognitive deficits commonly found in these patients. Importantly, the studies supported the use of SCN to comprehensively study brain networks after a brain injury and to characterise the global effect of a brain injury on the developing brain.

Moreover, from previous brain injury studies, it is well-established that brain injury often leads to widespread structural changes in the brain, as evidenced by grey matter structural changes in five large-scale networks (including the DMN and CEN) as well as by regional volume loss in paediatric patients (Dennis et al., 2013). Given the diffuse effect paediatric brain injury has across the whole structure of the brain, SCN is appropriate for examining changes in the brain following injury, as it models the extent to which the structural morphology of brain regions statistically correlates across every possible pair of ROIs. Despite the potential of SCNs in providing new knowledge regarding brain changes following injury, no other studies have examined SCN in a brain injury cohort. This constitutes a research gap that must be filled so as to further deepen our understanding of the disruptions to the networks that are known to support sustained attention.

1.8 Aims of Thesis

Sustained attention plays a vital role in cognitive functions and ultimately functional outcomes, including academic performance. Across different types of brain insults, including TBI and non-traumatic brain injuries such as epilepsy and stroke, sustained attention deficit is the most commonly reported problem following brain injury in children. The vulnerability of sustained attention to brain injury is because the neuronal substrates supporting attention, such as the frontal and parietal brain regions, are commonly damaged by brain insult. Given that sustained attention impairments are found across brain insults, it is likely that there are overlapping neural alterations in these patients that underlie the impairments. Current literature has, however, highlighted the presence of disorder-specific neural changes in the networks associated with sustained attention. It is therefore important to explore different injury types, characterised by different lesions or pathologies, in order to obtain a better understanding of attention and its underlying networks. Doing so would also allow for the identification of patients likely to struggle with long-term attention impairments and make it possible to provide them with early interventions. Based on the current literature, resting-state fMRI has proven useful in predicting cognitive performance across healthy and patient populations, including patients with brain injury. Moreover, recent studies have demonstrated a relationship between functional and structural alterations. Given that structural MRI is more commonly acquired than fMRI, the thesis will also examine structural connectivity using structural covariance network analysis. This thesis therefore examines structural and functional alterations in the brain regions underpinning sustained attention (DMN and CEN) across different types of paediatric brain insults, including TBI, non-traumatic brain injuries such as epilepsy, and neurological disorders.

In the following chapters, studies examining alterations in the functional and/or structural connectivity in the brain regions underlying sustained attention in patients with a brain insult are presented. Chapter 2 presents results from a pilot study that examined resting-state fMRI functional changes *between* regions *within* the DMN in children with TBI compared to typically developing children. Based on the current literature, the study expected to find reduction in the functional connectivity *within* the DMN in paediatric patients. Given this thesis's interest in early brain insults, Chapter 3 further explores resting-state fMRI changes in the DMN and CEN in children with epilepsy as compared to typically developing children. Based on the present studies, Chapter 3 hypothesises reduced functional connectivity *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions in paediatric patients. Given the relationship between functional and structural connectivity, Chapter 4 examines structural covariance network alterations across the whole-brain, and specifically *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions, in children with epilepsy as compared to healthy children. Based on recent studies, the study expected to find alterations in the SCN in paediatric patients. Finally, Chapter 5 examines changes in both SCN and resting-state fMRI across the whole-brain, and specifically *between* regions *within* the DMN and

within the CEN, and *between* the DMN and CEN regions, in paediatric patients with a brain insult compared to typically developing children. The chapter hypothesise 1) functional and structural alterations in paediatric patients, and 2) similarities across the brain regions that demonstrate functional and structural alterations. The final chapter in the thesis, Chapter 6, discusses the overall findings of the experimental chapters, the implications of these findings, and the limitations and directions for future studies.

Chapter Two: A Pilot Study using Resting-state Functional Magnetic Resonance Imaging to Explore Differences in Functional Connectivity In the Default Mode Network and Correlations with Sustained Attention Performance between the Paediatric Traumatic Brain Injury and Control Cohorts

2.1 Introduction

The impact of brain injuries sustained early in life and their resultant effects on brain structural development and function can vary according to the nature of the injury. The current chapter focuses on a highly prevalent type of brain insult- traumatic brain injury. Traumatic brain injury (TBI) results from a strong head force, inducing physiological interruption to the brain function (Faul, Wald, Xu & Coronado, 2010). Based on the mechanism of the injury, TBI can be divided into focal or diffuse injury. Examples of focal injuries include the 'coup' and 'contrecoup' injury, where 'coup' injury occurs at the actual impact site of the head, and 'contrecoup' injury occurs at the site remote (i.e., opposite) from the actual impact site of the head (McKee & Daneshvar, 2015; Payne, De Jesus & Payne, 2022). In contrast to focal injuries, diffuse injuries like the diffuse axonal injury cause widespread axonal damage within the white matter, and the axonal damage results from mechanic forces shearing the fibres during the impact, also known as shearing injury (Blumbergs, Jones & North, 1989). Across the different types of injuries, the Glasgow Coma Scale (GCS), which measures the level of consciousness, is normally used to assess and classify the brain dysfunction severity and outcome after a head injury (Mena et al., 2011). The GCS assesses TBI patients based on three main areas of responsiveness—eye opening, motor and verbal response. The total coma score is between 3 and 15, 3 being the lowest and 15 being the highest; based on the scores, TBI would be classified into mild (GCS 3-8), moderate (GCS 9-12) and severe (GCS 13-15), and these scores were found closely related to patients' outcomes (Jain & Iverson, 2018). Despite the wide use of the GCS in classifying the injuries' severities and outcomes, the GCS should not be used alone to predict a patient's outcome, as there are other clinical indices that can affect the prognosis of TBI like imaging findings (Jain & Iverson, 2018). This is supported by a review, which has suggested that the GCS does not allow the inference of the underlying brain pathology, which is important as the review reported similar clinical outcomes resulting from different structural abnormalities as a result of either a focal or diffuse injury (Andriessen, Jacobs & Vos, 2010). This suggests that rather than just the use of GCS alone, incorporating imaging metrics like functional magnetic resonance imaging (fMRI) can help in acquiring complementary information on TBI outcome, and provide greater insight into the pathophysiology of TBI, and importantly better identify long-term TBI outcomes, and guide rehabilitations (Lee & Newberg, 2005).

Paediatric TBI is classed as a major health problem as it is the leading cause of death and disability in children, and especially in the severe paediatric TBI population that has an estimated 20% mortality and 50.6% unfavourable 6-month outcome rates (Popernack, Gray &

Reuter-Rice, 2015). Despite showing some neurocognitive recovery over time, children with severe TBI failed to catch up with their peers across most neurocognitive domains, and even fell further behind over time (Babikian & Asarnow, 2009). In comparison, children with moderate TBI performed better than the severe TBI group, albeit worse than the mild TBI group; importantly, despite showing modest neurocognitive recovery, these children still showed persistent deficits in attention and intellectual functioning in the long term, which suggests that they never reached parity with their typically developing peers (Babikian & Asarnow, 2009). Moreover, despite the general view of fewer and less severe impairments in the paediatric mild TBI group, meta-analysis and systematic reviews have reported that a subset of these patients may also show long-term adverse outcomes in some domains like attention (Babikian & Asarnow, 2009; Lloyd, Wilson, Tenovuo & Saarijärvi, 2015). Overall, there is a general consensus that whilst the outcome after an injury is highly related to the severity of the injury, long-term impairments are however highly prevalent across the different severities. The frequency of TBI in children is particularly concerning because of the long-term impacts of TBI on physical health, cognitive abilities, school performance and social skills (Mayfield & Homack, 2005; Taylor et al., 2008). Attention impairments are common following traumatic brain injury, and the deficits appear to be persistent for years after the injury (Catroppa, Anderson, Morse, Haritou & Rosenfeld, 2007; Ginstfeldt & Emanuelson, 2010). Sustained attention, in particular, seems to be most vulnerable and has been frequently reported by children with TBI (Ginstfeldt & Emanuelson, 2010). Despite this, there are few studies of advanced imaging techniques in children with TBI, and these may provide insight into the susceptibility of the paediatric brain to long-term cognitive deficits post-TBI.

As discussed in Chapter 1, there is strong evidence for a relationship between the resting-state functional connectivity of the default mode network (DMN) and attentional performance in adults with TBI. Bonnelle et al. (2011)'s study showed that alterations in the functional connectivity within the DMN are a sensitive predictor of sustained attention impairments (as inferred from the longer reaction time when performing a simple choice reaction time task) in adult TBI patients. Their study further highlighted the notion that neural alterations involving the posterior cingulate cortex of the DMN are critical to the development of attention problems after injury. Nevertheless, owing to the undeveloped paediatric brain, which has potential for more rapid adjustments in reorganisation of the connectivity networks after TBI (see Chapter 1), those findings cannot be applied directly to paediatric cohorts. Indeed, it is likely that the pattern of results will differ in children. However, few studies have examined the DMN activity following paediatric TBI, and those that did were task-based studies. No known studies have examined DMN activity following paediatric TBI during resting-state fMRI.

Task-based fMRI studies that examine the role of DMN in attention have yielded mixed results. One study found that compared to paediatric mild TBI patients who were found to be clinically unrecovered (based on the Post Concussive Symptom Inventory that assesses

symptoms in four domains—somatic, cognitive, emotional and sleep), there was increased deactivation in the dorsal posterior cingulate cortex (PCC) and increased activation in the ventral PCC in paediatric patients with mild TBI who were categorised as clinically recovered, which were associated with improved attention performance (Stein, Iyer, Khetani & Barlow, 2021). Others, however, have demonstrated findings that are inconsistent with this observation; there is a disparity in the brain regions that are associated with attention performance. For example Kramer et al. (2008) found increased activation in the frontal and parietal regions in paediatric patients with TBI, who demonstrated good behavioural recovery (as measured using the discriminability parameter of the continuous performance task (CPT) Identical Pairs version), compared to typically developing controls. In comparison, Strazzer et al. (2015) reported increased activation in the frontal regions and the anterior cingulate cortex in brain injury patients as compared to healthy children, and the greater activation in the frontal regions is found associated with increased response time and a lower percentage of correct response when performing a modified version of the Conners' CPT, which reflected poorer attention performance. The over-activation may suggest reduced attentional capacity in paediatric TBI patients, who may find the task more challenging and thus require more neural resources to perform at a comparable level to healthy children; it may also reflect subtle cognitive deficits that affects TBI patients to effectively match available neural resources to the task demands, leading to over-recruiting of neural resources without better task performance (McAllister et al., 2001). The current studies have however presented an inconsistency in the neural patterns underpinning attention in paediatric patients with TBI, which is highlighted by both Strazzer et al. (2015) and Kramer et al. (2008)'s papers. The inconsistency between the task-based studies could be because of differences in attention tasks between studies; the two studies have used different variations of the CPT to measure sustained attention, and as discussed in the earlier chapter, they may not share the same sustained attention construct, which again highlights the challenge in choosing an appropriate attention measure. Moreover, the attention task in Kramer et al. (2008)'s study only included one difficulty level as compared to the parametric task in Strazzer et al. (2015)'s study. According to the existing literature, the difficulty of task is found to affect the brain regions found activated and also the activation level of the brain regions, including attention tasks (Barch et al., 1997; Culham, Cavanagh & Kanwisher, 2001; Herath, Klingberg, Youung, Amunts & Roland, 2001). Studies have suggested that higher cognitive demand tasks, which have increasing difficulty levels, could lead to more noisy brain activation due to more changes in the brain activity that can reduce fMRI signals, thus affecting the reliability of the fMRI findings (Morrison et al., 2016). Taken together, this suggests that the task choice and/or difficulty level has a significant impact on the reliability of tasked-based fMRI, and can affect the consistency in findings across studies. Resting-state fMRI is sensitive to alterations in the functional connectivity between the DMN nodes in patient populations (Dichter, Gibbs & Smoski, 2015; Luo et al., 2011; Wang, Li, Wang, Chen & Huang, 2017), and is

therefore well suited to overcome the problems observed in task-based fMRI studies of DMN relevant to paediatric attention following TBI. Thus, the current study instead used resting-state fMRI to explore neural changes in paediatric patients with a TBI, and to examine the neural-behavioural relationship.

Resting-state fMRI (see Chapter 1) holds several other advantages over task-based fMRI, one of which is that the former involves no task, which may support investigation of brain changes in people with TBI who may otherwise not be able to participate in fMRI experiments. Many patients may have cognitive or physical problems, which would affect their ability to accurately perform tasks in the MRI scanner; therefore more impaired patients, like children with severe brain injuries who are known to have poor functional outcomes (i.e., physical and cognitive outcomes) as compared to those with moderate TBI (Stancin et al., 2002), who would show the greatest neural abnormalities, may be excluded from study (Fox & Greicius, 2010). Exclusion of these patients can reduce the sensitivity to detect disease related changes, and also affect the representation of the findings to the general population. Moreover, resting-state fMRI can also overcome confounds that can affect the interpretation of task-based studies like a disparity in task strategy and effort, or practice effects, and instead allow the examining of the fundamental alternations underlying the disease (Fox & Greicius, 2010). Taking these factors, there is an overarching support for the use of resting-state fMRI in this chapter to examine paediatric TBI cohort.

There are different approaches to analysis of resting fMRI data (as previously discussed in Chapter 1), with frequently used analysis methods, including seed-based analysis, independent component analysis (ICA) and graph theory, each having their own strengths and limitations. The key advantages of seed-based analysis include the simple computation and straightforward interpretation of results; however the need for *a priori* selection of seed regions makes it vulnerable to bias (Lv et al., 2018). The need for a pre-selection of specific seed regions in seed-based analysis suggests that the position of seed region can significantly influence the resulting functional network pattern, like identifying wrong regions and missing the right regions of the network (Lu et al., 2017). In comparison to seed-based analysis, the main advantage of ICA is that it does not rely on having prior selection of seeds, and it has shown to reliably extract common resting-state networks including the DMN (Lv et al., 2018). However, a key limitation of ICA is that because it extracts all detectable networks (typically 20), it can lead to issues related to multiple testing, including false positives. Furthermore, while independent components derived from ICA can be inferred as spatially correlated through functional connections, it does not provide information on the functional connectivity between specific pairs of regions within a network. Taken together, both ICA and seed-based analyses provide different information, and there is no one ideal way to approach DMN analysis, especially in smaller samples. Therefore the current study used both analysis methods, which also helps to establish whether the two methods would provide different information in the same cohort.

Moreover, as previously discussed in Chapter 1, combining methods can provide complementary information, as ICA allows us to examine changes as a network, and seed-based analysis allows us to examine changes in specific brain regions within the network (von dem Hagen, Stoyanova, Baron-Cohen & Calder, 2013).

2.1.1 Aims and Hypotheses of Study

Using ICA and seed-based analyses, the current study aimed to examine functional connectivity changes *between* regions *within* the DMN regions in paediatric TBI patients as compared to typically developing children. Whilst both analyses allow the measurement of functional connectivity, seed-based analysis measures only the functional connectivity between each of the DMN brain regions; the ICA performs at a voxel-to-voxel level measuring the connectivity of the entire resting state network (Kornelsen et al., 2020), therefore including both methods can allow a better understanding of the neural changes in the brain. Functional connectivity is broadly defined as a pair of brain regions that are synchronous (Joel, Caffo, van Zijl & Pekar, 2011), and is commonly used to describe the outputs of both ICA and seed-based methods (Palacios et al., 2013). This chapter has however referred to the functional connectivity derived from the ICA as functional activity, defined as blood-oxygen-level-dependent (BOLD) signal fluctuations in regions that are spatially correlated with the DMN (Gursel et al., 2020; Prestel, Steinfath, Tremmel, Stark & Ott, 2018). Functional connectivity, in this study, is defined as the correlation between the time series of one region of interest (ROI) and all other regions of interests (ROIs) in the DMN, measured using seed-based analysis. The secondary aim was to investigate the relationship between functional connectivity in the DMN and sustained attention performance.

Based on the current literature, the study hypothesised that there would be reduced functional activity (i.e., BOLD signal fluctuations) and functional connectivity *between* regions *within* the DMN regions in the patient group as compared to the healthy controls. The present study also hypothesised that there would be correlations between resting-state functional connectivity in the DMN and sustained attention performance.

2.2 Methodology

2.2.1 Design

The present study reported on data that were previously collected from a larger longitudinal prospective study that investigated social cognitive outcomes of paediatric TBI at baseline, 6- and 12- months following injury (Anderson et al., 2013).

2.2.2 Participants

The data used in this study are a subset of a previously acquired database of paediatric TBI. The dataset was acquired between 2007 and 2010, as part of the 'Prevention and Treatment of Social Problems following Traumatic Brain Injury (TBI) in Children and Adolescence' study.

The study comprised of 136 children: 93 TBI patients and 43 typically developing children (Anderson et al., 2013). Paediatric traumatic brain injury patients were recruited at the time of injury from the emergency department and intensive care unit of The Royal Children's Hospital (RCH), Melbourne, Australia. Typically developing children were recruited from the community via local schools, and were group matched for age, gender and socioeconomic status.

For the TBI cohort, the inclusion criteria included (i) age between 5.0 and 16.0 years at time of recruitment; (ii) written evidence of closed-head injury being sustained and a minimum of two post-concussive symptoms (e.g., headaches, dizziness, nausea, irritability, poor concentration); (iii) sufficiently detailed medical reports to deduce injury severity, including the Glasgow Coma Scale (Teasdale & Jennett, 1974), and neurological and radiological findings; (iv) No prior diagnosis of pre-injury neurological or developmental disorder (including learning or attentional disability, or autistic spectrum disorder), non-accidental injury or previously sustained TBI; and (v) English speaking. The control cohort needed to meet the above inclusion criteria (i), (iv) and (v).

Based on the research aims of the current study, the TBI patient and control cases were selected based on two criteria: (i) the acquisition of resting-state fMRI at 2-years follow up, and (ii) the acquisition of sustained attention measures at 2-years follow-up. 20 participants met these criteria for inclusion, consisting of eight TBI patients and 12 controls. However, after imaging quality control, only 14 participants were included in the study (patients n = 6, controls n = 8).

The final patient group included five males and one female (11–15 years, M = 12.88 years, SD = 1.46), and the final control group included three males and five females (10–15 years, M = 12.77, SD = 2.16). Imaging data and cognitive outcomes of all participants were obtained approximately either two years following injury or two years since the baseline-scan for the control cohort between 2009 and 2012.

The TBI patient cohort comprised of moderate and severe paediatric patients (moderate: n = 4; severe: n = 2). However, as the present study is only using a small cohort of the wider study resulting in a very small TBI population, the severity groups were collapsed into one TBI cohort.

2.2.3 Procedure

The Royal Children's Hospital Human Research Ethics Committee and the Victorian Department of Education Research Ethics Committee approved the TBI study. Data in the current study were later obtained under a Material Transfer Agreement between the Murdoch Children's Research Institute and Aston University. Aston University granted a favourable ethical opinion for the secondary analysis of neuroimaging data from the TBI dataset (reference number #1083).

Families were first contacted to confirm their willingness to participate in the study before study details were mailed to them. The study then obtained parents' written, informed consent for children to participate in the study, as well as for retrospective extraction of clinical data from the child's medical records at the time of recruitment. Verbal assent was also sought from children who were older than 8 years. To prepare the participants for scanning, a mock scanning session was carried out with each participant to aid in familiarising them with the scanner environment. During the scan, radiographers consistently checked on the participants and informed them if they were moving, and sequences were repeated if possible when excessive motion was detected on the image reconstruction.

2.2.4 MRI Acquisition

All neuroimaging data were acquired from a 3.0 Tesla Siemens Tim Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil at The Royal Children's Hospital, Melbourne, Australia. High-resolution T1-weighted structural MR images were acquired for each participant (repetition time (TR) = 1900 ms, time to echo (TE) = 2.15 ms, flip angle (FA) = 9°, 176 slices). To acquire BOLD functional magnetic resonance imaging (fMRI), T2 sensitive gradient-echo echo-planar imaging (EPI) sequence was also acquired for each participant (TR = 2200 ms, TE = 30 ms FA = 90°, 280 slices).

2.2.5 Cognitive Outcomes at 24-months following Injury

Sustained attention was assessed using Walk/Don't Walk and Sky Search Dual Task from The Test of Everyday Attention for Children (TEA-Ch), a standardised and reliable tool to access the components of attention (Manly et al., 2001). The two subtests (Walk/Don't Walk and Sky Search Dual Task) as compared to the other sustained attention measures (i.e., Score!) have showed to be sensitive to attention impairments in children with different disorders (i.e., attention deficit hyperactivity disorder (ADHD), and a range of psychological conditions) who exhibit attention deficits, and are therefore used to measure attention in the current study (Heaton et al., 2001). Walk/Don't Walk requires participants to listen to a tape that will play one sound ('go' tone) and another sound ('no-go' tone) unpredictably and make their response accordingly by dotting with a marker pen on an A4 sheet upon the go tone and stopping when the no-go tone appears. The Sky Search Dual Task requires participants to perform a visual search while simultaneously keeping a count of scoring sounds from an auditory counting task.

2.3 Data Analysis

2.3.1 T1 Quality Control

The quality of the T1 images was determined using MRI Quality Control (MRIQC), a tool for acquiring quality measures (Esteban et al., 2017), where several outputs particularly focusing on artifact detection and noise measurement were taken into consideration for the quality control (Sound-To-Noise Ratio, Contrasts-To-Noise Ratio, Full Width Half Maximum, Foreground to Background Energy Ratio, Entropy Focus Criterion, Quality Index, Intracranial Vault Volume and Residual Partial Volume Effect). Out of the 20 eligible participants, 3 were excluded due to poor imaging data because of motion artifact.

2.3.2 T1 Template Generation

Due to the differences in cortical thickness, cortical surface area and cortical folding between the brains of children and adults, there is the risk of potential confounds when using a standardised adult template (Yoon, Fonov, Perusse, Evans & Brain Development Cooperative Group, 2009). Therefore, the current study used Template-O-Matic 8 toolbox (Wilke, Holland, Altaye & Gaser, 2008), to isolate the influence of age and gender on brain structure to generate a T1 paediatric template based on the NIH database (including 404 children between the age of 5–18 years). As a matched-pair approach was used, the tissue probability maps (grey matter, white matter, and cerebrospinal fluid) for each individual control subject were averaged to generate the paediatric T1 template image (Wilke et al., 2008).

2.3.3 Pre-processing

Image pre-processing was performed using Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) software running under MATLAB, version 2017a. Pre-processing prepares the images for further analysis, as the various pre-processing steps aids in reducing noise and artifacts thus improving the power of subsequent analyses (Jenkinson & Smith, 2001). The study has followed the following pre-processing steps according to a previous study (Sladky et al., 2011), including realignment, slice timing correction, segmentation, spatial normalisation and spatial smoothing (Gaussian Kernel, FWHM = 6mm). To exclude participants with large head movements, participants with head motion exceeding 3mm of maximal translation or 3° of maximal rotation throughout the scanning duration were excluded from further analysis to ensure more stable data. Therefore, 3 participants were being further excluded from the study. The functional data then underwent band-pass filter (0.01-0.08 Hz) to reduce physiological noise and improve signal to noise ratio with resting-state fMRI data analysis toolkit (REST), version 1.8 (Song et al., 2011).

2.3.4 Independent Component Analysis of Resting-State Imaging

The pre-processed resting fMRI data of the final 14 participants then underwent group ICA using Group ICA of fMRI toolbox (GIFT) software, version 4.0b (Rachakonda, Egolf, Correa & Calhoun, 2007; http://icatb.sourceforge.net/). Using GIFT software, each participant's data were decomposed into 20 predefined independent components (ICs). The fMRI data for all participants were firstly concatenated, before the data reduction; ICA decomposition and back reconstruction were performed to attain 20 ICs for each individual participant (Calhoun, Adali, Pearlson & Pekar, 2001). Each independent component (IC) included a time course and a spatial map relative to the IC, and the values from the spatial map are the Z-score that represents the level of correlation of a specific voxel's fMRI signal with the time course of the IC (Greicius et al., 2007). To identify the DMN component, the ICs were spatially sorted by multiple regression and using a previously published DMN paediatric spatial template (Thomason et al., 2011). The independent component with the highest multiple regression value was visually checked and confirmed as the DMN component for each participant, an example of the DMN component is showed in Figure 2.1. A one-sample t-test (corrected for family wise error (FWE)) was performed on the individual default mode network component within the group before a 2-way t-test (FWE-corrected) was carried out to test for significant difference in the functional activity in the DMN between the patient and control groups.

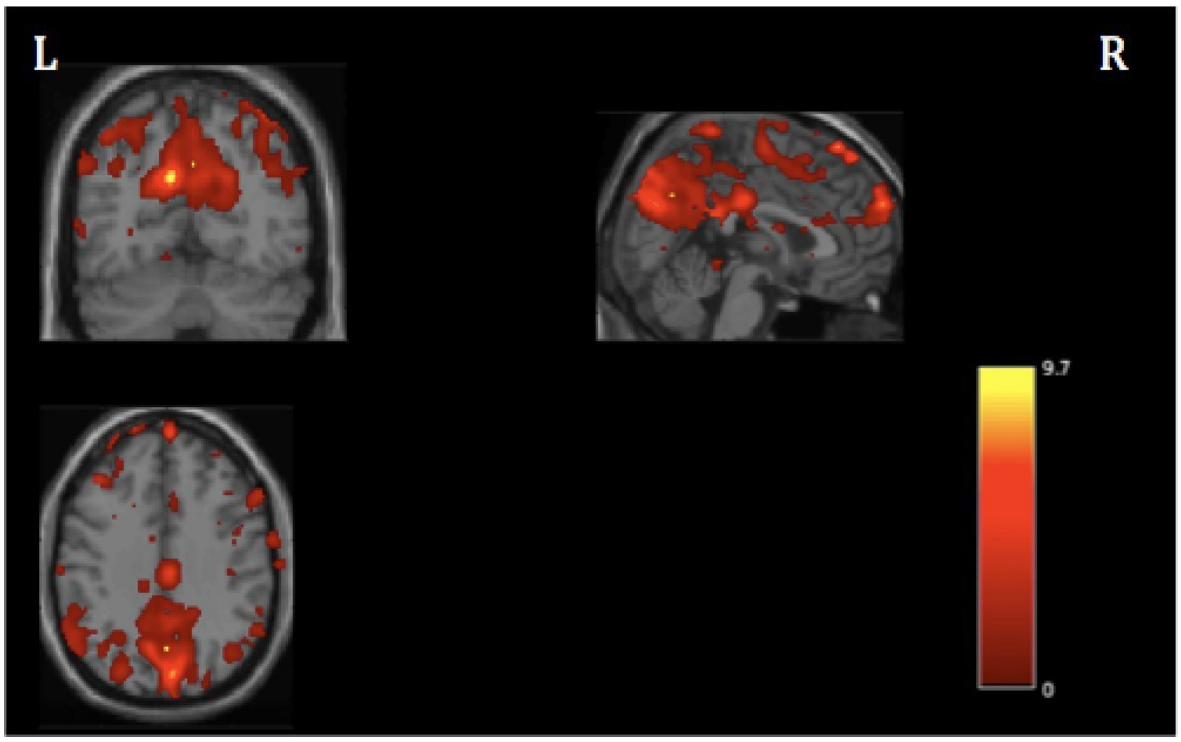

Figure 2.1. *The DMN component identified by the independent component analysis (ICA) in resting-state fMRI data* of a *single participant. The values of the colour scale to the right represent the minimum and maximum Z-values shown.*

2.3.5 ROI–ROI Analysis of the DMN Component

To further examine functional connectivity changes *between* regions *within* the DMN regions, the peak coordinates of the group DMN component identified by the ICA was used to generate 10mm spherical ROIs representing the main regions of the DMN. The regions selected were the medial prefrontal cortex (mPFC), parietal cortices, the precuneus and the PCC in each hemisphere. The coordinates of the ROIs making up the DMN are presented in Table 2.1. Each seed was generated using MarsBaR SPM Toolbox (Brett, Anton, Valabregue & Poline, 2002).

Using similar seed-based methods as previous studies (Iraji et al., 2016; Palacios et al., 2013), the current study extracted the average time series within each ROI from the individual pre-processed fMRI data. To examine any difference in functional connectivity *between* regions *within* the DMN between the patient and control cohort, correlations were performed within all the seeds in the DMN network in an 8x8 correlation matrix. In order to correct the underestimation caused by the skewedness of the correlation coefficients, the correlation values were then normalised and transformed into Z-scores using Fisher's r-to-Z transformation (Silver & Dunlap, 1987). The normalised correlation coefficient for each participant was then compared between the two groups using independent t-test to examine the between-group differences in the ROI–ROI functional connectivity *between* each seed *within* the DMN, corrected for false discovery rate (FDR).

Table 2.1.
MNI coordinates of the ROIs forming the DMN (in mm)

Brain Region	X	Y	Z
Left Parietal	-50	-56	34
Right Parietal	38	-70	54
Left mPFC	-6	40	16
Right mPFC	0	40	22
Left PCC	-8	-46	42
Right PCC	6	-40	34
Left Precuneus	-12	-64	44
Right Precuneus	16	-88	34

Note: Regions of the DMN: PCC = posterior cingulate cortex, mPFC = medial prefrontal cortex

2.3.6 Attention Measures

All statistical analyses were carried out using the Statistical Package for the Social Sciences, version 26 (SPSS, Chicago, Illinois). Independent t-test was carried out to investigate the differences in sustained attention scaled scores measured using subtests of the TEA-Ch (Walk/Don't Walk and Sky Search Dual Task Decrement score) between TBI patients and typically developing children.

2.3.7 Correlation between Functional Connectivity *within* the DMN and Attention Outcome

Foremost, Pearson's correlation was carried out between the sustained attention measures (Walk/Don't Walk and Sky Search Dual Task Decrement scaled scores) and all the ROI–ROI functional connectivity for each seed across all the subjects (including patients and controls). Pearson's correlation was then performed separately within each group (i.e., patient and control) to further examine the correlation between attention and the functional connectivity *within* the DMN, FDR-corrected.

2.4 Results

2.4.1 Age and Sex

The patient (M = 12.88, SD = 1.46) and control groups (M = 12.77, SD = 2.16) showed no significant difference in age ($t(12) = .10$, $p = .92$). Due to the small sample size, Chi-squared assumptions were not met, and Fisher's exact test was used to test for sex differences between groups. Patients (five males, one female) and controls (three males, five females) showed no significant difference in genders ($p = .14$).

2.4.2 Comparison of Group ICA (DMN)

20 components were generated via ICA for each group, and a back-construction step in GIFT produced individual subject images and time course. An established DMN template was used to identify the DMN component for further analysis. To examine functional activity differences in the DMN regions between the TBI and control cohort, voxel wise statistical analysis (two-sample t-test) was then carried out to examine the differences between the two groups. No significant difference in functional activity was found in the DMN between both groups ($p > .05$, FWE-corrected).

2.4.3 ROI–ROI Analysis of the DMN Component

The mean and standard deviation of the standardised Pearson's correlation between each of the eight ROIs (left/right PCC, left/right mPFC, left/right precuneus and left/right parietal) are presented below in Table 2.2. Despite majority being statistically non-significant, the mean of the standardised Pearson's correlation between the ROIs showed reduced functional connectivity across all the ROI–ROI pairs in paediatric patients with TBI as compared to typically developing children.

However after correcting for FDR based on Benjamini and Hochberg (1995)'s method, the present study only found significant group differences in functional connectivity *between* the left PCC and left mPFC ($t(12) = -3.74$, $p = .003$), and left PCC and right mPFC ($t(12) = -4.46$, $p = .001$). Compared to the control cohort, the patient cohort showed lower correlation *between* the left PCC and left mPFC, and *between* the left PCC and right mPFC, which may reflect reduced functional connectivity *between* these regions in TBI patients; presented in Figure 2.2 using BrainNet Viewer, version 1.63 (Xia, Wang, He, 2013).

Table 2.2.
Mean and standard deviation of standardised Pearson's correlation coefficients (Z-score) between each pair of ROIs for the patient and control cohorts

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
L_PCC–L_Precuneus	.47 (.17)	.76 (.35)
L_PCC–R_Precuneus	.55 (.37)	.84 (.36)
L_PCC–R_PCC	.55 (.16)	.91 (.35)
L_PCC–R_mPFC*	.22 (.11)*	.98 (.40)*
L_PCC–L_mPFC*	.36 (.18)*	.99 (.38)*
L_PCC–L_Parietal	.98 (.23)	1.21 (.31)
L_PCC–R_Parietal	1.83 (.24)	1.95 (.32)
L_Precuneus–L_mPFC	.40 (.24)	.68 (.38)
L_Precuneus–R_PCC	.73 (.11)	.88 (.46)
L_Precuneus–R_mPFC	.43 (.28)	.70 (.36)
L_Precuneus–R_Precuneus	.87 (.28)	1.09 (.26)
L_Precuneus–L_Parietal	.61 (.27)	.99 (.35)
L_Precuneus–R_Parietal	.70 (.19)	.83 (.23)
L_mPFC–R_PCC	.58 (.22)	.84 (.21)
L_mPFC–R_Precuneus	.70 (.19)	.83 (.23)
L_mPFC–R_mPFC	2.03 (.50)	2.06 (.31)
L_mPFC–L_Parietal	.68 (.24)	.85 (.35)
L_mPFC–R_Parietal	.77 (.30)	.99 (.35)
R_PCC–R_mPFC	.60 (.19)	.88 (.21)
R_PCC–R_Parietal	.98 (.23)	1.21 (.31)
R_PCC–L_Parietal	.63 (.12)	.89 (.25)
R_PCC–R_Precuneus	.70 (.16)	.91 (.20)
L_Parietal–R_Parietal	.63 (.12)	.88 (.20)
L_Parietal–R_Precuneus	1.83 (.24)	1.95 (.31)
L_Parietal–R_mPFC	.68 (.25)	.85 (.35)
R_Parietal–R_Precuneus	.68 (.20)	.90 (.29)
R_Parietal–R_mPFC	.59 (.19)	.65 (.30)
R_Precuneus–R_mPFC	.62 (.16)	.77 (.28)

Note: L/R = Left, Right. Regions of the DMN: PCC = posterior cingulate cortex, mPFC = medial prefrontal cortex *ROI–ROI pairs that were significantly different between patients and controls

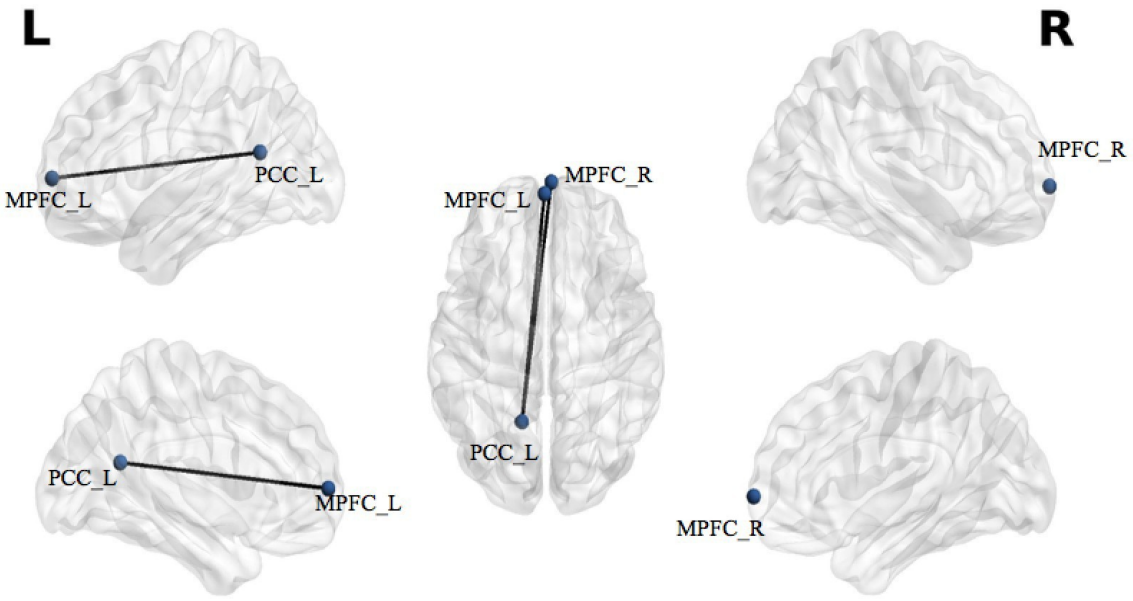

Figure 2.2. *Reduced correlation between the left MPFC and left PCC, and right mPFC and left PCC in patients compared to controls on a template brain generated using the BrainNet Viewer toolbox. MPFC_L = left medial prefrontal cortex, MPFC_R = right medial prefrontal cortex, PCC_L = left posterior cingulate cortex.*

2.4.4 Attention Measures

Using independent t-test, no significant difference was found between the paediatric TBI patients and typically developing children in the sustained attention subtests, Walk/Don't Walk and Sky Search Dual Task Decrement score ($p > .05$), as presented in Figure 2.3 below. No significant difference was observed in the scaled score between TBI patients ($M = 9.83$, $SD = 3.37$) and healthy children ($M = 9.75$, $SD = 3.81$) in the subtest, Walk/Don't Walk ($p > .05$). Similarly, in the subtest, Sky Search Dual Task, there was no significant difference in the decrement scaled score between TBI patients ($M = 8.33$, $SD = 1.37$) and healthy children ($M = 7.13$, $SD = 1.13$) ($p > .05$).

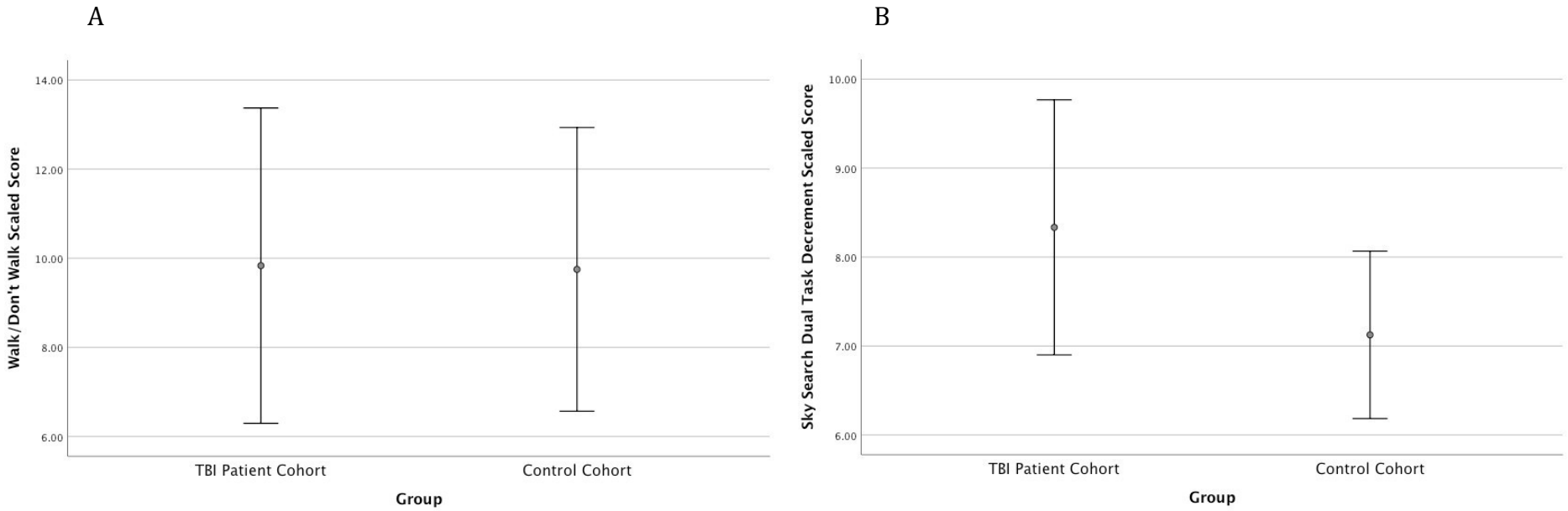

Figure 2.3. *Error bar chart showing the scaled score of the TEA-Ch subtests ((A) Walk/Don't Walk and (B) Sky Search Dual Task Decrement) in the TBI patient and control groups.*

2.4.5 Functional Connectivity *between* regions *within* the DMN and Attention Outcome

To examine the relationship between functional connectivity *between* regions *within* the DMN and sustained attention performance, Pearson's correlation analysis was then performed between the functional connectivity coefficients and attention measures across both groups and also within each group. Scatterplots (as presented in Figures 2.4, 2.5, 2.6 and 2.7) were generated to look at the relationship between functional connectivity of ROI–ROI pairs (left PCC and left mPFC, and left PCC and right mPFC) that previously showed significant differences (derived from standardised Pearson's correlation between ROI and ROI), and sustained attention measures (Walk/Don't Walk and Sky Search Dual Task Decrement score). The scatterplots suggested that there were no strong relationship between sustained attention performance and functional connectivity in the DMN in both patient and control cohorts.

The lack of relationship between sustained attention and functional connectivity in the DMN was further confirmed by the lack of significant correlations (FDR-corrected) between the Pearson's correlation between the sustained attention measures (Walk/Don't Walk and Sky Search Dual Task Decrement scaled scores) and the functional connectivity *within* the DMN across all the subjects. Similar findings were found when Pearson's correlation was performed within each group (i.e., patient and control). In TBI patients, there was no significant correlation between functional connectivity of the left PCC and left mPFC and (1) the Walk/Don't Walk subtest ($r(4) = .15$, $p = .78$), and (2) the Sky Search Dual Task ($r(4) = .38$, $p = .46$), and similarly, there was no significant correlation between functional connectivity of the left PCC and right mPFC and (3) Walk/Don't Walk ($r(4) = .79$, $p = .06$), and (4) the Sky Search Dual Task Decrement score ($r(4) = -.37$, $p = .47$) in TBI patients. In healthy children, there was no significant correlation between functional connectivity of the left PCC and left mPFC and (1) the Walk/Don't Walk subtest ($r(6) = .34$, $p = .41$), and (2) the Sky Search Dual Task Decrement score ($r(6) = -.54$, $p = .16$). There was also no significant correlation between functional connectivity of the left PCC and right mPFC and (3) Walk/Don't Walk ($r(6) = -.52$, $p = .19$), and (4) the Sky Search Dual Task Decrement score ($r(6) = -.14$, $p = .75$) in healthy children.

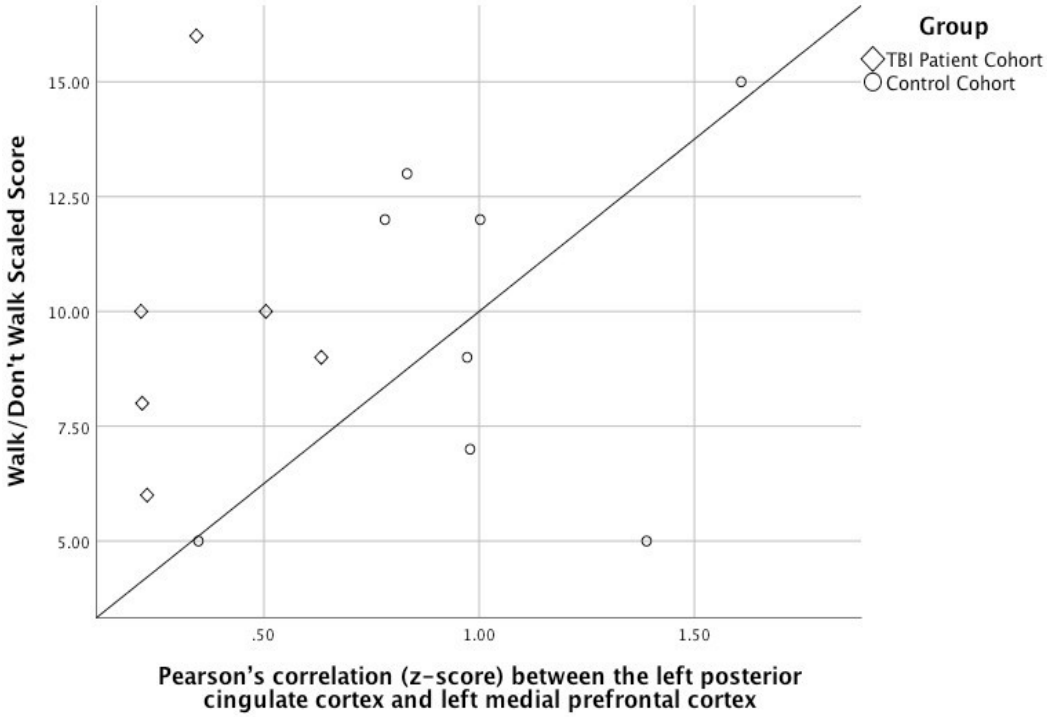

Figure 2.4. *Relationship between the standardised Pearson's correlation coefficients (Z-score) of the left PCC and left mPFC and the scaled score of the subtest, Walk/Don't Walk, in the patient and the control cohorts.*

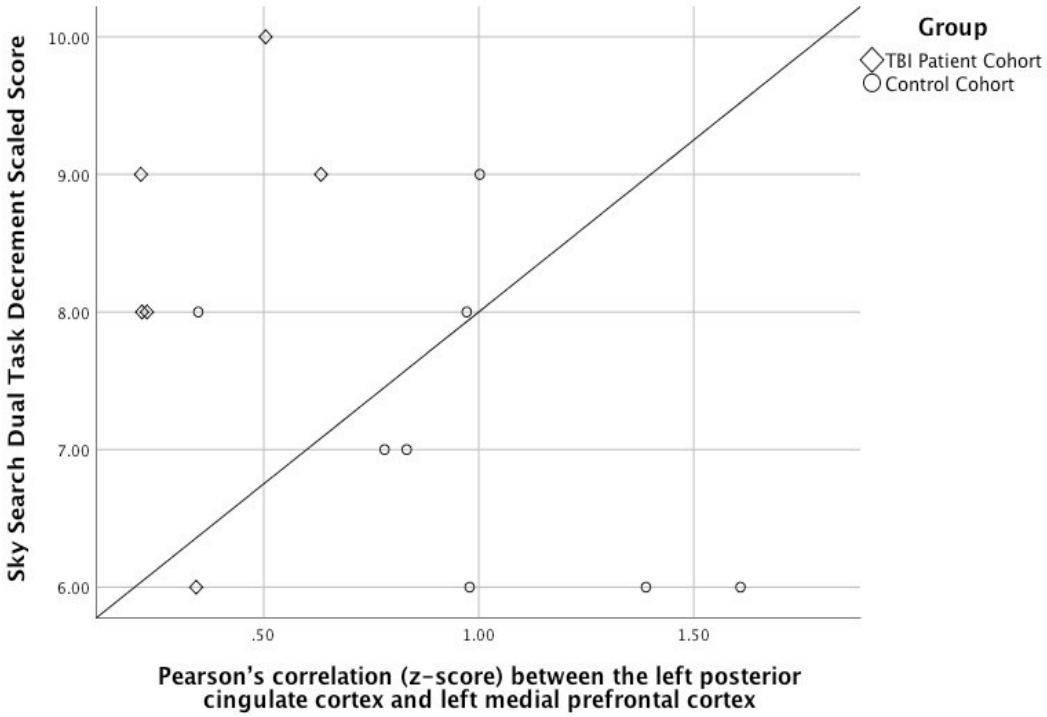

Figure 2.5. *Relationship between the standardised Pearson's correlation coefficients (Z-score) of the left PCC and left mPFC and the scaled score of the subtest, Sky Search Dual Task Decrement, in the patient and the control cohorts.*

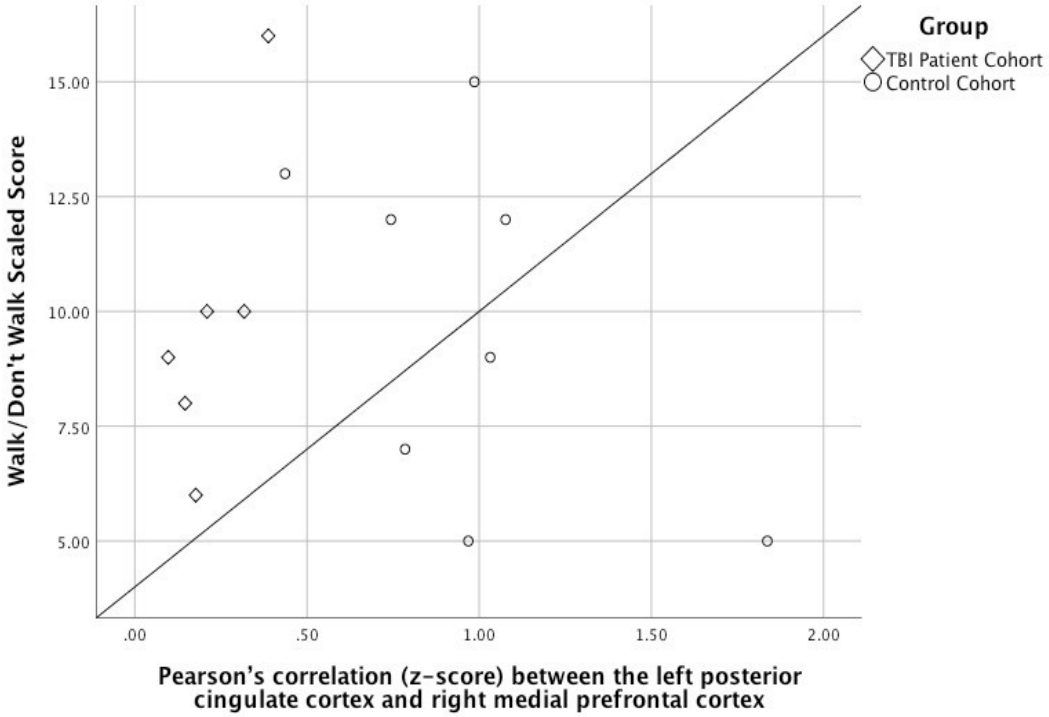

Figure 2.6. *Relationship between the standardised Pearson's correlation coefficients (Z-score) of the left PCC and right mPFC and the scaled score of the subtest, Walk/Don't Walk, in the patient and the control cohorts.*

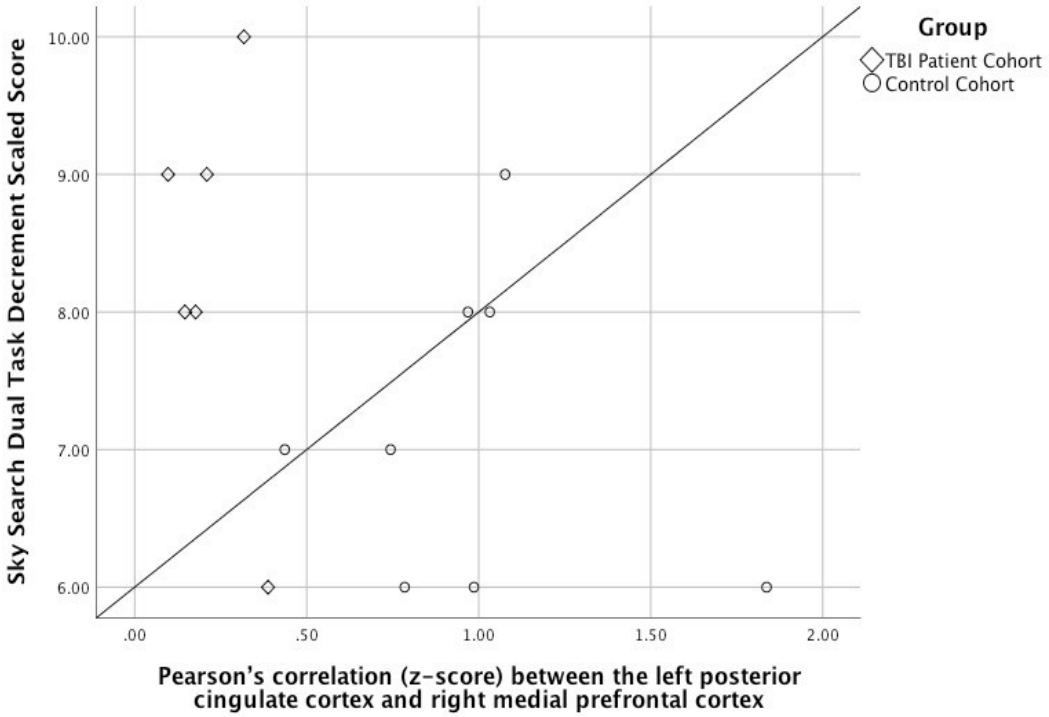

Figure 2.7. *Relationship between the standardised Pearson's correlation coefficients (Z-score) of the left PCC and right mPFC and the scaled score of the subtest, Sky Search Dual Task Decrement, in the patient and the control cohorts.*

2.5 Discussion

The purpose of this study was to examine the functional changes *between* regions *within* the DMN in paediatric TBI patients compared to control cohorts, and identify the relationship of DMN connectivity to long-term sustained attention outcome following paediatric traumatic brain injury. The implications of the current findings, and limitations that could have potentially affected the present findings are discussed below.

2.5.1 Present fMRI findings

To investigate neural changes in the paediatric patients after a brain injury, the study first used ICA to examine functional activity differences in the DMN regions between TBI patients and healthy children. The first hypothesis – that reduced functional activity (i.e., BOLD signal fluctuations in regions that are spatially correlated with the DMN) will be found in the patient group as compared to the control group – was not supported by the current study. Indeed, there was no significant difference in functional activity in the DMN between the groups. The current findings contradict previous studies, also using similar ICA methods, which reported activity alterations in the DMN regions (i.e., increased activity in the frontal regions, reduced activity in the PCC and parietal regions) in adults after a TBI (Palacios et al., 2013; Zhou et al., 2012). Moreover, using ICA, another study has found alterations across several resting-state networks including disruptions in the DMN (i.e., increased connectivity in the PCC, and decreased connectivity in the frontal and parietal cortices) in adolescents with a brain injury as compared to controls (Borich, Babul, Yuan, Boyd & Virji-Babul, 2015). The disparity in the present findings compared to previous TBI studies could be because of age differences, injury types, or time since injury between the studies, which can impact BOLD imaging metrics (Mayer et al., 2018). Importantly, the disparity in findings compared to previous adult studies could also be explained by the more plastic nature of the developing brain as compared to the adult brain (Stephenson et al., 2020), which might have led to different neural reorganisation in the two age groups, as discussed in Chapter 1. The current study however acknowledges that the small sample size has likely impacted its ability to detect differences, as small sample size would result in a low levels of power, consequently affecting the ability to detect significant activity difference (Cremers, Wager & Yarkoni, 2017). Moreover, the small sample size specifically impacts the analysis method used—independent component analysis. A small sample size will result in a small number of training samples, and as a result the ICA classifier, which is built on a training sample, is skewed and magnifies any bias in the data, leading to an unreliable performance of the ICA classifier (Cheng, Liu, Lu & Chen, 2006). As a result, the small sample size has likely affected the ICA performance and its ability to detect small differences.

The present study went on to use seed-based analysis to examine changes in the functional connectivity *between* the brain regions *within* the DMN. Consistent with this study hypothesis, the present findings illustrated functional connectivity alterations *between* regions

within the DMN, specifically *between* the left PCC and left/right mPFC, in the TBI patients as compared to typically developing children. The current findings are in line with adult TBI studies, which have also reported alterations *between* the mPFC and PCC (Zhou et al., 2012). Studies have further suggested that the PCC is most vulnerable to TBI, and alterations involving the PCC are associated with cognitive deficits (Sharp, Scott & Leech, 2014; Zhou et al., 2012). The vulnerability of the PCC is also evidenced in Bonnelle et al. (2011)'s study, which illustrated consistent neural alteration *within* the left PCC. Studies have suggested that the PCC plays a vital role in attention in healthy adults and monkeys, where the inability to suppress the PCC affects the performance of attention tasks (Hayden, Smith & Platt, 2009; Weissman, Roberts, Visscher & Woldorff, 2006). Bonnelle et al. (2011)'s study has extended the role of PCC in attention to the adult TBI population, where the inability to suppress the PCC is linked to poorer sustained attention performance. The study further suggested that the inability to suppress the PCC is also accompanied by problems with regulation *within* the DMN. This is evidenced in another study that demonstrated that the PCC, alongside the mPFC, is critical in regulating the brain connectivity with other DMN brain regions in the respective eyes-closed/eyes-opened state, which supports cognitive performance (Wang, Chang, Chuang & Liu, 2019). Moreover, it was suggested that during eyes-closed state, the PCC specifically influences the neural connectivity with the mPFC (Sharaev, Zavyalova, Ushakov, Kartashov & Velichkovsky, 2016). As the study did not collect data pertaining to the closed/opened state of the eyes, this study cannot confirm whether the present findings were a result of the eye-closed state. Taken together, the current results however are in line with the current studies, reiterating commonly reported alterations within the DMN in TBI populations, and also suggesting the vulnerability of the PCC after TBI. The results would have to be taken with caution given the very small sample size that could have led to an overestimation of effect size (Button et al., 2013; Cremers et al., 2017).

In contrast to prior studies, the present study however did not illustrate alterations in the parietal or precuneus regions of the DMN in the TBI sample compared to controls (Kramer et al., 2008). The disparity in findings could again be explained by the differences in the time since injury or age differences between the present study and Kramer et al. (2008) (which included younger paediatric patients) which can impact BOLD imaging metrics (Mayer et al., 2018). Another factor to consider is the impact of the ROIs selection on resting-state fMRI; despite common functional topographies shared across subjects, there is still variability between subjects (Sohn et al., 2015). Subject variability suggests that the position of a neural region is likely to be different between subjects, therefore a specific brain region that represents a functional region of one subject, could be unrepresentative in another subject (Mueller, Hong, Shepard & Moore, 2017). Therefore using standardised ROIs derived from ICA can affect the accuracy of functional connectivity measurements; a study has illustrated that standardised ROIs can lead to lower functional connectivity derived as a result of subject variability, and the

use of inaccurate ROIs have shown to lower measured connectivity and greater variance as the ROIs may exclude the correct functional regions for some subjects, which can affect the current findings (Sohn et al., 2015). The current study has however tried to reduce the influence of ROIs inaccuracy by deriving the ROIs from the ICA output, and data-driven ROIs are suggested to provide a better measurement of functional connectivity between seed regions (Cole, Smith & Beckmann, 2010).

2.5.2 Association between the DMN Functional Connectivity and Sustained Attention Performance

This study was also interested in examining the association between resting-state functional connectivity *between* regions *within* the DMN and sustained attention performance. The current literature suggests that the DMN regions, especially the PCC and mPFC, are crucial in performing attention tasks; the inability to suppress the DMN is associated with poor attention performance (as measured by the reaction time parameter of a global/local selective-attention task) in healthy participants (Mittner, Hawkins, Boekel & Forstmann, 2016; Weissman et al., 2006). The similar association is also presented in the TBI population (Bonnelle et al., 2011; Sharp et al., 2011; Zhou et al., 2012). Bonnelle et al. (2011)'s study has also suggested that alterations within the DMN are crucial in the development of sustained attention problems after a brain injury. The same was also observed in the paediatric TBI population, where Kramer et al. (2008)'s study illustrated greater activation of the DMN regions during sustained attention task in patients as compared to healthy children. Based on previous studies, the current study therefore hypothesised that there would be correlation between functional connectivity *within* the DMN and sustained attention performance. In contrast to previous findings, after correcting for false discovery rate, the current study did not find any significant correlation between functional connectivity *within* the DMN and attention performance. The lack of findings may be explained by several reasons; foremost, previous studies have suggested that the lack of association between functional connectivity and cognitive performance can reflect disorganization in TBI patients' neural network (Raizman et al., 2020). Raizman et al. (2020) suggested that TBI could disrupt the neural network patterns, and cause changes in the neural connectivity that are associated with specific cognitive performance. The changes in neural connectivity can result in a less effective network, consequently causing poorer cognitive performance (Hayes, Bigler & Verfaellie, 2016; Raizman et al., 2020). It was further suggested in a schizophrenia population that functional connectivity in patients might reflect different cognitive skills as compared to healthy controls (Honey, Bullmore & Sharma, 2002). Therefore, this suggests that the DMN regions examined may be unrepresentative of sustained attention processes in patients, which would explain the lack of correlations found in the current study. This however seems unlikely, as current studies have reported an association between neural disruption in the DMN and attention performance in TBI populations, and moreover the current

study have also found no correlations in the control group. This study has only examined the DMN based on the current TBI literature, particularly in the adult TBI studies, which have suggested that attention outcome after TBI is heavily reliant on disruptions in the DMN regions (Bonnelle et al., 2011). However, given the lack of significant findings, it is important for future studies to consider including other brain networks that are also crucial to sustained attention processes, as they might hold a closer association to attention performance, especially in the paediatric patient population which has little research on. As discussed in Chapter 1, sustained attention is reliant on the proper functioning of both the central executive network (CEN) and DMN, and the anti-correlation relationship both networks share may be most sensitive to attention performance (Fan et al., 2018). Given that the brain networks do not function independently, it would be important for future studies to simultaneously examine both the DMN and the CEN and their association to sustained attention in children with brain insults.

Notably, this study has also reported no significant association between sustained attention performance and functional connectivity in the DMN when Pearson's correlation was carried out across all the subjects (including patients and controls). Therefore, it is important to consider the appropriateness of the attention measures used to assess sustained attention, especially with the use of the Sky Search Dual Task Decrement score. This attention measure has been used widely in previous studies to assess sustained attention in children (Fathi, Mehraban, Akbarfahimi & Mirzaie, 2017; Kasirian, Mirzaie, Pishyareh & Farahbod, 2018; Lakomy, 2021). Whilst the Sky Search Dual Task is a sustained-divided attention task, the dual task has been found to fit better within the construct of sustained attention as compared to divided attention due to its' stronger link with the prolonged auditory performance demands of the sustained attention subtest measure (Passantino, 2011). However, it is important to acknowledge that as a dual task, Sky Search Dual Task reports a measure of sustained/divided attention, and may not tap into the same construct of sustained attention as other attention tasks. This is observed in Pasquali (2014)'s study, which looked at the relationship between the Sky Search Dual Task and other sustained attention measures (i.e., the Go-No-Go omission scores, Gordon Vigilance Task Omission scores and TEA-Ch Score task). Pasquali (2014)'s study reported only a very weak correlation between the Sky Search Dual Task, and the other sustained attention measures (i.e., Gordon Vigilance Task Omission scores and TEA-Ch Score task). The weak correlation suggests that these sustained attention measures may not represent the same construct, and instead may be tapping into different attention processes, which could explain the current findings. Taken together, Sky Search Dual Task may not be the most appropriate sustained attention measure, and future studies should consider including a measure that assess sustained attention as a separate domain.

The current study has examined the neural changes in the brain regions thought to underlie sustained attention as sustained attention impairment is one of the most commonly reported impairments after a brain injury. The study has however found no significant

differences in sustained attention performance between paediatric TBI patients and typically developing children. This could reflect that the TBI patients that returned 2-years after their injury may be patients with better cognitive outcomes, which is in line with previous studies that showed comparable cognitive performance in patients, especially those with less severe injury (classed by up to 6 days of length of coma), 2-years post injury as controls, suggesting cognitive recovery in these patients (Dikmen, Machamer, Temkin & McLean, 1990). While unexpected, there are previous studies that have also demonstrated no difference in attention performance via continuous performance task (using the discriminability measure) between paediatric TBI patients and controls, and the lack of difference was suggested to reflect good recovery in patients (Kramer et al., 2008). Moreover, studies have suggested that in mild and moderate TBI, deficits may become subtler in later stages, and standard measures may be less sensitive to detect the deficits in these TBI groups (Stephens, Salorio, Denckla, Mostofsky & Suskauer, 2017; Stephens et al., 2018). Given that the majority of the patients in the current study were diagnosed with moderate TBI, this could explain the lack of significant differences between the patient and control groups. This is further evidenced in previous studies, which found no differences in the same subtest used in the present study (Walk /Don't Walk) between controls and mild and moderate TBI patients (Hung et al., 2017), but illustrated differences in severe TBI patients and controls (Durish, et al., 2018; Hung et al., 2017). This also highlights that this subtest may not be the most appropriate measure for use with the mild/moderate populations, and may explain the current study's findings as most of the current patients had moderate TBI. It also emphasises the importance of examining moderate and severe TBI patients separately, as standardised subtests may be insensitive to subtle deficits, and therefore combining both groups together may mask deficits the study would otherwise find in the severe TBI cohort. However, given the small sample size in the current study, it was not feasible to separate the patient cohort into subgroups. Moreover, Kramer et al. (2008)'s study has also highlighted that despite good behavioural recovery in paediatric TBI patients, neural activities in the brain regions underpinning attention processes still remained disrupted 12-months following the injury. Taken together, these instead suggest that neuropsychological tests may not be a sensitive measure at identifying patients with attention problems, especially when the patient cohort is a heterogeneous sample, and instead examining neural disruptions in the brain regions underpinning attention processes may be more sensitive in identifying patients with potential attention problems.

2.6 Limitations

Several limitations could have affected the results of the current study. The patient sample was heterogeneous with regard to the mechanism of injury and TBI severity, which can influence the findings in regard to the contribution to the alteration in the network pattern, as studies have presented an association between increased brain activations in TBI patients and their injury

severity (Olsen et al., 2015), and more severe TBI patients have been associated with BOLD hypo-activations (Olsen et al., 2020). In addition, previous studies have demonstrated differences in the brain regions recruited between patients with moderate and severe TBI when carrying out cognitive tasks; severe TBI patients recruited brain regions that were not recruited in patients with moderate TBI (Scheibel et al., 2009). As a result of the small sample size, the current study had to collapse both severity groups into one, and it could not investigate neural changes in each group individually, which may result in overlooking subtle changes or changes only presented in severe TBI patients. Moreover, prior studies have also commonly combined moderate and severe TBI patients in their analyses, and found significant neural changes in patients compared to healthy controls (Gilbert et al., 2018; Konstantinou, Pettemeridou, Stamatakis, Seimenis & Constantinidou, 2018). Therefore, given the small sample size, it is reasonable for the current study to collapse the two severity groups together.

This also highlights another limitation of the present study, which is the small number of children in the TBI and control cohorts. As the present study used data previously collected, resting-state fMRI was not collected for every participant, consequently limiting the number of participants in the current study. Moreover, the study is of a longitudinal nature, where data were collected after 24-months, and consequently the study would have experienced participant attrition, which can reduce the study's statistical power because of the smaller sample size, and also introduce attrition biases as the patients who returned may not be representative of the patients who have dropped out, affecting the generalizability of the findings (Barry, 2005). However, the longitudinal approach was beneficial as it allowed the study to concurrently examine neural and cognitive changes 24-months post-injury, and the findings suggested that neuroimaging methods may be more sensitive in identifying deficits than cognitive tasks.

In addition, the current study may also be limited by the sample size, as a small sample reduces the ability to detect a true effect, and even if a true effect is discovered, the magnitude of that effect is likely to be exaggerated, and a small sample is also associated with low statistical power, which affects the ability to extend the current findings to the wider population (Button et al., 2013; Faber & Fonseca, 2014). However, the current study has used a statistical procedure, based on Benjamini and Hochberg (1995)'s method, to control for false discovery rate, and reduce the occurrence of false positives. Additionally, the study notes that the TBI cohort consisted mainly of male participants (n = 5) with only one female patient, however previous TBI studies have demonstrated gender differences in functional connectivity despite no differences in cognitive performance (Hsu et al., 2015). The authors have shown neural recovery in male, but not in female, which suggested poorer recovery and more severe injury in female than male. Unlike Hsu et al. (2015)'s study, this study was not able to examine gender groups separately due to a small sample size.

It is also important to consider whether the analysis method used in the current study (ROI–ROI analysis) could have influenced the current findings. While seed-based analysis, like

the method used in the current study, can effectively detect localised changes, it is spatially restricted and is less sensitive to clusters of altered connectivity (i.e., disruptions between segregated and connected brain regions/networks) (Clemm von Hohenberg et al., 2018). As seed-based analysis method like ROI–ROI analysis considers the brain as individual components rather than seeing the brain as a connected network, it does not provide a comprehensive examination of the network connectivity. Instead, future studies should consider using other analysis methods like the network-based statistics (NBS). NBS examines the whole-brain as a connected network whilst accounting for multiple comparisons during the connectivity analysis; therefore NBS allows a higher dimensional analysis, which provides a more thorough examination of network connections (Zhan, Chen, Gao & Zou, 2019). As a result, NBS holds greater statistical power in identifying between-group differences, and is thus may be more sensitive to identify functional connectivity differences between groups (Zhan et al., 2019).

Finally, it is important to acknowledge that the present study based its hypotheses on the current literature, which included a majority of studies with adult TBI patients; there are very few studies that have specifically examined the disruptions of brain regions underpinning sustained attention in children with a brain insult. Therefore it is fair to interpret the differences found between this study and the existing literature to result potentially from the disparity between an adult brain and a developing brain, and the influence this disparity has on responses to a brain injury. This instead highlights the gap in the literature, and especially suggests the need for more future studies to focus on the paediatric brain insult population.

2.7 Conclusion

In summary, the present study has shown alterations in the functional connectivity involving the regions of the DMN (PCC and mPFC) in TBI children when compared to typically developing children. The study however found no significant association between functional connectivity of the DMN regions and attention performance in both patient and control groups, and suggest that future studies include other relevant networks involved in attention like the task-positive network, also known as the central executive network. Moreover, while seed-based analysis like ROI–ROI method has its advantages, it may not be the optimal method when examining brain regions within or between brain neural networks, as it does not view the brain as a connected network. Additionally, as compared to ROI–ROI analysis, NBS is better equipped to control for multiple comparisons during connectivity analysis, therefore future work should consider using NBS. Furthermore, alongside the present findings, the existing literature has also suggested that examining neural changes may be a better way to identify children who may have subtle attention problems. The current chapter provided crucial pilot work to develop analysis pipelines that will be used in the following studies.

Chapter Three: Examining Resting-State Functional Connectivity Alterations in Neural Networks Associated with Sustained Attention in Children with Epilepsy

3.1 Introduction

Disordered brain networks in childhood can impact on different regions and yet still have a deleterious effect on key functions such as sustained attention. The previous chapter identified alterations in the default mode network (DMN), a network that is associated with sustained attention performance in children with traumatic brain injury (TBI). This acquired injury provides interesting insights into how a previously typically developing brain may be altered both structurally and functionally. The current chapter extends this work to focus on a different brain injury population that also has commonly reported attention problems—epilepsy. The pathophysiology is vastly different in both brain injury types. TBI is typically characterised by white matter connectivity disruption as a result of diffuse axonal injury (Kinnunen et al., 2011) to short- and long-range cortical networks. Conversely, the most common form of epilepsy across children and adults involves focal seizure onset (Beghi, 2020). However, there is ample evidence to show that epilepsy is also a network disorder; network alterations in this disorder have been shown to extend beyond the epileptogenic zone causing both regional and global connectivity disruptions, which underlie common cognitive problems found in people with epilepsy (Burman & Parrish, 2018; Englot, Konrad & Morgan, 2016; Hayes, Bigler & Verfaellie, 2016). Given the dependence of sustained attention on key cortical networks and the possibility that these are affected in children with epilepsy, the current chapter thus sought to examine changes in the resting-state functional connectivity in children with epilepsy as compared to typically developing children. First, an overview of epilepsy and seizures is given and then cognitive impairments are discussed with a focus on sustained attention and the brain networks supporting it. Following, the findings of existing literature are presented, before highlighting the current research gap, and finally addressing the main aims and hypothesis of the present study.

3.1.1 Epilepsy

Epilepsy is one of the most commonly diagnosed childhood neurological disorders, affecting 0.5-1.0% of children below 16 years and is characterised by epileptic seizures (Shinnar & Pellock, 2002). Seizures are sudden bursts of electrical activity in the brain, which can result in a brief interruption to the normal functioning of the brain (Stafstrom & Carmant, 2015). Even though the prognosis for the majority of people with epilepsy is favourable, some patients do not have seizure remission in spite of suitable treatment with antiepileptic drugs (Jiang et al., 2018; now referred to as anti-seizure medications). Patients with epilepsy, whose seizures are not controlled following trials of different antiepileptic drugs have refractory epilepsy, or also known as drug-resistant epilepsy (Laxer et al., 2014). This group of patients accounts for a substantial proportion of the burden of epilepsy in the population because of a range of factors: including

higher mortality rate, psychological disorders, social stigmatization and poorer quality of life as compared to patients with controlled epilepsy (Laxer et al., 2014).

Seizures experienced by patients with epilepsy are most commonly classified into focal seizures (previously known as partial seizure) and generalised seizures. Patients with focal onset epilepsy experience seizures confined to one hemisphere of the brain, and in comparison, patients with generalised onset epilepsy would experience seizures bilaterally across both hemispheres of the brain (Gloor & Fariello, 1988). Focal epilepsy can be characterised by seizure discharge originating from a specific part (lobe) of the brain, and is an umbrella term that commonly includes frontal lobe epilepsy (FLE), temporal lobe epilepsy (TLE) and parietal lobe epilepsy (Jokeit & Schacher, 2004). By comparison, generalised epilepsy is characterised by seizure discharge throughout the brain, and the new 2017 International League Against Epilepsy (ILAE) classification accounts for seizure types, etiology, comorbidities and general clinical outcome, thus expanding generalised seizure classification outside of motor and non-motor (absence) seizures (Fisher et al., 2017), and now encompasses generalised tonic-clonic seizures, absence epilepsy and myoclonic epilepsy (Gloor & Fariello, 1988; Jokeit & Schacher, 2004).

Regardless of the state of seizure control, people with epilepsy commonly present with cognitive impairments. The most frequent impairments reported by patients with epilepsy include memory problems, mental slowness and attention impairments, and these cognitive problems are found in both children and adults patients with epilepsy (Lodhi & Agrawal, 2012). While cognitive impairments are common comorbidities in epilepsy, there is increasing evidence that suggests that uncontrolled seizures worsen these impairments as frequent recurrent seizures often induced morphological and functional changes, which can disrupt the synchronization across neuronal networks, consequently affecting the cognitive functions supported by these regions (Holmes, 2015). This is in line with a previous study that suggested poorly controlled epilepsy leads to greater cognitive deficits (i.e., poorer intelligence quotient (IQ) performance) compared to well-controlled epilepsy (Berg, Zelko, Levy & Testa, 2012; Lagae, 2006). The greater proportion of cognitive deficits in children with refractory epilepsy is likely because the continuous seizures in refractory epilepsy are associated with progressive damage in the neural networks, which can lead to greater cognitive impairments in this epilepsy population (Caciagli, Bernhardt, Hong, Bernasconi & Bernasconi, 2014).

3.1.2 Left Seizure Focus Contributes to Greater Cognitive Impairments

Cognitive impairments (i.e., memory, language and executive function) are common consequences in patients with refractory epilepsy, and most patients (83%) have been found to be impaired in more than one cognitive domain (Rai et al., 2015; Thompson & Duncan, 2005). Studies have, however, demonstrated that patients with left focal epilepsy are more prone to brain activity abnormalities. For example, TLE, a common underlying pathophysiology that is

often associated with cognitive deficits (Doucet, Osipowicz, Sharan, Sperling & Tracy, 2013; Pereira et al., 2010) shows laterality effects; people with left mesial TLE presented with greater bihemispheric neural alterations than those with right mesial TLE; they presented with increased connectivity between the bilateral thalami and the posterior salience network, and decreased connectivity between the dorsal DMN and the visuospatial/dorsal attention network that were not found in people with right mesial TLE (de Campos, Coan, Yasuda, Casseb & Cendes, 2016), This is evidenced in studies showing that as compared to children with right focal epilepsy, cognitive deficits are reported more frequently and to be more severe in children with left focal epilepsy, including TLE (Baumer, Cardon & Porter, 2018; Nickels, Wong-Kisiel, Moseley & Wirrell, 2012). This is further evidenced by Gascoigne et al. (2017)'s study that reported that the presence of left focal seizures is a factor in poorer attention performance in children with epilepsy. The association between left focal epilepsy and poorer cognitive performance (in memory) was also present in adults with partial epilepsy (Blake, Wroe, Breen & McCarthy, 2000). A study has similarly found that across patients with TLE and FLE, patients with a left seizure focus performed worse than their right-sided counterparts (McDonald et al., 2005). More importantly, in contrast to the presumption that patients with FLE would perform poorer than those with TLE, McDonald et al. (2005) also found that patients with left TLE performed worse than right FLE. This suggests that the side of the seizure focus plays a bigger role as compared to the form of epilepsy in contributing to cognitive deficits (i.e., executive dysfunction) in patients with epilepsy. There is therefore strong evidence in the current literature that suggests whilst refractory epilepsy is prone to cognitive impairments, patients with left focal epilepsy are more vulnerable to poorer outcomes, and serves to be an important patient population to investigate.

3.1.3 Common Cognitive Impairments in Epilepsy

Cognitive deficits are also often reported following epilepsy diagnosis in children, and some of the most common cognitive deficits found in this cohort include memory, language and attention (van Rijckevorsel, 2006). Memory deficits have frequently been reported in children with epilepsy; despite differences in the extent of deficits between temporal lobe epilepsy, frontal lobe epilepsy and childhood absence epilepsy, children with these forms of epilepsy are all found vulnerable to verbal and/or visual memory impairments, measured using the Wide Range Assessment of Memory and Learning tool (Nolan et al., 2004). A systematic review carried out by Menlove and Reilly (2015) has further established the increased risk of memory impairments in children with epilepsy, the review demonstrated a general consensus of poorer memory performance in children with epilepsy as compared to healthy children in a range of visual, verbal and auditory memory tasks, including recall tasks, Wisconsin card sorting task, subtests from the Wechsler Intelligence Scale for Children amongst other standardised tests of memory. Similarly, language deficits have also been widely shown and demonstrated in different

subtypes of epilepsy in children, including refractory epilepsy (Baumer et al., 2018). In addition, attention problems in children with epilepsy are also well established, as evidenced by the increased risk for attention problems or inattention attention deficit hyperactivity disorder (ADHD) in children with epilepsy (Dunn & Kronenberger, 2005). The poor attention outcome has been evidenced in people with temporal lobe epilepsy, as measured using the Trail-Making test, the Stroop test, and the Continuous Performance Test (CPT) (Stella & Maciel, 2003), and have shown longer reaction times (RT) in a choice RT test and CPT (Fleck, Shear & Strakowski, 2002).

As previously discussed in Chapter 1, academic achievement and other cognitive skills rely heavily on attention therefore attention impairments can have significant consequences for children with epilepsy. As evidenced, attention has repeatedly been reported to be the more significant predictor of poor academic outcome as compared to other cognitive domains (i.e., executive functioning, language, memory, mathematics, psychomotor speed, spatial ability and general intelligence) in children with epilepsy (Cheng, Yan, Gao, Xu & Chen, 2017). Moreover, studies have found that attention problems may be, in part, responsible for memory deficits in children with lateralised epilepsy (Engle & Smith, 2010), which is consistent with the findings of a previous study that reported the influence of sustained attention and spatial attention in long-term memory encoding (deBettencourt, Williams, Vogel & Awh, 2021). Given the prevalence of memory impairments among people with epilepsy, it garners support for the importance of research surrounding attention in children with epilepsy, and is further elaborated in the next section.

3.1.4 Attentional Deficits in Epilepsy

There is strong evidence that children with epilepsy have attentional difficulties, and poorer performance is evidenced across the different forms of attention (sustained, selective and attentional control) relative to typically developing peers (Dunn & Kronenberger, 2005; Kang, Yum, Kim, Kim & Ko, 2015; Stella & Maciel, 2003). Using a range of cognitive tests (e.g., the Test of Variables of Attention – a computerized performance task, and vigilance and distractibility tasks from the Gordon Diagnostic System), sustained attention deficits are, however, the most consistently described impairments in paediatric epilepsy across different subtypes of paediatric epilepsy: complex partial seizure (Semrud-Clikeman & Wical, 1999), new-onset generalised and focal epilepsy (Triplett & Asato, 2015), and in focal/refractory epilepsy, including TLE and FLE (Smith, Elliott & Lach, 2002). This was also evidenced by Sanchez-Carpintero and Neville (2003)'s critical review which found that across the paediatric epilepsy literature that examined a range of attention domains (i.e., sustained, selective, divided, and response inhibition amongst others), sustained attention deficits were most consistently reported across studies even when no significant difference was found in the other

types of attention like selective attention and divided attention, suggesting epilepsy susceptibility particularly to sustained attention deficits.

The importance of sustained attention in academic performance is also well established in healthy children, and has been discussed in Chapter 1. For example, a study has suggested that, as sustained attention plays a key role in the learning process, therefore better sustained attention is associated with better academic performance (Bouzaboul, Abidli, Amri, Rabea & Ahami, 2021). This is further evidenced in Steinmayr, Ziegler and Träuble (2010)'s study that proposed the role of sustained attention in complex problem solving, which is an important skill in the school context, suggesting that school performance is reliant on sustained attention functioning. Given the key role sustained attention ultimately plays in academic performance, impairments in sustained attention would therefore likely result in poor performance in school. This relationship was presented in a previous study that found that impairments in sustained attention is a more significant predictor of poor academic performance in children with epilepsy as compared to other factors like impairments in memory (Williams et al., 2001).

Taken together, children with epilepsy are vulnerable to impairments in sustained attention, and as a result, are prone to poor academic performance, and it is therefore important to examine the underlying brain regions supporting attention to gain a better understanding of how disruptions in these regions may lead to attention deficits.

3.1.5 Susceptibility of the DMN and CEN in Epilepsy

Existing studies have suggested that the DMN may be particularly vulnerable to refractory epilepsy, as a study showed frequent/uncontrolled seizures can damage the cortex and disrupt the functional and casual connectivity of several networks, including the DMN, which results in cognitive dysfunction such as attention impairments in patients with epilepsy (Jiang et al., 2018). The susceptibility of the DMN to epilepsy may then explain the poor sustained attention outcome consistently reported in patients with epilepsy, as there is strong evidence that the DMN plays an important role in sustained attention in healthy participants, as discussed in Chapter 1, and disruptions in the DMN have been linked to poorer attention in the traumatic brain injury population. Alterations in the DMN, which is associated with spike and wave discharges in epilepsy (Gotman et al., 2005), have been reported in adults with TLE, and these alterations are suggested to reflect the pathophysiology of cognitive problems in patients with epilepsy (Gao et al., 2018). Compared with controls, right TLE patients showed reduced functional connectivity (measured using network homogeneity) in the right middle temporal pole gyrus, but higher functional connectivity in the bilateral posterior cingulate cortex, but left TLE patients showed reduced functional connectivity in the left inferior temporal gyrus and left hippocampus. Alongside the differences in the DMN alterations between left and right TLE patients, Gao et al. (2018)'s study has also reported poorer performance (inferred from the slower reaction time obtained from the attentional network test) in the left TLE patients; the

differences in disrupted regions may account for the poorer outcome in left TLE patients as further evidenced by the significant correlations between the reaction time and connectivity measures. More importantly, this reiterates the greater vulnerability of patients with left focal epilepsy to poorer outcomes, and highlights a need to examine DMN changes in paediatric patients with left focal epilepsy.

In addition to the task negative network (DMN) reported in Chapter 2, the task positive network (central executive network (CEN)) may have an important role in understanding attention deficits (Kelly, Uddin, Biswal, Castellanos & Milham, 2008) because of the way in which the DMN and CEN work in combination to efficiently carry out sustained attention tasks. As discussed in Chapter 1, there is emerging evidence that along with deficits in the DMN, disruptions to the CEN and connectivity between the DMN and CEN are also likely to underpin sustained attention deficits. Abnormalities in the CEN have been frequently found in adults with TLE (Cataldi, Avoli & de Villers-Sidani, 2013), and reduced connectivity in the CEN is suggested to contribute to impairment in related cognitive processes such as working memory (Vlooswijk et al., 2011). Despite the existing studies finding disruptions in the CEN in adults with epilepsy, very few studies have looked at it in children, and given the importance of the CEN in attention, there is an important need to examine CEN changes in children with epilepsy. More importantly, previous studies have also illustrated disruptions in the connectivity *between* the DMN and CEN in adult patients with TLE, and found a correlation between reduced functional connectivity between the DMN and CEN and cognitive impairments (executive control function measured using the Wisconsin Card Sorting Test) (de Campos et al., 2016; Zhang et al., 2017). Zhang et al. (2017)'s study suggested that the disrupted connectivity between the two networks, which is a marker of reduced interaction between the two networks, is a core element contributing to cognitive impairments in patients with TLE. To date, no studies have examined this relationship in children with refractory left-sided epilepsy.

Disruptions to the DMN have been reported in studies of children with epilepsy, including TLE (Oyegbile et al., 2019), FLE (Widjaja, Zamyadi, Raybaud, Snead & Smith, 2013a), benign epilepsy with centrotemporal spikes (Oser et al., 2014), and also in patients with refractory epilepsy, including TLE and extratemporal epilepsy (Ibrahim et al., 2014) and FLE, TLE, right hemisphere, and parietal-occipital lobe epilepsy (Widjaja, Zamyadi, Raybaud, Snead & Smith, 2013b). There are some data that examine the impact of disruptions in the DMN (less deactivations of the DMN regions – posterior cingulate cortex (PCC) and precuneus – during task (i.e., N-back task) as compared to healthy controls) on cognition, with impaired working memory and executive function performance (as measured using the accuracy and reaction time variables of the N-back task, and Delis-Kaplan Executive Function System Colour-Word Interference and Card Sort tests) in children with TLE (Oyegbile et al., 2019). Thus, these data highlight the relationship of key brain networks evaluated in resting state studies and their relevance to attention skills in children with epilepsy.

3.1.6 Disparity in DMN Changes across Epilepsy Subtypes

Despite disrupted DMN commonly reported across epilepsy groups, there are disparities in the disruptions between generalised epilepsy and focal epilepsy, and it is important to examine both epilepsy groups separately. For example, reduced connectivity is observed in the PCC, precuneus, anterior/mid-cingulate cortex and bilateral lateral parietal cortex in children with focal refractory epilepsy (Widjaja et al., 2013b), while reduction is identified in the precuneus, PCC, bilateral inferior lateral parietal and prefrontal cortex (PFC) in medial TLE (Zeng, Pizarro, Nair, La & Prabhakaran 2013), and reduction is found in the PCC, inferior parietal cortex and medial PFC (mPFC) in absence epilepsy (Luo et al., 2011), a form of generalised epilepsy in children. Adult epilepsy studies have further highlighted differences in the DMN alteration between patients with left and right focal epilepsy, and the disparity between both patient groups may be associated with the poorer cognitive outcomes in patients with left focal epilepsy, as discussed earlier (Gao et al., 2018). Current studies that have examined DMN connectivity in children with refractory epilepsy have however often combined data from patients with both left and right-hemisphere epilepsy (Widjaja et al., 2013b). Taken together, it warrants the need for studies to focus on patients with left focal epilepsy, as there is recurring evidence suggesting poorer outcomes in these patients and only examining this patient group will allow more accurate identification of neural changes that are specific to left focal epilepsy.

3.1.7 Existing Paediatric Epilepsy Literature

Given that previous studies have not distinguished between different patient groups, there are limited data on the specific relationship between abnormalities in DMN connectivity and other networks underlying sustained attention, particularly the CEN. The findings of studies that have examined connectivity between the DMN and CEN in adults with left-hemispheric epilepsy, as discussed in Chapter 1, are not directly translatable to children due to the differences in the development of the functional connectivity of the DMN and CEN between both age groups (Sherman et al., 2014; Supekar et al., 2010). One study compared healthy children and children with epilepsy (childhood absence epilepsy), and looked at the functional connectivity between the DMN and CEN (Li et al., 2015). In contrast to the current literature that has found reduced functional connectivity between the DMN and CEN in populations with known sustained attention deficits, their study found an increase in connectivity between the DMN and CEN (Cieri & Esposito, 2018; Fan et al., 2018; Mills et al., 2018). However, studies have illustrated how absence epilepsy, a form of generalised epilepsy in children, (Luo et al., 2011) affects the functional connectivity of the brain differently from focal epilepsy (Widjaja et al., 2013a). The DMN regions showing reduced connectivity differed between both epilepsy types; reduced connectivity was found between the fronto-parietal regions and between the temporal-fronto-parietal regions in generalised epilepsy, and reduced connectivity was found in the right anterior cingulate, left medial superior frontal and right superior frontal gyri, along with an increase in

connectivity in the left inferior parietal lobule in focal epilepsy (Luo et al., 2011; Widjaja et al., 2013a). Thus existing research does not address the question of whether alterations of the DMN and CEN connectivity occur in left focal epilepsy in children.

Given the impact of sustained attention impairments on school performance and achievement, it is important to examine neural changes in the brain regions that could underpin these impairments, and allow us to identify children with epilepsy who may be at risk of impaired attention. There is strong evidence that children with left focal refractory epilepsy, have worse cognitive outcomes than their right focal refractory, or generalised epilepsy counterparts, making them an important group to study.

3.1.8 Aims and Hypotheses of Study

The current study aimed to use resting-state fMRI to examine 1) functional activity changes in the DMN and CEN between patient and control cohorts, 2) functional connectivity changes *between* specific brain regions the DMN and the CEN between patient and control cohorts, and 3) functional connectivity changes *between* the regions of the DMN and CEN between patient and control cohorts. Similar to Chapter 2, this chapter also referred to functional connectivity measured using the independent component analysis (ICA) as functional activity, defined as blood-oxygen-level dependent (BOLD) signal fluctuations in regions that are spatially correlated with the DMN and CEN (Gursel et al., 2020; Prestel, Steinfath, Tremmel, Stark & Ott, 2018); and functional connectivity (derived from the seed based analysis) is defined as the correlation between the time series of one region of interest (ROI) and all other regions of interests (ROIs) of the DMN and CEN.

Based on the current literature, it was hypothesised that there would be 1) reduced functional activity *between* regions *within* the DMN, and *between* regions *within* the CEN in patients with epilepsy as compared to controls, 2) reduced functional connectivity *between* specific brain regions of the DMN and the CEN in patients with epilepsy as compared to controls, and 3) reduced functional connectivity *between* the DMN and CEN regions in patients with epilepsy as compared to controls.

3.2 Methods

3.2.1 Participants

Healthy children were recruited either from the Birmingham community by contacting families who have previously indicated their interest in research being carried out at the Aston Brain Centre, Aston University, or are controls for another study. Paediatric patients with epilepsy were recruited via Birmingham Children's Hospital, where they were referred to the Aston Brain Centre for pre-surgical evaluation as part of the Children's Epilepsy Surgery Service program. In total, 24 healthy children and 26 patients with drug-resistant epilepsy (four right-hemisphere)

were recruited. The four right-hemisphere patients were removed, leaving 22 patients with left-hemispheric epilepsy.

Following imaging quality control (described below in data analysis), only 13 healthy children (8–16 years, *M* = 11.31, *SD* = 2.72, four males, nine females) and 14 patients (13–17 years, *M* = 14.64, *SD* = 1.28, six males, eight females) were included in the final analyses. The patient group in this study primarily comprised of patients with TLE and FLE; detailed demographic information is presented in Table 3.1 below. Due to the small sample size, the current study was not able to perform further sub-analysis to examine each epilepsy subtype. Medication and seizure frequency information has not been included, as the study did not have access to them. None of the patients had undergone epilepsy surgery prior to the study, but were surgical candidates.

Table 3.1.
Demographic information for patients and controls

Participant (Group)	Gender	Age at Scan (years)	Onset Age (years)	Lesion	Seizure Location
001 (Patient)	Male	14	12	Left FCD	Left frontal FCD
002 (Patient)	Female	17	13	Likely no	Left temporal lobe
003 (Patient)	Male	15	3	Yes	Left temporal lobe
004 (Patient)	Female	17	8	No	Left temporal lobe
005 (Patient)	Female	13	10	No	Left frontal-insular
006 (Patient)	Female	14	5.5	Mesial temporal sclerosis	Left temporal lobe
007 (Patient)	Female	14	Not available	Likely no	Left hemisphere
008 (Patient)	Female	15	Not available	Left parieto-temporal lesion	Left temporal lobe
009 (Patient)	Male	16	Not available	Maybe (abnormalities in temporal lobe structure)	Left medial temporal lobe
010 (Patient)	Female	14	Not available	Likely no	Left temporal lobe
011 (Patient)	Male	15	Not available	Left tumour	Left tumour
012 (Patient)	Female	14	Not available	Yes (previous stroke)	Left temporal lobe
013 (Patient)	Male	16	Not available	No	Left temporal lobe
014 (Patient)	Male	13	6	Likely no	Left insula
015 (Control)	Male	8	-	-	-
016 (Control)	Female	9	-	-	-
017 (Control)	Male	15	-	-	-
018 (Control)	Female	13	-	-	-
019 (Control)	Female	13	-	-	-
020 (Control)	Female	14	-	-	-
021 (Control)	Female	16	-	-	-
022 (Control)	Female	11	-	-	-
023 (Control)	Male	11	-	-	-
024 (Control)	Female	8	-	-	-
025 (Control)	Female	8	-	-	-
026 (Control)	Female	11	-	-	-
027 (Control)	Male	10	-	-	-

Note: FCD = focal cortical dysplasia

3.2.2 Procedure

Ethical approval was obtained separately for both the healthy children and patient group. Ethical approval was obtained from Aston University Ethics Committee (reference number #888) for the controls, and ethical approval for patients was sought from West Midlands- Black Country NHS Research Ethics Committee (IRAS reference 206601).

Parents' written informed consent for their child's participation in the study were obtained. Verbal assent was sought from children below the age of 16, while consent was also obtained from children over 16 years and deemed capable of giving consent.

3.2.3 MRI Acquisition

All neuroimaging data were acquired from a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil at the Aston Brain Centre, Aston University. High-resolution T1-weighted structural MR images were acquired with the following parameter: repetition time (TR) = 1900 ms, time to echo (TE) = 2.4 ms, flip angle (FA) = 9°. To acquire BOLD functional magnetic resonance imaging (fMRI), T2 sensitive gradient-echo echo-planar imaging (EPI) sequence was also acquired with the following parameters: TR = 3051 ms, TE = 30 ms, FA = 90°, 44 slices, and 100 volume with a total scan time of five minutes. To increase the power of the study, 6 of the controls used are part of the control group for a different study; therefore they were scanned on the same scanner but at a later time and have different T1/fMRI parameters. The T1 parameters are as follows: TR = 1500 ms, TE = 3.4 ms, FA = 15°. The fMRI parameters are as followed: TR = 2680 ms, TE = 30 ms, FA = 80°, 41 slices, and 150 volume with a total scan time of six minutes. Despite the disparities in acquisition parameters, studies have shown that functional MRI is insignificantly affected by differences in many acquisition parameters, including the TR and FA (Gonzalez-Castillo, Roopchansingh, Bandettini & Bodurka, 2011; Van Dijk et al., 2010). Furthermore, five minutes of resting-state is suggested to be sufficient to examine resting-state networks, therefore the disparity in acquisition time should not cause significant differences (Allen et al., 2014). Lastly, as the scans were resting-state fMRI, participants did not complete any task during the scan period, but were instructed to keep their eyes open during the scan.

3.3 Data Analysis

3.3.1 T1 Template Generation

Adopting the same approach as Chapter 2, the current study has used the Template-O-Matic 8 toolbox to generate a T1 paediatric template (Wilke, Holland, Altaye & Gaser, 2008).

3.3.2 Pre-processing

Image pre-processing was performed using Statistical Parametric Mapping (SPM12) (Ashburner et al., 2014; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) software running under MATLAB, version 2011b. Pre-processing prepares the images for further analysis, as the various pre-processing steps aids in reducing noise and artifacts thus improving the power of subsequent analyses (Jenkinson & Smith, 2001). The images first underwent slice time correction, before realignment. As the study includes patients who are difficult to recruit, it is important to retain as many participants as possible, therefore scrubbing was carried out using the data processing and analysis of brain imaging (DPABI) toolbox, version 3.1, in line with a previous paper (Power, Barnes, Snyder, Schlaggar & Petersen, 2012). However, as part of the imaging quality control in the present study, participants with more than 25% of their data that exceeded the pre-decided framewise displacement (FD)-threshold of 0.5mm were excluded from further steps. This threshold was defined based on previous research (Cheng, Rolls, Gu, Zhang & Feng, 2015). Following this, common pre-processing steps were carried out, including co-registration, segmentation, spatial normalisation to the generated T1 paediatric template and spatial smoothing (Gaussian Kernel, FWHM = 6mm). Briefly, co-registration is the alignment of the fMRI to the corresponding structural T1, and segmentation refers to the segmenting of the structural T1 image into the distinct brain tissues—grey-matter, white matter and cerebrospinal fluid (Esteban et al., 2020). Following, the normalisation step aligns the brain images of each subject to be in the same standardised space, and finally, smoothing is performed to increase the signal-to-noise ratio. The functional data then underwent band-pass filter (0.01-0.08 Hz) to reduce physiological noise and improve signal to noise ratio with resting-state fMRI data analysis toolkit (REST), version 1.8 (Song et al., 2011).

3.3.3 Independent Component Analysis of Resting-State Imaging

Adopting the same approach as Chapter 2, Group ICA of fMRI toolbox (GIFT) software, version 4.0b, was used to carry out independent component analysis (ICA) on the pre-processed resting state fMRI data in the current study (Rachakonda, Egolf, Correa & Calhoun, 2007; http://icatb.sourceforge.net/). The technical steps in carrying out ICA have been discussed in detail in Chapter 2.

Similar to Chapter 2, the DMN and CEN components were identified using previously published DMN and CEN paediatric spatial template (Thomason et al., 2011). After visual confirmation, the current study conducted statistical analysis of the ICA similar to a prior study (Gursel et al., 2020). Foremost, one-sample t-test (FWE-corrected) was performed on the ICA components (DMN and CEN) for each group (patient and control). To test for group differences within these networks between the patient and control groups, the spatial maps were compared using a 2-way t-test (family wise error (FWE)-corrected), with age as a covariate.

3.3.4 Network Based Statistics Analysis

To run further analysis, the seed coordinates from the ICA output were determined by the peak Z-values in the spatial maps of the functional networks of interest (DMN and CEN). The regions being identified in the DMN were the mPFC, parietal cortices, the precuneus and the PCC; the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PCC) were identified in the CEN. The coordinates of the ROIs making up the DMN and CEN are presented in Table 3.2. Based on the peak coordinates of the DMN and CEN identified from ICA, 10 mm spherical regions of interest (ROIs) representing the main nodes of the DMN and CEN were created using resting state fMRI data analysis toolkit (REST; Song et al., 2011). Using Fisher's r-to-Z transformation via the REST toolbox, the Z-score of the resting-state functional connectivity was then measured *within* the DMN and CEN respectively, and also *between* the DMN and CEN using the averaged extracted time series of the nodes.

The current study then used advanced network analysis approaches as established in the Network based Statistics (NBS) toolbox, version 1.2, to examine the differences in functional connectivity *between* regions *within* the DMN and *within* the CEN respectively, and *between* the DMN and CEN regions between healthy children and patients. NBS was used because it is a validated statistical methodology to counter issues with multiple comparison when examining connectivity graphs, and allows the identification of sub-networks and connections showing between-group differences (Gaudio, Olivo, Beomonte Zobel & Schioth, 2018). As a result of NBS mass-univariate statistics approach, only one single global test that accounts for each connection encompassing the network would be conducted, eliminating the issue of multiple comparisons which was a challenge with the ROI–ROI method, another form of seed-based statistics used in Chapter 2 (Kim, Wozniak, Mueller, Shen & Pan, 2014). Using T-test, NBS was used to identify brain regions with significantly altered functional connectivity in patients (p <0.05). Whilst NBS findings are highly reliant on the inputted test statistics threshold as it changes the extremity of the deviation in a connection between groups, however no standard value has yet been established, and the selection of the threshold is arbitrary (Zalesky, Fornito & Bullmore, 2010). The present study has therefore performed additional series of NBS analysis with a range of thresholds (t = 1.5–3.0), which is recommended and practiced in previous studies (Gaudio et al., 2018; Pascual-Belda, Diaz-Parra & Moratal, 2018). As per the practice of previous studies, the threshold with the most significant results of the NBS analysis will be discussed. Age was added as a covariate of non-interest during NBS analysis. The significance for individual connectivity was estimated using the non-parametric permutation method (5,000 permutations).

Moreover, in order to increase the statistical power, this study has included five controls with different fMRI acquisition parameters from the other subjects (discussed earlier in section *3.2.3*), which could have increased the within-group variability in controls. Therefore, to control for any potential impacts the differences in acquisition parameters may have on the results, the

current study has ran additional NBS analyses (as per above method) with acquisition parameter added as another covariate.

Table 3.2.
MNI coordinates of the ROIs forming the DMN and CEN (in mm)

Brain Region	Network	X	Y	Z
Left Parietal	DMN	-40	-70	28
Right Parietal	DMN	42	-68	32
Left mPFC	DMN	-6	42	18
Right mPFC	DMN	0	36	26
Left PCC	DMN	-6	-48	16
Right PCC	DMN	2	-50	28
Left Precuneus	DMN	-4	-62	22
Right Precuneus	DMN	4	-60	26
Left dlPFC	CEN	-24	26	48
Right dlPFC	CEN	32	12	50
Left PPC	CEN	-44	-58	40
Right PPC	CEN	50	-56	42

Note: Regions of the default mode network (DMN): mPFC = medial prefrontal cortex , PCC = posterior cingulate cortex; Regions of the central executive network (CEN): dlPFC = dorsolateral prefrontal cortex, PPC = posterior parietal cortex

3.4 Results

3.4.1 Age and Sex

Using Fisher's exact test, the sex distribution of the patient group (six males, eight females) was not significantly different from the control group (four males, nine females) (p = .70). However, the two groups were not age-matched ($t(25) = 4.13$, $p < .0001$). The data showed that the controls in the current study (M = 11.31, SD = 2.72) were significantly younger than patients with epilepsy (M = 14.64, SD = 1.28). To eliminate potential confounding influences of age on the current findings, age was used as a covariate in the analyses.

3.4.2 Functional Activity in the DMN and CEN

ICA was carried out to address the first hypothesis—reduced activity would be found in the regions of the DMN and CEN in patients compared to healthy children.

There was lower activity in the DMN, in the left parietal ROI, in patients with left-hemispheric epilepsy compared to healthy children ($p < 0.05$, FWE corrected), as shown in figure 3.1 using BrainNet Viewer toolbox, Version 1.63 (Xia, Wang, He, 2013). The lower functional activity reflects a decrease in the BOLD fluctuations in the DMN in children with epilepsy. There was however no significant difference in BOLD activity in the CEN regions between patients and controls.

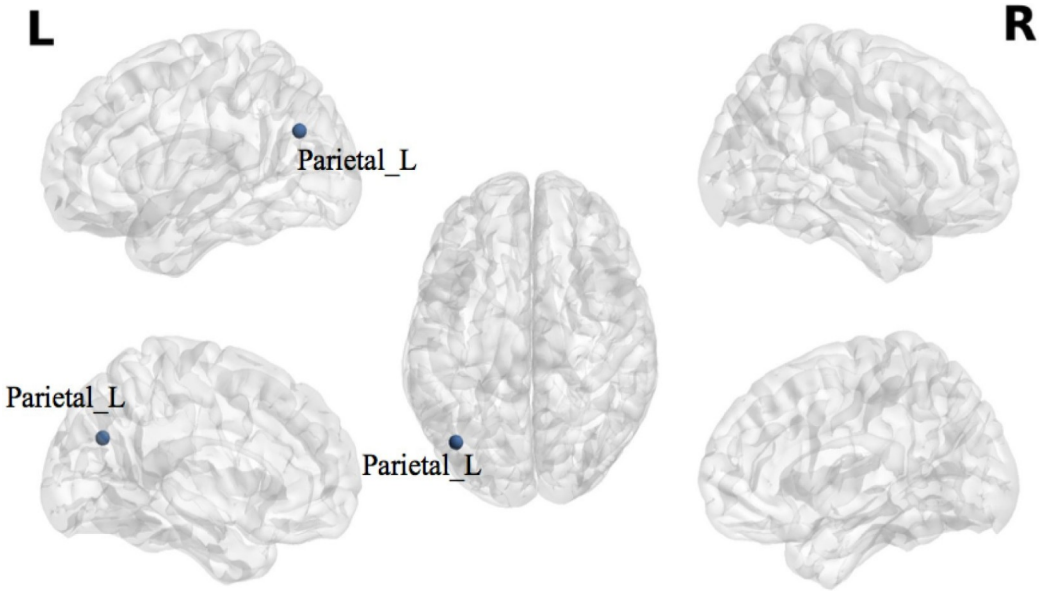

Figure 3.1. *The figure shows the left parietal ROI on a template brain generated using the BrainNet Viewer toolbox.*

3.4.3 Functional Connectivity *between* the regions *within* the DMN and *within* the CEN

The mean and standard deviation of the standardised functional connectivity (Z-score) between each of the main nodes of the DMN (left/right PCC, left/right mPFC, left/right precuneus and left/right parietal) and CEN (left/right dlPFC and left/right PPC) are presented below in Table 3.3 and Table 3.4 respectively. The data show a pattern of lower resting-state functional connectivity *within* the DMN and *within* the CEN in paediatric patients with epilepsy as compared to typically developing children.

NBS was performed to address the second hypothesis—patients with epilepsy would show reduced functional connectivity *between* the regions *within* the DMN and *within* the CEN as compared to healthy children. The NBS findings however showed no significant difference in the functional connectivity *within* the DMN or *within* the CEN between patients and controls.

Table 3.3.
Mean and standard deviation of standardised Functional Connectivity (Z-score) between each pair of ROIs in the DMN for the patient and control cohorts

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
R_mPFC–L_mPFC	1.31 (.20)	2.28 (1.59)
R_mPFC–R_Precuneus	.47 (.26)	1.27 (1.58)
R_mPFC–L_Precuneus	.40 (.21)	1.26 (1.60)
R_mPFC–R_PCC	.55 (.27)	1.38 (1.61)
R_mPFC–L_PCC	.46 (.25)	1.35 (1.68)
R_mPFC–R_Parietal	.39 (.26)	1.22 (1.67)
R_mPFC–L_Parietal	.43 (.27)	1.32 (1.70)
L_mPFC–R_Precuneus	.61 (.30)	1.33 (1.52)
L_mPFC–L_Precuneus	.56 (.30)	1.33 (1.56)
L_mPFC–R_PCC	.75 (.24)	1.46 (1.58)
L_mPFC–L_PCC	.73 (.31)	1.44 (1.62)
L_mPFC–R_Parietal	.50 (.27)	1.19 (1.64)
L_mPFC–L_Parietal	.62 (.37)	1.37 (1.67)
R_Precuneus–L_Precuneus	1.83 (.23)	2.62 (1.55)
R_Precuneus–R_PCC	1.40 (.32)	2.39 (1.40)
R_Precuneus–L_PCC	1.23 (.28)	2.06 (1.46)
R_Precuneus–R_Parietal	.84 (.32)	1.69 (1.64)
R_Precuneus–L_Parietal	.78 (.31)	1.61 (1.64)
L_Precuneus–R_PCC	1.06 (.27)	2.09 (1.50)
L_Precuneus–L_PCC	1.21 (.29)	2.15 (1.47)
L_Precuneus–R_Parietal	.72 (.31)	1.62 (1.65)
L_Precuneus–L_Parietal	.75 (.27)	1.67 (1.63)
R_PCC–L_PCC	1.39 (.26)	1.09 (1.58)
R_PCC–R_Parietal	.83 (.27)	1.63 (1.64)
R_PCC–L_Parietal	.84 (.35)	1.69 (1.64)
L_PCC–R_Parietal	.74 (.30)	1.56 (1.64)
L_PCC–L_Parietal	.78 (.31)	1.65 (1.72)
R_Parietal –L_Parietal	.93 (.30)	1.78 (1.73)

Note: L/R = Left, Right. Regions of the DMN: mPFC = medial prefrontal cortex, PCC = posterior cingulate cortex

Table 3.4.
Mean and standard deviation of standardised Functional Connectivity (Z-score) between each pair of ROIs in the *CEN for the patient and control cohorts*

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
R_dlPFC–L_dlPFC	.55 (.39)	1.67 (1.69)
R_dlPFC–R_PPC	.70 (.24)	1.61 (1.61)
R_dlPFC–L_PPC	.51 (.21)	1.50 (1.73)
L_dlPFC–R_PPC	.41 (.29)	1.39 (1.73)
L_dlPFC–L_PPC	.58 (.35)	1.67 (1.71)
R_PPC–L_PPC	.87 (.28)	1.79 (1.59)

Note: L/R = Left, Right. Regions of the CEN: dlPFC = dorsolateral prefrontal cortex, PPC = posterior parietal cortex

3.4.4 Functional Connectivity *between* the DMN and CEN Regions

The mean and standard deviation of the standardised functional connectivity *between* the DMN regions (left/right PCC, left/right mPFC, left/right precuneus and left/right parietal) and CEN regions (left/right dlPFC and left/right PPC) are presented below in Table 3.5. The data show a pattern of lower resting-state functional connectivity *between* the DMN and the CEN regions in paediatric patients with epilepsy as compared to typically developing children.

NBS was also performed to address the final hypothesis of the current study—patients with epilepsy would show significantly reduced functional connectivity *between* the DMN and CEN as compared to healthy children. The NBS findings however showed no significant difference in the functional connectivity *between* the regions of the DMN and the CEN between patient and controls.

3.4.5 Functional Connectivity Analyses with Acquisition Parameter as a Covariate

To account for the differences in imaging acquisition, additional NBS analyses were ran with acquisition parameter added as a covariate. The NBS findings similarly showed no significant difference in the functional connectivity *between* the regions *within* the DMN and *within* the CEN, and *between* the regions of the DMN and the CEN between patient and controls. The similar lack of findings suggests that disparities in the imaging acquisition may not have significant impact on the functional connectivity findings, providing support to Van Dijk et al. (2010)'s study which suggested that functional connectivity is minimally affected by most acquisition parameter differences.

Table 3.5.
Mean and standard deviation of standardised Functional Connectivity (Z-score) between each pair of ROIs between the DMN and CEN for the patient and control cohorts

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
R_mPFC–R_dlPFC	.48 (.22)	1.34 (1.70)
R_mPFC–L_dlPFC	.76 (.26)	1.65 (1.65)
R_mPFC–R_PPC	.50 (.29)	1.34 (1.67)
R_mPFC–L_PPC	.40 (.21)	1.22 (1.64)
L_mPFC–R_dlPFC	.41 (.25)	1.20 (1.69)
L_mPFC–L_dlPFC	.98 (.23)	1.21 (.31)
L_mPFC–R_PPC	.40 (.21)	1.22 (1.64)
L_mPFC–L_PPC	.52 (.31)	1.32 (1.70)
R_Precuneus–R_dlPFC	.37 (.26)	1.32 (1.66)
R_Precuneus–L_dlPFC	.39 (.24)	1.34 (1.55)
R_Precuneus–R_PPC	.39 (.24)	1.26 (1.70)
R_Precuneus–L_PPC	.47 (.27)	1.25 (1.64)
L_Precuneus–R_dlPFC	.31 (.28)	1.29 (1.66)
L_Precuneus–L_dlPFC	.38 (.19)	1.34 (1.56)
L_Precuneus–R_PPC	.29 (.21)	1.19 (1.72)
L_Precuneus–L_PPC	.40 (.25)	1.22 (1.66)
R_PCC–R_dlPFC	.36 (.30)	1.35 (1.72)
R_PCC–L_dlPFC	.51 (.26)	1.42 (1.64)
R_PCC–R_PPC	.43 (.23)	1.35 (1.73)
R_PCC–L_PPC	.56 (.29)	1.34 (1.66)
L_PCC–R_dlPFC	.30 (.23)	1.36 (1.74)
L_PCC–L_dlPFC	.50 (.30)	1.47 (1.63)
L_PCC–R_PPC	.29 (.23)	1.19 (1.73)
L_PCC–L_PPC	.46 (.30)	1.29 (1.74)
R_Parietal–R_dlPFC	.65 (.38)	1.56 (1.66)
R_Parietal–L_dlPFC	.38 (.24)	1.32 (1.65)
R_Parietal–R_PPC	.68 (.21)	1.60 (1.71)
R_Parietal–L_PPC	.54 (.27)	1.41 (1.67)
L_Parietal–R_dlPFC	.41 (.38)	1.35 (1.84)
L_Parietal–L_dlPFC	.53 (.29)	1.48 (1.75)
L_Parietal–R_PPC	.40 (.19)	1.31 (1.75)
L_Parietal–L_PPC	.60 (.30)	1.54 (1.79)

Note: L/R = Left, Right. Regions of the DMN: mPFC = medial prefrontal cortex, PCC = posterior cingulate cortex; Regions of the CEN: dlPFC = dorsolateral prefrontal cortex, PPC = posterior parietal cortex

3.5 Discussion

The present study examined resting-state brain alterations *within* and *between* the DMN and CEN in a group of children with left focal drug-resistant epilepsy relative to a group of healthy control children. Two approaches were adopted, ICA and then NBS. The latter was used to examine differences in resting-state functional connectivity *between* the regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions in patients, relative to healthy children. NBS was used because it has shown to be effective in demonstrating differences in inter-regional functional connectivity between patients and healthy participants (Goldbeck et al., 2018; Zhan, Chen, Gao & Zou, 2019). The networks (DMN and CEN) were selected because they have been identified to be involved in sustained attention, and the ROIs identified are main regions of these networks. The current findings demonstrated reduced resting-state functional activity in the left parietal ROI of the DMN in the patient group compared to control, however no other significant differences in either regional activity or connectivity were found between the groups. In this section, the implications of the current findings, possible explanations for the lack of other findings, main limitations and future directions are discussed.

3.5.1 Current Findings

Compared with typically developing children, children with drug resistant epilepsy showed significant reduction in functional activity in the left parietal ROI, which is part of the DMN. As discussed in Chapter 1, the DMN is known as a task-negative network, therefore when carrying out tasks, deactivation within the DMN (reflecting reduced activity in the DMN regions during task conditions as compared to a resting baseline) is functionally relevant for cognitive performance, and lower DMN activity is associated with better performance (Anticevic et al., 2012). In contrast, the DMN regions show simultaneous activation at rest (Ramirez-Barrantes et al., 2019), and reduced activation in the DMN during rest is instead associated with poorer cognitive performance (Kanno et al., 2021). In relevance to patients with epilepsy, epileptic discharges have been found to affect the DMN (i.e., deactivation in the brain regions), and the reduced activity in the DMN has been linked to cognitive deficits in these patients (Fahoum, Zelmann, Tyvaert, Dubeau & Gotman, 2013; Gotman et al., 2005; Liao et al., 2010). Given the importance of DMN in cognitive performance, the next sections further discuss the relevance and implications of the current study's findings, especially in regard to attention.

3.5.2 Role of the Parietal Lobe in Cognitive Functioning

The present study examined the DMN because the network is known to support carrying out sustained attention tasks (Danckert & Merrifield, 2018). Therefore, the current finding of reduced activity in the parietal lobe in the DMN may suggest cognitive impairments in children with epilepsy. The parietal lobe is important in carrying out tasks effectively across several

cognitive skills; it is vital in integrating sensory information from different modalities and cognitive functions (Humphreys & Lambon Ralph, 2017). For example, the parietal lobes are active when carrying out tasks involving visuomotor control, attention and eye movements (Culham & Kanwisher, 2001). Studies have also reported the parietal lobes to be crucial in visuospatial abilities and attention (Critchley, 1953; Mesulam, 1981); while Posner, Walker, Friedrich and Rafal (1984) found the parietal lobes to be pertinent in carrying out tasks involving orienting attention. Given the importance of the parietal lobe in several cognitive functions, including attention, disruption to the region could result in impairments in these cognitive skills, as evidenced in Posner et al. (1984)'s study; the study reported that alterations to the parietal lobe resulted in difficulty to disengage attention from one focus and to reorient it elsewhere. This is further evidenced in Castiello and Paine (2002)'s study, which reported that left parietal injury could lead to impairments in covert orienting of attention. The following section will further discuss the potential implications of disruptions to the left parietal lobe, in relevance to the existing epilepsy literature.

3.5.3 Alterations in the Left Parietal Lobe in Patients with Epilepsy

The present finding of reduced activity in the left parietal lobe in patients is consistent with existing studies that included adults with epilepsy; these studies have reported reduced activity in the left parietal lobe in patients with epilepsy compared to control across epilepsy types—TLE and idiopathic generalised epilepsy (Moeller et al., 2008; Zhu et al., 2016). Zhu et al. (2016) have found reduction in activation in the left parietal lobe, and suggested that there is a correlation between neural activity pattern and epilepsy duration. Importantly, Zhu et al. (2016) have highlighted that neural alterations are not constrained to the epileptogenic regions, and that long duration of epilepsy induces further neural changes in patients with epilepsy. This is in line with the current findings of reduced activity in the left parietal lobe, which was not the seizure location of most of the patients in the present study. However, as the duration of epilepsy was not known in the current study, it was not possible to examine whether there was an association between the epilepsy duration and neural changes in the current study.

Disruptions within the DMN, including the reduced activity in the left parietal lobe in the current study, often result from the disruption of neuronal activity, and commonly reflect associated impairments in brain diseases (Mohan et al., 2016). People with epilepsy often report abnormal psychological symptoms associated with the functionalities of the DMN (Stretton et al., 2013), as well as in attention, memory, language and associative learning (Fahoum et al., 2013; Gao et al., 2018; Gauffin et al., 2013). The importance of effective information communication between the parietal regions and other brain regions like the frontal regions is highlighted by Jung and Haier (2007)—for example, effective communication between the frontal and parietal brain regions is needed to support gifted mathematical thinking skills (Prescott, Gavrilescu, Cunnington, O'Boyle & Egan, 2010). Coordination between the

parietal and temporal brain regions are also reportedly important for social processing (i.e., theory of mind) and the processing of stimuli in working memory (Bowyer, 2016; Schipul, Keller & Just, 2011). However, as there are no outcome data available, this study cannot confirm the association between altered neural activity and cognitive or functional deficits, but raises some questions which should be investigated in future studies.

3.5.4 Disruptions in Parietal Lobe may Reflect Common Neurobiological Characteristics in Focal Epilepsy

It is interesting to highlight that significance was only found in the left parietal lobe in the current study. A possible explanation is that abnormalities found in the parietal lobe may represent neurobiological characteristics common to different epilepsies. Yang et al. (2021) suggest that DMN abnormalities such as parietal activations may be common to different epilepsy types and therefore an important marker of neural dysfunction which could in turn help to explain attention impairments in this population. The study found that patients with focal epilepsy (i.e., temporal lobe epilepsy and frontal lobe epilepsy) shared common neural disruptions in the inferior parietal lobe, which was however not found in patients with genetic generalised epilepsy with generalised tonic-clonic seizures, a type of generalised epilepsy, suggesting common pathophysiology characteristic especially in focal epilepsy (Yang et al., 2021). Hu et al. (2017)'s study also suggested dysfunction in the left inferior parietal lobe as a common pathophysiology characteristic to focal epilepsy; in particular it could serve as a pathophysiology basis for attention deficits (i.e., lower concentration level as measured by a numerical depth test) in people with epilepsy. Hu et al. (2017) have used a combined regional homogeneity (ReHo) and functional connectivity analysis, which provides a more complete evaluation of the brain network by evaluating both the intra-nodal activity and inter-nodal connection of the brain network. They reported that only the left inferior parietal lobule has been identified by two techniques (ReHo and functional connectivity), all the other identified regions were different between these two techniques. As Hu et al. (2017)'s study did not categorise the patients into specific epilepsy subtypes, both ReHo and connectivity patterns may suggest most significant networks responsible for epilepsy progression that are common across patients with different subtypes of partial epilepsy, a type of focal epilepsy. Taking together poorer attention in patients with epilepsy being reported in the study with inferior parietal lobe being responsible for concentration and stimulus surveillance, the reduction in the ReHo and functional connectivity in the inferior parietal lobe may serve as the pathophysiology basis for poor attention across people with epilepsy. The current study however cannot confirm this, as there were no attentional measures involved.

3.6 Limitations

Limitations of the current experiment relate to a number of factors, some of which are disease specific, and others methodological. In the following section, an overview of these is provided in order to not only contextualise the current thesis findings but also to highlight the optimal study design that should be considered in future research. Due to the impact of the Covid-19 pandemic and requirement to redirect the data sampling contained in the current work, retrospect access to data were gained, which can prevent collection of variables that are known to or may potentially influence analysis and results. This account may explain the lack of support for the remaining study hypotheses.

3.6.1 Influence of Seizure Frequency

A disease variable that can affect functional connectivity in patients with epilepsy is seizure frequency; higher seizure frequency is associated with greater neural abnormalities, specifically reduced functional connectivity in the limbic system, between the ipsilateral ventral anterior cingulate cortex and hypothalamus, and ipsilateral subiculum and the contralateral ventral posterior cingulate cortex (Jo et al., 2019). For example, Cao et al. (2014) reported that higher seizure frequency is related to greater impairments in neural functional connectivity, particularly in the CEN. Furthermore, Bharath et al. (2015) have further supported the relationship between frequency of seizures with functional connectivity changes in the DMN. The authors found significant differences in functional connectivity abnormalities between patients with frequent-seizure and patients with infrequent-seizure. The study found reduced connectivity in the DMN in patients with frequent-seizure, in comparison they found increased connectivity in the DMN in patients with infrequent-seizure. This similarly suggests that connectivity changes seen in one group of patients may not be seen in another group of patients. The current study did not have access to the relevant information to include as a confounding variable in the analyses. Accordingly, it is not possible to determine whether differences in frequency of seizures in the patients, resulted in differences in functional connectivity changes within the patient group. Future studies should collect data to enable control for these effects in analyses.

3.6.2 Influence of the Duration of Epilepsy

Longer duration of epilepsy (that is, time since diagnosis) is associated with a greater overall seizure burden on brain development or – when seizure control is poor – a longer duration of persistent seizures, which as earlier discussed can affect functional connectivity. As a result, it can affect the connectivity of functional networks (van Dellen et al., 2009). van Dellen et al. (2009) found that patients with temporal lobe epilepsy with longer epilepsy duration showed reduced functional connectivity in the temporal lobe and more random network changes were also observed in those same networks. The study suggested that ongoing seizures could

influence the functional neural network changes following epilepsy to be more random; as recurring seizures from longer epilepsy duration can cause progressive neural reorganisation (Englot et al., 2016; Pitkanen & Sutula, 2002). This is further evidenced in studies which have suggested that the longer duration of epilepsy can lead to greater impairment in resting state networks including the DMN, as seen from Wang et al. (2011); suggesting the possible reorganisation of the default mode network as epilepsy duration increases. This is also evidenced in another study that reported that patients with a longer history of epilepsy showed greater functional connectivity alterations, particularly in the frontal regions, compared to patients with a shorter history (Maneshi, Moeller, Fahoum, Gotman & Grova, 2012). Therefore, possible differences in the functional connectivity alterations amongst the patient group as a result of differences in epilepsy duration could have contributed to the current study's non-significant findings. However, the current study did not have access to the relevant information to include as a confounding variable in the analyses, future studies should acquire them to enable control for these effects in analyses.

3.6.3 Medication Influence on Functional Connectivity

The current study was also limited by the lack of information on medication intake by the patients included, and the current findings may also be impacted by some of the patients being on medication that could have affected the neural activity (Haneef, Levin & Chiang, 2015). There are data that suggest that some medications may affect cognition, and particularly attention (Eddy, Rickards & Cavanna, 2011). The effect of anti-seizure medications (ASMs) on functional connectivity is inconclusive, and in particular it is uncertain whether these medications affect connectivity within the DMN (Kay et al., 2013). Some studies have observed no significant drug effect, and suggest that functional changes more plausibly reflect disease-specific processes rather than as a result of medications used to treat seizures (Braakman et al., 2013; Pedersen et al., 2017; Yasuda et al., 2013). It would be useful for future studies to include the use of ASMs, and to elucidate the effect the ASMs on neural networks when examining functional connectivity changes in children with epilepsy.

3.6.4 Influence of Age on Functional Connectivity

Another factor to consider is the effects of age on neural connectivity networks. Studies have reported age effects on intrinsic functional connectivity across all neural networks (Sole-Padulles et al., 2016). Comparing children (7–12 years) and adolescents (13–18 years), Sole-Padulles et al. (2016) found a relationship between connectivity in both the DMN and CEN regions and age. The study suggested that connectivity between DMN regions are less connected when younger, and as age increases, connectivity between these regions increases. Based on current literature, the current study would have expected reduced functional connectivity in the DMN resulting from epilepsy when compared to an age-matched group. In

the current study, the age of both patient and control group was not matched; The current study compared patients with epilepsy to a group of younger children who have exhibited weaker connectivity, thus the differences may not have been large resulting in the current non-significant findings. However, age was used as a covariate in the present analyses, so it is unlikely that the present findings have been affected by the age factor. Instead, it is more pertinent to consider other more important factors that could have influenced the present lack of significant findings, like having a small sample size, which would be discussed in the following section.

3.6.5 Impact of a Small Sample Size

While the current study may also be limited by the small sample size, it has ensured reliable results by including permutation tests when carrying out the t-test, which is recommended when having a small sample size to reduce type-1 error occurrence (Önder, Şahin, Çankaya, Tahtali & Cebeci, 2003). The combination of a small sample size, a large number of dependent variables, and correcting for multiple comparisons can however drastically reduce the study's statistical power (Cremers, Wager & Yarkoni, 2017). This in turn affects the reliability of the research as it reduces the chance of detecting a true effect (Button et al., 2013). It is also argued that underpowered studies are vulnerable to analytical and reporting biases; smaller effects may be less likely to be revealed, which can explain the lack of findings in the current study (Button et al., 2013). Therefore, the small sample size could have impeded the current study's ability to detect other meaningful differences between control and epilepsy children.

The small sample size is however also a result of the stringent quality checks of the imaging data practiced in the present study. Given the challenge in recruitment for both healthy children and children with epilepsy, the present study has attempted to retain as many participants by carrying out scrubbing alongside motion correction to maximally correct for motion. This study has however had to remove approximately half of the original participants recruited due to excessive motion during scanning. Motion during fMRI scans, especially in the epilepsy population, is common (Lemieux, Salek-Haddadi, Lund, Laufs & Carmichael, 2007), and studies have established the importance to exclude those with high motion as motion reduces reliability of the results (Du et al., 2015; Guo et al., 2012). Removing these participants has however resulted in a small sample size, which may have impacted the study's ability to detect differences between patients and groups, as discussed earlier. This also highlights the challenge of scanning the paediatric population and also suggests the importance of minimising motion during scans, for example with methods that allow the child to practice holding still or the use of a mock scanner, which has been widely discussed in existing literature (Greene, Black & Schlaggar, 2016; Greene et al., 2018; Pua, Barton, Williams, Craig & Seal, 2020). It is therefore pertinent for future studies to consider utilizing methods to minimise scanning movements, in order to reduce attrition rate in the post-processing steps.

3.6.6 Influence of A Heterogeneous Patient Sample on Functional Connectivity

Lastly, while epilepsy is known as a disease of network dysfunction, studies have however suggested that the epileptic region is the key indicator of the brain network; thus regional differences in epileptic focus can lead to differences in neural changes (Adebimpe, Bourel-Ponchel & Wallois, 2018). This is in line with Yang et al. (2021)'s study, which identified that while different epilepsy subtypes (TLE, FLE and genetic generalised epilepsy with generalised tonic-clonic seizures) share some common disruptions in the DMN, there are also distinct dysfunctions in the DMN that are specific to the different subtype. The differences in functional connectivity disruptions in different types of epilepsy are also suggested by Fu et al. (2021)'s study that showed differences in the functional connectivity patterns in the resting-state networks in patients with mesial temporal lobe epilepsy and benign epilepsy with centrotemporal spikes. Therefore, this could explain the lack of findings as the patient cohort comprised of patients with different subtypes of epilepsy, who may present with distinctly different neural networks, and heterogeneous clinical sample group can lead to false negative as a result of lack of power to detect subtle differences (West et al., 2010). However, due to the small number of patients with the different types of epilepsy, it was not viable to perform subgroup analysis. Instead, future studies should look at including a larger sample size and examine the different focality of refractory epilepsy separately to conclusively report the neural alterations in individual epilepsy types. Having a larger sample size would also increase the study power, and reduce the risk of reporting a false negative finding (Biau, Kerneis, & Porcher, 2008).

3.7 Summary

In summary, the reduction in the left parietal found in the current study may represent neurobiological characteristics common to different epilepsies; this reduction could also be associated with cognitive deficits in patients with epilepsy.

The existing literature illustrates strong evidence in the relationship between functional and structural connectivity in the human brain, which has been discussed in Chapter 1. Briefly, the inter-regional correlation map driven by cortical thickness has been found to strongly reflect the underpinning functional connectivity of the medial prefrontal cortex in healthy adults (Park et al., 2017). In addition, another study has further suggested that changes in the cortical thickness may be related to alterations in the functional connectivity between two specific brain regions in patients with epilepsy, which is reflective of the long-term functional reorganisation in these patients (Ogren et al., 2018). Despite fMRI holding the potential to be a useful tool in understanding and predicting the course of diseases or injuries, it is still not used routinely in clinical practices unlike structural MRI (Specht, 2019). Given that structural MRI data are more commonly acquired, along with the known structure-function relationships in the brain, future studies could examine alterations to the structural connectivity after a brain insult, which in turn

can provide information on functional connectivity disruptions (Parsons, Hughes, Poudel & Caeyenberghs, 2020). More importantly, structural measures (i.e., cortical thickness) may be less susceptible to some of the earlier discussed limitation factors that could have influenced the functional connectivity measurements. Previous studies have showed that the duration of epilepsy, frequency of seizures and number of medication were not significantly related to the cortical thinning found in children with both left/right frontal lobe epilepsy (Widjaja, Mahmoodabadi, Snead III, Almehdar & Smith, 2011), and in children with left-hemisphere focal epilepsy (Boutzoukas et al., 2020).

The next study in this thesis therefore examined structural connectivity alterations in patients with epilepsy, using structural covariance network (SCN), which was earlier discussed in Chapter 1. Unlike fMRI studies, there are very few SCN studies in children with epilepsy, there is therefore limited knowledge in the current literature of SCN in the epilepsy or brain injury cohort, and SCN alterations in these patients compared to healthy controls is still unclear. A previous study has suggested that compared to ROI analysis, whole-brain analysis (i.e., voxel based morphometry) is more sensitive to subtle structural changes between groups, and has recommended combining both whole-brain analysis and ROI analysis (Seyedi et al., 2020). Based on previous studies (Duzel et al., 2019; Seyedi et al., 2020), the next study would therefore use SCN to acquire new knowledge on whole-brain structural changes following epilepsy, and given this thesis interest in sustained attention, the study would further examine structural connectivity changes in the DMN and CEN regions.

3.8 Conclusion

Using resting-state fMRI, the current study demonstrated reduced functional activity in the left parietal lobe in children with refractory epilepsy relative to healthy children. Neural alterations in children with epilepsy may result from various reasons like medication and frequency of seizures, which future studies should include into their analyses. The current findings highlight possible disparity in functional connectivity between the different subgroups of epilepsy. However, the current finding of reduced activity in the left parietal lobe may represent common neurobiological characteristics between epilepsy subtypes. In line with the current literature, the reduction in neural activity may underlie cognitive impairments (i.e., attention) in children with refractory epilepsy. Though this study has only found significance in one region, this study's work is important because it is the first known study that examined connectivity changes *between* and *within* the DMN and CEN in children with refractory epilepsy. An absence of clinical information (i.e., epilepsy duration/seizures frequency/medication), small sample size and heterogeneous patient group however may explain the present lack of other significant findings. The present study has highlighted the difficulty in recruitment in this vulnerable and important population, and also the challenge in scanning children due to excessive movements that led to a high attrition rate. Therefore, it is pertinent for future studies to not only aim to

recruit a larger sample, but also to consider steps that may reduce motions during scanning. More importantly, given that structural connectivity may be the substrate for functional connectivity, the next study in this thesis will be using SCN to examine structural alterations in children with epilepsy.

Chapter Four: Examining Structural Covariance Network Alterations in the Whole-Brain and in the Neural Networks Associated with Sustained Attention in Children with Epilepsy

4.1 Introduction

In healthy adults and children, studies have found a relationship between resting-state functional connectivity and structural magnetic resonance imaging (MRI) derived measures, like the grey matter volume and cortical thickness (Filevich et al., 2020; Moayedi et al., 2021), and has previously been discussed in Chapters 1 and 3. For example, the grey matter structure may be related to the brain's ability to engage and coordinate large-scale functional networks, which are crucial for proper cognitive functioning, across the life span in the default mode network, fronto-parietal network and salience network (Marstaller, Williams, Rich, Savage & Burianova, 2015). The relationship between the structural and functional connectivity is also widely presented in patient populations, and there is strong evidence that alterations in the functional connectivity are closely linked to disruptions in the structural connectivity in similar brain regions (Anurova, Renier, De Volder, Carlson & Rauschecker, 2015; Scheepens et al., 2020).

Similarly, epilepsy studies have also established that functional connectivity changes commonly follow from structural MRI changes (i.e., grey matter volume) (Liao et al., 2013). The relationship is evidenced across grey matter volume and cortical thickness; studies have found that disruptions in these anatomical measures are often accompanied with altered functional connectivity in similar brain regions in adults with temporal lobe epilepsy (Holmes et al. 2013; Labudda, Mertens, Janszky, Bien & Woermann, 2012), adults with juvenile myoclonic epilepsy (Zhong et al., 2018), and patients with generalised tonic-clonic seizures (Wang, Li, Wang & Huang, 2018). This therefore highlights that disruptions in the structural MRI likely underpin functional changes in patients with epilepsy, which may account for the common cognitive impairments reported like sustained attention (Gascoigne et al., 2017; Hernandez et al., 2003).

Cognitive impairments after a brain injury, such as those in attention, are traditionally assessed using relevant neuropsychological tests like the computational performance task and the Test of Everyday Attention for Children (Catroppa, Anderson, Morse, Haritou & Rosenfeld, 2007; Sanchez-Carpintero & Neville, 2003). These tests may however be less sensitive to detect mild or subtle cognitive deficits in less severe patients (Barr, 2001; Karr, Areshenkoff & Garcia-Barrera, 2014), as a result of various factors like tiredness and anxiety level, and also pain and potential medication side effects in patients (Barr, 2001). Instead, studies have suggested that imaging techniques (like functional MRI (fMRI) and structural MRI) may be more suitable to detect subtle cognitive changes, as they are sensitive to detect the impacts of brain injury on brain morphometry or function (Yaouhi et al., 2009). This was also presented in Chapter 2 where neural disruptions were identified in children with a brain injury despite not finding any differences in cognitive performance. The present study will therefore be utilising

imaging techniques to examine neural changes in children with epilepsy that may underpin attention impairments.

4.1.1 Disruptions in the Brain Regions underpinning Attention in Patients with Epilepsy

Functional imaging studies have demonstrated that the vulnerability of attention in patients with epilepsy is related to the susceptibility of the brain regions supporting attention particularly in the fronto-parietal regions, as discussed in Chapter 3 (Cheng et al., 2017; Qin et al., 2020). Aligned with functional studies, cortical thinning in patients with frontal and temporal lobe epilepsy has also been frequently reported in the frontal and parietal regions (Boutzoukas et al., 2020; Widjaja, Mahmoodabadi. Snead III, Almehdar & Smith, 2011). Given that alterations in the functional connectivity patterns in epilepsy is suggested to be a result of structural (e.g. grey matter thickness) changes in the same brain regions (Maneshi, Moeller, Fahoum, Gotman & Grova, 2012), this suggests that structural brain regions commonly associated with sustained attention may be vulnerable to epilepsy, in turn disrupting normal functional connectivity patterns of these regions, and resulting in attentional deficits.

Specifically, studies have suggested an association between functional connectivity disruptions in the default mode network (DMN) and central executive network (CEN), and cognitive impairments, including attention, in adult patients with frontal and temporal lobe epilepsy (two of the most common forms of epilepsy), which was discussed in Chapter 3 (de Campos, Coan, Lin Yasuda, Casseb & Cendes, 2016; Fahoum, Zelmann, Tyvaert, Dubeau & Gotman, 2013; Zhang et al., 2017). Few studies, however, have examined disruptions between these networks in the paediatric population, and Chapter 3 sought to rectify this shortcoming in the literature by examining the DMN and CEN in paediatric patients with a focal epilepsy (frontal and temporal lobe epilepsy). Given the relationship between structural and functional connectivity, it is informative to look at the structural disruptions in these networks in children with epilepsy to better understand the association between changes in the brain regions and potential attention deficits, however there are very few existing studies (discussed in the later sections), which is the motivation behind this study.

4.1.2 Left-Hemisphere Epilepsy is related to More Severe Outcomes

Consistent with previous research examining functional connectivity/activity (presented in Chapter 3), there also appears to be more pronounced structural disruption (i.e., grey matter volume) in adult patients with left-hemispheric epilepsy, compared to patients with right-hemispheric epilepsy (Yasuda et al., 2015). The study suggested that patients with left-hemispheric epilepsy demonstrated greater global disorganization in the volumetric neural network, and the less severe global network disruptions observed in patients with right-hemispheric epilepsy are likely related to better compensational mechanism, thus supporting

the better cognitive outcomes in these patients compared to patients with left-hemispheric epilepsy. Indeed, more severe structural alterations (i.e., grey matter volume) may be associated with greater reduced functional connectivity in patients with left-hemispheric epilepsy (Fan et al., 2016). Interestingly, patients with right-hemispheric epilepsy showed greater interhemispheric connectivity especially between the anterior temporal lobe, (which Fan et al. (2016) interpreted as more compensatory connectivity in place of the damaged or abnormal connectivity) and they argued that this better supported cognitive skills than was the case for patients with left-hemispheric epilepsy. These data support the literature that patients with left-hemispheric epilepsy suffer from more severe cognitive deficits likely because of the greater neural disruptions (Fernandes et al., 2014). Therefore, it was suggested that the severe structural changes disrupt interconnection between hemispheres, which cannot be compensated for by increased connectivity between regions in the same hemisphere, and the breakdown of interhemispheric connections is the cause of cognitive deficits (i.e., naming disability). Fan et al. (2016)'s study suggested severe anatomical changes in cognitive specific regions result in failed compensatory strategy in left-hemispheric patients, and their worse cognitive impairments, highlighting the potential value of examining structural neural changes in patients with left-hemispheric epilepsy.

4.1.3 Structural Covariance Networks

The past decade has seen a range of techniques developed that enable sophisticated analysis of regional structural co-variation. That is, morphological brain changes (i.e., grey matter volume, surface area or cortical thickness) in one brain region can be correlated with changes in other regions of the brain (Lerch et al., 2006; Mechelli, Friston, Frackowiak & Price, 2005). These correlations are suggested to form the underlying anatomical network reflecting interregional correlations of cortical thickness, also known as the structural covariance network (SCN). Chapter 1 has previously discussed SCN in detail, but briefly SCN relies on the assumptions that axonally connected regions show consistency in their development and maturation, resulting in similar morphology patterns (Bernhardt, Hong, Bernasconi & Bernasconi, 2013), and is useful in identifying disease-related changes in structural brain network topology (Alexander-Bloch, Giedd & Bullmore, 2013). This is evidenced in Drenthen et al. (2018)'s study, which showed relations between stronger clustering of the cortical network and more severe epilepsy, and also poorer cognitive performance in patients with focal seizures. Furthermore, as epilepsy is known to be a brain network disorder (Richardson, 2012), and widespread brain regions changes have been documented in temporal lobe epilepsy (Bernhardt et al. 2013; Li et al., 2021; Taylor, Han, Schoene-Bake, Weber & Kaiser, 2015) in frontal lobe epilepsy (Widjaja et al., 2011), and in idiopathic generalised epilepsy (IGE) (Bernhardt et al., 2009), SCN is potentially very useful in assessing overall brain network integrity as compared to only examining localised, regional changes.

Compared to other common neuroimaging techniques like diffusion tensor imaging (DTI) and fMRI, structural MRI offers higher anatomical resolution and is more accessible as it is essential in clinical evaluations, allowing hypothesis-driven, population based network analyses like SCN (Bernhardt, Bernasconi, Hong, Dery & Bernasconi, 2016). Moreover, SCN may provide new information on anatomical changes in epilepsy across networks, and thus provide insight that is different from that available with fMRI and DTI. Using the same subject dataset (adults with focal epilepsy), Drenthen et al. (2018)'s SCN findings contrasted with Vaessen et al. (2012) and Vlooswijk et al. (2011),'s DTI and fMRI findings. Whilst Drethen et al. (2018) found a correlation between stronger clustering within the SCN and cognitive performance, the other studies have instead found that poorer cognitive performance (similarly measured using Weschler Adult Intelligence Scale) was associated with weaker network clustering in the structural (derived from DTI) and functional networks (Vaessen et al., 2012; Vlooswijk et al., 2011). Drethen et al. (2018)'s study suggested that the disparity in their findings as compared to the DTI and fMRI studies could be because epilepsy is associated with morphological changes, thus SCNs could be used to examine the inter-regional cortical relationships in epilepsy, which could provide intrinsically different but complementary information to fMRI and DTI. While there is evidence that suggests a relationship between structural correlation and anatomical connectivity between brain regions, Gong, He, Chen and Evans (2012) have found disparity between cortical thickness measures and DTI. Gong et al. (2012) reported that SCN does not fully explain the networks derived from DTI, and the two measures are only moderately similar. This suggests the importance to examine SCN changes as they can provide complementary important information to better understand the brain and how diseases affect the brain.

More importantly, structural covariance – the correlation between regional grey matter volume or thickness across regions – is a novel technique which reflects the functional connectivity between these brain regions (Alexander-Bloch et al., 2013; Evans, 2013; He, Chen & Evans, 2007; Lerch et al., 2006). Therefore, SCN can provide an alternative method to examine functional networks by identifying brain regions with shared neural recruitment. This is especially useful because optimal cognitive performance relies on appropriate functional connectivity between brain regions. This means abnormal functional connectivity may underlie cognitive impairments, which may have resulted from structural damage (i.e., white matter demyelination and grey matter atrophy); this can help in identifying individuals with cognitive impairments (Sheffield & Barch, 2016; Yin et al., 2016; Zhou et al., 2016). fMRI, which is more often used to explore functional connectivity, is however not always available or most appropriate in a clinical imaging routine (Nelson, 2008). Alternatively, SCN is reliant on the structural T1 MRI, which compared to fMRI and DTI, is more available as they are a part of clinical routine, and may be a useful alternative to examine neural changes that may underpin cognitive impairments in patients with epilepsy (Bernhardt et al., 2016).

4.1.4 Structural Covariance Networks in Adult Epilepsy Population

Though studies have established the association of network changes and cognitive performance using MRI techniques like fMRI and DTI (Vaessen et al., 2012; Vlooswijk et al., 2011, fewer studies have examined network changes using SCN. Drenthen et al. (2018) was one of the few papers that examined SCN in patients with frontal and temporal lobe epilepsy, and the study found a correlation between stronger clustering within the SCN (i.e., cortical thickness) and lower cognitive performance (i.e., lower Full-scale IQ scores measured using the Wechsler Adult Intelligence Scale). Despite finding cortical thinning in several regions, Drenthen et al. (2018) have however found no differences in SCN between patients with focal onset epilepsy and healthy adults. This is not in line with other epilepsy studies that have found differences in SCN between healthy controls and adults who were previously diagnosed with childhood absence epilepsy (CAE), a form of childhood-onset generalised epilepsy (Curwood et al., 2015) and patients with temporal lobe epilepsy (Yasuda et al., 2015). Whilst neural disruptions were primarily found in the limbic/temporal areas in patients with temporal lobe epilepsy, patients with CAE however showed greatest disruptions in their frontal regions, and the differences in neural abnormalities may be driven by the differences in the origin of the epileptiform activity (Curwood et al., 2015). More importantly, the disparity in findings between Drenthen et al. (2018)'s study, which included both patients with frontal and temporal lobe epilepsy and Yasuda et al. (2015)'s studies, which only included patients with temporal lobe epilepsy, may suggest differences in structural changes between patients with different forms of focal epilepsy, which may have affected the sensitivity/ability to detect differences in patients and controls in Drenthen et al. (2018)'s study. This further suggests that different epilepsy subtypes likely result in distinct structural changes, highlighting that SCN finding in one epilepsy subtype is not representative across all epilepsy subtypes.

4.1.5 Structural Covariance Network in Paediatric Epilepsy Populations

Given the inconsistency of findings in present SCN studies, it is impossible to infer that findings from adult epilepsy studies are transferable to children with epilepsy. Furthermore, there have been only a few studies that examined SCN in children with epilepsy, specifically in generalised tonic-clonic seizure (Li et al., 2020), benign childhood epilepsy with centrotemporal spikes (BECTS) (Jiang et al., 2018) and new-onset epilepsy (Bonilha et al., 2014). Moreover despite drug-resistant epilepsy being one of the most common epilepsy subtypes and accounting for a substantial proportion of the burden of epilepsy in the population, no known studies have examined SCN in children diagnosed with drug-resistant epilepsy thus leading to the need for the present study (Laxer et al., 2014). Additionally, the findings of studies vary according to the group studied so whilst they underscore the potential novel insights from examining SCN in children with epilepsy, they are limited in their ability to offer specific insights into those with left focal seizure onsets. The current studies highlight that SCN is affected by differences in patient

populations, and it suggests that variations in SCN between studies may reflect specific epilepsy subtypes characteristics (Drenthen et al., 2018). For example, Li et al. (2020) studied (i.e., grey matter volumes), and found local network differences in the right thalamus, bilateral temporal pole and some regions of the DMN including the anterior cingulate cortex, precuneus and interior temporal gyrus (i.e., reduction) between patients with benign childhood epilepsy with centrotemporal spikes, and controls but found no significant global differences, whereas Bonilha et al. (2014) found both local and global differences (i.e., reduction) between patients with new-onset epilepsy and controls. Taken together, these studies highlight the inconsistencies in the existing paediatric SCN studies, and suggest that the technique is sensitive to identifying neural changes, which may underpin cognitive impairments commonly reported in these patients.

4.1.6 Aims and Hypothesis

The overall aim was to investigate structural connectivity changes in children with left focal epilepsy as compared to typically developing children. Despite potential differences in structural changes between different forms of epilepsy (i.e., temporal lobe and frontal lobe), attention impairments are well established in both epilepsy types, and comparable impairments have been suggested between both groups (Longo, Kerr & Smith, 2013). Taking into account that dysfunctions in similar brain regions are suggested to underpin sustained attention (as discussed earlier) in these groups, it is likely that attention impairment is not specific to an epilepsy type, and there would be common structural changes accompanying these impairments in these patients. Therefore, the current study examined paediatric patients with frontal lobe epilepsy and temporal lobe epilepsy together as a group.

Therefore, the primary aim of the present study was to compare whole-brain SCN between controls and patients with left-hemispheric drug-resistant epilepsy. Given the focus of the current thesis on sustained attention in patients with left-hemispheric drug-resistant epilepsy, the secondary aims included: 1) comparing cortical thickness between controls and patients with left-hemispheric drug-resistant epilepsy in the DMN and CEN regions; 2) comparing SCN between controls and patients with left-hemispheric drug-resistant epilepsy *between* regions *within* the DMN; 3) comparing SCN between controls and patients with left-hemispheric drug-resistant epilepsy *between* regions *within* the the CEN; 4) comparing SCN between controls and patients with left-hemispheric drug-resistant epilepsy *between* the DMN and CEN regions.

Based on the literature, the current study hypothesised that it would find significant differences in the whole-brain SCN between patients and controls. The study also hypothesised reduction in the SCN in patients compared to controls *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions. Lastly, the present study expected to find cortical thinning in DMN and CEN regions in patients with epilepsy compared to controls.

4.2 Methods

4.2.1 Participants

Healthy children were recruited either from the Birmingham community by contacting families who have previously indicated their interest in research being carried out at the Aston Brain Centre, Aston University, or are controls for a different neuroimaging study described in Chapter 5. Patients with paediatric epilepsy were recruited via Birmingham Children's Hospital, where they were referred to the Aston Brain Centre for pre-surgical evaluation as part of the Children's Epilepsy Surgery Service program. In total, 29 healthy children and 34 patients with drug-resistant epilepsy (four right hemisphere) were recruited. Four right-hemisphere patients were removed, leaving 30 patients with left-hemispheric epilepsy.

However, following imaging quality control (discussed below), only 10 healthy children (9–16 years, *M* = 12.50, *SD* = 2.17, three males, seven females) and 17 patients (10–18 years, *M* = 14.76, *SD* = 1.82, seven males, 10 females) were included in the final analyses. The patient group in this study primarily comprised of patients with temporal and frontal lobe epilepsy; detailed demographic information is presented in Table 4.1 below. Due to the small sample size, the current study was not able to perform further sub-analysis to examine each epilepsy subtype. Medication and seizure frequency information had not been included, as the study did not have access to them. None of the patients had undergone epilepsy surgery prior to the study, but were surgical candidates.

Table 4.1.
Demographic information for patients with epilepsy and controls

Participant (Group)	Age at Scan (years)	Onset Age (years)	Lesion	Seizure Location
001 (Patient)	16	2	Left Medial frontal	Left frontal
002 (Patient)	15	Not available	No	Left temporal lobe
003 (Patient)	16	Not available	No	Left temporal lobe
004 (Patient)	15	Not available	Yes	Left temporal lobe
005 (Patient)	17	8	No	Left temporal lobe
006 (Patient)	18	3	Yes	Left hemisphere
007 (Patient)	13	10	No	Left frontal-insular
008 (Patient)	14	5.5	Mesial Temporal Sclerosis	Left temporal lobe
009 (Patient)	14	Not available	Not available	Left hemisphere
010 (Patient)	16	Not available	Not available	Left medial temporal lobe
011 (Patient)	14	Not available	Not available	Left temporal lobe
012 (Patient)	15	Not available	Left tumour	Left tumour
013 (Patient)	16	Not available	No	Left temporal lobe
014 (Patient)	10	Not available	No	Left hemisphere
015 (Patient)	13	6	Likely no	Left insula
016 (Patient)	15	4	Left hippocampal sclerosis and right persylvian polymicrogyria	Left temporal lobe
017 (Patient)	14	Not available	FCD	Left frontal
018 (Control)	12	-		-
019 (Control)	12	-		-
020 (Control)	9	-		-
021 (Control)	13	-		-
022 (Control)	10	-		-
023 (Control)	13	-		-
024 (Control)	15	-		-
025 (Control)	14	-		-
026 (Control)	16	-		-
027 (Control)	11	-		-

Note: FCD = focal cortical dysplasia

4.2.2 Procedure

Ethical approval was obtained separately for both the healthy children and patient group. As per previous chapter, ethical approval was obtained from Aston University Ethics Committee for the former, and ethical approval for patients was sought from NHS Research Ethics Committee.

Parents' written, informed consent for their child's participation in the study was obtained. Assent was sought from children below the age of 16, while consent was also obtained from children over 16 years and deemed capable of giving consent. During the scan, radiographers checked on the participants and informed them if they were moving, and sequences were repeated if possible when excessive motion was detected on the image reconstruction.

4.2.3 MRI Acquisition

All neuroimaging data were acquired from a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil at the Aston Brain Centre, Aston University. High-resolution T1-weighted structural MR images were acquired with the following parameter: repetition time (TR) = 1900 ms, time to echo (TE) = 2.38 ms, flip angle (FA) = 15° for most of the participants. Three of the participants (two patients; one control) were scanned with slightly different parameters while on the same scanner: TR = 1900 ms, TE = 2.38 ms, FA = 9°. Though there is a difference in the scanning parameters, but as the participants were all scanned on the same Siemens scanner and have similar acquisition parameters, the compatibility would be highest with studies showing small error for whole brain measurements when including data with different parameters (Reig et al., 2009). Reig et al. (2009) has suggested that to improve consistency between T1 images scanned with different parameters, T1 tissue segmentation should be used which is carried out in this study.

4.3 Data Analysis

4.3.1 MRI Processing

T1 images were processed with the Freesurfer 6.0 software suite. Freesurfer is a freely available online software, and it is commonly used in studies examining cortical and subcortical anatomy. 3D tissue segmentation and estimation of cortical thickness from the acquired T1-weighted MR images was carried out using an established Freesurfer pipeline (Fischl, 2012). The T1-weighted anatomical MRI images were processed using Freesurfer default processing stream (recon-all) for cortical reconstruction and volumetric segmentation (Fischl & Dale, 2000; Fischl et al., 2004). The technical steps involved in Freesurfer's procedures for morphometric analysis are detailed in prior publications (Fischl et al., 2002; Fischl, 2012).

Briefly, the process included motion correction of volumetric T1-weighted images, the removal of non-brain tissue from the T1-weighted images (i.e., skull stripping), using a hybrid

watershed/ surface deformation process (Segonne et al., 2004), and automated Talairach transformation. The process also involved the segmentation of subcortical white and grey matter regions (Fischl et al., 2002; Fischl et al., 2004), intensity normalisation, tessellation of the boundaries between the grey and white matter and automatic topology correction (Fischl, Liu & Dale, 2001; Segonne, Pacheco & Fischl, 2007). Additionally, surface deformation was performed following intensity gradients to optimally define the grey/white and grey/cerebrospinal fluid at the greatest intensity shift to define the boundaries of these tissue classes (Dale & Sereno, 1993; Dale, Fischl & Sereno, 1999; Fischl & Dale, 2000).

In this study, Freesurfer was used to estimate the cortical thickness for 34 regions-of-interest for each hemisphere, based on the cortical parcellation of the Desikan-Killiany (DK) atlas (Desikan et al., 2006). The DK atlas is a well-studied atlas and is the standard atlas used in Freesurfer for analysing cortical thickness data (Perlman et al., 2017); it is also used in many adult and paediatric epilepsy studies (Lariviere et al., 2020; Mithani et al., 2020; Taylor et al., 2018), and also in studies including paediatric patients with a brain injury (King et al., 2020), supporting the use of the DK atlas with paediatric data. Freesurfer calculates cortical thickness as the closest distance from the grey matter (GM)–white matter (WM) boundary to the GM–cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl & Dale, 2000).

4.3.2 T1 MRI Quality Check

The quality of Freesurfer outputs were checked using Qoala-T, a supervised learning tool that assesses the accuracy of Freesurfer outputs and informs cases that require manual editing (Klapwijk, van de Kamp, van der Meulen, Peters & Wierenga, 2019). Visual inspection was also carried out on the output for motion artifact, and manual editing was carried out on the surfaces of participants with over-inclusion of the skull, pial matter or white matter. After manual editing, the recon-all script was re-run in order to regenerate final surfaces. As a result of either excessive motion, or poor quality, 32 participants (19 patients; 13 controls) were removed from further analyses.

4.3.3 Differences in Cortical Thickness between Patients with Epilepsy and Controls

Statistical Package for the Social Sciences, version 26 (SPSS, Chicago, Illinois) was used to perform statistical analyses. Due to the current study's interest in the DMN and CEN, a general linear model (GLM) was generated for each of the ROIs forming the DMN (n = 16), and the CEN (n = 12). GLM was carried out with each of the ROIs to examine the effect of group (patient versus control) on cortical thickness, whilst controlling for the effects of age at scanning, gender and estimated total intracranial volume (eTIV), as they are suggested to influence cortical thickness (Giedd & Rapoport, 2010). The region of interest (ROI) of each network (DMN and CEN) was chosen based on Ryan et al. (2017)'s paper that has established the neural networks

and their associated Freesurfer regions (presented in Table 4.2), based on Desikan-Killiany atlas, adapted from a previous paper (Dennis et al., 2013). Specifically, the DMN regions of interests (ROIs) comprised of the bilateral frontal pole, medial orbitofrontal cortex, posterior cingulate, cingulate isthmus, inferior parietal lobe, precuneus, entorhinal cortex and parahippocampal cortex; the CEN ROIs comprised of the bilateral superior frontal cortex, caudal and rostral middle frontal cortex, inferior and superior parietal cortex and precuneus. To control for multiple comparisons across all ROIs, false discovery rate (FDR), based on Benjamini and Hochberg (1995)'s method, was used when calculating *p*-values to keep the Type 1 error at 5% overall. Due to the unequal sample size, Levene's test of the homogeneity of group variances was also carried out as having both unequal sample sizes and variances can significantly affect the study's statistical power and increase Type 1-error rates (Rusticus & Lovato, 2014).

Table 4.2.
Freesurfer regions associated to the DMN and CEN

Neural Network	Freesurfer Regions
Default Mode Network	
Ventromedial prefrontal cortex	Frontal pole, medial orbitofrontal cortex
Posterior cingulate cortex	Posterior cingulate, cingulate isthmus
Inferior parietal lobule	Inferior parietal lobe, precuneus
Hippocampal formation	Entorhinal cortex, parahippocampal cortex
Central Executive Network	
Dorsolateral prefrontal cortex	Superior frontal cortex, caudal middle frontal cortex, rostral middle frontal cortex
Posterior parietal cortex	Inferior parietal cortex, superior parietal cortex, precuneus

4.3.4 Graphs of Structural Covariance

The current study's analysis plan follows a previous paper (King et al., 2020). All network analyses were carried out using several packages in R version 3.5.0 (R Core Team, 2016). Network analyses were specifically carried out using 'brainGraph' version 2.2.0 (Watson, 2016), which is an extension of the iGraph package (Csardi & Nepusz, 2006). Analyses were carried out between group-contrast, patients and controls, to examine patient–control differences.

Structural covariance analysis is widely used to infer the structural connectivity strength between cortical regions (Alexander-Bloch et al., 2013). In line with the current SCN literature, a general linear model was generated to test the effect of group (patient versus control) on cortical thickness across all ROIs (n = 68), while controlling for age at scanning, gender and estimated Total Intracranial Volume (eTIV). This is because these variables can affect cortical thickness; cortical thickness has shown to decrease with age (Sowell et al., 2004), gender differences in cortical thickness have been mapped (Sowell et al., 2007), and increased cortical thickness has been found with greater estimated total intracranial volume (Im et al., 2008). The studentised residuals were then used for analysis and to generate graphs of structural

covariance. Pearson's correlations were carried out between residuals of each ROI, resulting in a single 68x68 adjacency matrix.

The strength of structural covariance for each node was measured as node strength; that is the sum of the connectivity weights of all edges connected to the specific node (Fornito, Zalesky & Bullmore, 2016). The average nodal strength across all nodes was then calculated to derive an estimate of graph level strength. To generate confidence intervals for each group, these measures were bootstrapped over 5000 resamplings. To examine significant differences in structural covariance, permutation testing (5000 permutations) generated a null distribution of differences (t-values) in graph metrics between the two groups (patient versus control) with a two-tailed α-level of .05. These comparisons were conducted at the graph-level (mean graph strength) and at the nodal level. *p*-values for the graph level comparisons between groups and nodal-level comparisons were also FDR-corrected over the 68 nodes.

The same analysis was repeated three more times *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions respectively. The ROI inputted for the general linear model of each network (DMN and CEN) was selected based on previous papers that have described the Freesurfer regions representing these neural networks based on the neural structures of these networks established by earlier studies (Dennis et al., 2013; Ryan et al., 2017).

4.4 Results

4.4.1 Age and Sex

Using Fisher's exact test, the patient group (seven males, 10 females) and the control group (three males, seven females) were sex matched (p = .69). The present study has however included gender as a covariate based on the existing literature that has commonly controlled for gender in cortical thickness analysis (Fujiwara et al., 2018; Saute et al., 2014; Wang et al., 2019), in addition to the established gender differences in cortical thickness in both children and adults (Sowell et al., 2008). The two groups were however not age-matched ($t(23) = 2.77$, p = .01). The data showed that the controls in the current study (M = 12.50, SD = 2.17) were significantly younger than the patients with epilepsy (M =14.80, SD =1.93). To eliminate potential confounding influences of age on the current findings, age was used as a covariate in the analyses.

4.4.2 Differences in Cortical Thickness between Patients with Epilepsy and Controls in the DMN and CEN

The present study found increased cortical thickness in patients with epilepsy compared to healthy children in two regions—left rostral middle frontal cortex and right rostral middle frontal cortex. According to Ryan et al. (2017), the left and right rostral middle frontal cortices represent the left and right dorsolateral prefrontal cortex in the CEN. Increased cortical thickness was found in patients with epilepsy with a large effect size in the left rostral middle frontal cortex, $F(1, 22) = 7.52$, $p = .012$, partial $\eta 2 = .26$. Patients with epilepsy ($M = 2.68$, $SD = .20$) showed an increase in cortical thickness compared to healthy children ($M = 2.48$, $SD = .19$). Increased cortical thickness was also found in patients with epilepsy with a large effect size in the right rostral middle frontal cortex, $F(1, 22) = 12.21$, $p = .002$, partial $\eta 2 = .36$. Patients with epilepsy ($M = 2.75$, $SD = .40$) showed an increase in cortical thickness compared to healthy children ($M = 2.49$, $SD = .18$). To reduce Type-1 error, *p*-values were FDR-corrected.

These findings (increase in cortical thickness in the left and right rostral middle frontal cortices) were however in contrast with the current literature and the present hypotheses. The study therefore looked at potential reasons that could have driven these findings. Another round of visual checks were carried out, by two individuals in the research team on Freesurfer outputs, particularly on the ones with manual edits, to check for any under or over-inclusion of the skull, pial or white matter. The study then looked through the medical information of the patients and identified two participants with diagnosis that could have explained the unexpected findings. Two of the patients with epilepsy were diagnosed with left frontal focal cortical dysplasia and a right perisylvian polymicrogyria respectively. Literature has shown that increase in focal cortical thickness is one of the most prominent features of focal cortical dysplasia; cortical thickening is also established in patients with cortical dysplasia (Feng, Zhao, Tian, Lu & Wen, 2020). Therefore, it is reasonable to assume that the patient with frontal cortical dysplasia would also have cortical thickening in the frontal regions, which may then explain the current findings. The other patient was diagnosed with temporal lobe epilepsy, and right perisylvian polymicrogyria that is known to affect the cerebral cortex. Patients with right perisylvian polymicrogyria have shown increased cortical thickness in both the left and right hemispheres (Kotini et al., 2004). Specifically, unilateral and bilateral patients with perisylvian polymicrogyria have shown increased cortical thickness in the left frontal pole, right middle frontal gyrus and right frontal lobe (Oliveira, Valente, Shergill, Leite Cda & Amaro, 2010). Therefore, including patients with perisylvian polymicrogyria and frontal cortical dysplasia may have driven the current findings of increased cortical thickness in the left and right rostral middle frontal cortices, which is not representative across patients with epilepsy.

To remove these variables that could have confounded the findings, the analysis was re-run excluding these patients with perisylvian polymicrogyria and frontal cortical dysplasia, resulting in 15 patients with epilepsy in the final analyses. The new results showed no

significant cortical thickness differences in any of the regions of the DMN (presented in Table 4.3) and the CEN (presented in Table 4.4) between patients with epilepsy and controls. The non-significant (p >.05) and reduced effect size of the right (partial η2 = .11) and left (partial η2 = .05) rostral middle frontal cortices further highlight that the patients with perisylvian polymicrogyria and frontal cortical dysplasia affected the initial results by exaggerating the cortical thickness of those regions. The original large effect size became smaller (especially in the case of the left rostral middle frontal cortex) after removing the two patients which suggests that it was likely the two patients who contributed to the increase in cortical thickness and driven the initial group findings.

Table 4.3.
Mean and standard deviation of cortical thickness of DMN regions for the patient and control cohorts

Brain Region	Patient Mean (SD)	Control Mean (SD)
Ventromedial prefrontal cortex		
L_FrontalPole	2.93 (.51)	2.77 (.34)
L_MedialOrbitoFrontal	2.78 (.18)	2.83 (.19)
R_FrontalPole	3.14 (.46)	2.96 (.40)
R_MedialOrbitoFrontal	2.84 (.22)	2.88 (.19)
Posterior cingulate cortex		
L_PosteriorCingulate	2.79 (.24)	2.86 (.12)
L_IsthmusCingulate	2.59 (.19)	2.58 (.06)
R_PosteriorCingulate	2.80 (.13)	2.81 (.15)
R_IsthmusCingulate	2.63 (.26)	2.65 (.17)
Inferior parietal lobule		
L_InferiorParietal	2.73 (.14)	2.67 (.18)
L_Precuneus	2.67 (.17)	2.75 (.13)
R_InferiorParietal	2.65 (.16)	2.56 (.19)
R_Precuneus	2.72 (.16)	2.76 (.10)
Hippocampal formation		
L_Entorhinal	3.22 (.27)	3.42 (.28)
L_Parahippocampal	2.80 (.38)	3.10 (.33)
R_Entorhinal	3.47 (.47)	3.45 (.45)
R_Parahippocampal	2.91 (.30)	2.99 (.26)

Note: L/R = Left, Right

Table 4.4.
Mean and standard deviation of cortical thickness of CEN regions for the patient and control cohorts

Brain Region	Patient Mean (SD)	Control Mean (SD)
Dorsolateral prefrontal cortex		
L_SuperiorFrontal	3.06 (.18)	2.99 (.15)
L_CaudalMiddleFrontal	2.82 (.17)	2.70 (.19)
L_RostralMiddleFrontal	2.64 (.18)	2.48 (.19)
R_SuperiorFrontal	3.07 (.15)	2.98 (.15)
R_CaudalMiddleFrontal	2.80 (.20)	2.73 (.22)
R_RostralMiddleFrontal	2.64 (.18)	2.48 (.19)
Posterior parietal cortex		
L_InferiorParietal	2.73 (.14)	2.67 (.18)
L_Precuneus	2.67 (.17)	2.75 (.13)
L_SuperiorParietal	2.45 (.17)	2.49 (.14)
R_InferiorParietal	2.65 (.16)	2.56 (.19)
R_Precuneus	2.72 (.16)	2.76 (.10)
R_SuperiorParietal	2.46 (.19)	2.48 (.20)

Note: L/R = Left, Right

4.4.3 Graphs of Whole-Brain Structural Covariance

After FDR correction, no significant difference was found in the mean graph strength between patients with epilepsy and controls permuted difference (PermDiff = -.188, p_{fdr} = .396). The mean graph strength for the patient and control groups can be found in Table 4.5.

The only significant nodal difference was in the banks superior temporal sulcus before FDR correction. However after FDR correction across ROIs (n = 68), no nodal differences remained significant between patients with epilepsy and controls.

4.4.4 Graphs of DMN Structural Covariance

After FDR correction, no significant difference was found in the mean graph strength between patients with epilepsy and controls permuted difference (PermDiff = -.097, p_{fdr} = .317). The mean graph strength for the patient and control groups can be found in Table 4.5.

After FDR correction across the DMN ROIs (including the ventromedial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule and the hippocampal formation; n = 32), no nodal differences remained significant between patients with epilepsy and controls.

4.4.5 Graphs of CEN Structural Covariance

After FDR correction, no significant difference was found in the mean graph strength between patients with epilepsy and controls permuted difference (PermDiff = -.011, p_{fdr} = .599). The mean graph strength for the patient and control groups can be found in Table 4.5.

After FDR correction across the CEN ROIs (including the dorsolateral prefrontal cortex and posterior parietal cortex; n = 24), no nodal differences remained significant between patients with epilepsy and controls.

4.4.6 Graphs of DMN and CEN Structural Covariance

After FDR correction, no significant difference was found in the mean graph strength between patients with epilepsy and controls permuted difference (PermDiff) = -.081, p_{fdr} = .520). The mean graph strength for the patient and control groups can be found in Table 4.5.

After FDR correction across the DMN and CEN ROIs (n = 48), no nodal differences remained significant between patients with epilepsy and controls.

Table 4.5.
Mean graph strength and bootstrapped 95% confidence intervals (CI)

SCN	Graph Strength (Patient)	Graph Strength (Control)	PermDiff	p_{fdr}	Lower CI	Upper CI
Whole-Brain	15.16	12.81	-.188	0.396	-10.38	17.47
DMN	3.46	2.56	-.097	.317	-2.87	5.28
CEN	4.52	4.84	-.011	.599	-2.03	3.66
DMN and CEN	6.15	6.09	-.081	.520	-3.37	6.81

Note: fdr = false discovery rate. DMN = default mode network, CEN = central executive network

4.5 Discussion

The present study compared whole-brain SCN between children with left-hemispheric drug-resistant epilepsy and healthy children. Due to sustained attention being one of the most common cognitive impairments in children with epilepsy, the study focused on structural connectivity of brain regions involved in sustained attention. The current study has thus also compared SCN *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions between children with left-hemispheric drug-resistant epilepsy and healthy children. The study also compared regional cortical thickness in the regions of the DMN and also the CEN between children with left-hemispheric drug-resistant epilepsy and healthy children. The study's hypotheses were that reduced SCN would be observed across whole-brain, and between the regions involved in sustained attention (regions of the DMN and CEN), alongside reduced regional cortical thickness. In contrast to the hypotheses, the current findings found no significant differences in the whole-brain SCN or SCN *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions between patients with epilepsy and healthy children. No significant differences were found in the regional cortical thickness in the DMN and CEN regions between patients with epilepsy and healthy children either.

In contrast to literature that has reported cortical thinning in patients with epilepsy compared to healthy controls, the study found no significant differences (Galovic et al., 2019; Overvliet et al., 2013; Widjaja et al., 2012). Cortical thinning in early development is related to synaptic pruning, myelination and apoptosis, and these processes support cognitive and behavioural development (Jernigan, Baare, Stiles & Madsen, 2011). This means that cortical thinning may provide information on cognitive impairments commonly reported in patients with epilepsy. The absence of significant cortical thickness differences between the patients with epilepsy and controls may be because the differences are very subtle and were thus not detected due to several possible factors, which will be discussed below.

4.5.1 Influence of lesions on cortical thickness

Foremost, an important factor to consider is that the current study has included patients with lesions or known conditions that could affect cortical thickness measurement in the present study. In the original analyses, the study included two patients with known frontal focal cortical dysplasia (FCD) and a right persylvian polymicrogyria respectively. These conditions are known to cause cortical *thickening* which was evident in the original findings, and it was therefore useful to explore the influence that these individual cases had on the overall group results. Increased cortical thickness is a common feature in patients with cortical dysplasia, especially in FCD, and studies showed that cortical *thickening* occurs in 91% of patients with FCD (Bernasconi & Bernasconi, 2011). This instead suggests the importance of examining these cases in small cohorts rather than assuming that patients with FCD would all present with similar brain pathology.

By including participants with lesions, cortical thickness measurements can be affected, as lesions like cortical lesions can lead to global cortical thinning (Geisseler et al., 2016) therefore including these cases could result in an inaccurate representation. Nevertheless, when comparing patients with non-lesional epilepsy and controls, Whelan et al. (2018) found a similar pattern of cortical thickness differences (reduced thickness in the paracentral gyri, caudal middle frontal gyri, pars triangularis, superior frontal gyri, supremarginal gyri, and increased thickness in the cuneus, pars opercularis, precuneus and entorhinal gyrus) as when they compared patients with lesional and non-lesional epilepsy and controls, suggesting that lesions may not drastically affect findings. Therefore, the inclusion of lesional cases is unlikely to have led to the absence of any significant differences between controls and patients in the current study; as supported by Bigler et al. (2016)'s finding, which suggested that focal lesions do not uniquely affect cortical thickness because of their heterogeneous nature, and thus are unlikely to cause group-level effects. Importantly, the nature of the lesion seemingly has a bigger influence on cortical thickness; for example, white matter lesions may have no effects on cortical thickness (Komaromy et al., 2019), whilst subcortical lesions were found to affect regional cortical thickness depending on the lesion location in adults with stroke or multiple sclerosis (Charil et al., 2007; Tuladhar et al., 2015).

Lastly, lesions may also have an impact on the analyses tools used in this study, as they may affect the accuracy of cortical surfaces constructed and used by Freesurfer to generate volumetric measurements (Strangman et al., 2010). Freesurfer measures cortical thickness using the distance between the pial surface and the GM/WM boundary, which means inaccuracy in segmentation can also affect the cortical thickness measurement (Gerrits et al., 2016). However, the study ran a supervised learning tool (Qoala-T) to assess the quality of the Freesurfer output, and every Freesurfer output was also visually checked and manually corrected if needed or removed from further analyses if they had substantial anatomical distortions. The lesions in the patients with epilepsy may however have led to distortion in MRI

signal characteristics, which could affect Freesurfer surface reconstruction. Despite carefully examining data from each subject and applying the appropriate correction, Freesurfer semi-automated procedure, which incorporates atlas-based steps, may not take the lesion into account that may affect the accuracy of the cortical thickness measurement.

Lesion information is however not known for some of the patients due to incomplete medical information, but the current study excluded any patients with large lesions that are in line with TBI studies (Diamond et al., 2020). As a result of the lack of lesion information, this study cannot confirm whether the absence of significant findings has been influenced by the inclusion of lesional epilepsy cases. Instead, future studies should acquire the relevant information to enable control for these effects in analyses by carrying out supplementary sub-analysis with only non-lesional cases as per previous studies (Whelan et al., 2018).

4.5.2 Impact of Seizure Frequency on Cortical Thickness

Chapter 3 has previously mentioned that cortical thickness may be less susceptible to the impacts of seizure frequency as compared to functional connectivity measures (Boutzoukas et al., 2020; Widjaja et al., 2012). There are however a small number of studies that have found an association between cortical thickness and seizure frequency in children with complex partial epilepsy (Tosun et al., 2011). Moreover, it is important to consider the potential influence that seizure frequency may have on cortical thickness as many adult studies have shown correlations between the two; for example, seizure frequency correlated with the thickness of the cingulate cortex in adults with generalised tonic-clonic seizures (Ogren et al., 2018). Other studies have also corroborated Ogren et al. (2018)'s findings, as they have found more severe atrophy in individuals with more frequent seizures (Coan, Appenzeller, Bonilha, Li & Cendes, 2009). Furthermore, a meta-analysis (including children and adults with temporal lobe epilepsy) by Caciagli et al. (2017) suggests that more severe atrophy may be associated not only with more frequent seizures but also with longer epilepsy duration. This is further evidenced in Lin et al. (2007)'s study which found a link between longer epilepsy duration and greater cortical thickness thinning in several regions including the superior frontal and parahippocampal in adult patients with mesial temporal lobe epilepsy. This suggests that cortical thickness morphology, especially in adults, may be largely reliant on seizure frequency and duration, and the absence of any absolute cortical thickness changes may be because the patients with epilepsy are largely remitted from their seizures or experienced less frequent seizures (Curwood et al., 2015). The current study cannot confirm if this will explain the present absence of findings because the study does not possess the seizure information of the patients. Moreover, given that the existing studies involving children with epilepsy have suggested a less consistent association between seizure frequency and cortical thickness disruptions, it seems less likely that the present lack of findings is explainable by seizure frequency. Instead, it may be more important to examine other factors that may have an effect on the present lack of significant

findings, like the absence of attention impairments in the included sample of patients, which will be discussed next.

4.5.3 Absence of Sustained Attention Impairments

The absence of group differences in cortical thickness might indicate that this sample of children with epilepsy did not have sustained attention impairments. Hermann et al. (2006) found no initial significant grey matter volume differences between children with epilepsy and controls, but there was reduced grey matter volume when they separated patients with academic problems from patients without academic problems. Their data suggest that including patients with and without cognitive impairments (assessed over a range of cognitive skills including intelligence, language, verbal/visual memory, executive function, and motor function) would likely affect the ability to detect real differences, which may then explain the lack of significant findings in the current study. Unfortunately, the lack of availability of cognitive data precludes the ability to explore this hypothesis.

Nevertheless, the current study is the first to examine regional cortical thickness in the DMN and CEN which are important in sustained attention as demonstrated in healthy individuals; as previously discussed, greater cortical thicknesses of relevant brain regions (i.e., visual, somatomotor, frontal and parietal cortices) is important for the ability to maintain accurate performance in sustained attention tasks as measured using the gradual onset of continuous performance task and the Test of Variables of Attention (Mitko et al., 2019). However, as the present study did not conduct neuropsychological tests, it was not possible to confirm if the patients included had sustained attention deficits. Therefore alongside neuroimaging, future studies should also carry out neuropsychological tests to confirm the cognitive abilities of the patients.

4.5.4 Association between Regional Cortical Thickness and Structural Covariance Network

Unlike cortical thickness studies, fewer studies have looked at structural covariance networks in the epilepsy populations. In contrast to those few studies, the current study found no significant difference in either the overall structural covariance network or in the DMN, CEN, DMN and CEN regions between healthy children and children with epilepsy (Bernhardt et al., 2013; Curwood et al., 2015; Yasuda et al., 2015). Structural covariance networks are suggested to reflect common variations in grey matter morphology like cortical thickness and regional volume (Mechelli et al., 2005). Moreover, studies have found an association between regional cortical thickness reductions and structural covariance networks in both control and patient population (i.e., schizophrenia) (Wannan et al., 2019). The authors suggested that structural covariance networks could explain regional cortical thickness changes; they found an increase in structural covariance between regions with reduced cortical thickness in schizophrenia. Given the

suggested association between regional cortical thickness and SCN, the absence of significant differences in the structural covariance may be explained by the lack of significant difference in the regional cortical thickness between patients and healthy children in the present study (Marsh, Sullivan, Morrell, Lim & Pfefferbaum, 2001). This however is unlikely to explain the present absence of findings because despite not finding any significant differences in the cortical thickness between controls and patients with childhood absence epilepsy, Curwood et al. (2015) did find significant differences in connectivity patterns involving the lateral and medial frontal cortex, and they have suggested that the increased connectivity in patients are likely driven by differences in correlations across networks as compared to changes in regional thickness. This suggests that changes in the cortical thickness do not necessitate similar changes in SCN, which means that the absence of significant differences in SCN in the present study may not be because of the lack of changes in the cortical thickness. Instead, it is important to consider other factors like the developing brain trajectory, small sample size and also the influence of a heterogeneous patient sample, and is further discussed in the following sections.

4.5.5 Influence of the Developing Brain Trajectory on Structural Covariance Network

SCN measures reflect the influence of brain plasticity, including maturational timing, suggesting that SCN is sensitive to changes to the developing brain (Alexander-Bloch et al., 2013). This is in line with Curwood et al. (2015)'s work, which suggested that changes in cortical thickness during childhood and adolescence are prominent processes of cortical maturation that can differ according to the brain regions involved. As grey matter changes are not simultaneous, and instead vary across the cortex, it is expected to lead to significant differences in age-related trajectories across structural covariance networks (Krongold, Cooper & Bray, 2017). The effects of age on structural covariance networks is well established in the current literature, with reports age-dependent patterns of structural covariance across several networks including the DMN and fronto-parietal network (DuPre & Spreng, 2017; Li et al., 2013). For example, Li et al. (2013) reported age-related trajectories of eight large-scale networks via structural covariance network, and importantly, the study found that all the networks showed non-linear patterns across normal aging. Similarly, Zielinski, Gennatas, Zhou and Seeley (2010) have also reported age-related trajectories in structural covariance networks across children between the age of 5–8 years, 8.5–11 years, 12–14 years and 16–18 years. Zielinski et al. (2010) have reported that the different age group affects the varying brain networks differently; the study found more extensive covariance in the DMN and CEN in the older age groups as compared to the younger participants. For example, Zielinski et al. (2010) found covariance between the right and left angular gyrus in the 5–8 and 8.5–11 age groups, with the addition of the lateral temporal regions in the 12–14 age group, and a more extensive bilateral lateral temporal and PCC

covariance was found in the oldest age group (16–18 years). This suggests that younger children would have a less developed network, as compared to older children who would have a more intrinsic connectivity network pattern similar to adults. As the controls in the current study are significantly younger than the patients with epilepsy, they would likely possess a less developed structural covariance patterns which can affect the ability to detect changes in the patient group who were expected to show reduced structural covariance, and leading to the absence of any significant findings.

4.5.6 Impact of A Small Sample Size on Structural Covariance Networks

Importantly, in the context of covariance estimation, it is important to acknowledge that the small sample size may be a more salient basis for the observed lack of differences in structural covariance networks between patients with epilepsy and controls. Low sample sizes can result in an inherently noisy estimation of structural covariance (Carmon et al., 2020). The authors found that the sample size affects accurate covariance estimation, and note that a sample size below 30 subjects is not recommended. Moreover, Carmon et al. (2020) have also suggested that when using Desikan-Killiany parcellation, which was used in the current study, 30 subjects and more per group is also the ideal sample size to ensure the reliability of structural covariance. Given that the final sample size for the patient and control groups were below 30 (in part due to the strict quality control measures implemented in the current study), the absence of findings reflects the small sample size. Moreover, it is important to also point out that the current study had more patients (17) than controls (10), which may not be ideal because having more controls than patients (e.g. four controls for every patient have shown to increase statistical power (Kang, Choi & Koh, 2009). Though earlier research disagrees that having more than two controls per case is effective, Lewallen and Courtright (1998) have also agreed that having more than one control for every case adds power to the study. Future studies should aim to recruit equal number of patients and cases, and if not possible especially when the study involves a patient group that is difficult to recruit, they should try to recruit more controls to increase the study's statistical power.

4.5.7 Influence of A Heterogeneous Patient Sample on Structural Covariance

In addition to a small sample size, it is also important to consider the impact a heterogeneous patient group may have on structural covariance, as different pathology may affect cortical thickness differently. As evidenced in the original analyses, the study included two patients with known frontal focal cortical dysplasia (FCD) and a right persylvian polymicrogyria respectively. These conditions are known to cause cortical *thickening* which was evident in the original findings, and it was therefore useful to explore the influence that these individual cases had on the overall group results. Increased cortical thickness is a common feature in patients with cortical dysplasia, especially in FCD, and studies showed that cortical *thickening* occurs in 91%

of patients with FCD (Bernasconi & Bernasconi, 2011). This instead suggests the importance of examining these cases in small cohorts rather than assuming that patients with FCD would all present with similar brain pathology. It has also highlighted the challenge in examining a heterogeneous patient group, as the findings can be influenced by a small subset of the patients which is not representative of all patients. It also emphasises the importance for future studies to potentially remove these patients to assure the representability and reliability of their findings to the broader patient population.

Besides as discussed earlier in the introduction, it is likely that that structural covariance network changes may be specific to different epilepsy subtypes (Curwood et al., 2015; Drenthen et al., 2018). For example, despite having a relatively small sample size of 30 patients, Curwood et al. (2015) found increased connectivity primarily in the frontal regions in patients with childhood absence epilepsy (CAE), and the frontal cortex is suggested to play an important role in CAE, therefore the study has suggested that the cortical network disruptions may reflect the etiology of CAE. Similarly, Li et al. (2020)'s study, which has only included 13 patients and 30 controls, has found disruptions in the network in children with generalised tonic-clonic seizures, the disruptions specifically involved the temporal pole, which was suggested to play an important role in reflecting the effects of epilepsy on this group of patients. The current studies therefore suggest that structural covariance patterns are likely specific to each epilepsy subtype, and including patients with different epilepsy types can affect the study's ability to identify common changes across these patients, which may explain the study's current absence of findings.

With reference to the present study, the patient group mainly included children with temporal lobe epilepsy and frontal lobe epilepsy. As attention impairment is shared between both forms of epilepsy in children (Longo et al., 2013), it is fair to consider that temporal lobe and frontal lobe epilepsy would share common structural changes in brain regions relevant to attention, as supported by the existing literature (Bocquillon et al., 2009; Gutierrez-Colina et al., 2021). However, it is also pertinent to consider the potential brain structural differences between both forms of epilepsy as studies have shown distinct cortical thinning patterns in adults with temporal and frontal lobe epilepsy (Galovic et al., 2019). Whilst Galovic et al. (2019)'s study found structural changes extending beyond the epileptic focus in both groups, they have also found distinct patterns in each subgroup where regions interconnected with the epileptic focus is likely to be most affected; for example, cortical thinning was observed most in the medial temporal lobes in patients with temporal lobe epilepsy, while frontal lobe patients presented with a more widespread cortical thinning. This is corroborated by an earlier electroencephalography (EEG)–fMRI study that showed that patients with temporal and frontal lobe epilepsy showed similar patterns (activations in mid-cingulate gyri and deactivations in the DMN), however both forms of epilepsy also showed unique network changes (i.e., activation in brain regions known to be interconnected with the epileptic focus) (Fahoum, Lopes, Pittau, Dubeau & Gotman,

2012). This therefore suggests that whilst both forms of epilepsy may share common structural patterns, it is likely that they would be influenced by the seizure location; patients with temporal lobe epilepsy may present with more prominent changes in the networks involving temporal lobe. Sub-analysis was not carried out due to the small sample size in the present study, but future studies should examine the different epilepsy subtypes separately to gain a better understanding of structural changes that may have been missed when examining epilepsy subtypes together.

4.6 Limitations in the Present Study

In summary, the absence of any significant statistical differences in cortical thickness or structural covariance networks can be explained by a range of different factors: the presence of lesions, seizure frequency, variation in the patients with epilepsy, and a small sample size. In addition to these factors, one limitation that should be noted is the insufficient information the study had in regard to current medication usage in the patients with epilepsy, thus the current study does not know if all the patients are on medication or if only some of them are. Therefore, the study cannot rule out the possibility that medication could have influenced the brains of patients on medication differently from those who are not, creating variations in structural covariance between patients. It is well established that sodium valproate, a specific type of anti-epileptic medication, is associated with cortical thinning especially in the parietal lobe in adults with intractable focal epilepsy (Pardoe, Berg & Jackson, 2013). However, Pardoe et al. (2013)'s study did not find cortical thinning in patients who were on non-valproate anti-epileptic drugs (AEDs) or were previous valproate users. Pardoe et al. (2013)'s findings were supported by Tondelli, Vaudano, Sisodiya and Meletti (2020)'s study, which found cortical changes in the posterior cortex in patients with epilepsy (including genetic generalised epilepsy and focal epilepsy) who were on valproate. Similarly, Tondelli et al. (2020)'s study found that patients who were on non-valproate AEDs did not show similar cortical thinning. This is further supported by previous studies, which found that AEDs had no significant effect on cortical morphometry measures in children with childhood absence epilepsy (Tosun, Siddarth, Toga, Hermann & Caplan, 2011), and in adults with focal epilepsy (Galovic et al., 2019). This suggests that specific AEDs like valproate can have a differential influence on cortical thickness, and it would therefore be important for future studies to include the use of medication, and to account for the effect of medication on regional cortical thickness and structural covariance networks.

4.7 Implications of the Present Study

Despite the present hypotheses not being met, this study has highlighted an important factor that could have played a big role in the present absence of significant findings, which is including patients with different subtypes of epilepsy. As the existing literature has established that structural covariance network patterns are specific to the different subtypes of epilepsy, it supports that due to the different subtypes in the epilepsy group, there would be variations within the patients. As a result, there may be greater differences between the patient group as compared to between the patients and controls, thus resulting in the present absence of findings. Despite having a heterogeneous patient sample (i.e., idiopathic generalised epilepsy, mesial temporal lobe epilepsy), other studies have however found cortical thickness differences between patients and controls (Whelan et al., 2018), which suggest that the heterogeneous nature of patients would not solely explain the current absence of findings. In addition, given that the different subtypes of epilepsy shared common cognitive impairments like sustained attention, it would suggest shared structural changes between these patients, and therefore reasonable to examine these patients together as a group.

Moreover, the present study has also highlighted the challenge in carrying out MRI with a paediatric population, as demonstrated by the original recruited number for both the patient and control groups being halved after quality control of the imaging data. The poor quality of the imaging data were largely a result of large movement artefact during the scan, which is unsurprising, as the highest head motion during MRI scans have been found in children and patient populations (Dosenbach et al., 2017). It is however important to remove participants with excessive motion because motion is likely to impact the quality of the image, and affect the image processing and analysis, leading to the misinterpretation of results (Ware et al., 2021), specifically motion during T1 acquisition reduces the estimates of grey matter volume and cortical thickness (Reuter et al., 2015). Whilst excluding participants with excessive motion is important, this also means that the study may have excluded younger participants as increased motion artifacts are found in younger participants (Zaitsev, Maclaren & Herbst, 2015). Importantly, patients with potentially worse injuries may also be excluded, as brain injuries have been found to contribute to increased scanning motion (Ware et al., 2021). Additionally, studies have found an association between children with attention problems and greater movement during scans (Cahoon & Davison, 2014), and as worse attention outcomes are generally found in patients with greater injury severity, it does further suggest that patients with worse injuries would likely be excluded from the study. Therefore despite the potential of using neuroimaging to identify children with poor outcomes after a brain injury, the challenge with excessive motion would suggest that children with the poorest outcomes, who would benefit most from early interventions, may be unaccounted for.

As a result, this suggests that the utilising of neuroimaging methods to identify children with poor outcomes still require more research, which would also be further investigated in the next chapter. Moreover, studies have suggested that combining neuroimaging multi-modalities would provide more rounded information, and have higher predictive accuracy especially in distinguishing between patient and control groups, as compared to only using one modality, which may overlook important differences between groups (Guo et al., 2018). Therefore, given that structural connectivity may be the substrate for functional connectivity (as discussed in the earlier chapters), the next chapter examined novel tools which combine functional MRI (fMRI) and structural MRI (sMRI) network analysis, which may yield more power to understand neural changes that underpin cognitive impairments in children with a brain injury.

4.8 Conclusion

Using structural covariance networks, the current study found no significant differences between patients with epilepsy and healthy children. No differences in cortical thickness were observed either between the patient and control groups. The absence of finding likely demonstrates the disparity in structural covariance networks between the different subgroups of epilepsy, and highlights the importance of examining subtypes of epilepsy separately. The absence of clinical information (i.e., medication/seizure frequencies), the influence of lesions in patients and the heterogeneous patient group however could have influenced the current study's findings. Future studies should aim to recruit a larger sample size, allowing sub-analysis of the different epilepsy subtypes, whilst controlling for medication and seizure frequency. The current study has also highlighted the challenges in recruitment in this vulnerable yet important population, and also in the use of neuroimaging with the paediatric population. Lastly, to better understand neural changes in children with a brain injury, future studies should consider including more than one imaging modality, which will be examined in the next chapter.

Chapter Five: Examining Structural Covariance Network and Resting-state Functional Connectivity Alterations in the Whole-Brain and in the Neural Networks Associated with Sustained Attention in Children with an Early Brain Insult

5.1 Introduction

Strong associations exist between brain functional and structural changes following brain insults in childhood, as evidenced by structural magnetic resonance imaging (MRI) and functional MRI (fMRI) in patient populations (as discussed in Chapters 1 and 3). Most of these studies have examined local alterations in grey matter and/or functional activity, and the brain regions that show altered functional activity often overlap with the brain regions with altered structure. For example, using the same participants (youths with traumatic brain injury (TBI)), Urban et al. (2017) found that the brain regions with significant cortical thinning (i.e., the left dorsolateral prefrontal cortex and inferior parietal lobe) and their correlations with poorer task performance (i.e., slower reaction time during the dual task involving visuospatial working memory (i.e., n-back task) and motor tasks) overlapped with the fMRI activation abnormalities previously reported by Sinopoli et al. (2014). These findings suggest a close link between functional and structural local alterations following mild TBI, which may underpin the poor cognitive performance in these adolescents. This study also highlighted the use of the multi-modalities approach, which could allow for a more comprehensive understanding of pathological changes that would aid in the identification of biomarkers for the disease (Zhang et al., 2020), and – in the context of the current thesis – the contribution of network changes to cognitive outcomes. The current chapter focuses on whole-brain changes in the structural and resting-state functional connectivity, and changes in the networks (default mode network (DMN) and the central executive network (CEN)) known to underpin sustained attention, in children with acquired brain injury (ABI) as compared to typically developing children.

fMRI is often used to investigate altered functional brain responses (i.e., functional reorganisation) after a brain injury (discussed in Chapter 1), which may be associated with the cognitive outcomes in these patients (Medaglia, 2017). This technique is widely utilised to examine resting-state fMRI changes following ABI in paediatric patients, including for brain tumours, TBIs and ischemic stroke (Anandarajah et al., 2020; Ilves et al., 2016; Strazzer et al., 2015; Tuerk et al., 2020), which has also been extensively covered in Chapter 1. For example, Strazzer et al. (2015) reported activity changes in several brain regions in children with ABI, including an increase in activity in the frontal regions, which was found to be associated with poorer sustained attention (i.e., increased response time and lower percentage of correct response when performing the Conners' Continuous Performance Test); thus, highlighting the association between altered functional brain responses and cognitive outcomes.

However, more recent studies have suggested that cognitive skills like attention are, in fact, supported by large-scale brain networks. Zuberer et al. (2021) showed that optimal

sustained attention (as measured using the reaction time and latency of correct responses variables of a variation of the Continuous Performance Task (i.e. Gradual)) is associated with both integration and segregation across several large-scale intrinsic brain networks. Given that cognitive skills are underpinned by large-scale networks, it is possible that children with brain injuries are particularly susceptible to attention impairments because the networks underlying attention are still immature. In addition, as previously discussed in Chapter 1, brain injuries during developmental periods can affect subsequent neural and behavioural development. The development of network connectivity, especially in the task negative and task positive networks (i.e., the development of anticorrelations between these networks), between childhood and adulthood is crucial for the maturation of cognitive skills, and, therefore, atypical development of these network connections are likely to contribute to cognitive problems (Barber, Caffo, Pekar & Mostofsky, 2013). The relationships between disrupted networks and cognitive impairments have been presented by Anandarajah et al. (2020). This latter study reported disruptions within and between several networks, including reduced segregation between the dorsal attention network and the DMN, which was found to be associated with poorer cognitive performance (including attention as assessed using the National Institutes of Health (NIH) Toolbox Cognition Battery) in paediatric brain tumour patients. The previous chapters have also outlined similar neural disruptions in the DMN and CEN across various brain injuries. These disruptions are often associated with sustained attention deficits, suggesting the possibility of a shared pattern of network disruption across these injuries, as previously conceptualised by van den Heuvel and Sporns (2019). Given that brain function is highly reliant on effective communication between relevant brain networks, shared patterns of dysconnectivity in the brain would explain similar cognitive impairments in these patients (van den Heuvel & Sporns, 2019). Taken together, the shared attention impairments reported across different brain insults may be the result of similar disruptions in brain network organization. This conclusion highlights the importance of investigating the connectivity of large-scale brain networks supporting cognitive skills to provide insight into long-term cognitive impairments.

Compared to functional connectivity studies, there are far fewer studies that have examined the alterations in structural connectivity following an early brain injury. As discussed in previous chapters (specifically Chapters 1 and 4), structural covariance network (SCN) is a novel method that allows for analysis of the structural properties of networks (i.e., cortical thickness or grey matter volume) that may be altered in the pathological brain (Song et al., 2021). While there are fewer SCN studies, researchers have recently recognised disruptions in the grey matter structural covariance networks (SCNs), specifically in the DMN, executive control network (ECN), salience network (SN) and the sensorimotor network (SMN), in adults with a brain injury as compared to controls (Song et al., 2021). Song et al. (2021) have also suggested that the reorganisations of the structural covariance of these networks after a brain injury may either underpin cognitive deficits or reflect compensatory mechanisms. Along with

alterations in regional grey matter volume, Wei et al. (2020) have also found abnormal structural covariance patterns (involving the prefrontal cortex, parietal lobe, temporal lobe, paralimbic system and cerebellum) in adults with stroke. These authors suggested that examining both regional and SCNs changes can aid in better understanding the neurobiological mechanisms of behavioural recovery, which is related to cognitive functioning.

Taken together, SCNs have shown to be useful in providing network-level evidence that diseases/injuries have a widespread impact, causing changes beyond the lesion areas (Zhang et al., 2020). This is especially important in brain injury cohorts, as studies have established such injuries as disorders of brain networks, despite the injury being focal in nature. For example, widespread disruptions across the brain have been found in patients with focal epilepsy (Burman & Parrish, 2018), TBI (Hayes, Bigler & Verfaellie, 2016) or glioma (Derks et al., 2021). In addition, as compared to traditional univariate approaches that do not consider the relationships between cortical regions (e.g., the regions of interests (ROIs) approach; discussed in Chapter 1), SCN can better examine the complexity of the human brain by accounting for inter-regional correlations (Tur et al., 2018). Thus, this approach was adopted for the current study.

5.1.1 Structural Covariance Network Studies Examining the Atypical Developing Brain

As discussed in Chapter 4, SCNs are sensitive to changes in the developing brain. Structural covariance across the cortex can change due to neurodevelopment, age and maturational changes (Alexander-Bloch, Raznahan, Bullmore & Giedd, 2013; Zielinski, Gennatas, Zhou & Seeley, 2010). This is observed in autism, where its onset-age coincides with a critical brain development period that includes the maturation of structural covariance. Disruptions found in the structural covariance in children are suggested to reflect an early developmental insult that impacts the coordinated brain maturation of the social cognitive networks, thus leading to social functioning problems in these individuals (Alexander-Bloch, Giedd & Bullmore, 2013). Therefore, SCNs have been shown to be sensitive to the impacts of early childhood brain insults on the developmental trajectory of the structural brain and, thus, it may be informative to examine the effects of other insults like paediatric brain injury.

Zielinski et al. (2010) have further suggested an association between the development of SCNs and the maturation of the functional domains supported by the respective networks, indicating a close association between SCNs and functional skills. Moreover, studies have suggested that disruptions to the connectivity of developing neural networks as observed in early structural developmental brain abnormalities are likely to be responsible for long-term cognitive impairments (Birca et al., 2016). Taken together, this suggests that SCN may be sensitive to abnormalities in the brain, which would impact cognitive functioning. This is observed in a SCN study that examined preterm infants. This latter study showed that poorer

cognitive outcomes (measured by the Wechsler Preschool and Primary scale of Intelligence) in this group are associated with reduced structural covariance across the network, involving the fronto-insular, inferior parietal and middle occipital cortices, when measured using volumetric measurements; thus, supporting the use of SCN to examine structural network changes associated with cognitive outcomes (Vanes et al., 2021).

5.1.2 Structural Covariance Network Studies in Paediatric Brain Injury Cohorts

There are, however, very few studies that have looked at SCN alterations in children with a brain injury. King et al. (2020) found that paediatric TBI patients with poorer executive functioning (i.e., lower summary scores across several neuropsychological tests including The Everyday Attention of Children, Delis-Kaplan Executive Function System and Wechsler Intelligence Scale for Children) deviated from the age appropriate SCN, and greater deviation from the normative SCN was related to poorer executive function. Other studies have reported disrupted covariance across the networks (decreases in the left pars opercularis and dorsolateral prefrontal regions, and increases in the right anterior cingulate) when measuring cortical thickness, and that the disruptions in these regions may underlie cognitive deficits in speech, execution and language comprehension in children with bilateral cerebral palsy (Liu et al., 2019). Similarly, SCN disruptions (i.e., in the bilateral medial temporal gyrus, left caudate, left anterior cingulate cortex, right thalamus, right precuneus and inferior temporal gyrus) when measuring grey-matter volume were found in children with generalised tonic-clonic seizures have been suggested to be associated with cognitive decline in this group (Li et al., 2020). Moreover, a more recent paediatric TBI study found global changes in the SCN – measured by grey-matter volume – within the DMN (right angular gyrus, right middle frontal gyrus and left superior frontal gyrus) and the CEN (the right dorsolateral prefrontal cortex, calcarine sulcus and right occipital gyrus) in children with TBI 12–24 months post-injury as compared to typically developing children (Tuerk, Degeilh, Catroppa, Anderson & Beauchamp, 2021). These studies have shown that the SCN approach is sensitive to the widespread effects of the different brain injuries on the developing brain, further supporting the use of SCN to examine network changes in children after a brain injury.

The existing literature has therefore highlighted the potential of SCN for examining structural network disruptions. This approach could be used in clinical practice to identify patients who may have poor cognitive outcomes, especially as structural MRI is often part of the clinical routine and, therefore, widely available (Keightley et al., 2014). The potential use of SCN in clinical practice may allow clinicians to identify children who may benefit from support or early interventions that allow for a better prognosis. However due to the lack of studies that have examined SCNs in children with brain injuries, the alterations of SCNs in the brain following an early brain insult are still largely unknown. Given that SCN can reveal vulnerable networks and be used to early identify cognitive impairments in children with a brain insult, the current study

may improve our understanding of disruptions in the SCN following a brain injury. Moreover, studies have suggested that examining both regional and network changes may provide more comprehensive information about how the brain reorganises itself after a brain injury (Wang et al., 2021). Thus, the current study examines the brain regionally and from a network perspective.

5.1.3 Existing Multimodal Neuroimaging Studies

There is no single neuroimaging technique that can completely characterise the impact that brain injuries can have on the developing brain. However, by adopting a framework of multimodal neuroimaging, this might be achieved in a unified manner. Specifically, multimodal approaches combine data acquired from multiple imaging modalities to overcome the limitations of individual modalities and provide complementary findings from each modality, with the aim to better understand the structure and function of the brain (Zhang et al., 2020). As discussed in the previous chapters, functional and structural regional disruptions are frequently reported after a brain injury, and some studies have combined functional and structural measures to examine the neural disruptions. These studies have often looked at localised or regional alterations (i.e., fMRI activations and grey matter volumes derived from voxel-based morphometry) in patients with a TBI (Sanchez-Carrion et al., 2008) or medial temporal lobe epilepsy (Labudda, Mertens, Janszky, Bien & Woermann, 2012). There are, however, very few studies that have examined functional and structural connectivity changes at a network level after an early brain injury. It is important to examine these changes as these brain injuries are known to be a disorder of brain connectivity (as previously discussed) and are associated with alterations in network connectivity (Hayes, Bigler & Verfaellie, 2016).

Despite few studies having looked at both fMRI and SCN changes, those that have been conducted have provided evidence for an association between SCN and fMRI across developmental insults resulting from childhood maltreatment (Paquola, Bennett & Lagopoulos, 2018) or malformations in cortical development (Hong, Bernhardt, Gill, Bernasconi & Bernasconi, 2017). Specifically, Hong et al.'s (2017) results have suggested that the structural network largely determines the inter-regional functional interactions. The SCN and functional connectivity analysis in this latter study both revealed a similar pattern of gradual network changes, with the biggest rearrangement seen in polymicrogyria, moderate changes in heterotopia and subtle alterations in focal cortical dysplasia. However, this study also reported a divergence between the functional and structural connectivity, where the SCN results suggested inefficient global and excessive local connectivity, while the functional connectivity results suggested a decrease in both global and local connectivity. These findings suggest that a divergence may be present between structural connectivity and functional connectivity in adults with a brain insult. This could be due to a gradual loss of optimal functional connectivity patterns because of restrictions from a regularised structural topology, or it could reflect compensatory

mechanisms to maintain function (Hong et al., 2017). As discussed earlier, using the same cohort of youths with TBI, Urban et al. (2017) and Sinopoli et al. (2014) respectively examined the structural (i.e., regional cortical thickness) and functional alterations after a brain injury. The findings across both studies demonstrated that the brain regions showing structural and functional alterations overlapped, which suggests a structural substrate underlying the functional alterations (Urban et al., 2017). However, no studies have examined both fMRI and SCN in children with a known brain insult. Therefore, it is unknown whether SCN changes overlap with fMRI changes following a paediatric brain insult, which is the focus of the current study.

5.1.4 Aims and Hypotheses

Given the time and cost efficiency of structural MRI over fMRI, it is important to determine whether SCN changes can explain fMRI changes following a paediatric brain insult. Moreover, the current literature has shown that regardless of the nature of the brain injury, patients reported similar deficits in sustained attention, which might reflect shared brain functional and structural changes in these patients. Thus, the current study will look at patients with a range of brain injuries, inclusive of epilepsy, stroke, brain tumour and TBI.

As discussed earlier, SCN is sensitive to the developing brain and can reveal large-scale neural networks associated with cognitive functioning, which have been suggested to be similar to functional connectivity patterns (DuPre & Spreng, 2017). While it is well-established that brain injuries are likely to cause widespread structural and functional disruptions across large-scale, distributed networks (Cauda et al., 2018; Gratton, Nomura, Perez & D'Esposito, 2012), as previously discussed in Chapter 1, there are few paediatric brain injury studies that have investigated these network patterns using SCN, which is a relatively novel approach. Given that large-scale networks are defined by functional connectivity and structured covariance (Seeley, Crawford, Zhou, Miller & Greicius, 2009), the current study aimed to investigate the impacts of brain injuries by investigating changes across the whole-brain using SCN and fMRI in children with a brain insult.

Given the vulnerability of sustained attention to brain injuries, the current study also aimed to investigate structural (measured by structural covariance and regional cortical thickness) and functional changes in the brain regions of the DMN and CEN that are associated with sustained attention. Therefore, the aims of the current study also included: 1) examining regional cortical thickness changes in children with a brain injury in the brain regions of the DMN and CEN, 2) examining SCN changes in children with a brain injury *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions, and 3) examining resting-state fMRI changes in children with a brain injury *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions. Finally, given the suggested

relationship between structural and functional connectivity, this study will discuss whether significant disruptions to structural connectivity overlapped with functional connectivity changes.

Based on the current literature, it was hypothesised there would be significant differences in the whole-brain SCN and fMRI between children with a brain insult and typical developing children. It was also hypothesised that there would be a significant reduction in the SCN and fMRI between children with a brain insult and typical developing children *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions. Moreover, it was expected that there would be cortical thinning in DMN and CEN regions in children with a brain insult compared to typical developing children. Lastly, it was hypothesised that potential disruptions in the SCNs would overlap with functional connectivity changes in the corresponding brain regions.

5.2 Methods

5.2.1 Participants

Typical developing children were either recruited via Birmingham Children's Hospital outpatient clinics (children referred for non-neurological reasons like musculo-skeletal imaging or head/neck MRI where central nervous system involvement was not suspected) or through leaflets and posters placed throughout the community (i.e., schools, libraries, community group centres, and doctor's offices). Paediatric patients were recruited via Birmingham Children's Hospital when they were referred for routine MRI scans. These children were referred to radiology because of a suspected or known cerebral abnormality or brain lesion (i.e., CT evidence of a lesion, epilepsy, neurooncology, TBI, or stroke). Therefore, the imaging scans (namely fMRI) for this study were added to the patients' clinical scans. In total, 24 typical developing children and 50 patients with a brain insult were recruited. This study is part of a larger prospective study that included younger children who, as per standard clinical practice, were scanned while sedated or under general anaesthetic (GA), if recommended by the clinician. Sedation and GA have been shown to affect functional connectivity across the brain, including in the DMN. Therefore, patients who were scanned under either of these conditions were removed from the current study (Hudetz, 2012). As a result, 17 patients were removed and only 33 patients with no sedation or GA remained. In addition, fMRI was not acquired for 4 typical developing children and 1 patient, resulting in 32 patients with no sedation or GA and 20 typical developing children.

Following functional imaging quality control (refer to the section on *Functional MRI Quality Control* below), five controls and eight patients were removed from the final analysis due to excessive head motion during resting acquisition. After structural imaging quality control (refer to the section on *Structural MRI Quality Control* below*),* 10 patients and nine controls were removed from the final analysis due to excessive head motion or as a result of poor image quality during T1 acquisition. As a result, only 6 typical developing children and 14 patients

remained. However, 1 control and 1 patient were removed because the scans were obtained at a different location and on a different scanner. Thus, only 5 typical developing children (9–12 years, *M* = 10.20, *SD* = 1.10, 2 males, 3 females) and 13 patients (7–14 years, *M* = 10.31, *SD* = 2.18, 4 males, 9 females) were included in final analyses. The final patient group consisted of children with different suspected or known cerebral abnormalities and/or brain lesions (Table 5.1).

Table 5.1.
Demographic information for paediatric patients and controls

Participant (Group)	Age at Scan (Years)	Year of Diagnosis	Gender	Diagnosis	Lesion
001 (Patient)	9	2018	Female	Medulloblastoma	No
002 (Patient)	10	Congenital	Male	Prematurity, Perinatal Ischaemia, Haemorrhages	Yes
003 (Patient)	11	Not available	Male	Bilateral toe walker	No
004 (Control)	10	-	Female	Headache (Normal MRI)	-
005 (Patient)	9	Not available	Female	Tourette syndrome	No
006 (Patient)	12	Not available	Female	Hand tremor, Rathke's left cleft	No
007 (Control)	10	-	Male	Migraine (Normal MRI)	-
008 (Patient)	7	2019	Male	Traumatic brain injury	No
009 (Control)	10	-	Male	Headache (Normal MRI)	-
010 (Control)	9	-	Female	Headache (Normal MRI)	-
011 (Patient)	12	Not available	Female	Epilepsy (Unknown foci)	Yes
012 (Patient)	8	Not available	Female	Hypotensive hydrocephaly with seizures	Yes
013 (Patient)	13	Not available	Female	Relapsing remitting multiple sclerosis	Yes
014 (Patient)	14	Not available	Female	Transverse myelitis	No
015 (Patient)	8	Not available	Female	Learning difficulties (across attention, coordination, and visuospatial)	Yes
016 (Control)	12	-	Female	Headache (Normal MRI)	-
017 (Patient)	9	2019	Female	Autoimmune disorder	Yes
018 (Patient)	12	Not available	Male	Autoimmune ataxia	Yes

5.2.2 Procedure

Ethical approval was sought and obtained through an NHS Research Ethics Committee (Yorkshire and The Humber), and R&D management approval was also obtained from Birmingham Women's and Children's NHS Foundation Trust from where the participants in this study were recruited (REC reference 17/YH/0299). Aston University also acted as a sponsor for the study (IRAS reference 222771).

Consent to participate in this study was obtained from the parent and/or guardian, and also from the child themselves if they were deemed capable of giving consent. The study was

explained verbally to the children, and the written information sheet was either read to them or given to them. Child consent or assent, written or verbal depending on the child's abilities, was also sought from all participants who were not able to consent. Any signs of dissent from the child, verbal or non-verbal body language expressions, or an unwillingness to participate in the study was respected, and the child was excluded from the study.

The child was shown the MRI before the scan. Children were allowed to watch a DVD of their choice throughout the scan, except during the resting-state fMRI.

5.2.3 MRI Acquisition

All baseline neuroimaging data were acquired using a 3T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands) with a 32-Channel matrix head coil at Birmingham's Children Hospital. High-resolution T1-weighted structural MR images were acquired with the following parameters: repetition time (TR) = 8.10–8.30 ms, time to echo (TE) = 3.7–3.8 ms, flip angle (FA) = 8°. To acquire blood-oxygen-level dependent (BOLD) fMRI, a T2 sensitive gradient-echo echo-planar imaging (EPI) sequence was also acquired with the following parameters: TR = 2300 ms, TE = 35 ms, FA = 80°, 41 slices, and 150 volume with a total scan time of 6 minutes. As the scans were resting-state fMRI, the participants did not complete any tasks during the scan period.

5.3 Data Analysis

5.3.1 Structural MRI Pre-processing

T1 images were processed with the Freesurfer 6.0 software suite, which has been previously been described in Chapter 4. For controls and most of the patients without lesions (n = 17), T1-weighted anatomical MR images were processed using the Freesurfer default processing stream (recon-all) for cortical reconstruction and volumetric segmentation (Fischl & Dale, 2000; Fischl et al., 2004). The technical steps involved have previously been discussed in Chapter 4.

As lesions were present in the remaining brain injury patients (n = 15), Freesurfer's standard processing pipeline was not appropriate because lesions can affect the accuracy of reconstructed surfaces that volumetric measurements are based on (Diamond et al., 2020). To mitigate the issue of lesions on surface-based parcellations, an adjusted pipeline developed by other members of the research group was utilised instead (King, Seri, Catroppa, Anderson & Wood 2021). This pipeline is discussed in greater detail in Appendix A.

Similar to Chapter 4, Freesurfer (Fischl, 2012) was used to estimate cortical thickness based on the cortical parcellation of the Desikan-Killiany (DK) atlas (Desikan et al., 2006). More detailed information on the measurement of cortical thickness was presented in Chapter 4.

5.3.2 Structural MRI Quality Control

As per Chapter 4, Freesurfer outputs were quality checked using Qoala-T, before visual inspection and manual editing were carried out, which was presented in greater detail in the previous chapter. As a result of either excessive motion or poor image quality during T1 acquisition, 19 participants (10 patients, 9 controls) were removed from further analyses.

5.3.3 Functional MRI Pre-processing

Yeo, Tandi and Chee (2015) inspired the analysis plan for the resting-state fMRI data in the current study. The fMRI images for all the participants were first corrected for slice-acquisition-dependent time shifts in each volume by using Statistical Parametric Mapping 12 (Ashburner et al., 2014; http://www.fil.ion.ucl.ac.uk//software/spm12). Further pre-processing steps, including motion correction, masking, intensity normalisation and structural-functional data alignment (described in Yeo et al., 2011), were then carried out using the Freesurfer Functional Analysis Stream (FS-FAST) 6.0 (Fischl, 2012; surfer.nmr.mgh.harvard.edu/fswiki/FsFast).

Linear regression using multiple nuisance regressors, including global signal, six motion correction parameters, and the averaged signals of the whole brain, ventricles and white matter, were then applied. The whole brain, white matter and ventricular masks were defined based on Freesurfer segmentation of each participant's MRI scan and transformed into the participant's functional space. A band-pass filter (0.01-0.08 Hz) was then applied to the pre-processed data. The pre-processed data was then sampled to the template cortical surface of the left and right hemispheres (FreeSurfer fsaverage brain), and smoothed using a 6 mm full-width half-maximum kernel (Fischl, Sereno, & Dale, 1999).

5.3.4 Functional MRI Quality Control

Head motion is known to affect measures of functional connectivity and can be a confounding variable during group comparisons (Power, Barnes, Schlaggar & Petersen, 2012; Van Dijk, Sabuncu & Buckner, 2012). Therefore, to further reduce motion effects on functional connectivity, the current study applied motion scrubbing to the pre-processed fMRI data in line Power et al. (2012). However, to ensure the quality of the data, participants with more than 25% of their data that exceeded the pre-decided framewise displacement-threshold of 0.5 mm were excluded from further analyses. To calculate the framewise displacement, the study took the sum of the absolute derivatives of the 6-motion parameter for each time point derived from FS-FAST (Power et al., 2012). This threshold was defined based on a previous study (Cheng, Rolls, Gu, Zhang & Feng, 2015). As a result, twelve participants (5 controls, 8 patients) were excluded from further analyses because of excessive head motion during resting acquisition in the MRI scanner.

5.3.5 Differences in Cortical Thickness between Patients and Controls

As per Chapter 4, Statistical Package for the Social Sciences, version 26 (SPSS, Chicago, Illinois) was also used to perform statistical analyses in the current study. The present study carried out the same steps as outlined in Chapter 4 to examine the cortical thickness differences in the DMN and CEN between patients and controls.

5.3.6 Graphs of Structural Covariance

The structural covariance analysis in the present study also replicated Chapter 4's analysis pipeline, which was based on a previous paper (King et al., 2020). Network analyses were carried out using several packages in R version 3.5.0 (R Core Team, 2016), specifically 'brainGraph' version 2.2.0 (Watson, 2016), which is an extension of the iGraph package (Csardi & Nepusz, 2006).

5.3.7 Functional Connectivity Analysis

Seed regions were derived from the cortical parcellation of the Desikan-Killiany (DK) atlas (Desikan et al., 2006). Based on the DK atlas, 34 ROIs for each hemisphere were derived, resulting in a total of 68 ROIs. For each functional run, the time series were averaged across vertices within each ROI. Next, to derive the functional connectivity across the whole-brain, the mean time series of each region of interest (ROI) was correlated to the mean time series of every other ROI, resulting in a 68 x 68 correlation matrix. To normalise the correlation values, a Fisher r-to-z transformation was applied (Van Dijk et al., 2010).

Following this, the Network Based Statistics (NBS) toolbox was used to examine the differences in whole-brain functional connectivity between patients and controls. Age and gender were added as covariates of non-interest during the NBS analysis. NBS is a statistical toolbox that examines and identifies connections between brain regions that are interconnected, while controlling for the family-wise error rate. (Zalesky, Fornito & Bullmore, 2010). Importantly, NBS was used because it is a validated statistical methodology to counter issues with multiple comparisons when examining connectivity graphs, and it allows for the identification of sub-networks and connections showing between-group differences (Gaudio, Olivo, Beomonte Zobel & Schioth, 2018).

Due to the interest in regions associated with sustained attention, the same NBS analyses were carried out *between* regions *within* the DMN (ROI = 16) and *within* the CEN (ROI = 12), and *between* the DMN and CEN regions (ROI = 24). The ROI of each network (DMN/CEN) was chosen based on a prior paper that established the neural networks and their associated Freesurfer regions based on the DK atlas (Ryan et al., 2017).

5.4 Results

5.4.1 Age and Sex

The patient (*M* = 10.30, *SD* = 2.18) and control (*M* = 10.20, *SD* = 1.10) groups showed no significant difference in age, *t*(16) = -.10, *p* = .92. Using Fisher's exact test, patients (4 male, 9 female) and controls (2 male, 3 female) showed no significant difference in sex (*p* = .56). These findings indicate that the patient and control groups are both age- and gender-matched.

5.4.2 Differences in Cortical Thickness between Patients and Controls

In order to determine whether there were differences in the cortical thickness of the DMN and CEN brain regions between patients and controls, univariate analysis was carried out.

No significant cortical thickness differences in any of the DMN and CEN regions between children with a brain injury and typical developing controls were found. Statistical data, including the means and standard deviations of the cortical thickness for each region of the DMN and CEN are presented in Appendix B and Appendix C respectively.

5.4.3 Analysis of Whole-Brain Structural Covariance

In order to determine whether there were structural differences across the whole-brain between patients and controls, whole-brain SCN was carried out. For each network/graph, the strength of structural covariance for each node was measured as node strength; that is, the sum of the connectivity weights of all edges connected to the specific node (Fornito, Zalesky & Bullmore, 2016). The average nodal strength across all nodes was then calculated to derive an estimate of graph level strength.

At the graph level, no significant difference was found in the mean graph strength (false discovery rate (FDR) corrected) between children with a brain injury and typical developing controls, permuted difference (PermDiff) = -1.186, p_{fdr} = .239.

However, at the nodal-level, when uncorrected for FDR, a greater nodal strength was found in the patient group in the left banks superior temporal sulcus and left cuneus (regions derived from DK parcellation; Table 5.2). Nonetheless, after FDR correction across ROIs (n = 68), no nodal differences remained significant between children with a brain injury and controls.

Table 5.2
Nodal strength permuted difference between patients and controls

Brain region	Permuted difference	*p*-value	*p*-value (FDR corrected)
Left banks superior temporal sulcus	-1.06	0.03	0.52
Left cuneus	-1.06	0.04	0.52

Note: FDR = false discovery rate

5.4.4 Analysis of DMN Structural Covariance

Structural covariance analysis was then performed to test the hypothesis that there is a reduction in the SCN between children with a brain insult and typical developing children in the DMN.

At the graph level, no significant difference was found in the mean graph strength (FDR corrected) between children with a brain injury and typical developing controls, PermDiff = -.039, p_{fdr} = .502.

At the nodal level, there were also no significant nodal differences between children with a brain injury and typical developing controls across the DMN ROIs (including the ventromedial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule and the hippocampal formation; n = 16, FDR corrected).

5.4.5 Analysis of CEN Structural Covariance

Structural covariance analysis was also performed to test the hypothesis that there is a reduction in the SCN between children with a brain insult and typical developing children in the CEN.

At the graph level, no significant difference was found in the mean graph strength (FDR corrected) between children with a brain injury and typical developing controls, PermDiff = -.280, p_{fdr} = .843.

At the nodal level, there were no significant nodal differences between children with a brain injury and typical developing controls after FDR correction across the CEN ROIs (including the dorsolateral prefrontal cortex and posterior parietal cortex; n = 12).

5.4.6 Analysis of DMN and CEN Structural Covariance

Structural covariance analysis was also performed to test the hypothesis that there is a reduction in the SCN between children with a brain insult and typical developing children between the brain regions of the DMN and CEN.

At the graph level, no significant difference was found in the mean graph strength (FDR corrected) between children with a brain injury and typical developing controls, PermDiff = -.231, p_{fdr} = .661.

At the nodal level, there were no significant nodal differences after FDR correction between children with a brain injury and typical developing controls across the DMN and CEN ROIs (n = 24).

5.4.7 Whole-brain Functional Connectivity

In order to determine whether there were functional differences across the whole-brain between patients and controls, whole-brain NBS was carried out.

NBS found no significant difference in the functional connectivity across the whole-brain between children with a brain injury and typical developing controls.

5.4.8 Functional Connectivity *between* regions *within* the DMN

NBS was then carried out to order to address the hypothesis that there is a reduced functional connectivity in children with a brain insult as compared to typically developing children *within* the DMN.

NBS found no significant difference in the functional connectivity *between* regions *within* the DMN between children with a brain injury and typical developing controls. The statistical data are presented in Appendix D.

5.4.9 Functional Connectivity *between* regions *within* the CEN

NBS was also carried out to order to test the hypothesis that there is a reduced functional connectivity in children with a brain insult as compared to typically developing children *within* the CEN.

NBS found no significant difference in the functional connectivity *between* regions *within* the CEN between children with a brain injury and typical developing controls. The statistical data are presented in Appendix E.

5.4.10 Functional Connectivity *between* the DMN and CEN

NBS was finally used to test the hypothesis that there is a reduced functional connectivity in children with a brain insult as compared to typically developing children *between* the DMN and CEN.

According to the NBS *t*-test results, no significant difference was found in the functional connectivity *between* the DMN and CEN between children with a brain injury and typical developing controls. The statistical data are presented in Appendix F.

5.5 Discussion

To further understand the use of examining neural changes following a brain injury to identify children who would struggle with cognitive impairments, a prospective study involving children with a brain insult and typical developing controls was conducted. The present study investigated the functional and structural changes in children with a brain insult compared to typical developing controls. Given that sustained attention has commonly been reported across different types of brain injuries, the functional and structural changes in children with a brain

insult in the networks/regions known to underpin attention (i.e., the DMN and CEN) were also examined. Compared with typical developing controls, the current study found no significant differences in children with a brain insult in both whole-brain functional connectivity and SCN. In addition, no differences were found between patients and typical developing controls in functional connectivity and SCN across the attention networks (DMN and CEN). Given the current study's absence of significant findings, the current study is unable to discuss the structural-functional relationship in the brain regions/networks of the DMN and CEN, specifically if disruptions to structural connectivity would overlap with functional connectivity changes. Due to limitations/shortcomings of the novel analysis methods used (i.e., SCN and NBS), a direct correlation between the functional connectivity and structural connectivity was not possible. This is because the SCN was derived at a group-level, whereas the functional connectivity was attained at an individual subject-level, therefore a correlation analysis between both measures would be inappropriate. The current study has considered using group independent component analysis (ICA) as per previous chapters, but decided that it was inappropriate due to the different atlas used in the different analyses tools (i.e., ICA and Freesurfer), as the regions in the functional and structural analyses would not match. As a result, it would not be possible to directly examine the relationship between the functional and structural connectivity either across both groups, or between the patient and control groups. Overall, the current hypotheses have not been supported. Therefore, the following sections will discuss several factors that could explain the absence of significant differences between controls and patients.

5.5.1 Influence of Lesions on Functional Connectivity

Foremost, it is important to consider that all lesions are not the same. The pathological basis of a lesion contributes to its physiological and behavioural consequences (Anderson, Damasio & Tranel, 1990). Lesions that result from specific pathologies exhibit different characteristics. For example, low-grade gliomas often affect the medial prefrontal regions (Duffau & Capelle, 2004), but stroke rarely affects these regions (Sperber & Karnath, 2016). Furthermore, studies have also shown that gradual onset lesions (e.g., tumours) are likely to result in less severe cognitive and behavioural impairments as compared to sudden onset lesions (e.g., ischemic stroke; Desmurget, Bonnetblanc & Duffau, 2007). The differences in cognitive impairments may reflect a disparity in the brain's ability to compensate for lesions that develop differently (Desmurget et al., 2007). Desmurget et al. (2007) further suggested that the functional connectivity of the brain reorganises differently between acute and slow growing lesions (i.e., more efficient recruitment of remote brain regions in the ipsilesional and contralesional hemispheres for slow growing lesions than acute lesions), implying that neural patterns can differ between lesions caused by different brain insults. The current study included focal lesion patients with different pathological bases, which may have affected the neural networks differently. Therefore, there may have

been differences between patients that affected the ability to find any differences between the patients and controls.

Moreover, studies have suggested that functional connectivity disruptions are influenced largely by the location of the lesion (Alstott, Breakspear, Hagmann, Cammoun & Sporns, 2009). Alstott et al. (2009) illustrated that the degree of disruption in network organization is dependent on the structural network properties of the lesion site. Their study found that lesions along the cortical midline and temporo-parietal region led to more distributed changes, while lesions in the primary sensory and motor regions were more localised. This implies that functional connectivity alterations are very much dependent on the lesion location. Furthermore, Nomura et al. (2010) have shown that, while the effects of the anatomical damage extend beyond the region of the lesion, the functional connectivity disruptions (i.e., decrease) remains within the existing network connections. Thus, the non-lesioned network is spared from disruptions. This, therefore, suggests that functional connectivity changes are dependent on which region/network the lesion lies in. The fact that the patient cohort is heterogeneous, with lesions distributed across different networks, may have increased potential confounds for within-subject comparisons; therefore, affecting the ability to find any differences between the patients and the controls. However, all of these explanations seem unlikely as another study with a heterogeneous sample (focal lesions including stroke, TBI and tumour) found functional disruptions to the neural organization compared to healthy controls (Gratton et al., 2012). This latter study found global changes in brain organization after a focal injury to regions that are crucial for the communication between networks. This is also further evident in Nomura et al.'s (2012) study, which demonstrated neural changes in patients with heterogeneous focal lesions compared to controls. Given that the current literature has suggested an association between functional and structural substrates, it is expected that structural connectivity would also be affected by lesions in the current study, which will be discussed next.

5.5.2 Influence of Lesions on Structural Connectivity

Wang et al. (2019) demonstrated that, while stroke affects the structural covariance at a whole-brain level, alterations in the connection patterns are dependent on the lesion side. For example, Wang et al. (2019) found greater structural covariance alterations (e.g., in the infratentorial regions) in patients with left-sided lesions as compared to patients with a lesion on the right side. Similar to functional connectivity, this suggests that structural covariance is dependent on the location of the lesion. Therefore, the heterogeneous patient sample could have affected the ability to find any differences in the current study.

Previous studies have also suggested that for consistent alterations in cortical thickness to be exhibited within a specific brain region as a result of a brain injury, there would need to be consistency in the underlying pathology (Bigler et al., 2016). Similar to Bigler et al. (2016), the current study was comprised of a heterogeneous sample, with little or no consistency in the

distributions of lesions across the patients. Bigler et al. (2016) suggested that the combination of little overlapping regions of direct parenchyma damage, heterogeneity in the underlying pathology, along with individual differences across the group, could reduce the likelihood of any uniformity in the parenchymal damage from the injury. As a result of these factors, it can be difficult to detect any true differences between groups. However, a study by Bigler et al. (2013), which included TBI patients with heterogeneous lesions, found common neural features (grey matter reduction) despite group heterogeneity. Therefore, it is unlikely that the current heterogeneous patient group solely explains the absence of significant functional or structural findings. Instead, this highlights the importance of using data from patients with similar lesion pathologies to reduce the possibility of latent confounders in the analyses (Griffis, Metcalf, Corbetta & Shulman, 2019). Instead, it is important to consider other factors that could influence the current lack of significant findings, such as differences in injury severity between patients.

5.5.3 Influence of Injury Severity on Brain Networks

Another factor to consider is how disparity in severity across brain insults can affect neural changes differently. For example, the largest alterations in structural connectivity (grey matter volume loss/whole-brain volume loss) are observed in severe TBI patients (Bigler et al., 2013). In contrast, patients with complicated mild TBI showed few differences compared to controls, suggesting less severe alterations. This is further supported by Scheibel (2017), which suggested that, while moderate-to-severe TBI patients illustrate consistent functional alterations related to cognitive control, the functional alterations are not consistent in mild injury patients. Sharp et al. (2011) also suggested that patients with varying brain injury severities would likely show different patterns of functional connectivity changes. Severely injured patients may be unable to produce adaptive changes, and very mildly injured patients may have no motivation to do so. The relationship of severity to functional connectivity is also observed in van Meer et al. (2012)'s study. This latter study showed that, while rats with medium-sized and large-sized strokes showed similar changes at the beginning, a disparity was observed between groups after 21 days. In particular, rats with medium-sized strokes (characterised by mainly subcortical damage, occasionally involving some of the ventrolateral cortical tissue) showed a recovery to functional baseline levels, but the functional connectivity of rats in the large stroke group (characterised by extensive damage in the subcortical, ventrolateral and dorsolateral cortical tissue) remained elevated. Similarly, in tumour patients, van Dellen et al. (2012) found functional network differences between patients with low-grade gliomas and high-grade gliomas, and controls, where patients with low-grade gliomas showed decreased synchronizability and global integration. The study, however, found no network topology differences between high-grade glioma patients and controls, and suggested that the differences between patients could be explained by differences in plasticity that are guided by lesional growth patterns.

Given the heterogeneity of the present patient group, it is important to consider whether differences in severity may have influenced the group averages, which were used for both the functional and structural analyses. This is because the patients may be characterised by few distinct abnormalities; thus, there may be minimal overlap in these neural abnormalities, resulting in the current lack of significant findings. However, this also seems unlikely. Despite including patients with different severities, studies have found resting-state functional connectivity differences between the dorsomedial prefrontal cortex and fusiform gyrus, and the fusiform gyrus and superior frontal gyrus, between patients and controls (Tuerk et al., 2020). Regardless, the current study cannot confirm whether severity affected the ability to find significant differences, and future works should aim to include patients with similar injury severities. In addition to injury severity, it is also important to consider other factors that could explain the present findings, such as the time since injury, which will be discussed next.

5.5.4 Impact of Including a Prospective Patient Sample

As this study was a prospective study, it is also important to consider if acquiring the data at the acute stage can explain the lack of significant neural differences between patients and controls. As the brain scans acquired in this study were baseline scans or acquired at acute stage (children referred for a MRI scan to screen for a known/suspected cerebral abnormality or brain lesion), neural changes may have not yet occurred at the time of scan. Thus, there were no significant differences between patients and typical developing controls at the time of imaging.

The current lack of significant SCN differences between groups is consistent with Tuerk et al. (2021), which found no differences in the structural covariance between children with moderate-to-severe TBI and controls at the sub-acute stage (< 90 days). However, other studies have found early structural alterations (thinning in the cortical thickness in the superior parietal gyrus), alongside functional alterations (reduced activation in the superior parietal gyrus), within two weeks in adults after a TBI (Wang et al., 2017), and the neural disruptions were found to be related to the development of cognitive symptoms. This is in line with Tuerk et al. (2021), which suggested that regional structural damage at the acute stage might affect ongoing neural maturational processes, and, in the long-run result, disruptions at the global network level. This may manifest as reduced structural covariance (evident in their study at 12–24 months post-injury), and may underlie some of the observed cognitive deficits seen after a brain injury. Taken together, neural changes at the acute stage may only be found in patients who would go on to have long-term neural disruptions, which underpin their subsequent cognitive deficits.

In contrast to the current functional findings, previous studies have reported fMRI abnormalities in children with an ABI at the acute/sub-acute stage (< 6 months) when carrying out attention tasks (Strazzer et al., 2015). Alterations have also been found in resting-state fMRI in the DMN in patients with a brain injury at the acute stage (1–11 days; Sours, Zhuo, Roys,

Shanmuganathan & Gullapalli, 2015). However, unlike Strazzer et al. (2015), Sours et al. (2015) failed to show reduced functional connectivity in the DMN during the sub-acute stage (approximately one month post injury). Sours et al. (2015) suggested that the inconsistent findings across studies could be explained by the differences in the time of the scan since the injury, only including patients with cognitive impairments (measured using the overall measure of performance on the Automated Neuropsychological Asstssment Metrics that assessed processing speed, memory and attention), and variability in the rate of recovery of patients within the first month following a brain injury. This is evidenced in Wylie et al. (2015), which found disrupted connectivity during the first 72 hours after injury across brain injury patients, with no differences in their neurocognitive scores (i.e., Immediate Post-Concussion Assessment and Cognitive Testing computerized neurocognitive testing battery that assessed attention span, working memory, sustained and selective attention, response variability, non-verbal problem solving and reaction time). However, at 1 week following the injury, patients who showed cognitive recovery also illustrated little neural differences from controls, while patients who did not demonstrate recovery showed greater disruptions. The normalisation of functional connectivity following improved cognitive function was also observed by Tashjian, Goldenberg, Monti and Galvan (2018). This suggests that, unlike patients with persistent cognitive problems, the neural connectivity in patients who show cognitive recovery may normalise over a short period of time. This implies that there is a difference in recovery between patients, and a difference in neural networks between patients with persistent cognitive impairments and those without; thus, supporting Sours et al.'s (2015) explanation for the disparity in findings across studies.

The absence of significant findings in the present study may thus be explained by the disparity in patients' recovery profiles and/or cognitive impairment levels. Therefore, future investigations should aim to integrate neuroimaging and neuropsychology, which would allow the differentiation between patients with cognitive impairments and those without. This would allow for a sub-analysis of patients with cognitive impairments, as previous studies have consistently observed neural changes in these individuals. Furthermore, given that early brain responses to brain injury are likely to be subtle and dependent on the nature of the head trauma, the heterogeneity of the patient group and time of scan may have thus impacted the ability to detect subtle neural changes in the current study. In addition to considering the influence the patient sample may have had on the current findings, it is also important to consider whether the control group may have influenced this, which will be discussed in the next section.

5.5.5 Impacts of Using Orthopedically Injured Controls

The control group consisted of typical developing children who were mainly recruited via Birmingham Children's Hospital outpatient clinics (non-neurological referrals like musculo-skeletal imaging and head/neck MRI where central nervous system involvement was not suspected). Earlier studies that compared brain injury patients with orthopedically injured (OI) controls found that both groups are relatively similar (Bigler et al., 2013; Bigler et al., 2016). Bigler et al. (2016) suggested that having a brain injury at the group level of analysis for their study did not distinctively change or increase any expected age-related changes in cortical thickness. As OI controls share many similarities with brain injury patients, including premorbid characteristics, post-traumatic stress and the impact of pain and medication, including OI controls can control for predisposing factors in patients (Wilde et al., 2019). This could explain their generally similar longitudinal results, which actually reflect inherent, premorbid factors that are associated with increased injury risk instead of alterations as a result of the injury. Therefore, using OI controls may be more advantageous as it controls for the risk factors and the post-traumatic effects of an injury that could otherwise be mistaken as changes because of the injury, and increases the likelihood that any observed changes are brain-injury specific. However, given the similarities between both groups, it is also possible that comparing brain injury patients to the selected controls may have limited the ability to detect any less obvious changes that occur after a brain insult.

5.5.6 Lack of Significant Findings Linked to a Potential Absence of Attention Deficits

The current study examined structural and functional changes in attention networks (DMN/CEN) because sustained attention, which is commonly reported in brain injury patients, is known to affect learning and academic performance (Kokoç, Ilgaz & Altun, 2020; Steinmayr, Ziegler & Träuble, 2010). However, as discussed in previous chapters (see Chapters 3 and 4), one challenge with the current study was that no neuropsychological tests were carried out. Thus, this study was not able to confirm if the brain injury patients suffered from attention impairments. As altered functional connectivity of specific brain regions and networks are associated with cognitive impairments (Konstantinou, Pettemeridou, Stamatakis, Seimenis & Constantinidou, 2018), this suggests that patients without specific deficits may not display associated neural changes. Earlier studies have also suggested that the extent of cognitive impairment is associated with the functional changes observed in brain injury patients (Sharp et al., 2011). Furthermore, Mayer et al. (2012) found no group differences in visual attention (measuring using a multimodal selective attention task, numeric Stroop), along with no group-wise differences in functional activation within the associated brain regions, in patients with mild brain injuries compared to healthy controls. Similarly, Hermann et al. (2006) reported no total grey matter volumes changes, including in regions in the DMN, in children with epilepsy. However,

Hermann et al. (2006) carried out subgroup analyses and found that patients with academic problems had lower grey matter volume when compared controls and patients without academic problems. This suggests that, unlike patients with impairments, patients without impairments may not differ significantly compared to controls, thus suggesting that mixing patients with different levels of impairments can influence the ability to detect true differences between groups. This is also evident in Mayer et al. (2012), which showed that, despite near normal cognitive performance, within-group abnormalities were found during tasks in patients, such as an inability to exhibit task-induced deactivation within the DMN during higher attentional load. This implies that, when cognitive impairments are not severe, between-group comparisons may not detect subtle neural abnormalities. However, as attention skills were not measured, it is not possible to conclude if the patients suffered from cognitive impairments, which may explain the absence of significant findings in the current study. Future studies should therefore include neuropsychological tests to measure the cognitive level of patients. Future works should also aim to include patients with similar cognitive impairments to avoid their cognitive skills being a confounding variable in the analyses.

5.6 Current Limitations

There may be several additional limitations that could have affected the ability to detect true differences between the patient and control groups. Foremost, the lack of significant findings in this study may be the result of a small sample size. A small sample size reduces statistical power, limiting the ability to detect smaller effect sizes and potential differences between patients and controls (Cohen, 1988). Instead, studies have shown that a larger patient sample size not only increases power, but also stabilises effect estimates (Poldrack, 2012; Yarkoni, 2009). More importantly, as discussed in Chapter 4, a small sample size can greatly affect the accuracy and reliability of covariance estimation, particularly when using DK parcellation, which was used in this study (Carmon et al., 2020). Due to the small sample size, the current study was not able to carry out sufficiently powered sub-analyses or to control for injury-related confounding variables, such as the type of brain insult or lesion location/severity that could have affected the results.

The current study originally recruited a much larger sample size. However, the size was significantly reduced due to younger patients needing sedation/GA and a rigorous quality check of both the functional and structural data. Despite the quality check resulting in a small sample size, it is vital to exclude bad quality data as motion can affect the analysis and bias the results (Backhausen et al., 2016). The same is true for functional MRI data (Power et al., 2012; Maknojia, Churchhill, Schweizer & Graham, 2019). Therefore, it is more important to exclude poor quality data than to include these data for a larger sample. Earlier studies have also suggested that having a higher control-to-patient ratio can increase statistical power (Kang, Choi & Koh, 2009). As the number of controls in this study was relatively smaller when

compared to the brain injury patients, this could have also affected the power to find differences between groups. Regardless, this again highlights a challenge that was discussed in previous chapters in this thesis, which is the difficulty in acquiring good quality data from children, particularly paediatric patients, and the difficulty in recruiting paediatric controls. These difficulties may warrant incorporating steps to reduce motion, such as using a mock scanner (Greene, Black & Schlaggar, 2016). Future studies should also aim to recruit a much larger patient and control sample to allow for better statistical control of various demographic and injury relevant confounding variables that the current study was not able to address.

The current study's small sample size also prevented separating the heterogeneous patients into subgroups of patients with similar lesion pathologies. There are potential problems with analysing a heterogeneous patient sample, which have been discussed in detail earlier. A heterogeneous patient group suggests potential differences in the neural reorganisation mechanisms involved between patients (Tuerk et al., 2020), which can affect the ability to find uniform changes at the group level; thus, explaining the current lack of differences between the two groups. This is supported by Bigler et al. (2016), which that agrees that, while focal lesions do affect brain development to an extent, because of the heterogeneous nature of lesions, it is unlikely to find uniform cortical thickness changes at the group level. Moreover, studies like Eierud et al. (2014) have suggested that the heterogeneity of brain injuries affects the reliability when analyses rely hugely on group averages, which is pertinent to the current study. Due to the heterogeneity of the patient group, there may be minimal overlap in their neural abnormalities or changes, and thus a group average may not capture any abnormalities accurately. Therefore, is important for future studies to recruit a much larger sample size to allow for subgroup analyses to counter these problems.

Lastly, it is also crucial to consider if the analysis methodology could have been a limitation of this study. It was previously suggested that several factors such as the Freesurfer version, workstation type, operating systems, and automatic algorithms used for image quantification/cortical thickness measurement can limit the use of Freesurfer (Gronenschild et al., 2012). However, to minimise these problems, all analyses in this study were carried out using the same Freesurfer version and with a single type of hardware and operating system. Furthermore, studies have suggested that template based parcellations may influence the comparability of the estimations of area boundaries for all participants (Griffis et al., 2019). While prior studies have suggested the inter-individual variability in area boundaries and network topographies can affect the measures (Gratton et al., 2018; Marek & Dosenbach, 2018), Siegel et al. (2018) have shown that template based parcellation results in largely homogeneous functional regions across patients and controls. Moreover, it is challenging to create individual subject parcellations in brain injury patients because of the potential distortions caused by the lesions in these patients (Siegel et al., 2018) and the large amount of data/participants needed (Gordon et al., 2017). The current study based its parcellations on the

DK atlas, which is the standard Freesurfer atlas and has been widely used across paediatric and adult patient populations (Boes et al., 2012; Hoogman et al., 2019). Thus, the techniques used for parcellation should not have influenced the current results.

5.7 Implications of the Current Study

The current study is one of the very few that has examined SCN in children with a brain insult, which is important work because, in addition to being more readily available, SCN has been suggested to be less sensitive to noise compared to fMRI and DTI (Bernhardt, Chen, He, Evans & Bernasconi, 2011; Bethlehem, Romero-Garcia, Mak, Bullmore & Baron-Cohen, 2017). Thus, it is beneficial to examine the use of SCN to understand how the brain responds to insults. This study is also the first to have included both resting-state fMRI and structural MRI measures (SCN and cortical thickness) to examine neural changes in children with a brain insult. Previous studies have suggested the importance of including DTI or functional imaging alongside structural imaging to better understand neural changes resulting from brain injuries (Toledo et al., 2012). This is further supported by Irimia et al. (2012), who suggested that combining MRI with structural and functional measures (DTI and fMRI) has the potential to predict the outcomes of a brain injury, and also aid in formulating treatment and rehabilitation strategies. This highlights the importance of the current study, and suggests the need for future studies to include all three imaging modalities when examining neural changes following a brain injury.

Nonetheless, the lack of differences does suggest that the functional and structural characteristics of children with a brain insult may not differ significantly from typically developing children. However, the current findings are in contrast with existing functional and structural studies that have shown neural disparities between children with a brain insult and controls. Thus, several reasons that could explain the disparities between the current findings and other studies have been discussed, including the heterogeneous nature of the pathological basis of the lesions, the severity of injury, the time since the injury, and potential differences in cognitive level of the patients. In addition, the small sample size was an important limitation for this study, which consequently reduced statistical power and did not allow for subgroup analyses. Despite the heterogeneous nature of this study, it was expected differences would particularly be found in the attention networks, as attention problems have commonly been reported across all the brain injuries, suggesting common underlying neural changes. However, as no attention measures were carried out, the current study cannot confirm that the patients displayed attention problems, which could explain the lack of significant findings. Instead, the study has highlighted possible disparities in functional and structural neural patterns with few distinct abnormalities and minimal overlaps in the abnormalities between patients with a brain insult, leading to the lack of significant findings. In line with the current literature that suggests that different brain injuries can lead to distinct neural alternations, the heterogeneity in this study could have resulted in variations between patients. Therefore, the group averages may not have

accurately captured any abnormalities, and this may explain the lack of differences between patients and controls. This study has instead indicated that it is pertinent to include neuropsychology measures in future studies, and has highlighted the importance of recruiting a larger sample to allow for subtype analyses.

5.8 Conclusion

The current study found no significant differences in both the resting-state fMRI and SCN between patients with a brain insult and typically developing controls. No cortical thickness differences were observed between the patient and control groups. The lack of significant findings suggests that patients with lesions from different pathologies may exhibit different neural abnormalities, with minimal overlaps in the abnormalities between patients with a brain insult. Instead, the current study highlights the importance of recruiting a larger sample size to also carry out sub-analyses. The differences in the current findings compared to other studies may be explained by the heterogeneous nature of the patient group, differences in cognitive levels, and time since injury. Importantly, the small sample size limited statistical power and the ability to detect potential differences between groups. Thus, future studies should aim to recruit a larger sample size. The small sample size highlights both the challenges in recruitment in this vulnerable yet important population, and the difficulty in scanning a paediatric cohort, which is associated with poor imaging quality due to motion. Given the importance of sustained attention, future studies should carry out neuropsychological assessments to measure attention in order to determine whether there are common neural substrate underlying attention impairments across brain injuries in children. This is important because attention impairments have been associated with learning problems and poor academic achievement. Therefore, being able to separate children with a poor outcome (like attention problems) from those with a good outcome will allow for early treatment and a higher chance of recovery.

Chapter Six: General Discussion

This thesis examined changes in structural and functional connectivity in the brain regions and networks underpinning sustained attention after an early life brain injury, using structural and functional magnetic resonance imaging (MRI). This chapter recaps the main aims of the present thesis, briefly outlines the key findings of all four experimental studies, and discusses the contributions of the current findings towards new knowledge on neural changes following a brain insult in paediatric patients. It then highlights the clinical implications of the current findings, and discusses the limitations of the present thesis and future research directions.

6.1 Aims of the Thesis

Sustained attention impairments are common after paediatric brain injury, and have been reported to be the most vulnerable to brain injury compared to other cognitive skills (Catroppa, Anderson, Morse, Haritou & Rosenfield, 2007; Ginstfeldt & Emanuelson, 2010; Reddick et al., 2003; Robin, Max, Stierwalt, Guenzer & Lindgren, 1999). Compared to conventional behavioural measures that might be demanding especially for the clinical cohorts, and are heavily reliant on subjects' effort (Stulemeijer, Andriessen, Brauer, Vos & Van Der Werf, 2007), this thesis proposed the use of novel neuroimaging analysis methods that could be used in place of burdensome measures to identify patients who would go on to have attention problems.

Existing literature has suggested the importance of the coordination of brain regions in the default mode network (DMN) and central executive network (CEN) for sustained attention functioning in healthy adults (Danckert & Merrifield, 2018). The current thesis thus aimed to examine changes in these networks in children with an early brain insult, as they might reflect attention deficits, which is aligned to findings in patients with various psychiatric and neurological disorders, where studies have found an association between neural disruptions to the DMN and CEN, and sustained attention impairments (Christakou et al., 2013; Fan et al., 2018; Norman et al., 2017). The association between DMN disruptions and poorer attention performance has also presented in adults with a traumatic brain injury (Bonnelle et al., 2011), whilst disruptions in the DMN and CEN have been reported frequently in adults with a brain injury (McGill et al., 2012; Palacios et al., 2013; Sours et al., 2013; Sours, Zhuo, Roys, Shanmuganathan & Gullapalli, 2015; Sours, Kinnison, Padmala, Gullapballi & Pessoa, 2018; Stretton et al., 2013; Vollmar et al., 2011; Zhang et al., 2017). In contrast, two studies have examined the functional changes in these networks in childhood absence epilepsy (Li et al., 2015), and structural changes in the DMN and CEN in paediatric traumatic brain injury (TBI; Tuerk, Degeilh, Catroppa, Anderson & Beauchamp, 2021). However, as the pathophysiology of these brain injuries can be vastly different and might represent sample-specific characteristics, and is not representative across the range of early brain insults, there is thus more to learn about the functional and structural changes in the brain networks underlying sustained attention in these populations.

Besides being one of the first studies to use advanced network analysis approaches like network based statistics and structural covariance network (SCN) to examine functional and structural connectivity disruptions in the networks associated with attention following an early brain insult, this thesis was also one of the first to examine children with a range of brain insults. Overall, the researcher hoped that the findings would provide new information on shared pathophysiological characteristics across the different early brain injuries, which might underpin the common attention impairments reported across these cohorts, and aid in identifying children who may benefit from support or early intervention. Based on the existing literature, this thesis hypothesised that children with a brain injury would present with reduced functional and structural connectivity, especially *between* regions *within* the DMN and *within* the CEN, and *between* the DMN and CEN regions, as compared to typically developing children. The hypotheses were, however, not all supported: the studies in this thesis found only reduced functional connectivity in the DMN in children with TBI and focal epilepsy, as will be discussed in the following section.

6.2 Key Findings of the Thesis

Through a series of planned experiments to explore functional (Chapters 2, 3 and 5) and structural (Chapters 4 and 5) connectivity in focal (Chapters 3, 4 and 5) and generalised (Chapter 2) early brain insults, this thesis offers a unique lens to examine the potential use of advanced brain imaging techniques to examine brain networks that are crucial for attention functioning.

The thesis examined the CEN and DMN (also known as the task-positive and task-negative networks respectively), both of which are vitally important for successfully performing sustained-attention tasks. Existing fMRI studies have examined functional connectivity alterations *between* regions *within* the DMN and *within* the CEN, and *between* these networks and shown that these two key networks underlie attentional impairments in various psychiatric and neurological disorders. In children with early life brain insults, however, the present thesis found no evidence of functional alterations *between* the two networks. Specifically, experimental study 1 (Chapter 3) did not reveal any significant differences in the functional connectivity *between* the DMN and CEN, nor *between* regions *within* the CEN in epilepsy patients when compared to typically developing children. Similarly, experimental study 3 (Chapter 5) has also failed to support the hypothesised neural network alterations in children with a brain injury as compared to healthy subjects. Moreover, the structural studies (Chapters 4 and 5) failed to provide evidence of SCN alterations between patients with a brain insult and healthy children. The lack of confirmation can potentially be explained by different factors like small sample size, and heterogeneous patient sample, which are discussed in the limitations section below.

6.2.1 Do Alterations in the DMN Indicate Attention Impairments after an Early Brain Insult?

Disruptions in the DMN regions have been demonstrated across different paediatric brain insult types—epilepsy and traumatic brain injury in Chapters 3 and 2 respectively. Prior studies have suggested that normal functioning of the DMN is important for performing attention tasks, as the inability to suppress the DMN during attentional tasks may underpin poor attention performance (Moore & Malinowski, 2009). Current literature has similarly demonstrated the impact of this same inability to deactivate the DMN on task performance across healthy populations (Weissman, Roberts, Visscher & Woldorff, 2006), epilepsy (Gauffin et al., 2013), and traumatic brain injury (Bonnelle et al., 2011).

In line with the current literature, the pilot study (Chapter 2) demonstrated reduced resting-state connectivity *between* regions *within* the DMN (posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC)) in children with a TBI. Connectivity in the DMN regions, especially involving the PCC and mPFC, has been consistently demonstrated to be associated with cognitive performance, including attention function (Buckner, Andrews-Hanna & Schacter, 2008; Wang, Chang, Chuang & Liu, 2019). Moreover, the functional connectivity between the PCC and mPFC is critical in predicting outcomes of comatose patients, as connectivity strength between the two brain regions is associated with neurological recovery (Silva et al., 2015). The neural findings in Chapter 2 were, however, accompanied by statistically insignificant difference in attention performance between patients and controls, aligning with Kramer et al. (2008)'s study that examined long-term neural processes underlying attention after early brain injury. Despite finding increased activation in patients' frontal and parietal regions, Kramer et al. (2008) found comparable attention performance between patients and controls. The increased activation in children with a brain injury might reflect additional neural resources needed by them to perform at a comparable level as children without a brain injury (Kramer et al., 2008), suggesting that neural mechanisms might be a more accurate indicator of deficits after a brain injury, as neural alterations might persist for a long time after the injury despite good behavioural recovery, which conclusion also supported the decision, in this thesis, to use neuroimaging methods in place of behavioural measures to identify patients who would go on to have attention problems.

Unlike the pilot study, the first experimental study (Chapter 3) found reduced activity in the DMN (left parietal lobe) in paediatric epilepsy patients. This finding is consistent with previous epilepsy studies that have similarly reported reduced activity in the left parietal lobe in epilepsy patients (Moeller et al., 2008; Zhu et al., 2016;). Earlier studies have illustrated the important role of the left parietal lobe in visual attention for motor control (Castiello & Paine, 2002). As no neuropsychological tests were conducted, Chapter 3 cannot confirm whether the altered left parietal lobe was related to poorer attention for motor control. Regardless, the findings do suggest abnormalities *within* the DMN regions, and, taking into account the current

literature, it is possible that alterations in the DMN underpin cognitive impairments in paediatric brain insult patients.

6.2.2 Shared Connectivity Features in Functional Brain Networks

Studies have proposed that disorders with common physiopathology, for example schizophrenia, bipolar disorder and major depressive disorder, would also often share some similar neural functional connectivity patterns (Xia et al., 2019). This suggests that children with early life brain insults who present with similar clinical symptoms (in this case, attention problems) might have shared alterations in the functional brain networks. In line with previous epilepsy studies (Moeller et al., 2008; Zhu et al., 2016), the current thesis found shared functional alterations in the left parietal lobe in a group of heterogeneous epilepsy patients, in Chapter 3. This is consistent with a previous study, which found, using Regional Homogeneity (ReHo) and functional connectivity methods to examine the changes in DMN function in patients with partial epilepsy, the only brain region detected by both methods was the left parietal lobule, whilst the other identified regions differed between the two methods (Hu et al., 2017). Hu et al. (2017) proposed that the ReHo and functional connectivity findings suggest that disruptions in the left parietal lobule contribute to the pathophysiology mechanisms for attention problems in patients with partial epilepsy. Similar to Hu et al. (2017)'s study, the patient cohort in Chapter 2 also comprised patients with different seizure locations, therefore the current findings might further support that alterations in the left parietal lobes reflect a common functional alteration across patients with left-hemisphere focal epilepsy.

Connectivity between the DMN nodes, especially involving the posterior cingulate cortex (PCC) is also known to be associated with attention functions (Washington & VanMater, 2015), which suggests that disruptions to this node would potentially lead to attention dysfunction. The current thesis has also found reduced functional connectivity *between* the PCC and mPFC in children with TBI, as illustrated in Chapter 2, which has also been widely reported across TBI populations (Zhou et al., 2012). More importantly, as previously discussed in Chapter 2, the PCC has been suggested to be especially vulnerable to the impacts of TBI (Sharp, Scott & Leech, 2014; Zhou et al., 2012), and further evidenced in Bonnelle et al. (2011)'s study, which suggested that alterations in the functional connectivity between the PCC and the other DMN brain regions are crucial in the development of attentional impairments in TBI patients. Therefore, the current findings further support the vulnerability of the PCC to the impacts of TBI, which may reflect common pathophysiological characteristics that play a role in sustained attention outcomes in paediatric TBI patients. The findings in this thesis therefore do support the concept of shared connectivity disruptions in the functional brain networks in patients who might present with similar clinical symptoms. However, it is also important to consider that the lack of other significant findings does not necessarily reflect that absence of actual neural changes in the included brain injury patients. Instead, neural abnormalities that are not common across a

small and/or heterogeneous group may be undetected. This will be further discussed in the limitations section.

6.2.3 Neural Changes are not solely localised to the Injury Location

Studies suggest that focal brain injury can lead to damage beyond the primary lesion location, causing damage in brain regions remote from the lesion site (Nudo, 2013; Viscomi, 2020; Wieloch & Nikolich, 2006). Viscomi (2020) suggested that remote damage could be a result of an axonal lesion or transneuronal effects (that are commonly associated to brain injuries like TBI), which cause a spread of damage signals in the anatomical and functional connections, resulting in damage in remote parts of the brain. This thesis provides further support that neural disruptions are not localised to the injury location: the fMRI study (Chapter 3) found reduced activity in the left parietal lobe, which is outside of the patient groups' seizure onset location (namely the temporal and frontal lobes). Neural alterations outside the epileptic location are, however, unsurprising, as studies acknowledge that brain insults like epilepsy are unlikely to only cause focal alterations; these studies have instead established widespread neural changes extending beyond the seizure location in epilepsy patients (Caciagli, Bernhardt, Hong, Bernasconi & Bernasconi, 2014; Hatlestad-Hall et al., 2021). Caciagli et al. (2014) and Bernhardt, Bonilha and Gross (2015) have also suggested that epilepsy is a network disorder, commonly leading to functional connectivity changes rather than just focal alteration. This was, however, not present in the current findings, which will be further discussed in the limitations section.

Similarly, TBI has also been suggested to be a network disorder, brain injury has often led to widespread disruption of neural networks that are commonly linked to poor cognitive outcomes (Hayes, Bigler & Verfaellie, 2016; Venkatesan, Dennis & Hillary, 2015). In line with the current literature, the pilot study (Chapter 2) has illustrated network disruption in TBI patients, specifically in the brain regions forming the DMN (PCC and mPFC). Importantly, Venkatesan et al. (2015)'s study has demonstrated the PCC's vulnerability to traumatic brain injury in a network context, and suggested that greater widespread alterations of neural networks involving the PCC are likely to occur in patients when compared to healthy subjects, which were corroborated by the findings in Chapter 2. Additionally, as disrupted network connectivity involving the PCC is suggested to be associated to neurocognitive impairment (Venkatesan et al., 2015), it would be interesting for future studies to further examine the role of the PCC in other major brain networks, which can provide important information on neurocognitive outcomes post-injury. Taking all of these into account, the current thesis supports the move from conventional methods that examine functional and structural changes in single brain regions, which is unlikely to provide a complete perspective of network changes, to a network analysis approach.

6.2.4 Timing of Injury

Lastly, this section considered the influence of injury timing on the findings of the present thesis. For Chapters 2, 3 and 4, the included imaging data were acquired at approximately 2-years follow-up. In contrast, the imaging data in the last experimental study (Chapter 5) was acquired at the acute stage. The differences in the imaging acquisition time might affect this thesis' findings: as previously discussed in Chapter 1, brain injury can cause delayed onset of cognitive dysfunction for 'emerging' cognitive skills (Eslinger, Grattam, Damasio & Damasio, 1992), which was suggested to be because of the brain development during childhood. This is consistent with developmental studies that have showed that, whilst brain regions associated with attention are present from infancy, the connectivity between the regions continues to change into adulthood, leading to better behavioural performance (Posner, Rothbart, Sheese & Voelker, 2014). Therefore, it is possible that imaging scans acquired at the acute stage would not have captured these delayed neural changes, as compared to scans acquired at follow-up.

The lack of functional findings in Chapter 5 could therefore be because the imaging data of these patients were acquired at the acute stage, before neural changes had yet occurred (as previously discussed in Chapter 5). Brain plasticity occurs in three stages after a brain injury. In short, cell death occurs over one to two days, followed by the replacement of the damaged cells, and recovery and/or reorganisation usually begins weeks after the injury (Sophie Su, Veeravagu & Grant, 2016). This does suggest that initial recovery can be unpredictable, and can affect the neural patterns observed in the patients at acute stage. Wylie et al. (2015), however, suggested that functional recovery can occur immediately after brain injury; their study found that patients who had recovered between time point 1 (48 hours after injury) and time point 2 (1 week after injury) showed functional activation patterns comparable to healthy controls. In comparison, disparity in functional connectivity patterns is observed when comparing patients who have not recovered to healthy controls. The findings in Wylie et al. (2015)'s study suggested that patients' recovery profiles play a crucial role when examining neural changes after a brain injury, as short-term recovered patients might not show neural alterations.

As no neuropsychological test was performed for this thesis, it is unknown whether the patients have attentional deficits, which, according to previous studies could suggest comparable neural patterns between patients and controls, explaining why these outcomes were not observed. This instead highlights the importance for future studies to include neuropsychological measure in their study, discussed later.

6.3 Limitations

The key limitations of the thesis are addressed in this section along with the impacts they might have had on the current findings, briefly touching on how future works should address these limitations.

Foremost, the present studies share a limitation—an absence of clinical/medical information in regards to medication, age of diagnosis, lesion type and duration/frequency of seizure (for patients with epilepsy). As discussed in the previous chapters, these factors impact upon the structural and/or functional connectivity measured, and can affect the reliability of the derived measures and the study's ability to detect differences between groups. For example, studies have shown changes due to antiepileptic drugs in the brain function in people with epilepsy (Beltramini, Cendes & Yasuda, 2015). Due to the potential influence these clinical factors might have on the brain function, it is pertinent for future studies to include them as a confounding variable to account for their effect on functional and/or structural connectivity.

6.3.1 Sample Size

Another limitation that was highlighted throughout this thesis was the small sample size, leading to insufficient statistical power (Faber & Fonseca, 2014). There are several explanations for the small sample size in this thesis, one being the well-established challenge of recruiting patients (Sygna, Johansen & Ruland, 2015) due to factors like fatigue and being unwell, so they might be more focussed on recovery than joining a study, and the recruitment of paediatric patients is complicated by needing the interest of not just the patient but also the caregivers. Challenges in recruitment also extend to healthy children because of reasons like the unwillingness of parents to expose children to strong magnetic fields (Jiao, 2010). Moreover, the sample size of a study is also likely to be affected by subjects dropping out; longitudinal studies involving follow-ups are susceptible to high attrition rates of up to 70%, which can reduce statistical power whilst also introducing significant bias into the studies (Marcellus, 2004). Therefore, when attrition is expected, studies should increase their sample size, for example by 20-25% for when a 10% dropout rate is anticipated at each time point of the study (Vallejo, Ato, Fernandez & Livacic-Rojas, 2019).

The small sample size was highlighted in the experimental studies (Chapters 3 and 4), which had the specific inclusion criteria of left-hemisphere epilepsy patients because of the neural disparity between patients of a left- or right-side injury, which inevitably restricted the subject pool to 27 (14 patients) and 25 (15 patients) subjects respectively. Small sample size does not only reduce statistical power, but also impacts upon the analysis tools used. For example, studies have suggested that the reliability of the Desikan-Killany parcellations used for structural covariance estimation in Chapters 4 and 5 is reduced when used in studies with a small sample size (<30) (Carmon et al., 2020). The reliability of the later analyses would likely also be affected, as they are reliant on accurate structural covariance estimation, which may

explain the current lack of finding that is in contrast to the current literature. Importantly, the findings from a small sample might be less reliable, and thus affect the use in clinical care (i.e. assessing patients who might require intervention). Therefore, in order to increase the reliability of structural covariance estimates, Carmon et al. (2020) has recommended studies to include a larger sample size of at least 30 subjects per group (e.g., 30 patients and 30 controls), which future studies should aim for by potentially combining data from multi sites to account for low incidence of the injury.

Despite the potential confounding due to the use of multiple scanners, studies have shown that the effects of diseases were relatively greater than scanner effects, and their findings are not confounded by scanner differences (Stonnington et al., 2008). As scanner difference can be largely disregarded, a multi-site study would provide studies with a larger sample with a wider range of patient variety, consequently allowing a better representation of the wider patient population with greater generality for group-level functional/structural network maps (Van Horn & Toga, 2009).

The small sample size reported across the experimental studies in this thesis was also a result of the stringent quality-checking of both functional and structural data, which entailed removing subjects with poor-quality data from the final analyses. Stringent quality-checking is important to ensure the accuracy for functional activation maps in fMRI data (Soares et al., 2016). Previous studies showed that, when stringent motion correction is used, the short- and long-range connectivity found in development were reduced, and some of the connectivity became only weakly significant, improving connectivity findings in developmental studies (Fair et al., 2012). More importantly, Fair et al. (2012) also highlighted the importance of motion correction in clinical research to allow for better characterization and classification of disorders (e.g. attention deficit hyperactivity disorder), and allows for more accurate identification of neural distinctions underpinning the clinical heterogeneity of the disorder. In turn, this highlights the importance to practice stringent quality checks especially in clinical research, as poor-quality data can affect the accuracy of clinical classification and predictions, in turn affecting clinical care (Makowski, Lepage & Evans, 2019).

As a result of motion artefacts, a substantial proportion, approximately 50%, of the datasets was discarded in the current studies. The exclusion of subjects for poor image quality, however, highlights the challenge in acquiring paediatric-imaging data. The challenge of minimising motion during data acquisition is well documented in paediatric imaging; head motion in the scanner during functional and structural data acquisition can disrupt the signal, resulting in motion artefacts that lead to data loss (Greene, Black & Schlaggar, 2016; Raschle et al., 2012). However, studies have suggested that subjects with excessive motion tend to be subjects with greater cognitive impairments, so removing them from the group-level analyses could bias the sample bias against cognitive impairment (Wylie, Genova, DeLuca, Chiaravalloiti & Sumowski, 2014). Therefore, Wylie et al. (2014) suggested that findings would not be

representative of the disease as a whole, but instead be representative of subjects with better cognitive outcomes. Importantly, patients who would require the most aid or early rehabilitation would be dismissed, therefore, it is more important to include precautionary methods to minimise motion during scans. For example, it was suggested that sedation during scans could help reduce head movement in children, but sedation is not always an ethical option in neuroimaging research (Raschle et al., 2012). Instead, familiarising the child with the environment via videos or a mock scanner, or showing them how movements can affect images to illustrate the consequences of moving in the MR scanner, can help in reducing scanner movements, and hence reducing the number of images that do not pass the quality check.

6.3.2 Heterogeneous Patient Sample

As the present thesis was interested in neural changes following a brain injury in children, the experimental studies have, as expected, a heterogeneous patient group. Despite the differences in pathology amongst early brain insults, sustained attention impairments have been commonly reported across all of them (as widely discussed in Chapter 1), suggesting that these patients might have shared neural alterations in the brain regions supporting the attention skill. This is evidenced in Norman et al. (2017)'s study illustrating that, despite disorder specific neural changes, patients with attention-deficit/hyperactivity disorder and obsessive-compulsive disorder shared similar neural changes in the DMN and CEN brain regions that are associated with sustained attention impairments. This was further evidenced in the first experimental study (Chapter 3), which found significant reduction in the functional activity only in the left parietal lobe, which was previously suggested to reflect a common neurobiological characteristic across different epilepsies (Yang et al., 2021).

However, the heterogeneity of the patient group in this thesis may also explain the lack of other findings in Chapter 3, along with the absence of any significant findings in the other studies, especially Chapters 4 and 5. For example, given that the present studies relied on group averages to understand the influence of a brain injury on the functional/structural connectivity, it is possible that the lack of significant neural differences between patients and controls resulted from neural variations amongst patients. The neural variations between patients could reflect the diseases characteristics, as suggested by Drenthen et al. (2018)'s study, which has similarly suggested that the lack of differences between their patients with epilepsy and controls were because of the variations in the SCN between patients. The issue of subject variability was further evidenced in Schnack and Kahn (2016)'s study that suggested a heterogeneous patient group will likely exhibit a heterogeneous pattern of functional and structural neural alterations, thus disease heterogeneity can lead to the inability to capture the whole range of alterations, and be limited to patterns shared by most patients. Other studies have however suggested that the heterogeneity could allow better understanding of variability sources like chronicity and imaging methods (structural and functional), and in turn reveal more

accurate insights into the brain network's function (Karnath & Rorden, 2012). The literature has further suggested that studies with a heterogeneous sample would require a larger sample size, thus reiterating the importance for similar future works to acquire a much larger sample, which should ease concerns surrounding variability between patients (Vallejo et al., 2019; Vasileiou, Barnett, Thorpe & Young, 2018).

6.3.3 Analysis Methods

Using different fMRI analysis pipelines (including different toolboxes) can lead to some variability in the findings when examining the same cohort of subjects (Botvinik-Nezer et al., 2020). Given the differences between analysis methods used to examine functional connectivity in this thesis, it is therefore important to consider the impacts that they could have had on the current findings. The pilot study (Chapter 2) served as a training pilot for developing analysis pipelines for subsequent studies. First, the imaging data were pre-processed using Statistical Parametric Mapping (SPM12), a well-established and commonly used pre-processing toolbox (Hoffmann, Carpenter, Williams & Sawiak, 2015). Following previous methods (Iraji et al., 2016; Palacios et al., 2013), the study then used the similar region of interest (ROI)–ROI method, a form of seed-based analysis, to examine functional connectivity in children with an early brain insult. Chapter 3 adopted the same pre-processing steps using SPM-12, however, to counter concerns surrounding multiple comparisons that arose from using the ROI–ROI method, the Network Based Statistics (NBS) toolbox, which accounts for multiple comparisons, was used (Gaudio, Olivo, Beomonte Zobel & Schioth, 2018).

The final experimental study (Chapter 5) used Freesurfer FS-FAST instead of SPM-12 for pre-processing. This decision was made because of the aims of the study, which was to find out whether structural changes (derived using a structural covariance network) overlapped with functional changes following a paediatric brain insult. As the brain regions in the structural covariance network were based on Desikan-Killany parcellation, to address the study's aims, the functional connectivity had to be derived from the same brain regions for fair comparison. It was therefore important to measure functional connectivity based on the same Desikan-Killany parcellation, via a Freesurfer atlas. Even though pre-processing involved different toolboxes, the pre-processing pipelines were similar, for example slice time correction was carried out before realignment/motion correction. For consistency, chapter 5 has also used NBS to examine the differences in functional connectivity between patients and controls. Further, it is important to remember that the experimental studies are independent studies, so the present findings are unlikely to be greatly impacted by the differences.

6.3.4 Lack of Attention Measures

Studies have proposed that the basic assumptions that form the basis of neuroimaging methods and analysis techniques require validation from behavioural tests (Karuza, Emberson & Aslin, 2014). This was, however, not always possible in this thesis due to the lack of neuropsychological measurements in most of the experimental studies (Chapters 3, 4 and 5) due to Covid19 restrictions on face-to-face testing and access to medical records. Despite the important knowledge neuroimaging provides, Bigler (2001) has suggested that it can be misleading when relying only on one measure (regardless of whether neuroimaging or neuropsychological). It is instead important to integrate and combine neuroimaging findings with neuropsychological measures to better understand the association between neuropsychological outcomes and neuroimaging findings, which was not possible in this thesis with the exception of the pilot study. Despite finding no association between functional connectivity and attention performance, Chapter 2 did find disruptions in the functional connectivity in the DMN, and, as discussed earlier, despite potential behavioural recovery, neural alterations are likely to still persist in the long-run, suggesting that neural mechanisms might be a more accurate indicator of deficits after a brain injury.

Moreover, the last experimental study (Chapter 5) was a part of a wider prospective study, which was interested in using neuroimaging to predict outcomes two years after injury. Neuropsychological measures were thus not yet collected for inclusion in this thesis due to unanticipated interruptions to testing in the relevant timeframe, owing to public health measures to address the Covid-19 pandemic. Examining outcomes two years post injury is appropriate because studies have suggested that recovery is most pronounced in the first two years following the brain injury, and recovery almost plateaus after that time frame (Chadwick, Rutter, Brown, Shaffer & Traub, 1981). Without neuropsychological measures, the studies in present thesis cannot conclude with certainty that the included patients suffered from sustained attention impairments. This is important because other studies have shown that TBI patients who were clinically recovered demonstrated different neural disruptions as compared to patients who were clinically unrecovered (Stein, Iyer, Khetani & Barlow, 2021), therefore including both recovered and unrecovered patients would likely affect group effects.

6.4 Future Studies

The studies included in this thesis have shed light on the neural changes following a paediatric brain insult, especially in the DMN, which is important in sustained attention function. However, the main take-home message of this research is that further exploration into the questions posed in this research is still necessary.

Developmental studies have established the association between the maturation of structural and functional brain networks, and age during childhood, which is linked to cognitive development (Haartsen, Jones & Johnson, 2016). However, the small sample sizes precluded

sub-group analysis to compare paediatric patients whose brain insult, or its diagnosis, was early childhood versus later childhood. This is, however, important because 'emerging' skills at the time of the brain injury are more vulnerable to deficits as compared to already 'established' skills before the injury (Anderson et al., 2010), which would likely be accompanied by different reorganisation of the brain. Given that sustained attention has been suggested to emerge and develop most between the ages of 5 to 10 years (Betts, McKay, Maruff & Anderson, 2006), future studies should compare younger paediatric patients (5–10 years) and older paediatric patients (11–16 years) to isolate the influence of development on brain function/structure. Furthermore, despite the problems with having a heterogeneous patient sample, the nature of the heterogeneity is pertinent to answering the questions posed in this thesis. As sustained attention deficits are a common outcome in various early brain insults, the current goal was to examine whether these injuries share some pathophysiology characteristics that may underpin the deficits. Thus, future studies should also aim to carry out sub-analyses with cohorts of different brain injuries to obtain information on disorder-specific neural changes, as these alterations are likely to be overlooked in group-level analyses, and, more importantly, would aid in providing more accurate and reliable predictors for clinical assessments.

Despite the potential of neuroimaging as prognostic tools for outcomes in early brain injuries, obtaining neuroimaging data without neuropsychological measures has limited the interpretation of the imaging findings. Integrating neuroimaging and neuropsychology would allow for a better understanding of the relationships between brain function and structure, and cognitive outcomes. Moreover, incorporating attention measures would also allow studies to separate patients with and without cognitive impairments, which is important because previous studies have shown that both cohorts exhibit different brain function and structure effects, so separating them would allow new knowledge on the neural changes associated with recovery and alterations that underpin long-term impairments.

Taking everything into account, future studies should examine the influence of development on the brain function in the networks underpinning sustained attention after a brain injury. More importantly, integrating neuropsychology and neuroimaging would allow future studies to investigate the use of neuroimaging as a prognostic tool, to allow the early identification of patients who would experience attention dysfunction and its far-reaching consequences on learning, emotional well-being, social relationships, and quality of life. Early identification could, importantly, allow these individuals to benefit from early behavioural intervention; studies have shown that remedial intervention for attention is effective in improving attention in children and adolescents with TBI, which, in turn, improved their adaptive skills (Galbiati et al., 2009).

6.5 Conclusion

In conclusion, this thesis has investigated the potential of novel neuroimaging network analysis methods that could be used in place of behavioural measures to identify children with a brain injury who would go on to have attention problems. The current understanding of the network disruptions underpinning attention function after a brain injury is limited, and most existing studies have examined the adult cohorts, which findings are not applicable to the paediatric populations. This thesis is one of the first studies to use network approaches (i.e., network-based statistics and structural covariance network) to better understand the brain structure and function changes after an early brain insult, which is important, given that cognitive skills like attention are supported by large-scale brain networks. The current findings have demonstrate altered functional connectivity in the DMN in children with an acquired brain injury; these children showed reduced connectivity in the DMN regions that have shown to be important for attention functioning. Importantly, these findings do suggest shared connectivity disruptions in the functional brain networks in a heterogeneous cohort of patients with brain injury (in this case, children with focal epilepsy), which was proposed in Chapter 1 of this thesis. Finally, the findings also highlight possible directions for future research, specifically the need to integrate neuropsychology and neuroimaging, which would provide further important clinical benefits in allowing early detection of children with attention dysfunction who would benefit most from early interventions.

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Appendices

Appendix A

Freesurfer Lesion Pipeline

In order to mitigate some of the problems with surface-based parcellations in the presence of lesions, members of our research team adapted the default Freesurfer pipeline (King et al., 2021). The newly adapted approach to Freesurfer segmentation that accounts for lesions, based on King et al.'s (2021) paper, is used in the present study. Lesions were first identified and confirmed by multiple raters in the research team by examining each of the constituent axial slices of each 3D scan. Lesion masks were then drawn by two raters using the region of interest (ROI) editor tool in the MRtrix 3.0 software (Tournier, Calamante & Connelly, 2012) on both T1-weighted and FLAIR magnetic resonance imaging (MRI) scans separately. The FLAIR scans were co-registered to the corresponding T1-weighted scans using FSL's FLIRT for rigid-body transformations (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady & Smith, 2002). Nearest neighbour interpolation was used to transform FLAIR lesion masks into T1-weighted space. The T1-weighted and FLAIR lesion masks were then combined to produce an overall binary lesion mask in the T1-weighted space, and all the masks were manually checked by one of the raters. The reason for preferring combined masks over the individual modality masks is because the former may contain lesion information that may otherwise not be visible in the latter.

Using the method by Nachev, Coulthard, Jager, Kennard and Husain (2008), the binary lesions masks generated were used to enantiomorphically fill the lesions. This method registers the lesioned hemisphere to the non-lesioned hemisphere, and fills the lesioned voxels with healthy appearing signal intensities from the non-lesioned hemisphere. It then produces an image with approximately normal T1-weighted voxel intensities, which replaces the lesioned tissue. The enanteomorphically generated T1-weight image was then processing using the Freesurfer cortical surface segmentation pipeline.

As lesion masks were drawn in the native space into the T1-weighted images, they could be projected onto the cortical surface vertices on the Freesurfer surface model. The projected lesion ROI was filled, and used as an ROI label for further analyses.

Individual-subject level atlas parcellations were masked with the surface projected lesion masks. Region labels that are completely or partially obstructed by lesion tissue are therefore replaced with the lesion label. The standard Freesurfer approach is used to calculate morphometric measures like cortical thickness. However, as a result of the relabelling, no measures are acquired from lesioned tissue and/or tissue filled with estimated voxel intensities in the enanteomorphically filled T1-weighted images.

The final output of this adapted pipeline is cortical morphology measures that are not affected by lesioned tissue or any error related to the processing of T1-weighted images with lesions. Cortical morphological measures were reported as zero for regions that were completely obstructed by lesion tissue. These regions were recorded as NaN so that when generating the structural covariance matrix, no covariance is estimated with these regions.

Appendix B

Mean and standard deviation of cortical thickness of DMN regions for the patient and control cohorts

Brain Region	Patient Mean (SD)	Control Mean (SD)
Ventromedial prefrontal cortex		
L_FrontalPole	3.29 (.24)	3.26 (.69)
L_MedialOrbitoFrontal	2.98 (.20)	2.91 (.30)
R_FrontalPole	3.28 (.28)	3.30 (.44)
R_MedialOrbitoFrontal	3.00 (.21)	3.01 (.34)
Posterior cingulate cortex		
L_PosteriorCingulate	2.91 (.19)	2.90 (.08)
L_IsthmusCingulate	2.65 (.23)	2.80 (.045)
R_PosteriorCingulate	2.90 (.24)	2.96 (.19)
R_IsthmusCingulate	2.79 (.21)	2.84 (.15)
Inferior parietal lobule		
L_InferiorParietal	2.97 (.15)	2.93 (.14)
L_Precuneus	2.90 (.11)	2.89 (.09)
R_InferiorParietal	2.96 (.15)	2.89 (.14)
R_Precuneus	2.86 (.12)	2.91 (.17)
Hippocampal formation		
L_Entorhinal	3.25 (.24)	3.20 (.28)
L_Parahippocampal	3.06 (.31)	3.10 (.16)
R_Entorhinal	3.27 (.17)	3.38 (.52)
R_Parahippocampal	2.93 (.23)	3.00 (.17)

Note: L/R = Left, Right

Appendix C

Mean and standard deviation of cortical thickness of CEN regions for the patient and control cohorts

Brain Region	Patient Mean (SD)	Control Mean (SD)
Dorsolateral prefrontal cortex		
L_SuperiorFrontal	3.29 (.13)	3.19 (.21)
L_CaudalMiddleFrontal	3.06 (.21)	3.00 (.16)
L_RostralMiddleFrontal	2.89 (.14)	2.89 (.27)
R_SuperiorFrontal	3.28 (.11)	3.26 (.16)
R_CaudalMiddleFrontal	3.04 (.16)	2.91 (.19)
R_RostralMiddleFrontal	2.93 (.16)	2.87 (.20)
Posterior parietal cortex		
L_InferiorParietal	2.97 (.15)	2.93 (.14)
L_Precuneus	2.90 (.11)	2.89 (.09)
L_SuperiorParietal	2.73 (.16)	2.68 (.16)
R_InferiorParietal	2.96 (.15)	2.89 (.14)
R_Precuneus	2.86 (.12)	2.91 (.17)
R_SuperiorParietal	2.70 (.13)	2.65 (.15)

Note: L/R = Left, Right

Appendix D

Mean and standard deviation of functional connectivity between ROIs of DMN regions for the patient and control cohorts

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
IPL_L–ENT_L	0.63 (0.16)	0.54 (0.25)
ICC_L–ENT_L	0.75 (0.10)	0.72 (0.04)
MOF_L–ENT_L	0.40 (0.19)	0.38 (0.30)
PARH_L–ENT_L	0.39 (0.23)	0.33 (0.22)
PCC_L–ENT_L	0.37 (0.24)	0.41 (0.28)
PCUN_L–ENT_L	0.13 (0.23)	0.21 (0.19)
FP_L–ENT_L	0.27 (0.19)	0.31 (0.21)
ENT_R–ENT_L	0.86 (0.07)	0.75 (0.18)
IPL_R–ENT_L	0.54 (0.26)	0.47 (0.35)
ICC_R–ENT_L	0.68 (0.11)	0.64 (0.15)
MOF_R–ENT_L	0.41 (0.20)	0.33 (0.34)
PARH_R–ENT_L	0.36 (0.25)	0.33 (0.22)
PCC_R–ENT_L	0.41 (0.23)	0.43 (0.27)
PCUN_R–ENT_L	0.15 (0.24)	0.19 (0.22)
FP_R–ENT_L	0.35 (0.18)	0.22 (0.26)
ICC_L–IPL_L	0.52 (0.21)	0.39 (0.28)
MOF_L–IPL_L	0.61 (0.13)	0.55 (0.13)
PARH_L–IPL_L	0.35 (0.22)	0.38 (0.07)
PCC_L–IPL_L	0.37 (0.23)	0.46 (0.21)
PCUN_L–IPL_L	0.09 (0.27)	0.11 (0.17)
FP_L–IPL_L	0.33 (0.18)	0.33 (0.12)
ENT_R–IPL_L	0.51 (0.20)	0.43 (0.22)
IPL_R–IPL_L	0.66 (0.29)	0.64 (0.17)
ICC_R–IPL_L	0.46 (0.25)	0.37 (0.28)
MOF_R–IPL_L	0.46 (0.22)	0.38 (0.19)
PARH_R–IPL_L	0.32 (0.24)	0.36 (0.07)
PCC_R–IPL_L	0.36 (0.20)	0.48 (0.15)
PCUN_R–IPL_L	0.16 (0.21)	0.05 (0.17)
FP_R–IPL_L	0.28 (0.25)	0.15 (0.18)
MOF_L–ICC_L	0.32 (0.22)	0.29 (0.23)
PARH_L–ICC_L	0.42 (0.26)	0.22 (0.13)
PCC_L–ICC_L	0.41 (0.26)	0.41 (0.20)
PCUN_L–ICC_L	0.11 (0.23)	0.18 (0.21)
FP_L–ICC_L	0.09 (0.18)	0.08 (0.21)
ENT_R–ICC_L	0.69 (0.10)	0.58 (0.15)
IPL_R–ICC_L	0.47 (0.19)	0.38 (0.29)
ICC_R–ICC_L	0.89 (0.08)	0.83 (0.18)
MOF_R–ICC_L	0.37 (0.18)	0.25 (0.32)
PARH_R–ICC_L	0.38 (0.29)	0.20 (0.17)
PCC_R–ICC_L	0.41 (0.28)	0.39 (0.20)
PCUN_R–ICC_L	0.16 (0.23)	0.11 (0.25)
FP_R–ICC_L	0.13 (0.19)	0.06 (0.21)
PARH_L–MOF_L	0.29 (0.23)	0.26 (0.20)
PCC_L–MOF_L	0.29 (0.22)	0.39 (0.22)

PCUN_L–MOF_L	0.30 (0.26)	0.30 (0.16)

FP_L–MOF_L	0.29 (0.23)	0.45 (0.16)
ENT_R–MOF_L	0.32 (0.22)	0.29 (0.17)
IPL_R–MOF_L	0.44 (0.29)	0.43 (0.21)
ICC_R–MOF_L	0.29 (0.24)	0.25 (0.25)
MOF_R–MOF_L	0.68 (0.28)	0.65 (0.14)
PARH_R–MOF_L	0.25 (0.25)	0.29 (0.18)
PCC_R–MOF_L	0.26 (0.25)	0.37 (0.26)
PCUN_R–MOF_L	0.28 (0.24)	0.31 (0.07)
FP_R–MOF_L	0.32 (0.16)	0.36 (0.21)
PCC_L–PARH_L	0.71 (0.14)	0.70 (0.06)
PCUN_L–PARH_L	0.19 (0.18)	0.23 (0.15)
FP_L–PARH_L	0.06 (0.21)	0.20 (0.14)
ENT_R–PARH_L	0.39 (0.21)	0.35 (0.19)
IPL_R–PARH_L	0.37 (0.23)	0.40 (0.13)
ICC_R–PARH_L	0.39 (0.26)	0.25 (0.12)
MOF_R–PARH_L	0.32 (0.20)	0.29 (0.28)
PARH_R–PARH_L	0.86 (0.07)	0.82 (0.15)
PCC_R–PARH_L	0.66 (0.15)	0.66 (0.12)
PCUN_R–PARH_L	0.23 (0.17)	0.17 (0.18)
FP_R–PARH_L	0.16 (0.20)	0.16 (0.13)
PCUN_L–PCC_L	0.13 (0.20)	0.24 (0.17)
FP_L–PCC_L	0.05 (0.19)	0.23 (0.08)
ENT_R–PCC_L	0.39 (0.21)	0.42 (0.23)
IPL_R–PCC_L	0.38 (0.21)	0.48 (0.20)
ICC_R–PCC_L	0.44 (0.25)	0.41 (0.21)
MOF_R–PCC_L	0.34 (0.18)	0.37 (0.35)
PARH_R–PCC_L	0.65 (0.16)	0.62 (0.11)
PCC_R–PCC_L	0.83 (0.08)	0.86 (0.17)
PCUN_R–PCC_L	0.18 (0.20)	0.17 (0.19)
FP_R–PCC_L	0.09 (0.22)	0.24 (0.12)
FP_L–PCUN_L	0.19 (0.19)	0.22 (0.19)
ENT_R–PCUN_L	0.16 (0.19)	0.14 (0.09)
IPL_R–PCUN_L	0.18 (0.20)	0.13 (0.17)
ICC_R–PCUN_L	0.12 (0.21)	0.18 (0.24)
MOF_R–PCUN_L	0.33 (0.22)	0.34 (0.20)
PARH_R–PCUN_L	0.15 (0.22)	0.21 (0.07)
PCC_R–PCUN_L	0.14 (0.23)	0.20 (0.09)
PCUN_R–PCUN_L	0.75 (0.13)	0.74 (0.20)
FP_R–PCUN_L	0.20 (0.20)	0.23 (0.20)
ENT_R–FP_L	0.26 (0.16)	0.23 (0.12)
IPL_R–FP_L	0.48 (0.14)	0.34 (0.19)
ICC_R–FP_L	0.09 (0.18)	0.09 (0.18)
MOF_R–FP_L	0.32 (0.20)	0.37 (0.18)
PARH_R–FP_L	0.06 (0.17)	0.27 (0.08)
PCC_R–FP_L	0.05 (0.20)	0.25 (0.10)
PCUN_R–FP_L	0.18 (0.20)	0.26 (0.15)
FP_R–FP_L	0.44 (0.23)	0.45 (0.13)
IPL_R–ENT_R	0.61 (0.19)	0.60 (0.14)

ICC_R–ENT_R	0.72 (0.07)	0.68 (0.10)
MOF_R–ENT_R	0.42 (0.19)	0.44 (0.19)
PARH_R–ENT_R	0.38 (0.22)	0.36 (0.18)
PCC_R–ENT_R	0.44 (0.23)	0.43 (0.22)
PCUN_R–ENT_R	0.15 (0.23)	0.14 (0.13)
FP_R–ENT_R	0.34 (0.18)	0.25 (0.27)
ICC_R–IPL_R	0.48 (0.18)	0.47 (0.32)
MOF_R–IPL_R	0.63 (0.16)	0.62 (0.14)
PARH_R–IPL_R	0.34 (0.21)	0.45 (0.08)
PCC_R–IPL_R	0.39 (0.21)	0.56 (0.15)
PCUN_R–IPL_R	0.22 (0.18)	0.23 (0.11)
FP_R–IPL_R	0.36 (0.29)	0.28 (0.15)
MOF_R–ICC_R	0.36 (0.17)	0.34 (0.39)
PARH_R–ICC_R	0.36 (0.27)	0.27 (0.11)
PCC_R–ICC_R	0.44 (0.25)	0.44 (0.17)
PCUN_R–ICC_R	0.13 (0.22)	0.15 (0.30)
FP_R–ICC_R	0.13 (0.20)	0.06 (0.24)
PARH_R–MOF_R	0.28 (0.21)	0.31 (0.21)
PCC_R–MOF_R	0.36 (0.21)	0.38 (0.36)
PCUN_R–MOF_R	0.36 (0.24)	0.48 (0.09)
FP_R–MOF_R	0.39 (0.24)	0.42 (0.13)
PCC_R–PARH_R	0.71 (0.12)	0.73 (0.11)
PCUN_R–PARH_R	0.20 (0.19)	0.20 (0.13)
FP_R–PARH_R	0.13 (0.19)	0.22 (0.06)
PCUN_R–PCC_R	0.20 (0.22)	0.17 (0.18)
FP_R–PCC_R	0.16 (0.22)	0.26 (0.13)
FP_R–PCUN_R	0.20 (0.23)	0.29 (0.18)

Note: IPL_L = left inferior parietal lobule, ICC_L = left isthmus cingulate cortex, MOF_L = left medial orbitofrontal, PARH_L = left parahippocampal, PCC_L = left posterior cingulate cortex, PCUN_L = left precuneus, FP_L = left frontal pole, ENT_L = left entorhinal, ENT_R = right entorhinal, IPL_R = right inferior parietal lobule, ICC_R = right isthmus cingulate cortex, MOF_R = right medial orbitofrontal, PARH_R = right parahippocampal, PCC_R = right posterior cingulate cortex, PCUN_R = right precuneus, FP_R = right frontal pole

Appendix E

Mean and standard deviation of functional connectivity between ROIs of CEN regions for the patient and control cohorts

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
rMFG_L–cMFG_L	0.71 (0.18)	0.72 (0.15)
SFG_L–cMFG_L	0.48 (0.24)	0.48 (0.30)
SPL_L–cMFG_L	0.41 (0.27)	0.43 (0.28)
cMFG_R–cMFG_L	0.63 (0.18)	0.65 (0.21)
rMFG_R–cMFG_L	0.56 (0.21)	0.54 (0.23)
SFG_R–cMFG_L	0.38 (0.32)	0.39 (0.34)
SPL_R–cMFG_L	0.41 (0.31)	0.42 (0.33)
IPL_L–cMFG_L	0.54 (0.20)	0.52 (0.21)
PCUN_L–cMFG_L	0.19 (0.23)	0.24 (0.09)
IPL_R–cMFG_L	0.38 (0.25)	0.40 (0.21)
PCUN_R–cMFG_L	0.21 (0.21)	0.19 (0.12)
SFG_L–rMFG_L	0.44 (0.22)	0.40 (0.37)
SPL_L–rMFG_L	0.49 (0.27)	0.59 (0.23)
cMFG_R–rMFG_L	0.54 (0.22)	0.51 (0.25)
rMFG_R–rMFG_L	0.78 (0.13)	0.75 (0.20)
SFG_R–rMFG_L	0.37 (0.27)	0.32 (0.40)
SPL_R–rMFG_L	0.46 (0.29)	0.59 (0.24)
IPL_L–rMFG_L	0.40 (0.25)	0.49 (0.14)
PCUN_L–rMFG_L	0.43 (0.18)	0.50 (0.07)
IPL_R–rMFG_L	0.42 (0.18)	0.41 (0.24)
PCUN_R–rMFG_L	0.43 (0.20)	0.42 (0.11)
SPL_L–SFG_L	0.35 (0.21)	0.31 (0.34)
cMFG_R–SFG_L	0.54 (0.22)	0.58 (0.24)
rMFG_R–SFG_L	0.44 (0.18)	0.39 (0.35)
SFG_R–SFG_L	0.91 (0.06)	0.86 (0.13)
SPL_R–SFG_L	0.38 (0.17)	0.31 (0.36)
IPL_L–SFG_L	0.57 (0.14)	0.51 (0.21)
PCUN_L–SFG_L	0.02 (0.23)	0.07 (0.26)
IPL_R–SFG_L	0.48 (0.16)	0.47 (0.20)
PCUN_R–SFG_L	0.10 (0.22)	0.03 (0.23)
cMFG_R–SPL_L	0.37 (0.25)	0.43 (0.29)
rMFG_R–SPL_L	0.47 (0.25)	0.59 (0.20)
SFG_R–SPL_L	0.35 (0.21)	0.32 (0.30)
SPL_R–SPL_L	0.82 (0.14)	0.77 (0.19)
IPL_L–SPL_L	0.37 (0.24)	0.41 (0.17)
PCUN_L–SPL_L	0.20 (0.24)	0.34 (0.16)
IPL_R–SPL_L	0.34 (0.25)	0.47 (0.19)
PCUN_R–SPL_L	0.25 (0.25)	0.30 (0.16)
rMFG_R–cMFG_R	0.72 (0.10)	0.70 (0.19)
SFG_R–cMFG_R	0.55 (0.21)	0.63 (0.16)
SPL_R–cMFG_R	0.41 (0.23)	0.42 (0.36)
IPL_L–cMFG_R	0.47 (0.24)	0.46 (0.18)
PCUN_L–cMFG_R	0.14 (0.28)	0.18 (0.15)
IPL_R–cMFG_R	0.51 (0.16)	0.61 (0.06)

PCUN_R–cMFG_R	0.23 (0.23)	0.22 (0.15)
SFG_R–rMFG_R	0.43 (0.22)	0.42 (0.29)
SPL_R–rMFG_R	0.48 (0.26)	0.62 (0.19)
IPL_L–rMFG_R	0.40 (0.20)	0.39 (0.15)
PCUN_L–rMFG_R	0.42 (0.20)	0.48 (0.16)
IPL_R–rMFG_R	0.46 (0.15)	0.56 (0.08)
PCUN_R–rMFG_R	0.54 (0.13)	0.56 (0.05)
SPL_R–SFG_R	0.39 (0.18)	0.32 (0.31)
IPL_L–SFG_R	0.51 (0.19)	0.44 (0.25)
PCUN_L–SFG_R	0.02 (0.24)	0.03 (0.23)
IPL_R–SFG_R	0.51 (0.14)	0.56 (0.19)
PCUN_R–SFG_R	0.10 (0.22)	0.02 (0.25)
IPL_L–SPL_R	0.35 (0.23)	0.38 (0.19)
PCUN_L–SPL_R	0.21 (0.22)	0.30 (0.14)
IPL_R–SPL_R	0.35 (0.24)	0.51 (0.12)
PCUN_R–SPL_R	0.27 (0.26)	0.31 (0.11)
PCUN_L–IPL_L	0.09 (0.27)	0.11 (0.17)
IPL_R–IPL_L	0.66 (0.29)	0.64 (0.17)
PCUN_R–IPL_L	0.16 (0.21)	0.05 (0.17)
IPL_R–PCUN_L	0.18 (0.20)	0.13 (0.17)
PCUN_R–PCUN_L	0.75 (0.13)	0.74 (0.20)
PCUN_R–IPL_R	0.22 (0.18)	0.23 (0.11)

Note: rMFG_L = left rostral middle frontal gyrus, SFG_L = left superior frontal gyrus, SPL_L = left superior parietal lobule, cMFG_L = left caudal middle front gyrus, IPL_L = left inferior parietal lobule, PCUN_L = left precuneus, rMFG_R = right rostral middle frontal gyrus, SFG_R = right superior frontal gyrus, SPL_R
= right superior parietal lobule, cMFG_R = right caudal middle front gyrus, IPL_L = right inferior parietal lobule, PCUN_L = right precuneus

Appendix F

Mean and standard deviation of functional connectivity between ROIs of DMN and CEN for the patient and control cohorts

ROI–ROI	Patient Mean (SD)	Control Mean (SD)
ENT_L–cMFG_L	0.40 (0.20)	0.39 (0.32)
IPL_L–cMFG_L	0.54 (0.20)	0.52 (0.21)
ICC_L–cMFG_L	0.40 (0.24)	0.36 (0.25)
MOF_L–cMFG_L	0.60 (0.16)	0.56 (0.21)
PARH_L–cMFG_L	0.42 (0.23)	0.44 (0.12)
PCC_L–cMFG_L	0.54 (0.21)	0.60 (0.21)
PCUN_L–cMFG_L	0.19 (0.23)	0.24 (0.09)
FP_L–cMFG_L	0.10 (0.18)	0.20 (0.19)
ENT_R–cMFG_L	0.36 (0.22)	0.41 (0.22)
IPL_R–cMFG_L	0.38 (0.25)	0.40 (0.21)
ICC_R–cMFG_L	0.41 (0.26)	0.41 (0.21)
MOF_R–cMFG_L	0.47 (0.23)	0.49 (0.22)
PARH_R–cMFG_L	0.33 (0.30)	0.42 (0.16)
PCC_R–cMFG_L	0.40 (0.30)	0.48 (0.28)
PCUN_R–cMFG_L	0.21 (0.21)	0.19 (0.12)
FP_R–cMFG_L	0.12 (0.22)	0.15 (0.24)
ENT_L–rMFG_L	0.37 (0.23)	0.34 (0.36)
IPL_L–rMFG_L	0.40 (0.25)	0.49 (0.14)
ICC_L–rMFG_L	0.36 (0.26)	0.27 (0.27)
MOF_L–rMFG_L	0.51 (0.24)	0.58 (0.21)
PARH_L–rMFG_L	0.60 (0.17)	0.61 (0.13)
PCC_L–rMFG_L	0.66 (0.17)	0.70 (0.16)
PCUN_L–rMFG_L	0.43 (0.18)	0.50 (0.07)
FP_L–rMFG_L	0.21 (0.19)	0.34 (0.13)
ENT_R–rMFG_L	0.37 (0.19)	0.31 (0.29)
IPL_R–rMFG_L	0.42 (0.18)	0.41 (0.24)
ICC_R–rMFG_L	0.40 (0.23)	0.31 (0.26)
MOF_R–rMFG_L	0.48 (0.22)	0.49 (0.33)
PARH_R–rMFG_L	0.52 (0.22)	0.54 (0.17)
PCC_R–rMFG_L	0.56 (0.26)	0.63 (0.23)
PCUN_R–rMFG_L	0.43 (0.20)	0.42 (0.11)
FP_R–rMFG_L	0.18 (0.25)	0.26 (0.17)
ENT_L–SFG_L	0.63 (0.17)	0.63 (0.11)
IPL_L–SFG_L	0.57 (0.14)	0.51 (0.21)
ICC_L–SFG_L	0.66 (0.20)	0.60 (0.14)
MOF_L–SFG_L	0.25 (0.24)	0.17 (0.34)
PARH_L–SFG_L	0.51 (0.26)	0.52 (0.15)
PCC_L–SFG_L	0.59 (0.16)	0.56 (0.24)
PCUN_L–SFG_L	0.02 (0.23)	0.07 (0.26)
FP_L–SFG_L	0.06 (0.19)	0.03 (0.25)
ENT_R–SFG_L	0.62 (0.13)	0.56 (0.15)
IPL_R–SFG_L	0.48 (0.16)	0.47 (0.20)
ICC_R–SFG_L	0.64 (0.21)	0.59 (0.19)
MOF_R–SFG_L	0.31 (0.16)	0.19 (0.42)

PARH_R–SFG_L	0.53 (0.22)	0.44 (0.17)

PCC_R–SFG_L	0.57 (0.15)	0.54 (0.25)
PCUN_R–SFG_L	0.10 (0.22)	0.03 (0.23)
FP_R–SFG_L	0.10 (0.20)	-0.02 (0.28)
ENT_L–SPL_L	0.34 (0.25)	0.47 (0.29)
IPL_L–SPL_L	0.37 (0.24)	0.41 (0.17)
ICC_L–SPL_L	0.37 (0.26)	0.36 (0.26)
MOF_L–SPL_L	0.55 (0.18)	0.63 (0.14)
PARH_L–SPL_L	0.48 (0.17)	0.50 (0.18)
PCC_L–SPL_L	0.59 (0.13)	0.68 (0.20)
PCUN_L–SPL_L	0.20 (0.24)	0.34 (0.16)
FP_L–SPL_L	0.14 (0.23)	0.37 (0.14)
ENT_R–SPL_L	0.31 (0.27)	0.40 (0.29)
IPL_R–SPL_L	0.34 (0.25)	0.47 (0.19)
ICC_R–SPL_L	0.37 (0.24)	0.32 (0.27)
MOF_R–SPL_L	0.53 (0.21)	0.54 (0.33)
PARH_R–SPL_L	0.47 (0.18)	0.49 (0.15)
PCC_R–SPL_L	0.57 (0.16)	0.64 (0.21)
PCUN_R–SPL_L	0.25 (0.25)	0.30 (0.16)
FP_R–SPL_L	0.19 (0.26)	0.42 (0.14)
ENT_L–cMFG_R	0.43 (0.18)	0.50 (0.24)
IPL_L–cMFG_R	0.47 (0.24)	0.46 (0.18)
ICC_L–cMFG_R	0.45 (0.19)	0.43 (0.20)
MOF_L–cMFG_R	0.33 (0.32)	0.36 (0.21)
PARH_L–cMFG_R	0.41 (0.21)	0.46 (0.21)
PCC_L–cMFG_R	0.47 (0.21)	0.50 (0.28)
PCUN_L–cMFG_R	0.14 (0.28)	0.18 (0.15)
FP_L–cMFG_R	0.10 (0.14)	0.13 (0.19)
ENT_R–cMFG_R	0.40 (0.19)	0.56 (0.16)
IPL_R–cMFG_R	0.51 (0.16)	0.61 (0.06)
ICC_R–cMFG_R	0.45 (0.20)	0.49 (0.15)
MOF_R–cMFG_R	0.53 (0.22)	0.52 (0.25)
PARH_R–cMFG_R	0.40 (0.23)	0.46 (0.17)
PCC_R–cMFG_R	0.50 (0.24)	0.56 (0.24)
PCUN_R–cMFG_R	0.23 (0.23)	0.22 (0.15)
FP_R–cMFG_R	0.12 (0.18)	0.13 (0.26)
ENT_L–rMFG_R	0.39 (0.20)	0.39 (0.29)
IPL_L–rMFG_R	0.40 (0.20)	0.39 (0.15)
ICC_L–rMFG_R	0.39 (0.22)	0.31 (0.19)
MOF_L–rMFG_R	0.44 (0.24)	0.46 (0.18)
PARH_L–rMFG_R	0.52 (0.17)	0.54 (0.17)
PCC_L–rMFG_R	0.54 (0.18)	0.58 (0.23)
PCUN_L–rMFG_R	0.42 (0.20)	0.48 (0.16)
FP_L–rMFG_R	0.20 (0.19)	0.32 (0.08)
ENT_R–rMFG_R	0.37 (0.21)	0.39 (0.23)
IPL_R–rMFG_R	0.46 (0.15)	0.56 (0.08)
ICC_R–rMFG_R	0.39 (0.23)	0.35 (0.23)
MOF_R–rMFG_R	0.60 (0.16)	0.63 (0.20)

PARH_R–rMFG_R	0.51 (0.19)	0.59 (0.18)
PCC_R–rMFG_R	0.57 (0.21)	0.65 (0.17)
PCUN_R–rMFG_R	0.54 (0.13)	0.56 (0.05)
FP_R–rMFG_R	0.25 (0.24)	0.34 (0.13)
ENT_L–SFG_R	0.58 (0.17)	0.57 (0.15)
IPL_L–SFG_R	0.51 (0.19)	0.44 (0.25)
ICC_L–SFG_R	0.63 (0.20)	0.59 (0.17)
MOF_L–SFG_R	0.21 (0.27)	0.14 (0.37)
PARH_L–SFG_R	0.50 (0.26)	0.45 (0.14)
PCC_L–SFG_R	0.56 (0.16)	0.52 (0.25)
PCUN_L–SFG_R	0.02 (0.24)	0.03 (0.23)
FP_L–SFG_R	0.05 (0.17)	0.03 (0.25)
ENT_R–SFG_R	0.60 (0.15)	0.61 (0.10)
IPL_R–SFG_R	0.51 (0.14)	0.56 (0.19)
ICC_R–SFG_R	0.64 (0.20)	0.66 (0.09)
MOF_R–SFG_R	0.33 (0.16)	0.20 (0.44)
PARH_R–SFG_R	0.56 (0.20)	0.48 (0.14)
PCC_R–SFG_R	0.65 (0.12)	0.61 (0.18)
PCUN_R–SFG_R	0.10 (0.22)	0.02 (0.25)
FP_R–SFG_R	0.12 (0.17)	-0.03 (0.29)
ENT_L–SPL_R	0.34 (0.25)	0.36 (0.31)
IPL_L–SPL_R	0.35 (0.23)	0.38 (0.19)
ICC_L–SPL_R	0.38 (0.23)	0.28 (0.28)
MOF_L–SPL_R	0.44 (0.24)	0.46 (0.20)
PARH_L–SPL_R	0.49 (0.15)	0.50 (0.20)
PCC_L–SPL_R	0.61 (0.10)	0.66 (0.19)
PCUN_L–SPL_R	0.21 (0.22)	0.30 (0.14)
FP_L–SPL_R	0.11 (0.28)	0.30 (0.08)
ENT_R–SPL_R	0.34 (0.25)	0.45 (0.27)
IPL_R–SPL_R	0.35 (0.24)	0.51 (0.12)
ICC_R–SPL_R	0.38 (0.23)	0.34 (0.27)
MOF_R–SPL_R	0.54 (0.19)	0.60 (0.24)
PARH_R–SPL_R	0.51 (0.14)	0.52 (0.10)
PCC_R–SPL_R	0.61 (0.13)	0.69 (0.12)
PCUN_R–SPL_R	0.27 (0.26)	0.31 (0.11)
FP_R–SPL_R	0.19 (0.28)	0.46 (0.14)
IPL_L–ENT_L	0.63 (0.16)	0.54 (0.25)
PCUN_L–ENT_L	0.13 (0.23)	0.21 (0.19)
IPL_R–ENT_L	0.54 (0.26)	0.47 (0.35)
ICC_L–IPL_L	0.52 (0.21)	0.39 (0.28)
MOF_L–IPL_L	0.61 (0.13)	0.55 (0.13)
PARH_L–IPL_L	0.35 (0.22)	0.38 (0.07)
PCC_L–IPL_L	0.37 (0.23)	0.46 (0.21)
PCUN_L–IPL_L	0.09 (0.27)	0.11 (0.17)
FP_L–IPL_L	0.33 (0.18)	0.33 (0.12)
ENT_R–IPL_L	0.51 (0.20)	0.43 (0.22)
IPL_R–IPL_L	0.66 (0.29)	0.64 (0.17)
ICC_R–IPL_L	0.46 (0.25)	0.37 (0.28)

MOF_R–IPL_L	0.46 (0.22)	0.38 (0.19)
PARH_R–IPL_L	0.32 (0.24)	0.36 (0.07)
PCC_R–IPL_L	0.36 (0.20)	0.48 (0.15)
PCUN_R–IPL_L	0.16 (0.21)	0.05 (0.17)
FP_R–IPL_L	0.28 (0.25)	0.15 (0.18)
PCUN_L–ICC_L	0.11 (0.23)	0.18 (0.21)
IPL_R–ICC_L	0.47 (0.19)	0.38 (0.29)
PCUN_R–ICC_L	0.16 (0.23)	0.11 (0.25)
PCUN_L–MOF_L	0.30 (0.26)	0.30 (0.16)
IPL_R–MOF_L	0.44 (0.29)	0.43 (0.21)
PCUN_R–MOF_L	0.28 (0.24)	0.31 (0.07)
PCUN_L–PARH_L	0.19 (0.18)	0.23 (0.15)
IPL_R–PARH_L	0.37 (0.23)	0.40 (0.13)
PCUN_R–PARH_L	0.23 (0.17)	0.17 (0.18)
PCUN_L–PCC_L	0.13 (0.20)	0.24 (0.17)
IPL_R–PCC_L	0.38 (0.21)	0.48 (0.20)
PCUN_R–PCC_L	0.18 (0.20)	0.17 (0.19)
FP_L–PCUN_L	0.19 (0.19)	0.22 (0.19)
ENT_R–PCUN_L	0.16 (0.19)	0.14 (0.09)
IPL_R–PCUN_L	0.18 (0.20)	0.13 (0.17)
ICC_R–PCUN_L	0.12 (0.21)	0.18 (0.24)
MOF_R–PCUN_L	0.33 (0.22)	0.34 (0.20)
PARH_R–PCUN_L	0.15 (0.22)	0.21 (0.07)
PCC_R–PCUN_L	0.14 (0.23)	0.20 (0.09)
PCUN_R–PCUN_L	0.75 (0.13)	0.74 (0.20)
FP_R–PCUN_L	0.20 (0.20)	0.23 (0.20)
IPL_R–FP_L	0.48 (0.14)	0.34 (0.19)
PCUN_R–FP_L	0.18 (0.20)	0.26 (0.15)
IPL_R–ENT_R	0.61 (0.19)	0.60 (0.14)
PCUN_R–ENT_R	0.15 (0.23)	0.14 (0.13)
ICC_R–IPL_R	0.48 (0.18)	0.47 (0.32)
MOF_R–IPL_R	0.63 (0.16)	0.62 (0.14)
PARH_R–IPL_R	0.34 (0.21)	0.45 (0.08)
PCC_R–IPL_R	0.39 (0.21)	0.56 (0.15)
PCUN_R–IPL_R	0.22 (0.18)	0.23 (0.11)
FP_R–IPL_R	0.36 (0.29)	0.28 (0.15)
PCUN_R–ICC_R	0.13 (0.22)	0.15 (0.30)
PCUN_R–MOF_R	0.36 (0.24)	0.48 (0.09)
PCUN_R–PARH_R	0.20 (0.19)	0.20 (0.13)
PCUN_R–PCC_R	0.20 (0.22)	0.17 (0.18)
FP_R–PCUN_R	0.20 (0.23)	0.29 (0.18)

Note: ENT_L = left entorhinal, IPL_L = left inferior parietal lobule, ICC_L = left isthmus cingulate cortex, MOF_L = left medial orbitofrontal, PARH_L = left parahippocampal, PCC_L = left posterior cingulate cortex, PCUN_L = left precuneus, FP_L = left frontal pole, ENT_R = right entorhinal, IPL_R = right inferior parietal lobule, ICC_R = right isthmus cingulate cortex, MOF_R = right medial orbitofrontal, PARH_R = right parahippocampal, PCC_R = right posterior cingulate cortex, PCUN_R = right precuneus, FP_R = right frontal pole, cMFG_L = left caudal middle front gyrus, rMFG_L = left rostral middle frontal gyrus, SFG_L = left superior frontal gyrus, SPL_L = left superior parietal lobule, cMFG_R = right caudal middle front gyrus, rMFG_R = right rostral middle frontal gyrus, SFG_R = right superior frontal gyrus,

SPL_R =

right superior parietal lobule, IPL_L = left inferior parietal lobule, PCUN_L = left precuneus, IPL_R = right inferior parietal lobule, PCUN_R = right precuneus