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Fronto-striatal Network Dysfunction in Children with Developmental Coordination Disorder and Attention-Deficit/Hyperactivity Disorder

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Fronto-striatal Network Dysfunction in Children with Developmental Coordination Disorder and Attention-Deficit/Hyperactivity Disorder

by

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Abstract

Developmental coordination disorder (DCD) and attention-deficit/hyperactivity disorder (ADHD) are common neurodevelopmental disorders that significantly impact a child's physical and mental health. Importantly, DCD and ADHD frequently co-occur. Behavioral, genetic and neuroimaging research have identified commonalities between children with these disorders. This thesis used resting-state functional magnetic resonance imaging (rs-fMRI) to determine the functional connections of the motor network of children with DCD, ADHD, and combined DCD and ADHD, in comparison to healthy children. In the first study, common and distinct alterations in the functional connections with the left motor cortex were identified in children with these disorders, including regions involved in sensorimotor processing and motor control. In the second study, differences in the hemispherical asymmetry of functional connections within the motor networks were also identified. These findings suggest that common brain functional networks are involved in DCD and ADHD, and that rs-fMRI is a valuable tool for furthering our understanding of the neurological underpinnings of these disorders.

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Dedication

I would like to dedicate this thesis to my friends, family and most of all, my girlfriend Michelle, for the providing the support and encouragement to see this project through to the end.

Table of Contents

List of Tables

List of Figures and Illustrations

List of Abbreviations

ADHD – attention-deficit/hyperactivity disorder

ATP – Adenosine Triphosphate

BOLD – blood oxygenation level dependent

BOTMP - Bruininks-Oseretsky Test of Motor Proficiency

DCD – developmental coordination disorder

DCD-Q – developmental coordination disorder questionnaire

DICA – Diagnostic Interview for Children and Adolescents

DSM-IV/V – Diagnostic and Statistical Manual of Mental Disorders – IV/V

DTI – diffusion tensor imaging

FA – fractional anisotropy

fMRI – functional magnetic resonance imaging

GABA – gamma-aminobutyric acid

GLM – general linear model

GPi – globus pallidus internus

HRF – hemodynamic response function

ICA – independent component analysis

IFG – inferior frontal gyrus

LM1 – left motor cortex

M-ABC – movement assessment battery for children

MAND - McCarron Assessment of Neuromotor Development

M1 – primary motor cortex

MRI – magnetic resonance imaging

NMDA – n-methyl-d-aspartate

ODD – oppositional defiant disorder

PFC – prefrontal cortex

RD – reading disorder

RM1 – right motor cortex

rs-fMRI – resting-state functional magnetic resonance imaging

SMA – supplementary motor area

SN – substantia nigra

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Overview and Statement of the Problem

Developmental coordination disorder (DCD) affects approximately 5-8% of children and is characterized by deficits in fine and gross motor ability(American Psychiatric Association, 2013). Attention-deficit/hyperactivity disorder (ADHD) is identified by difficulties with inattention, hyperactivity and impulsivity, and has a prevalence of 5% in school-aged children (American Psychiatric Association, 2013). Both DCD and ADHD have implications for educational outcome (Cantell et al., 2003) and long-term physical (Cairney et al., 2012; Cantell et al., 2008) and mental health (Lingam et al., 2012; Pratt and Hill, 2011; Rasmussen and Gillberg, 2000). DCD and ADHD display a high rate of co-occurrence, close to 50% (Kadesjo and Gillberg, 1998; Pitcher et al., 2003), suggesting that there may be common risk factors towards developing the conditions. Indeed, behavioural (Lingam et al., 2010; Piek and Pitcher, 2004), genetics (Fliers et al., 2009, 2012; Martin et al., 2006), and neuroimaging (Langevin et al., 2014, 2015) research have demonstrated overlap between the disorders. For example, children with DCD have been shown to have deficits in attention (Lingam et al., 2010), and motor problems have been identified in children with ADHD (Piek and Pitcher, 2004). However, little is understood about the brain regions involved in comorbid motor and attention disorders, and how such changes affect brain function.

Functional magnetic resonance imaging (fMRI) studies using motor tasks have observed altered activity in brain structures associated with inhibition in individuals with ADHD (Booth et al., 2005; Durston et al., 2006, 2003; Mostofsky et al., 2006; Suskauer et al., 2008) and altered

activity within visuospatial regions in children with DCD (Kashiwagi et al., 2009; Zwicker et al., 2010). Resting-state functional magnetic resonance imaging (rs-fMRI) is a method to identify the functional connections of brain networks while a participant is at rest, by analyzing the correlation of low frequency signals between structures. Zang *et al.* demonstrated altered resting-state patterns within sensory and motor structures in children with ADHD, suggesting the underlying neural network is altered in these children (Zang et al., 2007). To date, however, rs-fMRI studies have not exclusively studied the motor network in children with ADHD, and no rs-fMRI studies have been performed at all in children with DCD or children with both DCD and ADHD. Such rs-fMRI studies may provide important information on brain regions common to DCD and ADHD.

1.2 Thesis Structure

In addition to the above general introduction and statement of the problem, Chapter 1 provides a review of the current literature. The first section of the literature review summarizes the basics of functional and rs-fMRI, and these methods were the primary modalities used in the experimental studies. The final section describes brain networks, with emphasis on the motor network, DCD and ADHD and their high rate of co-occurrence, and current neuroimaging research in these populations.

Chapter 2 describes the first study, entitled "Functional connectivity of neural networks is disrupted in children with developmental coordination disorder and attention-deficit/hyperactivity disorder". This study has been published (McLeod *et al.*, Neuroimage Clinical 2014;4:566-575).

Chapter 3 describes the second study, entitled "Hemispheric asymmetry of motor cortex functional connections in children with developmental coordination disorder and attention-deficit/hyperactivity disorder". The study is currently in preparation for submission to a peer-reviewed journal.

Chapter 4 summarizes the findings of these studies and discusses how together these studies advance our knowledge of the neurological underpinnings of these disorders. Limitations of our studies and directions for future research are also discussed.

1.3 Functional MRI and Resting-state fMRI

Magnetic resonance imaging (MRI) is a non-invasive imaging modality that can provide exquisite images of the structure and function of the human brain. Structurally, MRI can identify grey and white matter, and can thus measure parameters such as cortical thickness and brain region volumes MRI has few risks or contraindications to its use, and does not use ionizing radiation. While the physics of MRI are beyond the scope of this thesis, the methods of functional imaging (fMRI) and resting-state fMRI will be discussed here.

As its name suggests fMRI is capable of localizing and quantifying the function of regions of the human brain. It typically does this by recording MR images sensitive to blood oxygenation while the participant performs mental or motor tasks inside the MR scanner. Thus, this type of fMRI is referred to as blood-oxygenation level dependent, or BOLD fMRI. That is, BOLD fMRI does not measure the electrical neuronal activity of the brain directly. However, there is a tight coupling between the synaptic activity of the brain and the accompanying increase in blood oxygenation and blood flow in the immediate area, as follows (Jezzard, 2004). Neurons communicate using neurotransmitters, which generate electrochemical gradients that lead to

polarization and depolarization of membranes. Energy is needed to restore membrane potentials, and this energy primarily comes from the oxygen-dependent breakdown of glucose. Glucose breakdown, or glycolysis, ultimately creates energy in the form of adenosine triphosphate (ATP) following oxidative phosphorylation in mitochondria. Oxidative phosphorylation is a series of chemical reactions that creates the majority of ATP available to neurons, and requires oxygen in the final synthesis stage. Likewise, oxygen is required for energy homeostasis of neurons. The source of this oxygen comes from the vasculature of the brain, in the form of oxygenated haemoglobin (oxyhemoglobin). That is, there is an increase in blood flow; however, increased blood flow does not necessarily correlate directly with increased oxygen delivery. While the mechanics and specifics of this process are beyond the scope of this review, there is a link between oxygen, glucose consumption and neuronal activity (Jezzard, 2004). Oxygen delivery to neurons happens because of a disproportionate increase in blood flow to a brain region, which increases the pressure of oxygen on capillaries, thus creating a pressure gradient favouring oxygen delivery to neurons. Oxyghemoglobin in the blood then becomes paramagnetic deoxyhemoglobin. Therefore, the increased energy demand of neurons, such as during task performance or when restoring homeostasis, results in elevated oxygen requirements from the vasculature to carry out oxidative phosphorylation to generate ATP in response to neural synaptic activity.

The BOLD fMRI surrogate of neuronal activity can be described by the hemodynamic response function (HRF) (Jezzard, 2004) (Figure 1.1). In response to neural activity, the HRF has an immediate “initial dip” that lasts less than two seconds because of the increase in the concentration of paramagnetic deoxyhemoglobin. This is followed by an increase in cerebral blood volume (CBV) and cerebral blood flow (CBF), creating a surge in diamagnetic

oxyhemoglobin, thus decreasing the concentration of deoxyhemoglobin. This leads to a positive BOLD response, which lasts five to eight seconds, and accounts for signal measured in fMRI studies. The hemodynamic response ends with a negative undershoot phase, lasting about ten seconds, before returning to baseline. The characteristics (duration, amplitude) of each phase of the HRF are dependent on physiological (brain regions, oxygen levels) and physical (MRI scanner used, field strength) factors.

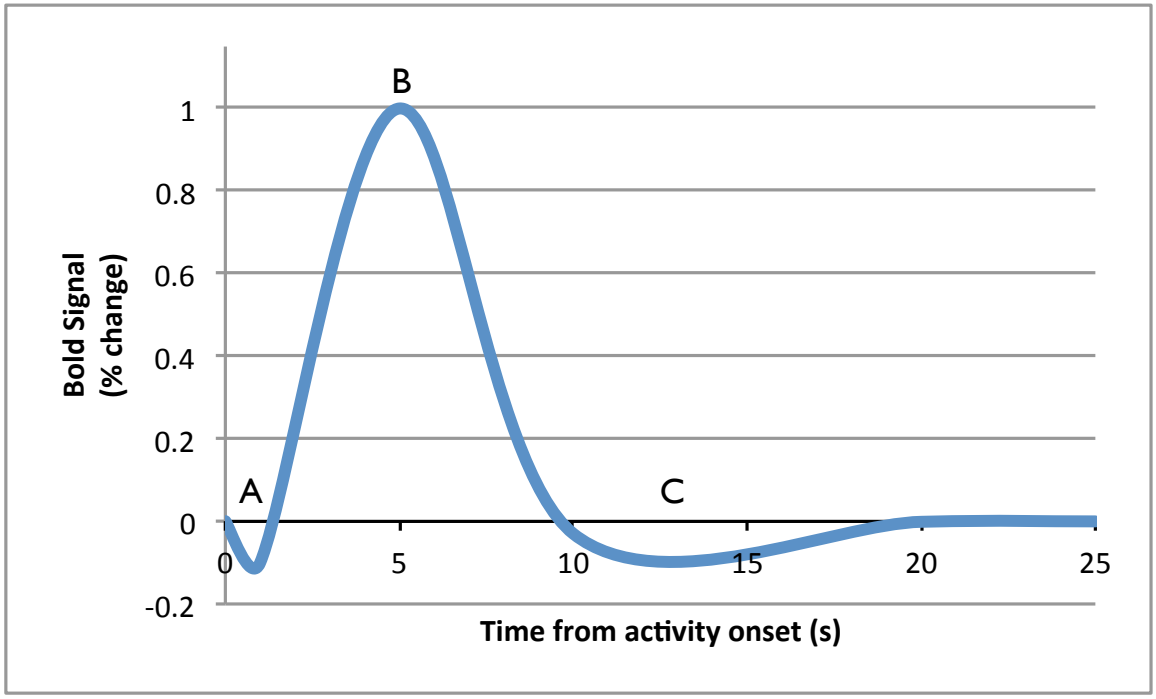

Figure 1.1: Hemodynamic Response Function. At the beginning of the response is the "initial dip" (A), followed by an increased BOLD signal resulting from increased CBV and CBF (B). Next is the undershoot phase (C), then a return to baseline (Jezzard, 2004).

In a typical fMRI experiment, neural activity is elicited by presenting repeated trials of a task for the participant to perform while in the MR scanner. FMRI thus localizes the brain regions

associated with performing a task. Alternatively, fMRI can determine how brain regions interact or are functionally connected, even in the absence of a task. This approach is called resting-state fMRI (rs-fMRI). Regions are considered to exhibit a functional connection if their rs-fMRI signals over the duration of a scanning session are highly synchronous, or demonstrate a significant temporal cross-correlation (Friston et al., 1993). The level of significance of the correlation is thought to indicate the strength of the functional connection, and is termed connectivity. Biswal *et al*. were the first to demonstrate connectivity of the motor networks during rest (Biswal et al., 1995) and their findings have since been replicated in multiple rs-fMRI studies. In addition, other networks such as visual (Beckmann et al., 2005), auditory (Biswal et al., 1997), default-mode (Raichle et al., 2001), and fronto-parietal networks (Fox et al., 2005) have been identified. These connectivity signals are thought to represent a baseline level of brain activity, or a means for related structures to 'check-in' with other parts of their networks. Their function may also be to keep the brain circuitry 'active' in order to lessen the time to respond to a given stimulus or prepare for task performance (Fox and Raichle, 2007).

Reduced or increased connectivity, relative to normal, is thought to represent a disruption within brain networks. For example, rs-fMRI has demonstrated altered cortico-basal ganglia connectivity in patients with Parkinson's disease (Baudrexel et al., 2011), specifically in the subthalamic nucleus, which receives dopaminergic input from the substantia nigra and is key for regulating movement (Kandel et al., 2000). Rs-fMRI may thus be a valuable tool to determine the impact of neurological and neurodevelopmental disorders on the functional networks of the brain.

1.4 The Brain as Networks

1.4.1 Overview

For an in-depth description of the network organization of the human brain, the reader is referred to neuroscience and neuropsychology texts, such as Kandel *et al.* (Kandel et al., 2000) and Kolb and Whishaw (Kolb and Whishaw, 1996), from which much of this section originates. The human brain consists of many functionally distinct regions and structures, from those associated with language processing and generation to those that decipher visual information. However, human interaction with the world is not simply the sum of individual processes, but instead are the integration of what is seen, known, and felt about stimuli in the environment. While specific brain regions may be specialized for given functions, it is the interaction and transfer of information between brain regions that create the human experience. Brain regions form networks, consisting of functionally related structures that are interconnected, such as the motor and visual networks (Beckmann et al., 2005; Biswal et al., 1997; Fox et al., 2005; Raichle et al., 2001). Sensory information is received in primary sensory regions – the visual, auditory and somatosensory cortices, for instance – and this input is passed to secondary and tertiary regions where the information is refined (Felleman and Van Essen, 1991). The information is incorporated in tertiary areas, such as the polymodal/multimodal cortices. It is then sent through subcortical structures such as the basal ganglia and amygdala for further processing, such as emotional relevance of the event. This information travels to the prefrontal cortex and then to the supplementary motor area to initiate and plan a response, and finally to the primary motor cortex, which is responsible for execution of our actions (Felleman and Van Essen, 1991). The frontal lobe is where the usefulness of behaviours are evaluated and adapted to fit the environment, based on higher cognitive abilities such as learning and memory. The understanding of how

neural structures are connected and how they form networks is important for understanding results obtained from functional neuroimaging.

1.4.2 Sensorimotor Integration

Each lobe of the brain contributes to sensory experience and how behaviours are shaped. This section will focus primarily on how each lobe contributes to movement. Firstly, the occipital lobe primarily deciphers visual stimuli. Three neural pathways exit from the occipital lobe: the dorsal pathway is used for the visual guidance of movement, the ventral pathway is for object recognition, and the superior temporal sulcus pathway is used for processing complex, multimodal stimuli (Goodale et al., 1991; Kandel et al., 2000). Next, the temporal lobe is responsible for a number of functions associated with language, hearing, vision and memory, but also has sensorimotor function and contributions to behavior, particularly in the insular cortex and limbic system. The insular cortex is a multimodal area that plays a role in attention and sensorimotor processing (Cauda et al., 2012). The limbic system contains the hippocampus and amygdala, which incorporate memories and emotions with behavioral responses in the frontal lobe (Kolb and Whishaw, 1996).

The parietal lobes have a number of structures involved in sensorimotor integration. The anterior parietal lobe consists of the postcentral gyrus and the parietal operculum, which together are known as the somatosensory cortex (Kolb and Whishaw, 1996). Posterior regions consist of the supramarginal and angular gyri, which together are referred to as the inferior parietal and superior parietal lobules (Kolb and Whishaw, 1996). The parietal lobes perform a wide variety of functions. First, the somatosensory areas receive sensory stimuli from throughout the body regarding pain, temperature, vibration and proprioception. As such, there are many connections

throughout the brain, and these have been described by Felleman and van Essen (Felleman and Van Essen, 1991). The somatosensory area connects to the motor areas of the frontal lobe, and also to posterior parietal areas. The parietal lobes also have areas that receive neuronal projection from the dorsal pathways of the occipital lobes. These areas are primarily in the inferior parietal lobules, where sensory information regarding balance (vestibular), proprioception/position, somasthetic, auditory (from temporal lobe), eye position (oculomotor) and motivation are integrated (Kolb and Whishaw, 1996). This wealth of information is used to guide movements and behaviours in space, such as orientation of hands to grasp objects and how attention is directed. Finally, information is transferred to the prefrontal cortex (PFC) (Felleman and Van Essen, 1991). Therefore, the parietal lobes act as a multimodal centre for visuomotor control. The ability of the parietal lobes to interpret spatial information significantly influences the interpretation of written language and performing written arithmetic (Kolb and Whishaw, 1996); persons with lesions in these areas demonstrate deficits in these areas. This shows the diverse nature of parietal lobe functions.

1.4.3 Frontal Lobes

The vast amount of information from the occipital, parietal and temporal lobes eventually reaches the frontal lobes, which is responsible for behaviour performance and movement execution. Anatomically, the frontal lobes are defined as the cortical areas in front of the central sulci, and are functionally divided into three primary areas: the motor cortex, the premotor cortex, and the prefrontal cortex (Kolb and Whishaw, 1996). The motor and premotor cortices form a system for the control of movement. Limb, digit and facial movements are executed by the motor cortex via white matter corticospinal projections (Kandel et al., 2000). The premotor

cortex influences movement directly and indirectly by connections with the primary motor cortex (M1) (Felleman and Van Essen, 1991). The premotor cortex also contains the frontal eye fields, which control eye movement and visual attention (Schall, 2004). Neuronal input from the inferior parietal lobe is received throughout the premotor cortex and guides the execution of limb and eye movements (Felleman and Van Essen, 1991). Input is also received from the PFC, which itself receives information from multimodal regions of the posterior parietal lobe, the superior temporal sulcus and the limbic regions (Felleman and Van Essen, 1991). Functionally, the PFC is responsible for controlling cognitive processes to ensure movements are selected at appropriate times, in accordance to internal goals (Miller and Cohen, 2001). In addition, the dorsolateral PFC is responsible for temporal or short-term memory, action selection, movement planning, and permits the incorporation of non-sensory information (i.e., distractors) before behaviours are performed (Mars and Grol, 2007). Behaviour is context-dependent; sensory information from the temporal and parietal lobes, in addition to emotional input from the amygdala, help guide actions in different situations.

Patients who have lesions or damage to the frontal lobe have provided tremendous insight into the location of functions. For example, damage to the motor cortex can result in the loss of fine movements, and damage to the supplementary motor area (SMA) may disrupt the voluntary performance of movement (Kolb and Milner, 1981). Insults to the prefrontal cortex, meanwhile, can result in a range of symptoms that influence goal-directed behaviours, including difficulties with response inhibition, following instructions, short-term memory, and regulating behaviour in response to stimuli (Knight, 1984). Personality changes, similar to those seen in frontotemporal dementia, often accompany frontal lobe damage or degeneration (Kolb and Whishaw, 1996).

Ultimately, the frontal lobe is responsible for the temporal regulation of behaviour and movement.

1.4.4 The Motor Network

Humans begin to develop finer movements, such as grasping objects, at a very young age. The coordination, planning and execution of such movements involve the spinal cord, brainstem, cerebellum, basal ganglia, the neocortex and other structures (Kolb and Whishaw, 1996). Damage to individual structures can result in unique symptoms. Of particular interest in the present discussion are the cortical motor areas, the basal ganglia, and cerebellum.

The cortical motor areas include M1, SMA, premotor cortex, sensorimotor cortex and the posterior parietal cortex. The cortical areas are thought to act in a hierarchical manner, with input from multiple cortical areas converging on M1, which ultimately integrates various signals from visuospatial, sensory and motor control regions of the cortex for the sequencing and timing of movements (Felleman and Van Essen, 1991; Kolb and Whishaw, 1996). M1 also receives neuronal projections from the thalamus via the basal ganglia and cerebellum to control movements (Kolb and Whishaw, 1996). The corticospinal white matter tracts that descend from M1 control movement execution of the contralateral side of the body.

The basal ganglia – which include the caudate, putamen, globus pallidus, and substantia nigra - act as a link between other cortical areas and M1 (Kolb and Whishaw, 1996). The primary function of the basal ganglia is the control of movement amplitude, which is impacted in medical conditions such as Parkinson's disease and Huntington's disease. In Parkinson's disease there is neuronal loss in the substantia nigra that leads to tremor, rigidity, akithesia and postural instability (Kandel et al., 2000; Kolb and Whishaw, 1996). In contrast, in Huntington's disease,

where there is degradation of the caudate and putamen, uninhibited, random movements known as chorea are produced (Kolb and Whishaw, 1996). The involvement of the basal ganglia in movement starts at the neostriatum, or caudate and putamen (Kandel et al., 2000). These structures receive glutaminergic input from throughout the cortex and thalamus, which is then relayed as inhibitory signals to the globus pallidus internus (GPi) and substantia nigra (SN), which regulates movement (Figure 1.2). This happens because the GPi and SN inhibit the motor cortex via the ventral thalamus; the striatum essentially "inhibits the inhibitor" to produce movement. Excess movement is prevented using tonic inhibition by the GPi and SN on M1 using the neurotransmitter gamma-aminobutyric acid (GABA). This is the direct pathway; the indirect pathway involves the globus pallidus externa and subthalamic nucleus, which results in activation of GPi for movement inhibition. Input to the basal ganglia can originate from any region of the neocortex (Kandel et al., 2000). As such, sensory information from varying stimuli can influence movements, such as tactile feedback from the somatosensory cortex to visual cues from the occipital lobe.

The cerebellum influences aspects of motor control such as movement accuracy, balance, timing and creating coordinated movements. It receives peripheral sensory input via the brainstem and contralateral M1, and therefore, each cerebellar hemisphere controls coordination of the ipsilateral side of the body (Kolb and Whishaw, 1996). Functions of the cerebellum are demonstrated with clinical examples. For instance, the cerebellum is susceptible to alcohol; intoxicated persons have difficulty performing "tandem gait" or coordinated walk, which the cerebellar vermis controls. The most lateral section of the cerebellum controls fine motor and visually guided movements (Kolb and Whishaw, 1996). When this function is impaired, for example through a cerebellar lesion, intention tremors, where persons have uncontrollable

shaking as they approach a target with their hand or finger, can occur. The details of the cortico-thalamic-cerebellar pathways are beyond the scope of this review.

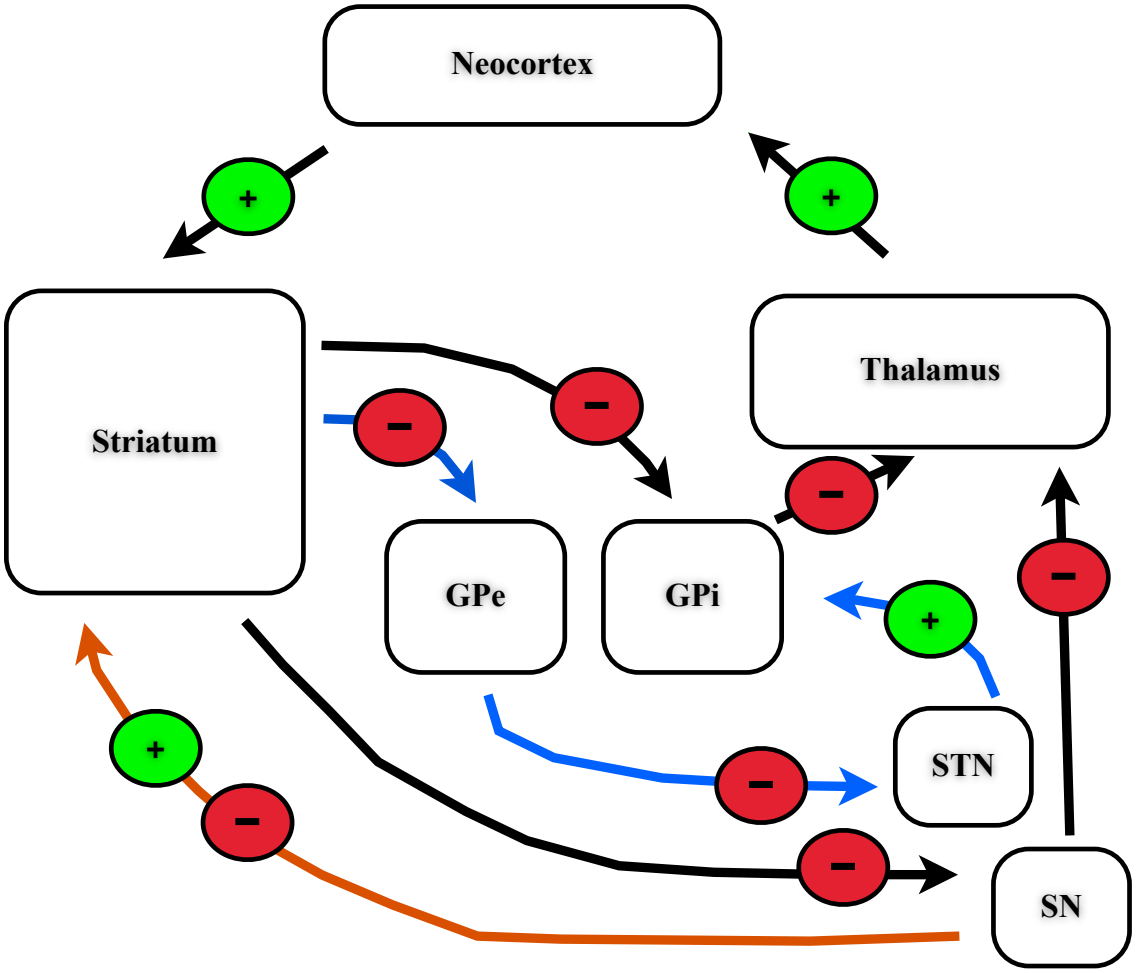

Figure 1.2: How the basal ganglia control movement. Excitatory (glutaminergic) signals are received in the striatum. Two pathways are depicted from the striatum – the direct (black) and indirect (blue) pathways. The direct pathway inhibits the globus pallidus internal (GPi) which in turn inhibits the thalamus. The indirect pathway inhibits the globus pallidus external (GPe), which inhibits the subthalamic nucleus (STN), which then excites the GPi,, and then inhibits the thalamus. The substantia nigra (SN) pars compacta produces dopamine which excites the direct pathway and inhibits the indirect pathway (orange arrow) in the striatum.

1.5 DCD, ADHD and Comorbidity

1.5.1 Developmental Coordination Disorder

In the literature, developmental coordination disorder (DCD) has been referred to by a number of names – such as clumsiness, motor awkwardness or weakness, psychomotor syndrome, and developmental dyspraxia. The Diagnostic and Statistical Manual of Mental Disorders III-R first defined DCD in 1987 and created a concrete set of criteria for the diagnosis of the disorder (American Psychiatric Association, 1987). These criteria remain similar to those included in the DSM-V. The DSM-V criteria for a diagnosis of DCD are as follows: (1) acquisition and execution of motor skills being below age level, with clumsy, slow and inaccurate movements, (2) having a negative impact on daily living, (3) symptom onset during early development, and (4) not explained by intellectual disability, visual impairment or a neurological disorder (e.g., cerebral palsy) (American Psychiatric Association, 2013). Children are typically diagnosed with DCD using standardized tests and school reports. The primary characteristics of DCD are impairments in motor coordination, fine motor abilities, cross-modal integration (incorporating vestibular, proprioceptive and kinesthetic feedback into responses), and motor visualization (Dewey and Wilson, 2001; Wilson and McKenzie, 1998). These deficits lead to challenges in academic settings, specifically in mathematics, reading, writing, and activities like physical education, which are associated with poorer educational outcomes and physical health (Cairney et al., 2012; Cantell et al., 2008). Tasks of daily living are also a challenge, such as fastening zippers or tying shoelaces. These difficulties can have a negative effect on self-esteem and may lead to long-term psychosocial and mental health concerns such as depression (Lingam et al., 2012) and anxiety (Pratt and Hill, 2011).

Approximately 5-8% of children exhibit symptoms of DCD and males are more commonly affected (American Psychiatric Association, 2013). The etiology of DCD is unknown, but neuroanatomy, neurochemistry and genetics likely contribute to the disorder. The central nervous system, which has a large number of structures that contribute to movement, is likely impacted given the deficits in motor coordination, sensorimotor integration and fine motor control in DCD (Wilson et al., 2013; Wilson and McKenzie, 1998). These deficits may arise due to abnormalities in neurotransmission, and animal models have helped elucidate the relationship between neurochemistry and movement. For example, n-methyl-d-aspartate (NMDA) receptor (a major excitatory neurotransmitter receptor) knockout mice display striatal abnormalities and deficits in motor learning (Dang et al., 2006). Also, reducing activity of the neurotransmitter gamma-aminobutyric acid (GABA) in mice has been found to result in impaired motor skills, sensorimotor integration and spatial learning (Leppä et al., 2011). Genetics is also a contributor to DCD, particularly to fine motor control (Martin et al., 2006). DCD has been found to have a high rate of heritability; 70%, identified in a twin study (Lichtenstein et al., 2010). These findings suggest that DCD is a multifactorial disorder.

A number of diagnostic tests are used in research studies to identify children with motor difficulties. The common standardized assessment measures include the Motor Assessment Battery for Children (M-ABC) (Henderson et al., 2007), the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) (Bruininks, 1978), the McCarron Assessment of Neuromotor Development (MAND) (McCarron, 1997), and the DCD questionnaire (DCD-Q) (Wilson et al., 2000). Part of the challenge of diagnosing DCD with these tests is the variability of symptom expression in children and differences in the motor functions measured by the various tests (Crawford et al., 2001). Comparing the different assessment tests, Dewey and colleagues found

that resulting scores and potential diagnoses differed both amongst healthy children and children with motor difficulties, possibly because of factors such as attention, memory and visuomotor challenges (Dewey and Wilson, 2001). Therefore, children a diagnosis of DCD should not rely on the results of an assessment using only one measure. Further, interventions provided to children with DCD should be geared towards their individualized needs with help from occupational therapists, psychologists, physicians, teachers, and family (Dewey and Wilson, 2001).

The focus of much of the research on DCD over the past two decades has been on identifying impairments in function. Meta-analyses of these studies by Wilson *et al*. identified a number of areas where children with DCD struggle, including problems with coordination, executive function, postural and gait control, sensoriperceptual function, catching and interceptive action, and forward modeling (Wilson et al., 2013; Wilson and McKenzie, 1998). Visuospatial and coordination impairments suggest involvement of the sensory and motor networks in DCD. For example, poorer sensory processing from visuospatial centres could impact the coordination of motor movements required for catching a ball.

1.5.2 Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that has three distinct behavioural subtypes defined in the DSM-V (American Psychiatric Association, 2013). These subtypes are (1) predominantly inattentive, (2) predominantly hyperactive and/or impulsive, and (3) combined inattentive and hyperactive. Inattentive symptoms include careless mistakes during schoolwork and activities, difficulties sustaining attention and following through on instructions, being easily distracted, and frequently losing

things needed for activities (American Psychiatric Association, 2013). Hyperactive/impulsive symptoms include fidgeting, inappropriately leaving one's seat or running, inability to play quietly, frequently interrupting others, excessive talking, and restlessness (American Psychiatric Association, 2013). Both symptom domains negatively impact children's academic and social development, and if left unmanaged, often persist into adulthood and can lead to other problems such as drug abuse, challenges at work, difficulties in post-secondary education, and antisocial behavior (Shaw et al., 2012).

Symptoms of ADHD are present in approximately 5% of school aged children (American Psychiatric Association, 2013). Despite this high prevalence, the exact etiology of ADHD is unclear. It is thought to be a multifactorial disorder with influences from genetics, neurochemistry, neuroanatomy and environment. ADHD is highly heritable, with twin studies suggesting a heritability rate of 76%-79% (Faraone et al., 2005; Lichtenstein et al., 2010). Genetics research has identified roles for genes involved in neuronal transport of dopamine and norepinephrine (Cortese, 2012). These neurotransmitter pathways are targeted by pharmaceutical interventions that can result in improvement in ADHD symptoms. Furthermore, the neurobiology of ADHD has been described through neuroimaging studies as consisting of deficits in three major pathways – the frontostriatal, fronto-temporal-parietal, and fronto-cerebellar networks (Cortese, 2012; Nakao et al., 2011; Vaidya, 2012), which control inhibition and goal directed behaviours. Presently, however, genetic, neurobiological and neuroimaging methods are not used to diagnose ADHD. Standardized measures such as the Conner's Parent Rating Scale – Revised (Conners et al., 1998) and Diagnostic Interview for Children and Adolescents (DICA) (Reich et al., 1997) are utilized alongside information from parents, teachers and clinicians to diagnose the condition.

Children with ADHD, particularly children with the inattentive and combined subtypes, frequently exhibit challenges with motor function, control and coordination (Harvey and Reid, 2003; Pitcher et al., 2003), suggesting a majority of the children with ADHD have motor difficulties (Kaiser et al., 2015). Additionally, children with the inattentive subtype of ADHD have been found to have lower scores on the MABC (Kaplan et al., 1998). This has led to research investigating whether inattention causes motor difficulties. For example, children with ADHD were found to have poorer handwriting ability compared with controls (Adi-Japha et al., 2007). These children required more time to complete longer words and were more prone to errors, indicating that problems existed in both inattentive and motor skills. A systematic review by Kaiser *et al.* indicated that when ADHD co-occurs with other disorders such as DCD, reading disorder (RD) or oppositional defiant disorder (ODD), and is often associated with greater motor difficulties (Kaiser et al., 2015). Additionally, ADHD may more commonly co-occur with other developmental disorders rather than on its own, including DCD, RD and autism spectrum disorder (Piek and Pitcher, 2004). Multiple studies have also identified significant overlap between ADHD and learning disorders, between 31-45% (DuPaul et al., 2013). As an example of one study, thirteen of fifteen children diagnosed with ADHD were identified as having comorbidities such as RD or DCD (Kadesjo and Gillberg, 2001). On standardized measures of motor function, children with ADHD and ODD and/or RD had significantly poorer motor performance compared to healthy children (Kooistra et al., 2005). Overall, motor deficits are a common feature of ADHD.

1.5.3 Comorbidity of DCD and ADHD

DCD and ADHD have been found to co-occur in up to 50% of affected children (Kadesjo and Gillberg, 1998; Pitcher et al., 2003). The co-occurrence of these disorders has also been referred to as DAMP (i.e., deficits in attention, motor control and perception). It has been suggested that DCD+ADHD occurs in approximately 5-7% of school-aged children (Landgren et al., 1996) and is more frequent in males (Kadesjo and Gillberg, 1998). Children with DCD are likely to have problems with attention (Lingam et al., 2010), and inattentive symptoms in children with ADHD has been associated with motor problems (Piek and Pitcher, 2004). This symptom overlap and high rate of comorbidity suggests that the disorders may have common developmental mechanisms. Supporting this, genetic research has found familial links between ADHD and motor problems (Fliers et al., 2009) and between fine motor and inattentive symptoms (Martin et al., 2006). A genome-wide association study in individuals with ADHD identified genes associated with aspects of motor coordination (Fliers et al., 2012). Interestingly, children with both disorders demonstrate improvement in both attention and motor symptoms with methylphenidate, demonstrating a possible neurological link between attention and motor control (Bart et al., 2013). Importantly, children with DCD+ADHD tend to experience much greater functional impairment than children with either disorder alone. They display higher rates of behavioural and academic problems (Kadesjo and Gillberg, 1998; Kadesjo et al., 2001), and poorer processing speed (Loh et al., 2011) and fine motor ability (Pitcher et al., 2003). Additionally, children with DCD+ADHD have poorer long-term outcomes, including higher rates of antisocial personality disorder, criminal activity, drug and alcohol abuse, and are more likely to require social support (pension) for psychiatric concerns (Rasmussen and Gillberg,

2000), reinforcing the need for early identification and management of children with comorbid DCD+ADHD.

1.6 Neuroimaging Research in DCD and ADHD

Neuroimaging research on children with DCD is an emerging field, but findings to date support the involvement of motor and sensory networks in this disorder. Two diffusion tensor imaging (DTI) studies have identified regions with altered fractional anisotropy (FA), which is a measure of white matter integrity, in children with DCD. One study observed lower FA bilaterally in the corticospinal tracts (Zwicker et al., 2012), whereas the other found lower FA in the region of the corpus callosum, which is connected to the superior parietal cortex (Langevin et al., 2014), and which is associated with motor output. A recent study investigating cortical thickness in children with DCD observed reduced thickness in the right medial orbitofrontal cortex and right temporal pole, which are regions associated with sensory integration and attention, respectively (Langevin et al., 2015). Studies using fMRI have also investigated children with DCD. Querne *et al.* used a Go/No Go task and found slower and more varied responses in children with DCD compared to control children, but similar BOLD activation patterns (Querne et al., 2008). This study also measured effective connectivity and reported higher levels of connectivity between middle frontal cortex and anterior cingulate cortex, and the inferior parietal cortex in the left hemisphere, whereas, in the right hemisphere they found lower connectivity between the striatum and parietal cortex in children with DCD (Querne et al., 2008). Using a visual tracing task, Kashiwagi *et al.* found lower BOLD signal in the left superior, inferior parietal lobes, and somatosensory cortex, in children with DCD, supporting the idea of altered involvement of sensory structures in this disorder (Kashiwagi et al., 2009). Zwicker *et al.* conducted two studies using trail-tracing tasks.

In the first, children with DCD displayed similar levels of task performance compared to healthy children; however, greater BOLD signal was noted in various frontal, parietal, and temporal regions, and in the cerebellum compared to controls and lower BOLD signal was found in the left precuneus, superior frontal, inferior frontal, postcentral gyri, and right superior temporal gyri and insular cortex (Zwicker et al., 2010). A follow-up study with the same group of children, who perform the task again following training, found that children with DCD displayed lower BOLD signal change in the right inferior parietal lobe and lingual gyrus, the left fusiform gyrus and inferior parietal lobule, and cerebellar regions compared to controls (Zwicker et al., 2011). This observation suggests that children with DCD may have impairments in motor learning as demonstrated by the reduced recruitment of brain regions during the follow-up task. Finally, in a task designed to elicit motor responses to visual stimuli, Debrabant *et al.* observed that with irregular stimuli, children with DCD had lower activation in the right IFG compared to control children. During task performance, control children also had higher activation in the left cerebellum and right-temporoparietal junction compared to children with DCD (Debrabant et al., 2013). Based on these findings, the authors suggested that children with DCD have impairments in predicting patterns for motor responses. To date, no research has used rs-fMRI to investigate brain functioning in children with DCD.

Neuroimaging research suggests that the most common alterations in brain structure and function observed in children with DCD are in the parietal lobes and cerebellum. The one study that reported reduced mean diffusivity in the corticospinal tract suggests impaired communication between M1 and the lower motor neurons used for movement execution in children with DCD. Alterations in the parietal lobes, which are essential for spatially guided movements, could result in the observed visuospatial impairments associated with DCD.

Cerebellar abnormalities could also underlie the symptoms associated with DCD and affect motor learning and coordination. Although the conclusions that can be drawn from these imaging studies are limited, due to the small number of studies conducted to date and the small sample sizes of these studies, they support for the contention that sensorimotor networks are involved in the pathophysiology of DCD.

In contrast to DCD, a significant number of neuroimaging studies have been conducted with children with ADHD using both structural and functional methods. These studies have found differences in the brains of children with ADHD, especially in areas associated with attention and inhibition, such as the frontostriatal, fronto-temporal-parietal, and fronto-cerebellar networks (Cortese, 2012; Nakao et al., 2011; Vaidya, 2012). This section will review imaging studies that observed structural and functional changes in the motor network of children with ADHD.

A number of structural imaging studies have found volumetric and white matter changes in motor areas in children with ADHD. The left and right hemispheres are smaller in individuals with ADHD (Castellanos et al., 2002), and children with ADHD have been reported to have a three-year delay in cortical thickness maturation in motor planning areas (Shaw et al., 2007). Castellanos *et al.* observed that children with ADHD had similar growth trajectories compared to healthy children for cerebral growth, but had a lower total cerebral volume (Castellanos et al., 2002). They also observed that the volume of the caudate nucleus was initially lower in children with ADHD, starting at age 5, and this persisted until age 16 where the caudate volume approached that of healthy children (Castellanos et al., 2002). This could be associated with resolution of hyperactive symptoms in some individuals as they mature (Biederman et al., 2000; Hart et al., 1995). Meta-analyses of volumetric imaging studies have consistently found reduced right hemisphere (Valera et al., 2007), right prefrontal cortex (PFC) (Valera et al., 2007), frontal

WM (Valera et al., 2007), right putamen/pallidus (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011) and caudate (Frodl and Skokauskas, 2012; Nakao et al., 2011) volumes in children with ADHD. Smaller volumes may be representative of a lower neural or neuropil density, or disproportionate grey/white matter ratios. DTI studies have shown FA alterations in children with ADHD; these include reduced white matter integrity in the corticospinal tracts (Hamilton et al., 2008) and in regions between the basal ganglia and the prefrontal cortex (de Zeeuw et al., 2012; Langevin et al., 2014).

Functional magnetic resonance imaging (fMRI) studies using motor tasks have implicated motor regions such as the inferior frontal gyrus in children with ADHD (Booth et al., 2005; Durston et al., 2006, 2003; Mostofsky et al., 2006; Suskauer et al., 2008). Resting state fMRI, studies have observed connectivity differences within frontostriatal circuits, attention circuits, and the default mode network (Cao et al., 2006, 2009; Tian et al., 2006; Zang et al., 2007); however, none have explicitly investigated the motor network. Specifically, research has found increased connectivity between the dorsal anterior cingulate cortex and the bilateral thalamus, cerebellum, insula and brainstem (Tian et al., 2006), as well as increased connectivity between the cerebellum and the right inferior frontal and left somatosensory cortices (Zang et al., 2007), supporting the involvement of sensory and motor pathways in the pathophysiology of ADHD. Finally, reduction of functional connectivity in the frontostriatal circuit has been observed in response to methylphenidate, supporting the role of dopamine in the motor symptoms that have been associated with ADHD (Hong et al., 2014).

1.6.1 Common Observations in DCD and ADHD Neuroimaging Research

Due to the relatively small number of neuroimaging studies of children with DCD, it is difficult to compare and contrast the findings of these studies with those of children with ADHD. However, subcortical structures such as the basal ganglia and parts of the sensorimotor pathway appear to be involved in both disorders. It also bears mentioning that few studies have explicitly investigated children with both motor and attention deficits. However, a recent DTI study found that children with co-occurring DCD and ADHD displayed similar alterations in white matter integrity in areas of the corpus callosum as children with DCD only or ADHD only (Langevin et al., 2014). Another recent study investigating cortical thickness observed more extensive decreases in thickness in children with both disorders compared to children with only one disorder, particularly in frontal, parietal and temporal lobes (Langevin et al., 2015). Therefore, children with DCD+ADHD may share common neurological substrates with children with only DCD or only ADHD, but also display unique structural changes in the brain. Research has reported children with co-occurring DCD+ADHD display more severe and unique behavioural and motor deficits than children with single disorder. This could be due to greater and/or distinct alteration in neural pathways.

1.7 Interhemispheric Communication and Atypical Brain Asymmetry in DCD and ADHD

Interhemispheric communication is a term used to describe the interaction between the left and right hemispheres while a person is performing a task. Simple motor tasks, such as finger tapping, require less bilateral activation, whereas complex tasks, like tracing a figure or catching a ball, require contributions from both hemispheres (Mostofsky et al., 2006; Scholz et al., 2000; Solodkin et al., 2001). The principal structure mediating this communication between

hemispheres is the corpus callosum, which allow for the interaction of brain regions throughout the cortex. In children with DCD and/or ADHD, behavioural and neuroimaging research have reported differences in motor performance on tasks that require input from both hemispheres such as movement planning, gait, postural control, visuoperception and coordination. Children with DCD have been found to display deficits on such tasks (Dewey et al., 2007; Wilson et al., 2013). The altered activity observed in visuospatial regions during performance of complex tracing tasks in children with DCD, could be due to interhemispheric communication deficits (Kashiwagi et al., 2009; Zwicker et al., 2010). In children with ADHD, Hale *et al.* demonstrated alterations in right-left hemisphere communication on a box checking task (Hale et al., 2009). When participants used their left hand, for instance, their right hemisphere required feedback from the left hemisphere. Children with ADHD had poorer performance on this task compared to controls, suggesting poorer interhemispheric communication.

Imaging studies in children with ADHD suggest the involvement of neuronal structures, particularly the corpus callosum, may negatively influence interhemispheric communication. Volumetric abnormalities have been observed in the corpus callosum in children with ADHD (Roessner et al., 2004). One meta analysis identified the splenium, or posterior corpus callosum, as having reduced volumes in comparison to healthy children (Valera et al., 2007). A second meta-analysis of DTI research reported lower white matter integrity in the right forceps minor near the corpus callosum and the anterior corona radiate (van Ewijk et al., 2012), and a recent study found reduced integrity in the anterior corpus callosum (Langevin et al., 2014). In children with DCD, irregularities in the corpus callosum have also been identified, specifically in the posterior region which is linked to the parietal lobes (Langevin et al., 2014). These changes in

the corpus callosum may negatively impact interhemispheric communication in children with DCD and ADHD.

Functional imaging studies offer another avenue to investigate how the brain's hemispheres interact during task performance. FMRI Go/No Go studies have consistently identified reduced activity in right inferior frontal gyrus (IFG) of children with ADHD (Booth et al., 2005; Garrett et al., 2008; Rubia et al., 2005). Historically, this is a task performed with the right hand in response to a visual stimulus, requiring left hemisphere motor activity, and inhibitory control from the right IFG. The reduced right IFG activity may result from poorer communication from the left hemisphere, leading to challenges with inhibition. With a complex finger tapping task, which requires interaction between hemispheres, Mostofsky *et al.* found reduced contralateral motor cortex activity in children with ADHD (Mostofsky et al., 2006). Transcranial magnetic stimulation (TMS) research has also demonstrated delayed inhibition in ADHD. When using TMS to innervate the motor cortex, there was delayed inhibition in the contralateral hand of children with ADHD (Buchmann et al., 2003). The findings of these studies support the contention that there is a delay in the interhemispheric motor network in ADHD and suggest that children with ADHD may have altered communication between hemispheres that influences their performance of complex motor tasks.

Atypical asymmetry of the motor networks may underlie the potential changes in interhemispheric communication in children with DCD and/or ADHD. Brain asymmetries have been observed in relation to handedness. Compared to left-handed individuals, imaging studies have found right-handed individuals have a deeper right sulcus (Amunts et al., 2000), have greater neuropil volume in the left motor cortex (Amunts et al., 1996), and greater left motor cortex activity for contralateral and ipsilateral movements compared to right motor cortex

activity (Kim et al., 1993). Term infants also demonstrate increased white matter integrity in the left corticospinal tract in comparison to the right (Dubois et al., 2009). It has been postulated that ADHD is one of a number of disorders with atypical asymmetry (Rubia et al., 2010), and research on children with ADHD has reported reduced cortical thickness in the right prefrontal cortex compared to healthy peers (Shaw et al., 2009). Neuroimaging research investigating asymmetry in DCD has yet to be performed.

No resting-state fMRI studies have investigated how the left and right motor networks interact in children with DCD and/or ADHD. Given the knowledge that children with DCD and/or ADHD have difficulties with complex motor behaviours that require communication between hemispheres, it is possible that that communication in these motor networks is altered. Resting-state fMRI, which eliminates the variability inherent in task-based fMRI, can be used to measure the left and right motor networks of children with DCD and/or ADHD to determine if communication in the motor networks of these children is fundamentally different from that of their healthy peers.

1.8 Thesis Objectives and Hypotheses

Objective 1: The first objective is to examine if there are functional connectivity changes in the primary motor network in children with DCD and/or ADHD and determine if there is a common neurological substrate between the disorders.

Rationale: DCD and ADHD frequently co-occur and children with these disorders are associated with deficits in motor abilities, including coordination, visuospatial perception, and fine motor control. Limited neuroimaging research has investigated the motor networks of children with

these disorders and whether there are common neurological changes. The left primary motor network will be targeted in children with DCD and/or ADHD using rs-fMRI. The left primary motor cortex will be used as a seed region, and children with DCD and/or ADHD will be compared to typically developing control children. Signals from structures of the motor network, such as the sensorimotor cortex and basal ganglia that eventually converge upon the primary motor cortices prior to the onset of movement will be investigated. The results of Objective 1 will support Objective 2, and also demonstrate the suitability of the rs-fMRI methods for use with children with DCD and/or ADHD.

Hypothesis: We anticipate that children with DCD and/or ADHD will have altered functional connectivity between the primary motor cortex and regions associated with sensorimotor processing and motor control, and that children with both motor and attention deficits will have larger changes in connectivity than children with single disorders (i.e., DCD only, ADHD only).

Objective 2: The second objective is to examine the difference in the strength of the functional connections between the dominant left motor cortex and the non-dominant right motor cortex in right-handed children with DCD and/or ADHD.

Rationale: Children with DCD and/or ADHD demonstrate difficulty in complex motor tasks that require interhemispheric communication, such as motor coordination, gait control and movement planning. A number of structural imaging studies have found white matter changes in the corpus callosum in children with these disorders. Further, children with ADHD are known to have atypical brain asymmetry in the right hemisphere, and this may further contribute to challenges

with complex tasks. Resting state fMRI targeting the connectivity differences between the left and right motor networks will be measured in children with DCD and/or ADHD and compared to typically developing control children. This will determine if there are connectivity differences and altered asymmetry of functional connections in children with motor and attention difficulties.

Hypothesis: We anticipate that children with DCD and/or ADHD will have functional connectivity patterns demonstrating asymmetry of the motor networks in comparison to typically developing children, with reduced connectivity between motor cortices and motor structures of the opposite hemispheres.

CHAPTER 2: FUNCTIONAL CONNECTIVITY OF NEURAL MOTOR NETWORKS IS DISRUPTED IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

2.1 Abstract

Developmental Coordination Disorder (DCD) and Attention Deficit/Hyperactivity Disorder (ADHD) are prevalent childhood disorders that frequently co-occur. Evidence from neuroimaging research suggests that children with these disorders exhibit disruptions in motor circuitry, which could account for the high rate of co-occurrence. The primary objective of this study was to investigate the functional connections of the motor network in children with DCD and/or ADHD compared to typically developing controls, with the aim of identifying common neurophysiological substrates. Resting-state fMRI was performed on 21 children with ADHD, seven with DCD, 18 with DCD+ADHD and 23 controls. Resting-state connectivity of the primary motor cortex was compared between each group and controls, using age as a co-factor. Relative to controls, children with DCD and/or ADHD exhibited similar reductions in functional connectivity between the primary motor cortex and the bilateral inferior frontal gyri, right supramarginal gyrus, angular gyri, insular cortices, amygdala, putamen, and pallidum. In addition, children with DCD and/or ADHD exhibited different age-related patterns of connectivity, compared to controls. These findings suggest that children with DCD and/or ADHD exhibit disruptions in motor circuitry, which may contribute to problems with motor functioning and attention. Our results support the existence of common neurophysiological substrates underlying both motor and attention problems.

2.2 Introduction

Developmental coordination disorder (DCD) occurs in approximately 5-6% of children and is associated with impairments in fine and gross motor functions (American Psychiatric Association, 2000). Attention-deficit hyperactivity disorder (ADHD), which affects approximately 5% of children, is characterized by age-inappropriate levels of inattention, hyperactivity and/or impulsivity (American Psychiatric Association, 2000). DCD and ADHD have been found to co-occur in up to 50% of affected children (Kadesjo and Gillberg, 1998; Pitcher et al., 2003), and have both been associated with neuropsychological deficits, academic difficulties and behavior problems that can lead to long-term issues in social and mental health (Able et al., 2007; Lingam et al., 2012). Early identification and intervention is therefore critical to improve outcomes.

Imaging studies suggest that disruptions in brain motor circuitry are associated with both ADHD and DCD. In children with ADHD, meta-analyses have consistently reported reduced volumes in the right hemisphere (Valera et al., 2007), including right prefrontal cortex (PFC) (Valera et al., 2007), frontal white matter (Valera et al., 2007), right putamen/pallidus (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011) and caudate (Frodl and Skokauskas, 2012; Nakao et al., 2011). Consistent with these findings, diffusion tensor imaging (DTI) studies of children with ADHD have reported reduced white matter integrity in the corticospinal tract (Hamilton et al., 2008) and in regions between the basal ganglia and PFC (de Zeeuw et al., 2012; Langevin et al., 2014). Functional magnetic resonance imaging (fMRI) studies have also implicated motor regions in children with ADHD (Booth et al., 2005; Durston et al., 2006, 2003; Mostofsky et al., 2006; Suskauer et al., 2008). Limited imaging research has been conducted on children with DCD; however, recent DTI studies have reported reduced white

matter integrity within the corticospinal tract (Zwicker et al., 2012) and superior/posterior parietal regions of the corpus callosum and the left superior longitudinal fasciculus (Langevin et al., 2014). Functional MRI studies have implicated motor regions immediately overlying the corticospinal tract (Kashiwagi et al., 2009; Querne et al., 2008; Zwicker et al., 2011, 2010) and one fMRI study investigating functional connectivity (FC) (i.e., temporal synchrony between brain regions, which is an indicator of functional connection strength) during a Go/No Go task reported children with DCD exhibit increased connectivity between the left middle frontal and inferior parietal cortices and reduced connectivity between the right striatum and parietal cortex (Querne et al., 2008). These findings suggest that the functional connections between the striatum and the parietal cortex, areas that integrate sensory information in motor responses, are altered in children with DCD.

Functional connectivity can also been examined when participants are not performing an explicit task during imaging, referred to as resting-state fMRI (rs-fMRI). Studies using rs-fMRI in children with ADHD have observed FC differences within frontostriatal circuits, attention circuits, and the default mode network (Cao et al., 2006, 2009; Tian et al., 2006; Zang et al., 2007). Findings of increased FC between the dorsal anterior cingulate cortex and the bilateral thalamus, cerebellum, insula and brainstem (Tian et al., 2006), as well as increased FC between the cerebellum and the right inferior frontal and left somatosensory cortices (Zang et al., 2007) support the involvement of motor pathways in ADHD. No studies, however, have specifically examined FC within the motor network. Furthermore, no rs-fMRI studies have investigated FC in the motor network of children with DCD or co-occurring DCD and ADHD.

In the present study, we used rs-fMRI to investigate brain regions that are functionally connected with the primary motor cortex (M1) in children with DCD and/or ADHD. The M1

was selected because motor circuitry converges upon M1 for movement execution and it is consistently identifiable on MR images because of its location and shape (Golestani and Goodyear, 2011; Yousry et al., 1995). We hypothesized that children with DCD and/or ADHD would exhibit altered FC between M1 and brain regions involved in motor functioning and sensorimotor processing compared to typically developing children. Regions exhibiting common FC alterations among children with DCD, ADHD or co-occurring DCD and ADHD compared to typically developing children would provide support for a common neurophysiological basis for these disorders.

2.3. Methods

2.3.1. Participants and Assessment

Participants eight to 17 years of age were recruited through advertisements posted in local communities, local schools and physicians' offices in Alberta, Canada that invited parents of children with motor or attention problems and parents of children who did not have motor or attention problems to contact the investigators regarding the study. Parents who responded were screened by telephone. Exclusion criteria included diagnosed metabolic or genetic condition, epilepsy or other seizure disorder, cerebral palsy, intellectual disability, autism spectrum disorder, fetal alcohol spectrum disorder, psychiatric disorder other than ADHD, prematurity (born at <36 weeks gestation), and very low birth weight (<1500 grams). Participants with a previous diagnosis of DCD and/or ADHD were included; however, all participants were classified as DCD, ADHD, DCD+ADHD or controls based on standardized psychometric measures (Table 1). Those who scored less than the 16th percentile on The Movement Assessment Battery for Children – Second Edition (Henderson et al., 2007) and were reported by

parents as exhibiting motor difficulties that interfered significantly with daily functioning on the Developmental Coordination Questionnaire (Wilson et al., 2000) were classified as DCD. Children were classified as ADHD if they met the diagnostic criteria on the Diagnostic Interview for Children and Adolescents-IV (Reich et al., 1997), or had a T score above the 95th percentile on the Conner's' Parent Rating Scale-Revised (Conners et al., 1998) and were diagnosed by a physician as having ADHD based on DSM-IV criteria (American Psychiatric Association, 2000). Children meeting our research criteria for both DCD and ADHD were classified as DCD+ADHD. Children not meeting our research criteria for DCD, ADHD or DCD+ADHD were assigned to the typically developing control group.

Table 1: Participant Characteristics

	Controls	*ADHD*	*DCD*	*DCD+ADHD*
Age in years	11.3 +/- 2.8	12.5 +/- 2.9	13.0 +/- 2.5	11.5 +/- 3.0
N (females)	23 (12)	21 (1)[a]	7 (2)	18 (4)
Left-Handed	2	2	1	4
WASI IQ	113.0 +/- 13.4	105.4 +/- 11.8	107.0 +/- 13.0	104.8 +/- 15.8
CPRSC-C Score	51.7 +/- 9.5	72.5[a,b] +/- 8.7	50.9 +/- 3.9	72.2[a,b] +/- 12.0
CPRSC-H Score	51.6 +/- 9.4	71.1[a,b] +/- 14.1	49.7 +/- 3.4	65.0[a,b] +/- 13.8
MABC-2 Score	10.1 +/- 2.2	9.5 +/- 1.6	5.1[a,c] +/- 2.0	4.4[a,c] +/- 2.2

WASI IQ = Wechsler Abbreviated Scale of Intelligence IQ; CPRSC-C = Conner's Parent Rating Scale Revised Children Cognitive Problems Inattention; CPRSC-H = Conner's Parent Rating Scale Revised /Hyperactivity ; MABC-2 = Movement Assessment Battery for Children - Second Edition. [a]represents significant differences from healthy controls, [b]represents significant differences from the DCD group, [c]represents significant differences from the ADHD group ($p < 0.05$, corrected for multiple comparisons). CPRSC Scores were not available for one child in the ADHD group.

Children who were on stimulant treatment for ADHD were asked to refrain from taking their medication on the day of assessment. No children in the control and DCD groups were on stimulant medication, 11 of 21 the children in the ADHD group were on stimulant medication, and 9 of 18 children in the ADHD+DCD group were on stimulant medication. A significant difference was found between the control and ADHD groups for sex [χ (1, N = 44) = 9.69, $p <$ 0.002]. This is consistent with research, which has reported higher prevalence of ADHD in males (Ramtekkar et al., 2010). No group differences were found for age, handedness or IQ (Table 2.1). This research was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. This study received approval from the Conjoint Health Research Ethics Board of the University of Calgary. Written consent was obtained from parents/guardians, and verbal assent was obtained from the participants.

2.3.2. Image Acquisition and Analysis

Images were collected using a 3 Tesla GE MR scanner (Signa VH/i, GE Healthcare, Waukesha, WI) with an eight-channel phased-array radiofrequency head coil. Resting-state fMRI consisted of five minutes of a T_2*-weighted gradient-recalled echo, echo planar imaging (EPI) sequence (TR/TE = 2000/30ms, flip angle = 70 degrees, matrix size 64 x 64, FOV = 220mm x 220mm, 4-mm slice thickness, 26 slices). Participants were instructed to look at a fixation cross at the center of a screen. T_1-weighted images were obtained for anatomical registration of the fMRI data (multi-slice fast spoiled gradient echo; TR/TE = 200/2.5ms, flip angle = 18 degrees, matrix size = 128 x 128, FOV = 220 x 220mm, 4-mm slice thickness, 40 slices).

Resting-state fMRI data were pre-processed prior to statistical analysis using with the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl). This included scalp and skull removal using the Brain Extraction Tool (BET) (Smith, 2002), motion correction using MCFLIRT (Jenkinson et al., 2002), interleaved slice timing correction, temporal high pass filtering (> 0.01 Hz), spatial smoothing using a Gaussian kernel of 6 mm, and registration to the MNI standard template. T_1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). MCFLIRT analysis revealed no group difference in head motion, M1 centre of gravity, or degree of correlation among voxels within the mask. The center of gravity of the M1 mask and the degree of correlation among the voxels of the mask did not differ between groups. Thus, the M1 mask represented an equivalent region across all groups.

For each participant, a mask of left M1 was manually drawn on the anatomical image using the FSLView drawing tool, with the omega-shaped anatomical landmark of M1 as a guide (Yousry et al., 1995). The mask was registered to the native resting-state data space using FLIRT, and then reduced to a final volume of 100 contiguous voxels using the process of intervoxel cross-correlation, which identifies the region with the greatest homogeneity in terms of temporal synchrony (Golestani and Goodyear, 2011). The center of gravity and the degree of cross-correlation within the mask were each tested between subjects groups using a Student's *t*-test, to determine if there was a group bias in this method of mask generation.

The average time series of all the voxels in the left M1 mask was generated from the preprocessed resting-state data, to act as the regressor of interest in a time-series analysis using the general linear model (GLM). This analysis generated a whole-brain voxel-by-voxel estimate of FC with M1. The average time series from the segmented white matter masks, CSF masks and

six head motion parameters were used as nuisance regressors. Groups were compared using a mixed effects GLM model. FC maps were created for each participant group and for the differences between each group, using age as a co-factor. Exploratory image data analysis revealed that no differences in FC were associated with sex or handedness in each group (i.e., males and females demonstrated no significant differences in FC patterns); therefore, these variables were not included as co-factors in the group analysis, in order to maintain sufficient degrees of freedom. Average Z-statistic images for each group were generated for clusters of 25 or more voxels and a Z-score greater than 3.1, corresponding to a corrected cluster significance of $p = 0.05$ (Woolrich et al., 2004; Worsley, 2003). For differences between participant groups, Z-statistic images were generated for clusters of 75 or more voxels and a Z–score greater than 2.3 ($p = 0.05$). Brain regions within these Z-statistic images were anatomically identified by Brodmann's area and the Harvard-Oxford Cortical and Subcortical Structural atlas (Lancaster et al., 2007, 2000).

2.4. Results

2.4.1. Resting-State fMRI

Each group exhibited resting-state connectivity of motor circuitry consistent with that reported by (Deco and Corbetta, 2011). Brain regions exhibiting significant FC with the left M1 included the contralateral motor cortex, bilateral premotor cortices, somatosensory cortices and striatum. Figure 1 shows brain regions that differed significantly between the control group and all diagnostic groups. Compared to the control group, the DCD group demonstrated decreased FC with M1 in the bilateral inferior frontal gyri, right frontal operculum cortex, right supramarginal gyrus, bilateral insular cortices and superior temporal gyri (Table 2). Subcortical structures

exhibiting decreased FC included the bilateral caudate and the right nucleus accumbens, pallidum and putamen. No regions exhibited increased FC with M1. In the ADHD group, decreased FC with M1 was observed in the bilateral frontal eye fields, bilateral inferior frontal gyri, left middle frontal gyrus, right anterior cingulate cortex and frontopolar cortex. More posteriorly, decreased FC was observed in the bilateral supramarginal gyri, right auditory cortex and bilateral insular cortices. Subcortical structures that exhibited reduced connectivity with M1 in children with ADHD included the left amygdala, bilateral putamen, globus pallidus and brainstem. No regions exhibited greater FC with M1. Relative to controls, the DCD+ADHD group exhibited lower FC in the right motor cortex, left supramarginal gyrus, bilateral postcentral gyri, left putamen, left pallidum and left amygdala. Regions exhibiting greater FC with M1 included the left frontopolar cortex and lingual gyrus.

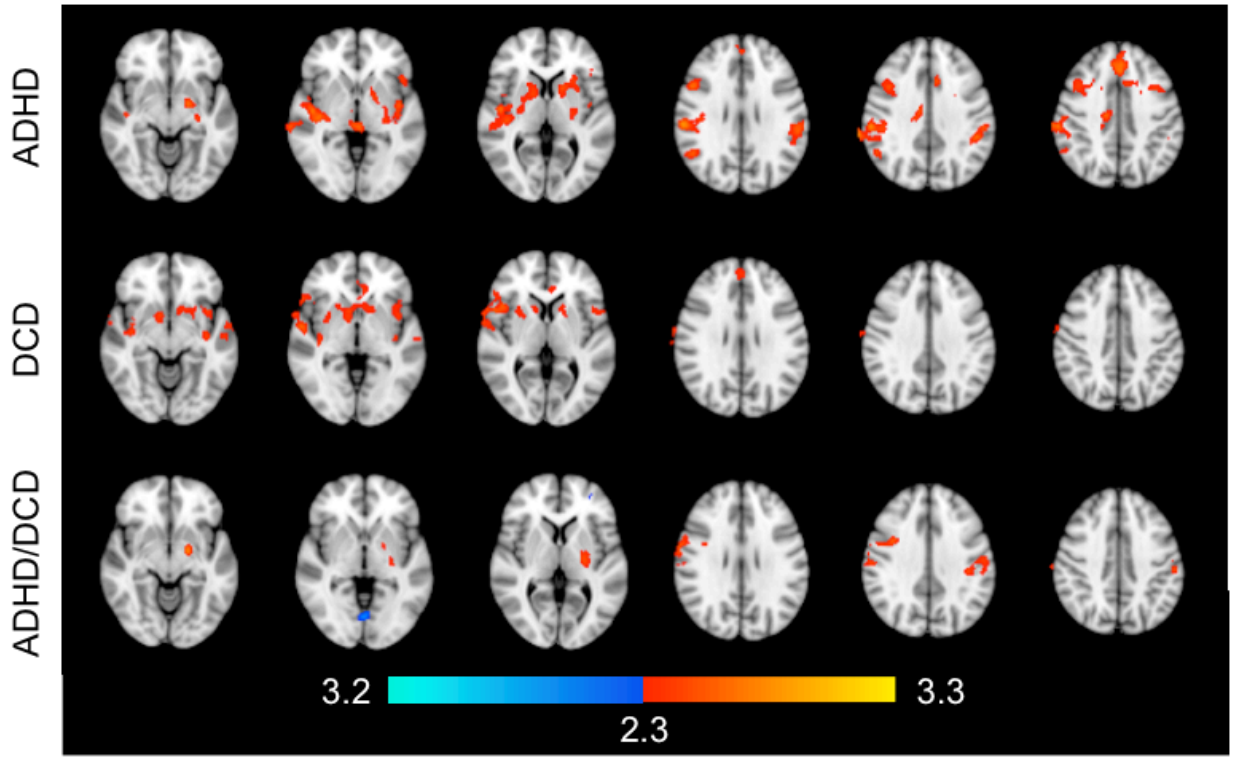

Figure 1. Regions exhibiting greater (red) and lower (blue) functional connectivity with left M1 in controls compared to children in the ADHD (top), DCD (middle), and DCD + ADHD (bottom) groups. Colors indicate statistical significance, expressed as *Z*-scores.

Table 2: Regions exhibiting altered functional connectivity with left primary motor cortex in children with DCD, ADHD and DCD+ADHD

Comparison	Brain Region	Z Score	x	y	z	BA
DCD < Controls	R Anterior Superior Temporal Gyrus/Planum Polare	3.16	58	-4	-2	6,22
	R Frontal Operculum Cortex	3.0	46	16	4	13
	R Inferior Frontal Gyrus/Precentral Gyrus	2.93	54	12	2	44,45
	R Caudate	2.88	8	10	0	-
	R Nucleus Accumbens	2.85	10	8	-6	-
	L Insular Cortex	2.79	-40	8	-6	13
	L Superior Temporal Gyrus (Anterior)	2.79	-56	-14	-6	-21
DCD < Controls	L Inferior Frontal Gyrus/Precentral	2.76	-54	10	2	13,44
	R Insular Cortex	2.71	38	0	-6	13
	L Anterior Cingulate Gyrus	2.71	-4	40	-4	24
	R Pallidum	2.66	14	4	-4	-
	L. Caudate (all)	2.66	-14	14	2	-
	Paracingulate Gyrus/Superior Frontal Gyrus	2.56	0	48	28	9
	R Putamen (ventral)	2.53	28	8	2	-
	R Parietal Operculum	2.53	52	-32	22	13
ADHD < Controls	R Parietal Operculum Cortex/Supramarginal Gyrus	3.69	60	-26	28	40
	R Auditory Cortex/Insular Cortex	3.58	46	-10	0	13
	Frontal Eye Fields	3.29	0	30	40	8
	L Pallidum	3.28	-18	-4	-8	-

Comparison	Brain Region	Z Score	x	y	z	BA
	R Inferior Frontal Gyrus	3.26	48	14	30	9
	L Angular/Supramarginal Gyri	3.26	-54	-52	22	22,39,40
	L Supramarginal Gyrus	3.21	-48	-40	34	40
	Brainstem	3.17	-2	-28	2	-
	L Amygdala	2.97	-20	-6	-10	-
	L Insular Cortex	2.96	-42	-6	-2	13
	L Inferior Frontal Gyrus	2.89	-44	32	2	45,47
	R Anterior Cingulate Gyrus	2.88	-8	18	34	24,32
	L Putamen	2.71	-28	-12	2	-
	R Putamen, Pallidum	2.67	20	4	6	-
	L Middle Frontal Gyrus	2.66	-38	10	40	6
DCD+ADHD < Controls	L Pallidum	3.55	-18	-6	-8	-
	R Postcentral Gyrus	3.49	64	-8	26	4
	R Motor Cortex	3.32	62	2	26	6
	L Supramarginal Gyrus (Anterior)	2.96	-56	-26	38	2,40
	L Putamen/Pallidum (Dorsal)	2.85	-26	-14	6	-
	L Amygdala	2.79	-20	-8	-12	-
	L Postcentral Gyrus	2.71	-56	-16	34	3
DCD+ADHD > Controls	Lingual Gyrus	3.46	0	-72	-2	-
	L Lingual Gyrus	3.41	-4	-84	-16	-
	L Frontopolar Cortex	3.22	-26	64	8	10

BA = Brodmann's Area, L = left, R = right. Coordinates (x, y, and z) given in mm of MNI template space.

Direct comparison of the clinical groups revealed greater FC with M1 in the left postcentral gyrus and left superior frontal gyrus in children with DCD compared to ADHD (Table 3). The ADHD group exhibited greater FC compared to the DCD group in the right caudate, middle frontal gyrus, left superior temporal gyrus and bilateral inferior frontal gyri. Compared to the DCD+ADHD group, children with ADHD exhibited greater FC between M1 and the left postcentral gyrus. Children with DCD+ADHD evidenced greater FC between M1 and the bilateral precuneus cortices and anterior cingulate gyri, the left premotor cortex and postcentral gyrus, and the right parietal operculum cortex and angular gyrus, compared to children with ADHD. In comparison with the DCD group, children with DCD+ADHD exhibited greater FC between M1 and the bilateral caudate nuclei and anterior superior temporal gyri, the left premotor cortex, postcentral gyri and frontopolar cortex, and the right inferior frontal gyrus and parietal operculum cortex.

Table 3: Regions exhibiting altered functional connectivity with left primary motor cortex between clinical groups

Comparison	Brain Region	Z Score	x	y	z	BA
DCD > ADHD	L Postcentral Gyrus	3.70	-32	-30	54	3
	L Superior Frontal Gyrus	2.67	-2	44	40	8
ADHD > DCD	R Caudate	3.33	8	12	-2	-
	R Middle Frontal Gyrus	3.01	52	44	4	10
	L Superior Temporal Gyrus	2.98	-56	-2	-10	22
	R Inferior Frontal Gyrus	2.79	48	20	16	44
	L Inferior Frontal Gyrus	2.72	-56	10	2	44
ADHD > DCD+ADHD	L Postcentral Gyrus	2.98	-58	-14	34	3
DCD+ADHD > DCD	R Caudate	3.27	8	12	-2	-
	L Premotor Cortex	3.25	-26	-12	70	6
	R Inferior Frontal Gyrus	3.10	52	12	4	44
	L Postcentral Gyrus	3.09	-50	-16	58	3
	L Anterior Superior Temporal Gyrus	3.02	-58	0	-8	22
	L Frontopolar Cortex	2.92	-28	62	8	10
	R Anterior Superior Temporal Gyrus	2.86	58	-4	-2	22
	R Parietal Operculum Cortex	2.75	54	-22	20	40
	L Caudate	2.62	-8	14	0	-
DCD+ADHD > ADHD	L Premotor Cortex	3.91	-28	-12	70	6
	L Anterior Cingulate Cortex	3.12	-12	20	36	32
	R Parietal Operculum Cortex	2.99	54	-24	24	40
	L Postcentral Gyrus	2.94	-28	-30	56	3
	R Precuneus Cortex	2.73	18	-72	40	31
	R Anterior Cingulate Cortex	2.66	4	32	28	32
	L Precuneus Cortex	2.60	-10	-72	30	31

Comparison	Brain Region	Z Score	x	y	z	BA
	R Angular Gyrus	2.59	54	-52	32	40

BA = Brodmann's Area, L = left, R = right. Coordinates (x, y, and z) given in mm of MNI template space.

2.4.2. Connectivity Association with Age

In controls, increasing age was associated with greater FC between M1 and the bilateral precentral and postcentral gyri as well as the right superior frontal gyrus (Figure 2, Table 4). Lower FC was observed in the bilateral occipital poles, left lingual gyrus, and right anterior cingulate cortex. In the DCD group, older age was associated with greater FC between M1 and the left frontal pole, left precuneus cortex and right paracingulate gyrus, and lower FC between M1 and the left occipital lobe, right motor cortex, left supplementary motor area and thalamus. In the ADHD group, age was positively associated with greater FC between M1 and a number of brain regions including the dorsolateral prefrontal cortices, paracingulate gyrus, right superior and middle temporal gyri, right insular cortex, lateral occipital cortices and precuneus. Older age was associated with lower FC between M1 and the angular gyri, left precentral and middle frontal gyri, right anterior cingulate cortex, and left superior lateral occipital cortex. In the DCD+ADHD group, increasing age was not associated with greater FC in any brain regions. Increasing age, however, was associated with lower FC between M1 and the right angular gyrus, lateral occipital cortex, and right superior and middle temporal gyri.

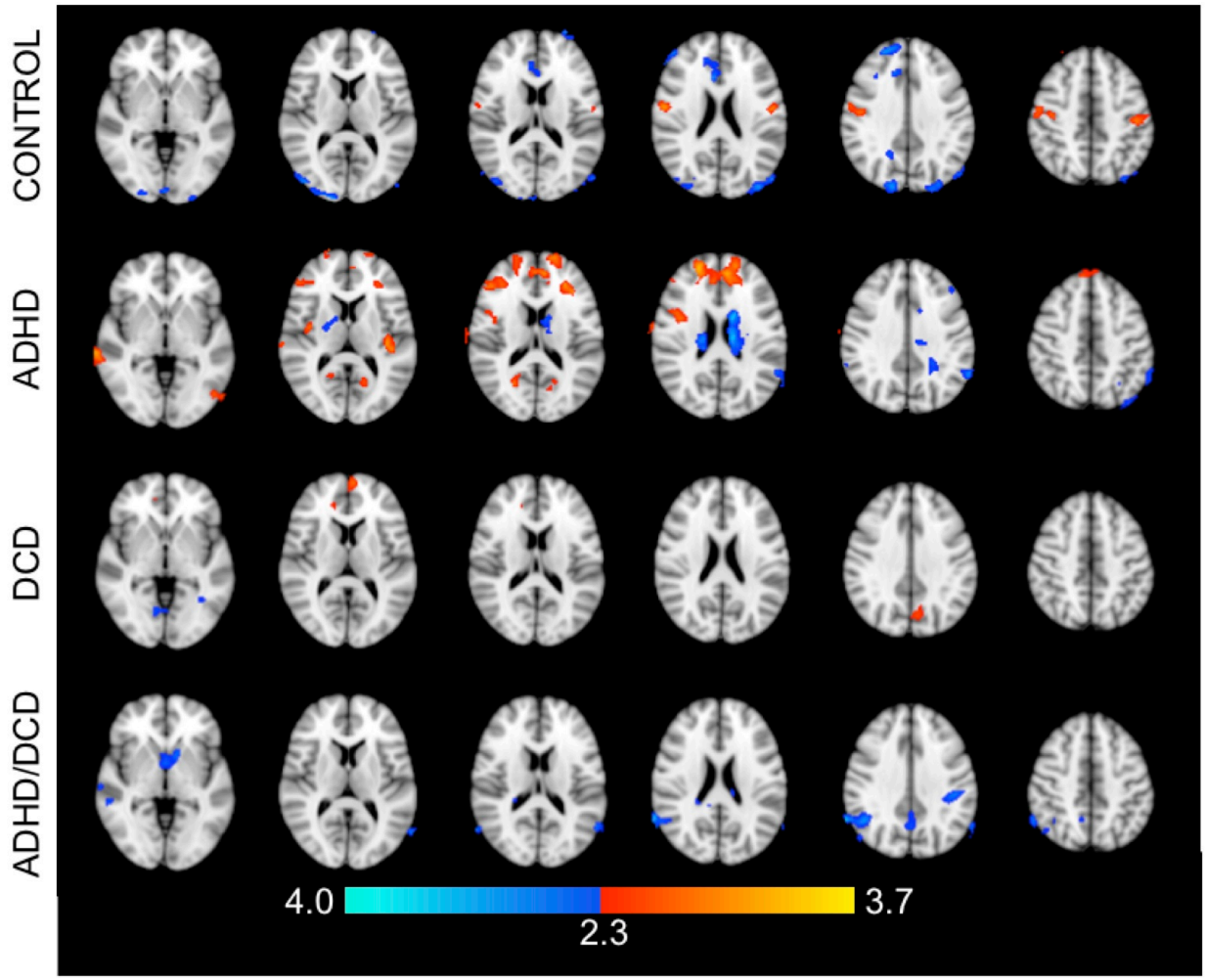

Figure 2. Regions exhibiting a significant association between age and functional connectivity with the left M1. Colors indicate statistical significance, expressed as *Z*-scores; red indicates a positive association with age; blue indicates a negative association with age.

Table 4: Regions exhibiting a dependence of functional connectivity on age

	Brain Region	Z Score	x	y	z	BA
Increase with Age (Controls)	R Precentral and Postcentral Gyrus (entire)	4.24	58	-8	24	4
	R Superior Frontal Gyrus	4.14	28	28	58	6
	L Precentral Gyrus	4.08	-34	-6	68	6
	L Postcentral Gyrus (entire)	3.41	-46	-22	46	1,2
	R Precentral Gyrus	3.36	40	-2	64	6
Decrease with Age (Controls)	L Lingual Gyrus	3.74	-6	-84	-10	-
	R Lateral Occipital Cortex/Occipital Pole	3.72	18	-88	36	19
	L Lateral Occipital Cortex (Superior)/ Occipital Pole	3.63	-42	-84	30	19
	R Anterior Cingulate Gyrus	3.59	6	22	22	24
	R Frontal Pole	3.56	20	50	34	9
Increase with Age (DCD)	L Frontopolar Cortex	3.19	-4	62	10	10
	L Precuneus Cortex	2.85	-8	-70	36	7
	R Paracingulate Gyrus	2.69	12	48	2	32
Decrease with Age (DCD)	L Occipital Fusiform Gyrus	3.28	-24	-74	-14	19
	L Occipital Pole/Lingual Gyrus/Occipital Fusiform Gyrus	3.2	-20	-92	-16	18
	R Precentral Gyrus	3.00	22	-22	58	4
	L Supplementary Motor Area	2.96	-10	-4	50	6
	L Intracalcarine Cortex	2.77	-4	-88	4	18
	R Thalamus	2.73	4	-18	4	-
Increase with Age (ADHD)	R Superior Frontal Gyrus/DLPFC	4.17	20	52	24	9
	Paracingulate Gyrus	3.95	-8	48	22	32

	Brain Region	Z Score	x	y	z	BA
Increase with Age (ADHD)	R Superior and Middle Temporal Gyrus, Posterior	3.94	70	-26	2	21, 22
	L Heschl's Gyrus	3.88	-38	-24	8	13
	L DLPFC	3.85	-18	62	20	9, 10
	Brainstem	3.78	0	-10	-12	-
	R Inferior Temporal Gyrus (temporooccipital)/ Lateral Occipital Cortex, Inferior	3.68	56	-54	-12	20
	L Lateral Occipital Cortex, Inferior	3.63	-40	-64	4	37
	L Temporal Occipital Fusiform Cortex	3.49	-30	-46	-16	37
	R Middle Frontal Gyrus	3.42	48	36	18	46
	R Supracalcarine/Precuneous Cortices	3.24	24	-64	16	30, 31
	R Insular Cortex	3.19	40	-4	12	13
	L Supracalcarine/Precuneous/ Intracalcarine Cortices	3.03	-16	-64	12	30
Decrease with Age (ADHD)	L Angular Gyrus/Supramarginal Gyrus	3.76	-58	-54	26	40
	R Anterior Cingulate Gyrus/Paracingulate Gyrus	3.45	8	12	38	32
	L Superior Lateral Occipital Cortex	3.29	-32	-76	52	7
	L Precentral Gyrus	3.11	-10	-14	68	6
	L Middle Frontal Gyrus	2.82	-38	32	42	8
	R Supramarginal Gyrus (posterior)/Angular gyrus	2.81	62	-44	32	40
Decrease with Age (DCD+ADHD)	R Angular Gyrus/Lateral Occipital Cortex (Superior)	5.16	66	-52	30	39, 40
	R Planum Polare/Superior Temporal Gyrus/Middle Temporal Gyrus (posterior)	3.96	52	-12	-12	13, 21, 22

Coordinates (x, y, and z) are given in mm of MNI template space; BA = Brodmann's Area.

2.5. Discussion

This study is the first to report that children with motor and/or attention problems exhibit altered FC with M1 within the motor network as well as with brain regions involved in cognitive control of movement and sensorimotor processing.

2.5.1. Resting-State Motor Connectivity of Children with DCD

The alterations in FC we observed in children with DCD are consistent with commonly reported deficits in motor execution, motor control, motor planning and sensorimotor processing. Reduced FC between M1 and the caudate, putamen, and globus pallidus in children with DCD suggests disrupted connectivity between regions associated with motor execution and motor control. Similarly, reductions in connectivity between M1 and the inferior frontal gyrus is consistent with disruptions in fine motor control, inhibition and integration of sensory input into action reported previously (Liakakis et al., 2011). Consistent with decreased insular cortex involvement during trail-tracing in children with DCD (Zwicker et al., 2010), we observed reduced FC between M1 and the posterior insular cortex, which could also be related to disruptions in sensorimotor processing and motor output (Cauda et al., 2012) . Cognitive control regions related to working memory and motor planning (i.e., prefrontal cortex) also exhibited altered FC in children with DCD. As a result, motor execution regions may receive degraded input from areas responsible for motor planning, organization and regulation (Christoff and Gabrieli, 2000).

2.5.2. Resting-State Motor Connectivity of Children with ADHD

Reduced FC in the striatum, putamen and other subcortical structures in children with ADHD is consistent with observations of previous imaging studies (Cao et al., 2009; Castellanos et al., 1996; Durston et al., 2003; Suskauer et al., 2008). Lower connectivity between M1 and the frontal eye fields, areas associated with visual attention (Schall, 2004), and the left post central gyrus, a key component of the neural network involved in working memory (du Boisgueheneuc et al., 2006), could be linked to deficits in visual attention and working memory observed in children with ADHD (Martinussen et al., 2005; Swanson et al., 1991). Decreased FC in the inferior frontal gyri could play a part in the motor inhibition difficulties associated with ADHD (Cao et al., 2006; Zang et al., 2007), which is further supported by previous task-related fMRI studies (Booth et al., 2005; Durston et al., 2006; Liakakis et al., 2011). Previous imaging research has reported reduced grey matter volume of the left insular cortex in children with ADHD (Brieber et al., 2007). Further, increased cortical thickness (Duerden et al., 2012) and increased activity during an fMRI-based attention-reorientation task (Konrad et al., 2006) have been reported in the right insular cortex. Given the multiple functions performed by the insular cortices, it is not surprising that abnormal connectivity between the M1 and the insular cortices are associated with attention difficulties.

2.5.3. Resting-State Differences in Single versus Co-occurring Disorders.

Compared to typically developing controls, children with co-occurring DCD and ADHD evidenced lower FC between M1 and the somatosensory cortices, left supramarginal gyrus, striatum and amygdala, suggesting poor integration between sensorimotor input, motor execution and movement regulation. In contrast, compared to children with only DCD or ADHD, the

DCD+ADHD group exhibited greater FC between M1 and brain regions involved in motor control (bilateral caudate, left premotor cortex, right inferior frontal gyrus), speech processing and prosody (bilateral anterior superior temporal gyri), sensorimotor processing (left postcentral gyrus, right parietal operculum cortex, bilateral precuneus cortices, angular gyri) and attention and error detection (bilateral anterior cingulate cortices) compared to children with only DCD or ADHD. These findings, though unexpected, may suggest that some connections between M1 and processing areas may be erroneous, such that greater involvement of these regions is needed to successfully plan and execute movement (Zwicker et al., 2010). More research is needed that examines the influence of erroneous connectivity between brain areas on motor output.

2.5.4. Common Neurophysiological Substrates

Our findings support the hypothesis that common neurophysiological substrates may underlie both motor and attention problems. We found that a number of brain regions (i.e., bilateral inferior frontal gyri, the right supramarginal gyrus, angular gyri, insular cortices, amygdala, putamen and pallidum) exhibited similar FC alterations in children with DCD and/or ADHD, which may represent putative targets for future study and potential biomarkers for DCD and ADHD.

The angular gyri act as multimodal integration centers active during tasks such as reading, comprehension, spatial cognition and attention (Vannini et al., 2004). Imaging research has implicated these regions in both DCD (Kashiwagi et al., 2009; Querne et al., 2008; Zwicker et al., 2011, 2010) and ADHD (Dickstein et al., 2006). The angular gyri are also part of the fronto-parietal network, which is responsible for integrating internal and external information for response generation (Binkofski et al., 1999). In individuals affected by ADHD, fMRI tasks

involving motor inhibition have been found to result in decreased activity within this network (Dickstein et al., 2006). Our observation of lower FC between M1 and the angular gyri in the DCD and ADHD groups compared to the controls suggests that the information provided by this region to M1 may be degraded, which in turn could impact motor performance. The putamen and pallidum, key regulators of movement and motor learning (Kandel et al., 2000), exhibited lower FC with M1 in all diagnostic groups. Reduced FC between this region and M1 could also contribute to the movement difficulties associated with DCD and ADHD, as striatal structures receive information from regions throughout the brain and directly interact with M1.

The supramarginal gyri (secondary somatosensory cortices) are responsible for integrating tactile or pain-based stimuli with higher order functions such as attention (Chen et al., 2008). Decreased FC with M1 was observed in the right supramarginal gyrus (secondary somatosensory cortex) in the DCD and ADHD groups, and in the left supramarginal gyrus in the DCD+ADHD group. Other sensorimotor regions also displayed decreased FC with M1. In the DCD and ADHD groups, decreased FC was observed with the insular and secondary somatosensory cortices. In contrast, in the DCD+ADHD group decreased FC was observed with the primary somatosensory cortices. Further, the posterior insular cortices exhibited lower FC in the DCD and ADHD groups; however, a similar decrease in FC was not observed in the DCD+ADHD group. These findings suggest that alterations in FC between primary motor cortex and sensory networks differ between children with isolated DCD or ADHD and children with co-occurring DCD+ADHD. The functional consequences of these differences needs to be investigated further; however, they could be associated with differences in severity of the sensory processing dysfunction (Crawford and Dewey, 2008).

2.5.6 Connectivity Association with Age

Volumetric MRI studies of children with ADHD have reported decreased volume and delayed cortical thickness changes as age progresses, particularly in regions associated with motor control (Castellanos et al., 2002; Shaw et al., 2012, 2007), In our study, typically developing children exhibited increased FC between M1 and the bilateral motor and sensorimotor cortices as age increased; a finding not observed in children with DCD and/or ADHD. This is a novel finding and may provide the basis for a subjective biomarker of motor and attention problems in future studies. Our findings of increasing FC with age between M1 and frontal and parietal regions involved in executive functions, memory and visuospatial imagery in children with DCD is consistent with the research that has reported symptom remission in adolescence in children with milder symptoms of motor impairments (Cantell et al., 2003). In the ADHD group, increasing FC with age between M1 and regions of the frontal cortex is consistent with a delay in the development of regions associated with inhibition, impulsivity, and attention. Increased FC between M1 and frontal cognitive areas such as the dorsolateral prefrontal cortex, could be associated with the remission of symptoms such as hyperactivity, impulsivity and inattention, in children with ADHD as they mature (Biederman et al., 2000). Finally, in the DCD+ADHD group, the absence of increased FC with age between M1 and any brain structures suggests that brain development in children with co-occurring attention and motor disorders could be disrupted to a greater extent than that of children who present with only one disorder.

2.5.7. Limitations and Future Research

Cortical development in children is influenced by many factors, including environmental and social occurrences not covered by our exclusion criteria. Our seed based correlation approach is

a highly reliable and allows for straightforward interpretation of the results; however, it is prone to spatial confounds and structural noise (motion, scanner artifacts), and may under represent the data due to the strict area selected. One future alternative approach would be independent component analysis (ICA), which is less prone to noise but is susceptible to statistical complexities (Cole et al., 2010). Our limited sample size and cross-sectional design limits the validity of the findings; however, the feasibility of the design provides a strong foundation upon which future, longitudinal study paradigms cam be built, including investigations of DCD and ADHD subtypes.

FC alterations may reflect atypical brain development in children with DCD and/or ADHD and could explain the activation differences frequently observed in task-based fMRI studies (Booth et al., 2005; Durston et al., 2006, 2003; Kashiwagi et al., 2009; Mostofsky et al., 2006; Suskauer et al., 2008; Zwicker et al., 2011, 2010). Future research investigating the relationship between FC and task-based fMRI activity is warranted to shed light on how abnormal inter-regional communication may lead to the observed deficits.

Our findings of altered FC between M1 and the insular, somatosensory cortices, striatum, and inferior frontal gyri in children with DCD supports the hypothesis that DCD is a disorder of sensorimotor processing (Wilson and McKenzie, 1998). Central problems in DCD are movement control and visuospatial processing, which rely on integrated information from visual, kinesthetic and vestibular systems (Wilson and McKenzie, 1998). The results of studies investigating kinesthetic and sensorimotor ability in children with ADHD have been inconsistent, possibly because of the confounding effect of unacknowledged motor problems (Piek and Dyck, 2004). Future research is needed to determine if children with only ADHD have overt problems with sensorimotor processing.

2.5.8. Conclusions

Compared to typically developing controls, children with DCD and/or ADHD exhibit FC alterations between M1 and brain regions involved in motor functioning and sensorimotor processing. Our findings support the hypothesis that common neurophysiological substrates underlie both motor and attention problems. The decreased FC between the primary motor cortex, and the striatum and angular gyrus observed in all groups of children with motor and attention problems suggests that the these brain regions are common neurophysiological substrates underlying DCD and ADHD. Our results also indicated that children with co-occurring DCD and ADHD appear to have unique alterations in FC between primary motor cortex and sensory networks compared to children with DCD or ADHD alone; suggesting that co-occurrence of neurodevelopmental disorder may have a distinct impact on FC.

CHAPTER 3: HEMISPHERIC ASYMMETRY OF MOTOR CORTEX FUNCTIONAL CONNECTIONS IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

3.1 Abstract

Developmental coordination disorder (DCD) and attention-deficit hyperactivity disorder (ADHD) are highly comorbid neurodevelopmental disorders. Behavioural and neuroimaging research suggest that children with DCD and ADHD have altered brain region communication, particularly with the motor network. Studies of typical populations have established that there is structural and functional hemispheric asymmetry in motor network of the brain. Alterations in hemispheric asymmetry in the motor network could be associated with DCD and ADHD. The present study used resting-state fMRI to examine hemispheric asymmetry of functional connectivity (FC) with the primary motor cortex in children with DCD, ADHD, and DCD+ADHD, relative to typically developing children. Our findings revealed that typically developing children had greater FC between the right motor cortex and left cerebellar regions V and VI compared to children with DCD, ADHD and DCD+ADHD. In contrast, children with DCD and/or ADHD exhibited greater FC between the left motor cortex and right cerebellar regions V and VI relative to controls, suggesting that there are consistent interhemispheric connectivity changes in the left and right motor networks in these children. These findings suggest that children with DCD and/or ADHD display reduced input from the right hemisphere for motor functions; supporting the hypothesis that atypical motor network asymmetry is associated with these disorders.

3.2 Introduction

Developmental coordination disorder (DCD) is one of the most common neurodevelopmental disorders of childhood, affecting 5-6% of school-aged children (American Psychiatric Association, 2013; Blank, 2012). DCD is characterized by an impairment of motor coordination that significantly interferes with activities of daily living, and impacts academic/school productivity, prevocational and vocational activities, as well as leisure and play (American Psychiatric Association, 2013; Blank, 2012). Clinical presentation of DCD is diverse (Kaplan et al., 1998; Schoemaker et al., 2013; Vaivre-Douret, 2014; Visser, 2003), but up to 50% of children with DCD also meet the criteria for attention-deficit/hyperactivity disorder (ADHD) (Kadesjo and Gillberg, 1998; Pitcher et al., 2003). ADHD occurs in approximately 5% of children (Kadesjo and Gillberg, 2001) and is associated with age-inappropriate levels of inattention, hyperactivity and/or impulsivity (American Psychiatric Association, 2013). The etiology behind the comorbidity of DCD and ADHD, however, is not well understood.

Children with DCD often exhibit functional deficits in cross-modal integration (integration of information from different sensory modalities), specifically during tasks that demand visual feedback for motor control (Wilson and McKenzie, 1998), internal/forward modeling (i.e., movement planning), gait and postural control, visual perception and motor coordination (Dewey et al., 2007; Wilson et al., 2013). A finger tapping switch task demonstrated that children with DCD displayed poorer inhibition in tapping with their left finger in comparison to control children. Further children with DCD showed less improvement in motor inhibition with age compared to controls (Tallet et al., 2013). Similar deficits on a task used to examine cross-modal integration were observed in children with ADHD (Hale et al., 2009). Studies of typical individuals and split-brain patients indicate that tasks requiring successful integration of motor,

cognitive and emotional processing, rely on inter-regional brain region communication, both within and between hemispheres (Compton et al., 2008; Sauerwein and Lassonde, 1997; Toro et al., 2008), especially as tasks become more complex (Mostofsky et al., 2006; Scholz et al., 2000; Solodkin et al., 2001; Weissman and Banich, 2000). For example, simple unilateral movements of the fingers recruit the contralateral motor network, whereas complex movements, like catching a ball, running or riding a bicycle, elicit bilateral activation of both the cortical and subcortical components of the motor network, and are reliant on proficient communication between and within hemispheres (Mostofsky et al., 2006; Scholz et al., 2000; Solodkin et al., 2001). Thus, it is plausible that the motor deficits observed in children with DCD and ADHD could be associated with disruptions in inter-regional brain communication.

Evidence from structural neuroimaging studies supports the presence of inter-regional communication deficits in children with DCD and ADHD. One neuroimaging study using diffusion tensor imaging (DTI) identified reduced white matter integrity in children with DCD within the posterior corpus callosum, which connects the parietal lobes of the two hemispheres (Langevin et al., 2014). Given the important role of the parietal lobes in visuospatial function and sensorimotor integration, degraded integrity of the posterior corpus callosum could be a contributor to visuomotor deficits associated with DCD. Imaging studies have reported reduced volume of the corpus callosum in children with ADHD (Roessner et al., 2004), as well as significantly reduced volumes of the splenium and the right cerebral hemisphere (Valera et al., 2007). A meta-analysis of DTI studies of children with ADHD found reduced white matter integrity within the right forceps minor near the corpus callosum and the anterior corona radiate (van Ewijk et al., 2012). Another study reported reduced integrity within the anterior corpus callosum (Langevin et al., 2014).

The findings of functional magnetic resonance imaging (fMRI) studies also support the presence of inter-regional communication deficits in children with DCD and ADHD. Altered levels of brain activity have been found during the performance of tasks known to engage brain networks that have extensive connections between and within hemispheres. For example, two studies of children with DCD using complex tracing tasks observed altered activity within visuospatial regions (Kashiwagi et al., 2009; Zwicker et al., 2010). In children with ADHD, studies using Go/No Go tasks, which require responses using the right hand and thus the left hemisphere activation, noted reduced activity of the right inferior frontal gyrus (IFG) during task response inhibition (Booth et al., 2005; Garrett et al., 2008; Rubia et al., 2005). Reduced right parietal lobe and motor cortex activation were also observed in children with ADHD relative to controls, during complex finger tapping and finger sequencing tasks, which demand inter-regional communication (Mostofsky et al., 2006).

Communication among brain regions involved in the planning and execution of motor behaviors ultimately converges upon the primary motor cortex (M1) to generate movement. Hence, one possible way of probing inter-regional communication between brain regions of the motor network in children with DCD and/or ADHD is to observe how M1 communicates with these regions. Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive imaging technique that can be used for this purpose. Resting state fMRI examines the temporal synchrony of low-frequency (< 0.1 Hz) fMRI activity between brain regions while a participant is at rest. The degree of synchrony is referred to as functional connectivity. Greater synchrony (typically measured using temporal cross-correlation or a similar approach) is thought to reflect a stronger functional connection between regions.

Our recent study found reduced functional connectivity between left M1 and structures of the basal ganglia, including the caudate, putamen and globus pallidus in children with DCD, ADHD, and DCD+ADHD, compared to controls (McLeod et al., 2014). In the DCD and ADHD groups, reduced functional connectivity was also found between left M1 and the insular cortices. In the DCD+ADHD group, reduced functional connectivity was observed between left M1 and the right motor cortex. These results strongly support the assertion that inter-regional communication deficits of the motor network are indeed associated with ADHD and DCD, and may involve altered communication between the motor cortex and basal ganglia.

It is well established that there is hemispheric asymmetry in the normal development of the motor network of the brain, which is associated with handedness. Structurally, right-handed individuals have a deeper left central sulcus than left-handed individuals (Amunts et al., 2000). The left motor cortex in right-handed individuals also has greater neuropil volume, which reflects the amount of dendrites, axons and synapses (Amunts et al., 1996). In term infants, a DTI study demonstrated that the left corticospinal tract is more structurally developed than the right (Dubois et al., 2009). Functionally, fMRI in typically developing individuals has demonstrated that the left motor cortex exhibits greater activation with both ipsilateral and contralateral movements compared to the right motor cortex in right-handed adults (Kim et al., 1993). One hypothesis why this asymmetry in the motor network develops is based on the "cortical activation theory", that postulates that early in childhood development the left motor cortex inhibits the right motor cortex to prevent mirror movements of the left hand (Todor and Lazarus, 1986). Subcortical regions of the motor network likely play a key role in this process.

Abnormalities in the development of structural and functional asymmetry of the motor network could be associated with DCD and ADHD (Rubia et al., 2010). In children with ADHD,

the normal pattern of asymmetric cortical thickness of prefrontal cortex is not observed (Shaw et al., 2009). Instead children with ADHD have reduced cortical thickness in this region. Hence, it is possible that typical hemispheric asymmetry of motor function is altered in the presence of DCD and/or ADHD.

In light of this evidence, the main purpose of this study was to determine if the differences with connectivity in the left and right motor cortices found in typically developing children are altered in children with DCD, ADHD or DCD+ADHD. We hypothesized that asymmetry of functional connectivity between M1 and the left and right motor cortices would be altered in children with ADHD, DCD, and ADHD+DCD, specifically within the motor cortices and subcortical regions of the motor network (thalamus and basal ganglia). In children with DCD, we hypothesized that functional connectivity between the motor network and parietal lobes would also be affected.

3.3 Methods

3.3.1 Participants and Assessment

Participants were recruited from local schools and community advertisements in locations such as hospitals and physician's offices in Calgary, Alberta, Canada. Children were classified as DCD, ADHD, DCD+ADHD or controls based on performance on standardized psychometric measures (Table 3.1). Children who scored below the 16th percentile on The Movement Assessment Battery for Children (MABC) – Second Edition (Henderson et al., 2007) (which indicates children who are at risk for or have significant motor difficulty) and were reported by their parents as exhibiting motor difficulties that interfered significantly with daily functioning on the Developmental Coordination Questionnaire (Wilson et al., 2000) were classified as DCD.

Children were classified as ADHD if they met diagnostic criteria as described in the Diagnostic Interview for Children and Adolescents-IV (Reich et al., 1997), or had a T-score above the 95th percentile on the Conners Parent Rating Scale-Revised (Conners et al., 1998) and were diagnosed by a physician as having ADHD based on DSM-IV criteria. Children meeting criteria for both DCD and ADHD were classified as DCD+ADHD. Children not meeting the criteria for DCD, ADHD or DCD+ADHD were assigned to the control group. In total, 6 participants were classified as DCD, 19 as ADHD, 14 as DCD+ADHD, and 21 as typically developing controls. All participants were right handed. Exclusion criteria included: history of a diagnosed metabolic or genetic condition, epilepsy or other seizure disorder, cerebral palsy, psychiatric disorder other than ADHD, intellectual disability, autism spectrum disorder, fetal alcohol spectrum disorder, prematurity (born at <36 weeks gestation), very low birth weight (<1500 grams), or severe traumatic brain injury. There were no group differences for age or IQ (see Table 1); however, the control group had a significantly higher proportion of females compared to the other groups [$\chi(1, N=60) = 13.1, p < 0.05$]. Children on stimulant treatment for ADHD were asked to refrain from taking medication on the day of imaging. No children in the control and DCD groups were on stimulant medication, 19 of the children in the ADHD group were on stimulant medication, and 13 of children in the DCD+ADHD group were on stimulant medication. This research was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. The appropriate institutional review board for the ethics of human research approved this study. Consent and verbal assent were obtained from parents and children, respectively, after study procedures were fully explained.

Table 3.1: Participant Data

Demographic	*Controls*	*ADHD*	*DCD*	*ADHD/DCD*
Average Age	11.05 +/- 2.84	12.37 +/- 3.06	13 +/- 2.76	11.29 +/- 3.81
(range)	(8-17)	(8-17)	(9-17)	(8-16)
N (females)	21 (11)	19 (1)	6 (1)	14 (3)
IQ	111.7 +/- 13.3	107.1 +/- 11.0	108.3 +/- 13.7	103.5 +/- 16.5
CPRSC-C Score	51.90 +/- 9.77	73.67 +/- 8.01*	50 +/- 3.52	70.64 +/- 12.6*
CPRSC-H Score	50.71 +/- 7.96	72.0 +/- 14.5*	49.3 +/- 3.50	64.1 +/- 14.5*
M-ABC2 Score	10.3 +/- 2.23	9.47 +/- 1.65	5.50 +/- 1.87*	4.07 +/- 2.37*

No significant differences for age. CPRSC-C/H, Connor's Parent Rating Scale Revised Children Cognitive Problems/Inattention (C), Hyperactivity (H), MABC-2, Movement Assessment Battery for Children - Second Edition. * represents significant differences observed between study groups and controls (student's t-test, $p < 0.05$, corrected for multiple comparisons). CPRSC Scores were not available for one child with ADHD.

3.3.2 Image Acquisition and Analysis

Images were collected using a 3 Tesla GE MR scanner (Signa VH/i, GE Healthcare, Waukesha, WI) with an eight-channel phased-array radiofrequency head coil. Resting-state fMRI consisted of five minutes of a T_2*-weighted gradient-recalled echo, echo planar imaging (EPI) sequence (TR/TE = 2000/30ms, flip angle = 70 degrees, matrix size 64 x 64, FOV = 220 mm x 220 mm, 4-mm slice thickness, 26 slices). Participants looked at a fixation cross at the center of a screen during imaging. T_1-weighted images were obtained for anatomical registration of the fMRI data (multi-slice fast spoiled gradient echo; TR/TE = 200/2.5ms, flip angle = 18 degrees, matrix size = 128 x 128, FOV = 220 mm x 220 mm, 4-mm slice thickness, 40 slices).

Prior to statistical analysis, resting-state fMRI data underwent pre-processing using with the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl), which included scalp and skull removal using the Brain Extraction Tool (BET) (Smith, 2002), motion correction using MCFLIRT (Jenkinson et al., 2002), interleaved slice timing correction, temporal high pass filtering (>0.01 Hz), spatial smoothing using a Gaussian kernel of 6 mm, and registration to the Montreal Neurological Institute standard template. T_1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001).

Masks of the left (LM1) and right (RM1) primary motor cortices were manually drawn for each participant on the anatomical images using the FSLView drawing tool, with the omega-shaped anatomical landmark of the motor cortex as a guide (Yousry et al., 1995). Masks were registered to the participants native resting-state data space using FLIRT, and then reduced to a final volume of 100 contiguous voxels using the process of intervoxel cross correlation, which identifies the region within the mask with the greatest homogeneity in terms of temporal synchrony (Golestani and Goodyear, 2011). The center of gravity and the degree of cross-correlation within masks were each tested between subjects groups using a Student's *t*-test prior to analysis. This analysis revealed there was no group bias in this method of mask generation.

The average time series of all the voxels in the final masks was generated from the preprocessed resting-state data, to act as the regressor of interest in a time-series analysis using the general linear model (GLM). The average time series from the segmented white matter and CSF masks were used as nuisance regressors. Separate analyses were performed for each of the LM1 and RM1 masks. These analyses generated whole-brain voxel-by-voxel estimates of functional connectivity with left M1 and right M1. Group comparison analysis was performed

using a mixed effects GLM model. Preliminary image analysis revealed no group differences for sex, and as such sex was not included as a factor in the group analysis. Functional connectivity maps were created for: 1) each of left and right M1 for each participant group, 2) the difference between left and right M1 for each group, and 3) the difference between groups in the asymmetry of connectivity with left and right M1. These maps were computed as Z-statistic images, and were corrected to a significance level of $p = 0.05$ using *AlphaSim* of the AFNI analysis package (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim). Brain regions were anatomically identified by Brodmann's area and using the Harvard-Oxford Cortical and Subcortical Structural atlases within FSLView (Lancaster et al., 2007, 2000).

3.4 Results

Functional connectivity maps for each group are shown in Figure 3.1. Significant functional connections with M1 are consistent with those reported previously, including the contralateral and ipsilateral primary motor, somatosensory and premotor cortices, as well as the putamen, thalamus and cerebellum (Biswal et al., 1995; Deco and Corbetta, 2011). As expected, there was also considerable overlap in regions connected to both left and right M1 (shown in green) for each participant group. Visual inspection of the maps demonstrated that there were differences between the DCD, ADHD, DCD+ADHD and control groups; these differences were tested statistically on a voxel-by-voxel basis, as described above. The results of these analyses are shown in Figure 3.2, and all brain regions exhibiting significantly different connectivity with left versus right M1 (i.e., exhibiting asymmetry) are listed in Table 3.2.

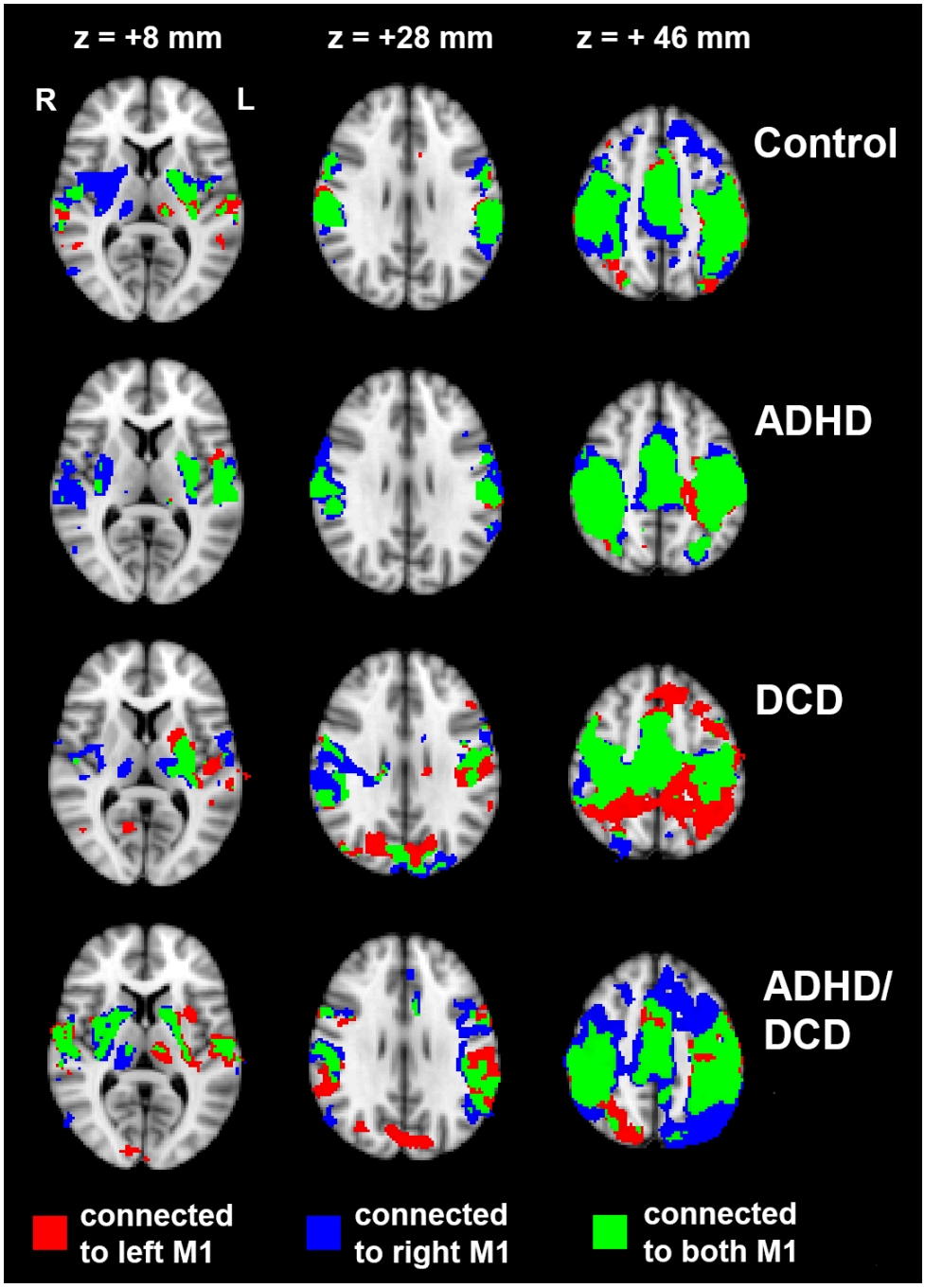

Figure 3.1. Functional connectivity maps demonstrating regions connected with the left motor cortex (red), right motor cortex (blue) and to both the left and right motor cortices (green).

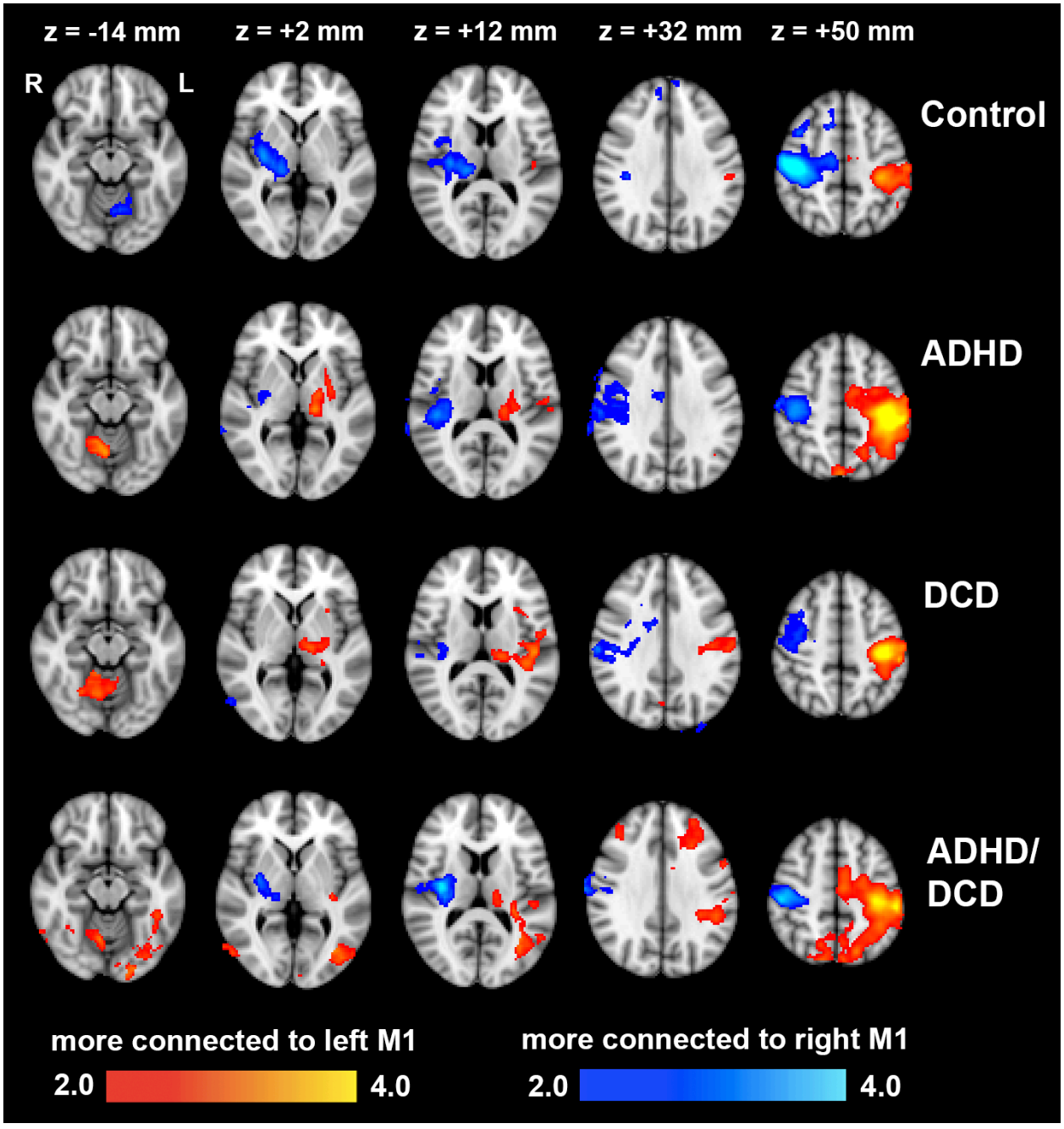

Figure 3.2: Brain regions with higher functional connectivity to the left (orange) and right (blue) motor cortices in each study group.

Table 3.2: Brain regions exhibiting significantly different functional connectivity with the left primary motor cortex as compared to the right primary motor cortex

	Z-score	x	y	z	BA	Brain Region
Controls						
L > R	3.8	-38	-22	60	4	Left Precentral Gyrus
	2.9	-46	-32	48	2	Left Postcentral Gyrus
	2.9	-40	-24	18	13	Left Posterior Insula
R > L	5.0	44	-16	58	4	Right Precentral Gyrus
	5.0	46	-24	52	2	Right Postcentral Gyrus
	3.5	44	-22	40	2	Right Somatosensory Cortex
	3.3	14	-24	0	--	Right Thalamus
	3.1	32	-12	-2	--	Right Putamen
	2.7	36	-14	12	13	Right Posterior Insula
	2.3	10	26	54	6	Right Superior Frontal Gyrus
	2.5	-6	-62	-14	--	Left V Cerebellum
ADHD						
L > R	4.9	-34	-22	58	4	Left Precentral Gyrus
	5.2	-44	-32	50	2	Left Postcentral Gyrus
	3.3	-14	-26	6	--	Left Thalamus
	2.6	-28	-6	2	--	Left Putamen
	3.3	8	-60	-12	--	Right V Cerebellum
	3.0	8	-72	42	7	Right Precuneus
R > L	3.7	40	-18	54	4	Right Precentral Gyrus
	36	46	-20	46	2	Right Postcentral Gyrus
	3.1	60	-18	32	2	Right Somatosensory Cortex
	2.3	30	-12	2	--	Right Putamen
	2.7	40	-22	12	13	Right Posterior Insula
DCD						
L > R	4.1	-38	-18	52	4	Left Precentral Gyrus
	4.6	-40	-28	50	2	Left Postcentral Gyrus
	3.2	-48	-20	40	2	Left Somatosensory Cortex
	2.7	-10	-20	2	--	Left Thalamus
	2.2	-28	-16	4	--	Left Putamen

	Z-score	x	y	z	BA	Brain Region
	2.9	-42	-18	14	13	Left Posterior Insula
	3.1	10	-62	-14	--	Right V Cerebellum
	2.4	12	-62	26	31	Right Precuneus
R > L	2.5	48	-8	48	4	Right Precentral Gyrus
	3.3	52	-20	40	2	Right Postcentral Gyrus
	2.9	46	-24	26	2	Right Somatosensory Cortex
	2.8	36	-20	14	13	Right Posterior Insula
	2.9	8	2	38	24	Right Anterior Cingulate Cortex
ADHD/DCD						
L > R	4.1	-36	-22	60	4	Left Precentral Gyrus
	4.4	-46	-28	52	2	Left Postcentral Gyrus
	2.3	-14	-26	10	--	Left Thalamus
	2.7	-6	-22	70	6	Left Supplementary Motor Area
	3.7	-44	-24	18	13	Left Posterior Insula
	3.1	-6	-10	46	31	Left Anterior Cingulate Cortex
	3.1	-18	-70	50	7	Left Precuneus
	2.5	-32	36	30	9	Left Middle Frontal Gyrus
	2.6	-10	-92	-8	18	Left Visual Cortex Area V2
	2.9	-46	-78	0	19	Left Inferior Lateral Occipital Cortex
	2.9	10	-62	-14	--	Right V Cerebellum
	2.7	10	-74	50	7	Right Precuneus
	2.4	40	38	30	9	Right Middle Frontal Gyrus
	2.4	10	-80	-6	18	Right Visual Cortex Area V2
	2.7	54	-72	0	19	Right Inferior Lateral Occipital Cortex
R > L	4.3	42	-20	58	4	Right Precentral Gyrus
	4.1	48	-22	52	2	Right Postcentral Gyrus
	2.5	54	-16	34	2	Right Somatosensory Cortex
	2.5	16	-24	2	--	Right Thalamus
	2.5	28	-14	8	--	Right Putamen
	2.7	40	-12	8	13	Right Posterior Insula

Coordinates are in mm of the MNI standard template brain atlas; BA = Brodmann's Area. Green indicated regions common to all groups; yellow indicates regions common to controls and DCD; blue indicates regions common to controls and ADHD; red indicates regions common to DCD and ADHD.

For all groups, the left precentral and postcentral gryi were more connected with left M1 than right M1, and the right precentral and postcentral gyri, right somatosensory cortex and right posterior insula were all more connected with right M1 than left M1. The left posterior insula was more connected with left M1 than right M1 in controls and children with DCD, but not in children in ADHD. The right putamen was more connected to right M1 in controls and in children with ADHD+DCD, and the right thalamus was more connected to right M1 in controls and children with ADHD and ADHD+DCD. Several regions exhibited significantly stronger connections with left M1 than with right M1 in the DCD, ADHD and DCD+ADHD groups, but not in controls; these regions included the left thalamus, left putamen (but not ADHD+DCD), right precuneus and lobule V of the right cerebellum. The right superior frontal gyrus and lobule V of the left cerebellum exhibited significantly stronger connections with left M1 in controls, but not in the DCD, ADHD and DCD+ADHD groups. Children with ADHD+DCD exhibited stronger connections with left M1 in a number of additional regions, including the anterior cingulate, supplementary motor area, and regions of the visual cortex (bilateral area V2 and bilateral inferior occipital cortex).

Although regions of the motor cortex exhibited common hemispheric asymmetry across all subject groups, we wished to determine if the magnitude of this asymmetry differed between the children with DCD, ADHD, DCD+ADHD and controls. Thus, we statistically tested the magnitude of the left minus right differences between groups, as described above. The results of these analyses are shown in Figure 3.3. For the DCD, ADHD, DCD+ADHD groups, the left motor cortices exhibited stronger connections with left M1 than with right M1, when compared to controls. The right motor cortices of control subjects exhibited stronger connections with right

M1 than with left M1, when compared to children with ADHD or DCD+ADHD; this was not significant when compared to children with DCD.

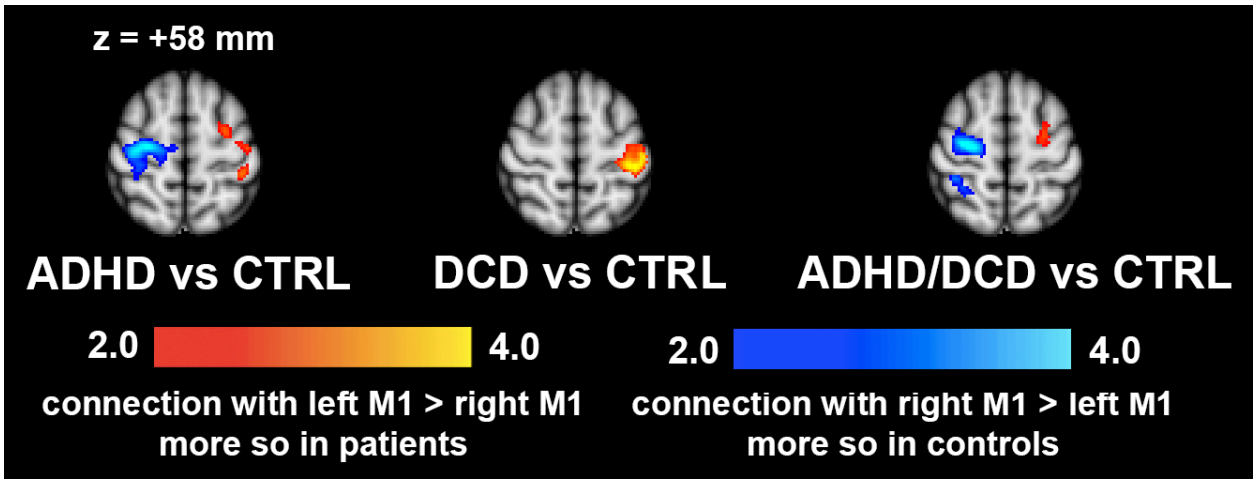

Figure 3.3: Differences in the magnitude of asymmetry of functional connections between left and right motor cortices in each participant group versus controls.

In summary, the results suggest that children with DCD and/or ADHD exhibit stronger ipsilateral functional connections between left M1 and cortical and subcortical brain regions of the motor network, when compared to contralateral connections. The children with DCD and/or ADHD have stronger connections between right cerebellum and left M1 than between right cerebellum and right M1. In contrast, in typically developing controls functional connections between left cerebellum and right M1 are stronger than between left cerebellum and left M1.

3.5 Discussion

This study examined whether children with DCD and/or ADHD displayed differences in left and right motor cortex connectivity compared to controls. Consistent with our hypotheses, we found

that children with ADHD had reduced connectivity of the right hemisphere M1 to left subcortical motor structures, representing reduced right hemisphere contribution to movement. In children with DCD, visuospatial regions, such as the parietal and occipital lobes, displayed similar connectivity to the left and right M1. However, in children with DCD+ADHD, stronger connectivity between the left motor cortex and bilateral visual areas was observed. In addition, children with DCD+ADHD displayed a connectivity pattern similar to the groups with only DCD or ADHD between the left motor cortex and right cerebellum. The opposite of this pattern was observed in control children, who had higher connectivity between the right motor cortex and left cerebellum. This suggests that in DCD and/or ADHD, that there is altered connectivity between the left motor cortex and cerebellum that could represent a neural correlate of these disorders. Furthermore, these findings support the hypothesis that there is abnormal asymmetry in the motor networks in children with DCD and/or ADHD (Rubia et al., 2010; Shaw et al., 2009).

Interhemispheric connectivity between the motor cortices and cerebellum is necessary to integrate sensory information from both sides of the body when coordinating and planning movements. Specifically, cerebellar lobules V and VI are associated with motor activity (Stoodley and Schmahmann, 2009). We observed connectivity changes between the motor cortices and cerebellar lobules V and VI in each study group. The children in our control group displayed higher functional connectivity between the RM1, the left thalamus and the left cerebellar lobules V and VI, compared to the LM1. This finding is consistent with cerebellar-thalamic-motor cortical pathway connectivity (Kandel et al., 2000). This higher connectivity suggests an increased contribution of the right hemisphere to cerebellar motor circuitry for coordinating movements of the non-dominant side in typically developing children. In contrast,

children with motor and/or attention disorders displayed higher functional connectivity between the LM1 and the right cerebellar lobules V and VI. This pattern suggests greater involvement of the left hemisphere in motor coordination of the right side of the body and less involvement of the right hemisphere. In terms of asymmetry, we observed that the DCD and/or ADHD groups had a reduced connectivity to LM1 from RM1, and the opposite was observed in the control group. This pattern of atypical connectivity of the right motor network could be associated with poorer coordination in the performance of tasks that require information from both hemispheres to be performed efficiently. This is supported by previous studies that suggest impaired connectivity between the left motor network and the right hemisphere in children with DCD and ADHD is due to abnormalities or alterations in the corpus callosum or the right hemisphere (Langevin et al., 2014; Roessner et al., 2004; van Ewijk et al., 2012).

The right superior parietal lobule, which is associated with spatial orientation, was found to have higher functional connectivity with LM1 in children with ADHD compared to controls. Children with DCD+ADHD displayed higher functional connectivity between LM1 and the bilateral lateral occipital cortices, the left occipital pole and the left inferior parietal lobule. These findings suggest that areas involved in vision and sensory functions are more highly connected with the left motor network than the right motor network in children with ADHD or DCD+ADHD compared to controls. As a result, sensory information may not be effectively relayed to the right motor network, or vice versa, possibly resulting in the reported visuospatial problems seen in children with these disorders, particularly DCD+ADHD (Crawford and Dewey, 2008; Wilson and McKenzie, 1998). Movement problems may also manifest due to greater FC between LM1 and the SMA/premotor areas in children with DCD+ADHD; if these structures are more connected with the left motor network, and thus receiving less right hemisphere input,

performance of complex motor tasks involving both hemispheres may be compromised. A larger sample size in the DCD group is necessary to determine if similar alterations in connectivity are characteristic of DCD or a unique feature of children with co-occurring motor and attention problems. The recent finding of white matter alterations in the posterior corpus callosum in children with DCD suggests, however, that interhemispheric communication may be impaired between visuospatial regions and the motor network (Langevin et al., 2014).

In the right motor network, higher functional connectivity was found between RM1 and the secondary somatosensory cortex and insular cortex in the temporal lobe compared to LM1 for all groups. This suggests a common pattern of motor network connectivity in children, which is preserved in children with DCD and/or ADHD. The left insular cortex has been implicated in motor learning (Mutschler et al., 2007), and connections between this region and M1 may be critical for executing learned movements. Interestingly, only the control group displayed this pattern of connectivity in the left motor network, which could be representative of the 'typical' pattern of connectivity in the left resting-state motor network. Its absence in children with disorders suggests these children have either altered or less efficient connections for motor learning. Finally, children in the control group and those with DCD+ADHD had higher functional connectivity between RM1 and the right putamen. In the control group, this may represent a 'normal' pattern of connectivity. However, in children with DCD+ADHD, it could represent a compensatory or alternate pattern of connectivity.

3.5.1 Limitations and Conclusions

A limitation of this study is the small sample size, particularly of the DCD group. As a result, the findings should be considered preliminary and need to be replicated. Future studies that explore

structural correlates for these findings are needed, particularly studies examining asymmetry in the integrity of the tracts that connect the motor cortices and cerebellum. The current results were obtained using rs-fMRI; future studies in children with DCD and/or ADHD should include both rs-fMRI and task-based fMRI to investigate whether the activity in currently reported regions of the motor network is altered under task conditions. Finally, due to the cross sectional design, we are unable to examine the impact of brain maturation on connectivity. Future longitudinal studies could address these issues.

In summary, we have found differences in interhemispheric functional connectivity between and within left and right motor networks in children with DCD, ADHD and DCD+ADHD, and typically developing controls. Our findings suggest that children with these disorders display reduced input from the right hemisphere for motor functions, supporting the contention that children with DCD and/or ADHD have atypical interhemispheric connectivity of the motor networks. It is possible that the corpus callosum plays a role given the previous findings that have reported white matter alternations in this structure in children with these disorders. Further exploration of functional connectivity between and within left and right motor networks may provide more information on how alterations in connectivity impact interhemispheric communication in children with DCD and ADHD.

CHAPTER 4: DISCUSSION AND FUTURE DIRECTIONS

4.1 Review of Thesis Goals

The goal of this thesis was to use rs-fMRI to investigate the functional connections of the motor networks in children with DCD and/or ADHD. This was performed using the motor cortices as the region of interest in our rs-fMRI analysis. In the first study, we identified differences in connectivity with the left motor cortex in children with DCD and/or ADHD compared to typically developing children. In the second, we contrasted connectivity with the left and right motor cortices to determine if there was atypical hemispheric asymmetry within the motor networks of children with DCD and/or ADHD compared to typically developing children. From these two studies we determined there is alterations within the left hemisphere and between hemispheres in the motor networks of children with these disorders.

4.2 Main Findings

In the first study, we observed that children with DCD and/or ADHD exhibit altered functional connections with the left motor cortex when compared to typically developing children. A number of brain regions exhibiting these altered connections were common to DCD and ADHD. Functional connectivity with the left motor cortex was decreased in areas involved in sensory integration, including the insular cortices, parietal operculum (secondary somatosensory cortices), and the angular and supramarginal gyri. Additionally, children with co-occurring DCD+ADHD also had reduced connectivity with the postcentral, or sensorimotor cortex, compared to controls. These findings support the contention that deficits in sensorimotor processing play a role in both DCD and ADHD (Piek and Dyck, 2004; Wilson and McKenzie,

1998), and will affect the performance of tasks that require such processing, such as coordination, movement timing and visuospatial ability, all of which have been identified as areas of concern in both DCD and ADHD (Pitcher et al., 2003; Wilson et al., 2013; Wilson and McKenzie, 1998). Connectivity reduction with the somatosensory cortex in children with co-occurring DCD and ADHD, which was not present in children with DCD or ADHD, is consistent with previous studies that identified children with DCD *and* other disorders, including ADHD as having poorer visual perceptual skills (Crawford and Dewey, 2008). Another alteration that was common among children with DCD and/or ADHD compared to typically developing controls was connectivity decreases between the left motor cortex and areas of motor control, including the putamen and pallidum. These structures directly interact with the motor cortex and help regulate movement, in addition to being involved in motor learning (Kandel et al., 2000). Children with DCD are known to struggle with motor learning (Bo and Lee, 2013). For example, they were found to display a slower learning rate compared to typically developing children in a dynamic balance game (Jelsma et al., 2015). We also identified connectivity increases in children with co-occurring DCD and ADHD relative to controls that were not present in children with single disorders. Children with co-occurring DCD and ADHD had increased connectivity between the left motor cortex and numerous structures relative to children with DCD or ADHD – including those involved in motor control, speech processing, sensorimotor processing and error detection. This increased connectivity may represent compensatory changes in the motor networks, meaning that these brain regions may be more actively recruited to plan and execute movements. Children with co-occurring disorders also had lower connectivity between the left motor cortex and both somatosensory cortices, indicating a greater potential disruption of sensorimotor processing involvement in this group.

In the second study, we found differences in the hemispheric asymmetry of the functional connections with the motor cortices in children with DCD and/or ADHD in comparison to typically developing controls. Abnormal motor network asymmetry was found in children with DCD and/or ADHD, with brain regions of the left motor network having less connectivity to the right motor cortex, which was in direct opposition to our findings for typically developing controls. This was true of the motor cortices themselves as well, where children with disorders had reduced connectivity from the right motor cortex to the left motor cortex motor; control children displayed the opposite pattern. Another alteration that was common to children with DCD and/or ADHD was greater connectivity between the left motor cortex and motor regions of the right cerebellum, suggesting that the right hemisphere has less input to this part of the motor network. Again, control children demonstrated the opposite pattern. This suggests there is altered interhemispheric communication, particularly from the right hemisphere to the left, in children with DCD, ADHD and co-occurring DCD and ADHD. Previous diffusion tensor imaging studies, which have reported alterations in the corpus callosum in children with DCD and/or ADHD, support the contention that these alterations may be contributory factors to impaired communication (Langevin et al., 2014).

Imaging research in children with ADHD has identified differences in the development of brain structural asymmetries in the prefrontal cortex. In healthy children, the right prefrontal cortex thickened in comparison to the left with age; children with ADHD did not display this pattern of asymmetry (Shaw et al., 2009). Functionally, poorer communication with the right hemisphere may manifest as difficulties with coordination and motor control (Gazzaniga, 2000). In summary, the findings of the present study are consistent with previous research and support the contention that DCD and ADHD are characterized by abnormal motor network asymmetry.

Both of the studies in this thesis provided information on how the motor networks are altered in children with DCD and/or ADHD, and together they suggest that disruptions in motor network functional connectivity in the left hemisphere and between hemispheres is associated with these disorders. The first study demonstrated poorer input from regions involved in sensorimotor processing and motor control to the left motor cortex. A number of these regions with lower connectivity to the left motor cortex were in the right hemisphere, such as the right insular cortex and right basal ganglia. These findings are consistent with the asymmetry differences observed in the second study, in that these regions had greater connectivity with the right motor network. However, a number of regions in the left hemisphere, such as the left basal ganglia and angular gyri, also demonstrated reduced connectivity with the left motor cortex. Overall, our findings suggest that there are motor network disruptions within the left hemisphere *and* between hemispheres in children with DCD and/or ADHD. This is supported by previous neuroimaging and behavioural research. Imaging studies have reported changes in the motor networks of the left hemisphere in children with DCD and ADHD. In children with DCD, white matter alterations have been found in the descending corticospinal tracts (Zwicker et al., 2012). In a simple tracking task using fMRI, right-handed children with DCD had lower activation in left somatosensory and posterior parietal cortices (Kashiwagi et al., 2009). In children with ADHD, multiple Go/No Go fMRI studies, which use a simple unilateral finger tapping of the right hand as the motor response, have found altered activity in the left basal ganglia (Booth et al., 2005; Durston et al., 2003; Garrett et al., 2008; Vaidya et al., 1998; Valera et al., 2010).

In probing interhemispheric communication, a finger tapping switch task in children with DCD observed that these children had poorer inhibition of left finger tapping compared to healthy controls (Tallet et al., 2013). A recent meta-analyses of behavioural research on children

with DCD identified struggles with coordination, gait control, and internal modeling (Wilson et al., 2013; Wilson and McKenzie, 1998), all of which are complex tasks requiring interaction between hemispheres. These findings support the hypothesis that there are motor network disruptions between hemispheres in children with DCD and/or ADHD. A mechanism for poorer interaction between hemispheres in DCD is suggested by poorer white matter integrity in the posterior corpus callosum (Langevin et al., 2014). Furthermore, right-handed children with DCD had altered activity in the right hemisphere during a complex tracing task using fMRI (Zwicker et al., 2010). Children with ADHD also demonstrate difficulties with motor coordination (Pitcher et al., 2003) and in these children, imaging studies have found that the corpus callosum is also affected, particularly in the frontal aspects (Langevin et al., 2014; Roessner et al., 2004; Valera et al., 2007; van Ewijk et al., 2012). A complex finger tapping task using fMRI observed lower activation in the contralateral motor and parietal cortices with both left and right finger tapping in children with ADHD (Mostofsky et al., 2006). Therefore, existing evidence supports that contention that there is poorer interhemispheric communication in children with DCD and ADHD. Finally, white matter changes have been observed in children with both DCD and ADHD in the anterior and posterior corpus callosum (Langevin et al., 2014). Children with comorbid DCD and ADHD demonstrate deficits in motor coordination and balance (Bart et al., 2013). These data support the assertion that there are two distinct processes affecting motor network connectivity, one within the left hemisphere and the second between hemispheres that results in the motor impairment seen in DCD and/or ADHD.

4.3 Strengths and Limitations

These were the first studies to using rs-fMRI to investigate functional connectivity in children with DCD and DCD+ADHD. Furthermore, this was the first research using rs-fMRI that explicitly investigated the motor network in children with ADHD. All participants were carefully assigned to the disorder groups based on the results from standardized assessments. The groups did not demonstrate any significant differences in age, gender, handedness, and IQ. Regarding the methodology, rs-fMRI is particularly user-friendly with pediatric participants, as the children are not required to perform complex and demanding tasks while in the scanner. The seed-based method used to measure functional connectivity of the motor cortex has been previously established in adults (Golestani and Goodyear, 2011), and the resting-state connectivity maps generated of the motor network were consistent with those described previously (Deco and Corbetta, 2011), indicating that our method was sound.

The main limitation in the two studies was the relatively low number of participants, particularly children with DCD only. Another limitation was that the studies were cross-sectional in design, looking at connectivity at a specific point in the children's development. Longitudinal studies that investigate changes in connectivity over time would be beneficial. Additionally, the age range of the participants (ages 8-17) was wide, and connectivity results could vary at different stages of development, as suggested in the results reported in the first study presented in this thesis. Other factors that could have contributed to variability in our participant groups, such as gender and handedness, demonstrated no significant differences in preliminary data analysis; however, future research with larger samples is needed to confirm these findings. Regarding seed-based analysis, while we were able to target the left motor cortex, we may have missed interesting and meaningful findings if other potential brain regions were used as seeds.

Additionally, the seed-based approach is susceptible to motion artifacts and spatial confounds. An alternative method would be to conduct an independent component analysis, which is less predisposed to noise, but presents challenges in relation to statistical analysis and data interpretation (Cole et al., 2010).

4.4 Future Directions

One of the long-term goals of neuroimaging research is the development of valid and reliable non-invasive measures for diagnosing neurodevelopmental disorders. One means of doing this is to identify unique functional and structural changes in the brain that are associated with specific neurodevelopmental disorders. The present research adds to a growing research literature on the neurological substrates of DCD, ADHD and DCD+ADHD. The next step is to replicate the alterations in functional connectivity that we have reported in a larger cohort of children, especially those with DCD and co-occurring ADHD. Additionally, it will be important to determine if there is any relationship between connectivity alterations, functional outcomes and performance on various neuropsychological measures. Finally, assuming that connectivity changes over time, longitudinal studies would be important – particularly those that examine connectivity between the motor cortex and striatum, between the motor cortex and sensorimotor regions of the parietal lobes, along the motor pathways linking the motor cortex and cerebellum, and the changes in left-right interhemispheric communication.

Recent imaging research has identified some anatomical differences in DCD and DCD+ADHD. Zwicker *et al.* found reduced white matter integrity in the corticospinal tracts in children with DCD using diffusion tensor imaging (DTI) (Zwicker et al., 2012). Langevin *et al.* (2014) also observed white matter alterations in the posterior corpus callosum and left

longitudinal fasciculus in children with DCD only, and in children with ADHD only, alterations in the anterior corpus callosum were observed (Langevin et al., 2014). In children with DCD+ADHD they found white matter changes in the anterior and poster corpus callosum, consistent with those of children with DCD only and ADHD only. These two studies suggest that structural changes in white matter tracts associated with the motor and sensorimotor networks may be the basis for the connectivity changes identified in this thesis. The recent findings of Langevin *et al.* (2015) provide additional support for this contention. They observed changes in cortical thickness in DCD and/or ADHD. In children with DCD or ADHD, relative to control children, decreases in thickness in regions associated with attention were observed; however, children with DCD+ADHD had more widespread cortical thinning in attention and motor regions, in comparison to children with the single disorders (Langevin et al., 2015). Thus, it would be prudent to include structural indicators as determined by DTI and volumetric analysis to better describe the neuroanatomical substrates of DCD and ADHD.

4.5 Final Conclusion

Neuroimaging has begun to elucidate the changes in the brains of children with DCD, ADHD and DCD+ADHD. By identifying structural and functional connectivity changes unique to DCD and/or ADHD through neuroimaging, there is the potential for earlier diagnosis, intervention and treatment. Based on our findings, investigations of sensorimotor function, motor control and how interhemispheric communication is affected have the potential to elucidate the mechanisms underlying these disorders. In conclusion, children with DCD and/or ADHD have motor network disruptions in the left hemisphere and in the communication between the left and right hemispheres.

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APPENDIX

A.1 Letter of Permission from Neuroimage Clinical

From: EP Support
Sent: April 29, 2014 5:16 AM
To: Deborah Dewey
Subject: The paper, "Functional Connectivity of Neural Motor Networks is Disrupted [YNICL_252] [140428-005488] [Reference: 140428-005488]

Subject
The paper, "Functional Connectivity of Neural Motor Networks is Disrupted [YNICL_252] [140428-005488]

Discussion
Response Via Email (Renato) 29/04/2014 11.16 AM
Dear Dr Dewey,

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