

**Characterizing the Neural Correlates of Children with Developmental Coordination
Disorder using Diffusion Tensor Imaging**

by

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Abstract

Developmental coordination disorder (DCD) is a neurodevelopmental disorder of unknown etiology characterized by poor motor coordination and difficulty learning motor skills. Recent research has shown brain differences in children with DCD compared to typically-developing children. Diffusion Tensor Imaging (DTI) is a neuroimaging technique used to identify diffusion properties of white matter of the brain. Only a handful of studies have started to elucidate the white matter pathways that are implicated in children with DCD. These studies used tractography to look at *a priori* white matter pathways. The objective of this thesis is to be the first to apply a DTI method called tract-based spatial statistics (TBSS), a user independent analysis of the whole brain white matter to investigate the neural correlates of children with and without DCD. We hypothesized that the white matter differences would be widespread and implicate white matter pathways such as the: corticospinal motor tract (CST); sensorimotor pathways of the posterior thalamic radiation (PTR); corpus callosum; and cerebellar pathways (CP).

To achieve our research goals, DTI data were collected from 61 children between 8-12 years of age (31 DCD; 30 TD) who had an MRI scan at a mean age of 10.02 years. Voxel-wise statistical analysis of diffusion metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) was conducted using TBSS. A two-group comparison design matrix with age and attention as covariates was used. Data were corrected for multiple comparisons across space and statistical significance was set at $p < 0.05$. Lastly, we investigated whether there was a relationship between the diffusion metrics and motor performance using Spearman's correlation coefficient.

Our findings suggest that children with DCD show altered, widespread diffusion

parameters of white matter in pathways associated with the CST, PTR and CP. Of clinical significance, FA and AD positively correlated with motor performance. Findings from this study will contribute to the scarcity of existing data on characterizing neural correlates of DCD. This research will help elucidate the pathophysiology of DCD and, also, inform intervention studies to investigate motor learning that will, ultimately, help optimize motor functioning in children with DCD.

Preface

Under the supervision of Dr. Jill Zwicker, the research undertaken for this Master's thesis project was completed by the candidate, Meisan Brown-Lum. As part of a larger research program, the experimental conception and design of this project was principally the work of Dr. Jill Zwicker. The candidate, Meisan Brown-Lum, was responsible for data acquisition, pre- and post-processing of diffusion data, statistical analyses, data interpretation, and documentation.

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Chapters 1 and 4 of this thesis contain sections from two published review papers: (1) Brown-Lum M, & Zwicker J. G. (2015). Brain imaging increases our understanding of developmental coordination disorder: A review of literature and future directions. *Current Developmental Disorders Reports*, 2, 131–140; and (2) Brown-Lum, M., & Zwicker, J. G. (2017). Neuroimaging and occupational therapy: Bridging the gap to advance rehabilitation in developmental coordination disorder. *Journal of Motor Behavior* [Epub ahead of print]. doi: 10.1080/00222895.2016.1271295. Meisan Brown-Lum conducted the literature review, synthesis of information, and wrote the first drafts of the manuscripts. Dr. Jill Zwicker supervised, co-wrote and edited both manuscripts. Findings from this thesis will be prepared for future publication as a multi-authored manuscript in a peer-reviewed journal.

Table of Contents

Abstract.....	ii
Preface.....	iv
Table of Contents	v
List of Tables	vii
List of Figures.....	viii
List of Abbreviations	ix
Acknowledgements	xi
Chapter 1: Introduction	1
1.1 DCD Definition and Prevalence	2
1.2 Neuroimaging Studies That Bridge Function to Theory.....	5
1.2.1 Domain specific dysfunction in motor learning impairment in children with DCD	6
1.2.2 Domain general dysfunction in motor learning impairment in children with DCD	7
1.3 Application of DTI and TBSS to Investigate Neural Correlates of DCD.....	9
1.3.1 Application of diffusion tensor imaging (DTI) to investigate DCD	11
1.3.2 Application of TBSS to investigate developmental disorders.....	12
1.4 Research Hypotheses and Aims.....	13
Chapter 2: Study Methods	15
2.1 Participants.....	15
2.2 Research Design.....	16
2.3 Clinical Measurements.....	17
2.4 Neuroimaging Protocol and Analysis	18

2.5	Statistical Analysis.....	20
Chapter 3: Results.....		22
3.1	Cohort Characteristics.....	22
3.2	Between-group Differences in Head Motion.....	22
3.3	Research Aim 1: Group Differences in DTI parameters	23
3.4	Research Aim 2: Correlation Analysis of DTI Parameters and MABC-2 Scores	25
Table 3.628		
Chapter 4: Discussion		32
4.1	Tract-Based Spatial Statistics Reveal Diffuse White Matter Abnormalities in Children With DCD	32
4.1.1	The corticospinal motor tract	32
4.1.2	The posterior thalamic radiation.....	33
4.1.3	The cerebellar pathway	34
4.1.4	Other white matter regions of significance – the attentional network	35
4.1.5	Atypical brain development theory of DCD	35
4.1.6	The role of the mirror neuron system theory in DCD	36
4.2	Possible Mechanisms That Drive Low FA and AD.....	37
4.2.1	DCD risk factors.....	37
4.3	Relationship Between FA and AD with Motor Performance	38
4.4	Limitations, Future Directions, Conclusion.....	39
References.....		41

List of Tables

Table 3.1 Cohort characteristics N = 61.....	22
Table 3.2 Between group differences in head motion parameters	23
Table 3.3 Between group differences in TBSS analysis of FA.....	24
Table 3.4 Between-group differences in TBSS analysis of AD.....	25
Table 3.5 Correlation of FA and MABC-2 scores, controlling for attention.....	26
Table 3.6 Correlation of AD and MABC-2 scores, controlling for attention.....	28

List of Figures

Figure 1.1 DTI diffusion tensor ellipsoid.....	10
Figure 2.1 Recruitment flow chart.....	16
Figure 3.1 TBSS analysis of FA and AD.....	24
Figure 3.2 Correlation analysis between fractional anisotropy (FA) and motor performance ...	27
Figure 3.3 Correlation analysis between axial diffusivity (AD) of the CST and motor performance.....	29
Figure 3.4 Correlation analysis between axial diffusivity (AD) of the PTR and motor performance	30
Figure 3.5 Correlation analysis between axial diffusivity (AD) of the CP and motor performance.....	31

List of Abbreviations

ADHD-	Attention Deficit Hyperactivity Disorder
ASD-	Autism Spectrum Disorder
AD-	Axial Diffusivity
BET-	Brain Extraction Tool
CP-	Cerebellar Pathways
CST-	Corticospinal Motor Tract
DCD-	Developmental Coordination Disorder
DCDQ-	Developmental Coordination Disorder Questionnaire
DSM-	Diagnostic and Statistical Manual of Mental Disorders
DTI-	Diffusion Tensor Imaging
DTI-TBSS	Diffusion Tensor Imaging – Tract-based Spatial Statistics
FA-	Fractional Anisotropy
fMRI-	Functional Magnetic Resonance Imaging
GLM-	General Linear Model
IFOF-	Inferior Fronto-Occipital Fasciculus
MRI-	Magnetic Resonance Imaging
MD-	Mean Diffusivity
MABC-2	Movement Assessment Battery for Children 2 nd Edition
MNS-	Mirror Neuron System
PLIC-	Posterior Limb of the Internal Capsule
PTR-	Posterior Thalamic Radiation

RD-	Radial Diffusivity
SLF-	Superior Longitudinal Fasciculus
TFCE-	Threshold Free Cluster Enhancement
TBSS-	Tract-based Spatial Statistics
TD-	Typically-Developing

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Chapter 1: Introduction

A significant number of children in Canada (5-6%) have a neurodevelopmental disorder called developmental coordination disorder (American Psychiatric Association, 2013). At the core of DCD is motor impairment that significantly interferes with activities of daily living. Children diagnosed with DCD have difficulty learning motor skills and performing everyday motor-related activities (Zwicker, Missiuna, Harris, & Boyd, 2012a). Longitudinal data on children with DCD have shown that, contrary to previous beliefs, children with DCD do not outgrow their motor difficulties, furthermore, motor difficulties persist into adulthood (Hill et al., 2015). Secondary consequences of DCD also emerge, such as anxiety, depression and low self-esteem (Zwicker et al., 2013). Little is known about the cause of DCD and how it develops, making it difficult to understand why children with DCD struggle to learn motor skills and to determine the best intervention to optimize function. Central nervous system pathology is suspected and, while preliminary research suggests that diffusion properties of white matter of the sensorimotor regions and pathways may be implicated in DCD (Zwicker Missiuna, Harris, & Boyd, 2012b), neural substrates of DCD remain to be fully characterized.

In the last few years, there have been tremendous advances in MRI technology that can safely and reliably capture details of the developing brain. Advanced MRI technology has enabled investigation into the relationship between brain structure, microstructure, and connective pathways with neurodevelopment and behaviour in the paediatric population (Dubois et al., 2014). Diffusion tensor imaging (DTI) is an MRI technique that enables the indirect exploration of white matter non-invasively at a detailed level not possible with conventional MRI. The diffusion properties of white matter that are assessed by DTI can provide a strong estimate of physical characteristics of axonal directionality and associated white matter

membrane permeability. In the paediatric population, DTI has been used to identify neural correlates of cognitive skill development, such as reading (Gebauer et al., 2012; Keller & Just, 2009; Beaulieu et al., 2005), but similar studies of motor development are rare. To our knowledge, little has been done to characterize whole brain white matter associated with motor development in children with and without DCD. By characterizing diffusion properties of white matter that would differentiate movement disorder across a spectrum of motor abilities, this project will increase clarity of motor pathway development in children with DCD, in addition to intervention strategies for rehabilitation.

In the subsequent sections of this thesis, DCD will be described in more detail. This will be followed by a brief overview of what neuroimaging is and will include a rationale of our choice to use DTI-TBSS to investigate our hypotheses. The research aims and hypotheses of this thesis will be discussed at the end of Chapter 1. In Chapter 2, the focus will be on an explanation of the study methodology. The results of the study, discussion, and conclusion will encompass Chapters 3 and 4 respectively.

1.1 DCD Definition and Prevalence

Developmental coordination disorder has gained increasing recognition as an important condition of childhood that is characterized by difficulty performing and learning motor skills, such as tying shoelaces, using a knife and fork, printing, and riding a bicycle. In children with DCD, the motor difficulties extend beyond being in the lower end of normal variance in motor abilities of typically-developing (TD) children; the motor impairment of children with DCD significantly impacts daily life (Polatajko, 1999). In 1996, Fox and Lent suggested that children with DCD outgrow their motor difficulties. However, longitudinal research has suggested

otherwise, reporting that without intervention these difficulties persist into adulthood (Cacola, 2016; Cantell, Smyth & Ahonen, 2003; Hellgre, Gillberg, Gillberg, & Enerskog, 1993; Losse et al., 1991; Zwicker et al., 2012a) and that secondary physical and psychological health concerns develop, such as greater risk for obesity and coronary vascular disease, difficulty in peer relationships, anxiety, depression, and low self-esteem (Cacola, 2016; Cairney, Hay, Faught, & Hawkes, 2005; Zwicker et al., 2013).

As early as the 1960's, many terms have been used to describe the DCD, including clumsy child syndrome, sensory integrative dysfunction, developmental dyspraxia, and perceptual motor dysfunction (Polatajko, 1999). Recognition of DCD is further complicated by an unknown etiology and heterogeneity of symptoms. Approaches to assessment and treatment vary, reflecting different theoretical assumptions of mechanisms and developmental course. To address this inconsistency, an international consensus meeting was held in 1994 to establish DCD as the accepted term with a set of diagnostic criteria for DCD that was recognized and added to the third edition of the DSM. DCD is broken down into four diagnostic criteria in the Diagnostic and Statistical Manual, fifth edition – (DSM-V; American Psychiatric Association, 2013):

- A. Acquisition and execution of coordinated motor skills are below what would be expected at a given chronologic age and opportunity for skill learning and use; difficulties are manifested as clumsiness (e.g., dropping or bumping into objects) and as slowness and inaccuracy of performance of motor skills (e.g., catching an object, using scissors, handwriting, riding a bike, or participating in sports)
- B. The motor skills deficit significantly or persistently interferes with activities of daily living appropriate to the chronological age (e.g., self-care and self-maintenance) and impacts academic/school productivity, prevocational and vocational activities, leisure and play
- C. The onset of symptoms is in the early developmental period
- D. The motor skills deficits cannot be better explained by intellectual disability or visual impairment and are not attributable to a neurologic condition affecting movement (e.g., cerebral palsy, muscular dystrophy, or a degenerative disorder)

The estimated prevalence of DCD is as high as 10% in school-aged children (Cacola, 2016). However, estimate in the range of 5-6% are more likely (American Psychiatric Association, 2013), which translates to at least one affected child per school classroom in Canada (Statistics Canada, 2006). DCD affects males more than females (American Psychiatric Association, 2013; Kadesjo & Gillberg, 1999).

DCD has been described as a “hidden problem,” because, relative to other disorders, DCD diagnosis happens later in childhood, and it can be masked by the co-occurrence of other disorders. Only about 25% of children with DCD are diagnosed before starting school (Missiuna, Rivard, & Bartlett, 2003). DCD are often diagnosed with other developmental disorders. The most common co-occurring condition is attention deficit hyperactivity disorder (ADHD); it is estimated that 50% of children with DCD also have ADHD (Kadesjo & Gillberg, 1998).

Learning disabilities and autism spectrum disorders have also been reported to co-occur with DCD. There is research evidence that the various developmental problems among children with DCD, ADHD and autism tend to co-occur (Gillberg et al., 2004; Kaplan, Wilson, Dewey, & Crawford, 1998; Piek et al., 2004) and that developmental problems exist along a continuum of symptom severity (Kaplan, Crawford, Cantell, Kooistra, & Dewey, 2006). Whether a child with these co-occurring problems displays two or more independent disorders or several symptoms associated with a single underlying condition remains equivocal (Kaplan et al., 2006). While some authors argue that DCD and ADHD share etiology (Kaplan et al., 1998; Langevin, MacMaster, Crawford, Lebel, & Dewey, 2014; Langevin, MacMaster, & Dewey, 2015; MacLeod, Langevin, Goodyear, & Dewey, 2014), others suggest that DCD and ADHD are separate disorders (Goulardins et al., 2015). This debate has important clinical implications. If

each disorder is distinct rather than sharing a common neural pathway, then different treatment approaches may be required (Goulardins et al., 2015). Given the frequency of concurrence of other developmental disorders with DCD, diffuse, rather than specific areas of the brain may be involved (Kaplan et al., 2006). The goal of this project is to apply neuroimaging techniques to investigate the white matter differences of the whole brain in children with and without DCD.

The ability to quantify imaging data accurately and reliably and, to relate these data to behavioural measures, will be critical to elucidating the underlying neural correlates of DCD. Advanced MRI techniques, such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), have enabled investigation into the relationship between brain structure, microstructure, connective pathways, and behavioural outcomes in both healthy and impaired paediatric populations (Dubois et al., 2014). In addition to advances in imaging techniques, there have also been advances in software packages to interpret the data. These advances have allowed for novel inferences to help facilitate a greater understanding of brain development in children with DCD. A handful of neuroimaging studies conducted in children with DCD have begun to bridge behavioral theories with associated brain regions and pathways that are associated with DCD (Brown-Lum & Zwicker, 2015).

1.2 Neuroimaging Studies That Bridge Function to Theory

Several theories have been proposed to explain the underlying mechanism that gives rise to DCD. Neuroimaging studies can help shed some light on the theories that have been proposed to explain the motor difficulties experienced by children with DCD. To explain motor skill learning difficulties in DCD, some researchers propose that a deficit in a specific cognitive process is compromised in DCD (Adams, Lust, Wilson, & Steenbergen, 2014). This is a domain specific

approach to understanding DCD. The internal modeling deficit hypothesis and the mirror neuron system theory are examples of this approach. There is, also, a domain general approach to understanding motor impairment in DCD. This approach suggests that the underlying mechanisms of DCD involve several separate deficits (Michel, 2012). For example, deficits in predictive motor control, rhythmic coordination, timing, executive function are examples of clusters of deficits that a child with DCD may have, whereby a child with DCD could be strong in one cluster and not in another. This type of clustering may help explain the heterogeneous nature of DCD (Michel, 2012; Visser, 2003; Wilson, Ruddick, Smits-Engelsman, Polatajko, & Blank, 2013). These theories are discussed in more detail in the next sections and describe how our current project will aim to shed some light on these theories.

1.2.1 Domain specific dysfunction in motor learning impairment in children with DCD

The internal modeling hypothesis is one predominant hypothesis that suggests children with DCD have difficulty with forming or updating an internal model of movement (Adams et al., 2014; Wilson et al., 2013; Zwicker et al., 2012a). Under this model, successful motor control is thought to result from an internal model that accurately predicts the sensory consequences of motor command (Wilson et al., 2004). The internal modeling deficit hypothesis has implications for occupational therapy intervention. Current evidence suggests that task-specific cognitive approaches are effective for children with DCD (Smits-Engelsman et al., 2013), which implies therapists are using compensatory strategies (explicit motor learning) to work around deficits in forming or updating internal models of movement (implicit motor learning) (Brown-Lum & Zwicker, 2017). Future innovations in rehabilitation may find ways to engage brain networks to promote internal modeling, which offers the potential to affect motor skill development beyond

task-specific therapy. Neuroimaging findings suggest fronto- and parietal cerebellar networks deficits in DCD, supporting the internal modeling hypothesis (Debrabant et al., 2013; Kashiwagi, Iwaki, Narumi, Tamai, & Suzuki, 2009; Zwicker, Missiuna, Harris, & Boyd, 2010, 2011). The involvement of the cerebellum has since been confirmed in fMRI studies reporting under-activation of the cerebellum in children with DCD relative to control children (Debrabant et al., 2013; Zwicker et al., 2011).

The MNS hypothesis posits that children with DCD have difficulty with learning motor skills due to MNS dysfunction, and that rehabilitation involving motor imagery may be a promising tool to promote motor learning in DCD. The mirror neuron system is comprised of a group of neurons that are activated during observation, motor imagery, execution, and imitation; the MNS circuit includes the pars opercularis in the inferior frontal gyrus, premotor cortex, and the inferior parietal lobule (Reynolds et al., 2015) that may also be related to the internal modeling hypothesis (Miall, 2003; Kilner, Friston, & Frith, 2007). MNS dysfunction in DCD fits with the domain specific theory and has gained momentum recently (Licari et al., 2015; Reynolds et al., 2015; Werner, Cermak, & Aziz-Zadeh, 2012). Preliminary evidence suggests that motor imagery may support development of motor skills in children with DCD (Wilson, Thomas, & Maruff, 2002), but to our knowledge, motor imagery has not been widely adopted in clinical practice.

1.2.2 Domain general dysfunction in motor learning impairment in children with DCD

The motor dysfunction in children with DCD could also be explained by impaired executive function. Using fMRI and performance on an attention inhibition task, Querne et al. (2008) reported that children with DCD engaged the attentional network differently (left > right) and less effectively than unaffected children. Licari et al. (2015) also reported fMRI findings that

support the theory of suspected deficits in cortical regions associated with working memory and executive functioning in children with DCD. In both these studies, children with co-occurring attention deficit hyperactivity disorder (ADHD) were excluded, which suggests that attentional difficulties are inherent in DCD. Other researchers have compared children with DCD, ADHD, and DCD + ADHD and suggest a shared neurobiological basis for motor and attention deficits. For example, reduced cortical thickness was found in the frontal, parietal and temporal lobes in children with DCD and ADHD (Langevin et al., 2015). Furthermore, reduced connectivity between the primary motor cortex, striatum, and angular gyrus was reported (McLeod et al., 2014) and the corpus callosum (Langevin et al., 2014) in both children with DCD and ADHD. For occupational and physical therapists, knowing whether attentional difficulties are part of DCD or another disorder may have important implications for therapy, as adjunct therapies may need to be considered by the team (e.g., stimulant medication). These studies, as well as an fMRI study by Zwicker et al. (2010), highlight that attention may have a significant role on motor performance and motor learning in children with DCD.

Together, the domain specific and domain general theories help to explain why some children with DCD have trouble performing and learning motor tasks. It has also been proposed recently, that in DCD, these theories exist in a dual role that reflects atypical brain development whereby widespread neurodevelopmental impairment affects both domain specific and domain general mechanisms (Karmiloff-Smith, 2015). Utilizing neuroimaging modalities to investigate the extent of atypical brain development in children with DCD continues to be an exciting area for exploration. To characterize white matter differences of the whole brain in children with DCD compared to their TD peers, the application of tract-based spatial statistics (TBSS) will help to identify the extent of atypical neurodevelopment. This will be the first study to look at the

whole brain white matter pathways in children with DCD.

1.3 Application of DTI and TBSS to Investigate Neural Correlates of DCD

Neuroimaging has provided preliminary support to some of the hypotheses that predominate DCD literature and has informed our understanding of the disorder. We propose to utilize DTI-TBSS to look at whether we can characterize differences in diffusion parameters of the whole brain in both typically developing children and children with DCD.

DTI is an indirect measure of molecular water diffusion and is an imaging technique that has been applied to infer information about gray and white matter microstructure (Mukherjee et al., 2002). During development, diffusion parameters in brain microstructure change. For example, water diffusion becomes increasingly restricted to the longitudinal axes of fiber tracts due to increasing fiber density and myelination (Salat et al., 2005), making it a marker of changes in diffusion properties of white matter over time. Maturation-dependent diffusion measures in white matter have been featured in neurodevelopmental studies as well as investigations about neuroplasticity in response to rehabilitation intervention in DCD (Jones, Knosche & Turner, 2013; Blumenfeld-Katzir et al., 2011). To date, commonly reported DTI measures in DCD research are measures of diffusion, such as mean diffusivity (MD) and fractional anisotropy (FA) (Debrabant et al., 2013; Debrabant et al., 2016; Langevin et al., 2014; Zwicker et al., 2012b). Mean diffusivity is an indirect measure of the overall magnitude of water diffusion in axons, whereas FA represents the relative direction of water diffusion. An FA value of 0 is interpreted to mean that diffusion is isotropic or freely moving whereas an FA value of 1 is representative of restricted diffusion that may indirectly reflect the degree of myelination in axons (Cascio, Gerig & Piven, 2007; Ciccarelli, Catani, Johansen-Berg & Clark, 2008; Dubois et al., 2014). As

described in Figure 1.1, subcomponents of FA include measures of axial and radial diffusivity that describe the movement of water molecules parallel and perpendicular to fiber bundles respectively. Increase axial diffusivity may reflect an increase in axon number or size (Song, 2003). During the development of white matter fibre pathways, mean diffusivity and radial diffusivity decrease, whereas FA and axial diffusivity steadily increase (Partridge et al., 2004, Schmithorst, Wilke, & Dardzinski, 2005). These diffusion parameters are thought to provide an indirect measure of white matter microstructure. Changes in water diffusion may be related to changes in fiber diameter, fiber density, membrane permeability, and/or myelination, which, in turn, may be associated with disease, development, learning, or rehabilitation (Jones et al., 2013).

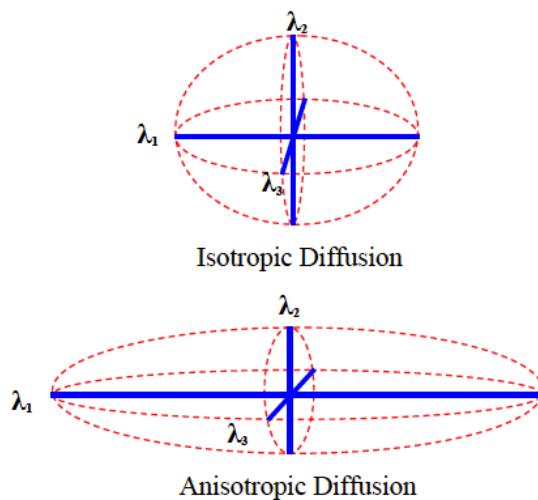


Figure 1.1 DTI diffusion tensor ellipsoid

The eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) describe the size, shape and orientation of the ellipsoid. The eigenvalue λ_1 represents diffusion that runs parallel or along the axon (axial diffusion or AD); eigenvalues λ_2 and λ_3 represent diffusion that is perpendicular to the axon (radial diffusivity or RD). Mean diffusivity is the average of eigenvalues $\lambda_1, \lambda_2, \lambda_3$. Fractional anisotropy or FA represents the variance of all three eigenvectors to represent the relative direction of water diffusion.

In cross-sectional DTI studies, diffusion parameters can be applied to help identify group differences of brain white matter that are implicated in neurodevelopmental disorders. As we hypothesized that DCD may be due to altered white matter development of the motor and

sensorimotor pathways, we expected that children with DCD would have lower FA in these pathways compared to TD children. While DTI is exquisitely sensitive to any change in diffusion parameters of white matter, it does not address the heterogeneity of fiber orientation at any given voxel and cannot provide information about what biological or physiological changes underlie these changes (Jones et al., 2013). Despite the limitations of DTI, this modality has the potential to help inform rehabilitation sciences and clinicians. For example, using serial DTI scans, indices of diffusion can be applied to track changes in brain white matter over time as a result of rehabilitative intervention strategies. A greater understanding of the implicated brain regions and how the brain responds to rehabilitation intervention may help to inform clinical practice.

1.3.1 Application of diffusion tensor imaging (DTI) to investigate DCD

DTI studies on children with DCD have reported differences in white matter compared to TD children. In a pilot study, Zwicker et al. (2012b) reported lower axial diffusivity (lower water diffusion along the axons) of the corticospinal tract (motor pathway) and the posterior thalamic radiations (sensory pathway) in children with DCD compared to TD children. Lower axial diffusivity was moderately to highly correlated with poorer motor outcomes as measured by the Movement Assessment Battery for Children - Second Edition (MABC-2) (Henderson, Sugden, & Barnett, 2007). Additionally, lower FA in the corpus callosum under the parietal lobe and in the left superior longitudinal fasciculus in children with DCD has been reported (Langevin et al. 2014), and was correlated with lower motor scores on the McCarron Assessment of Neuromuscular Development (McCarron, 1997). Langevin et al. (2014) also reported lower FA in the frontal region of the corpus callosum in children with ADHD. As a result, Langevin et al. (2014) suggest a shared neurobiological basis for DCD and attention disorders in children that

may explain the high co-occurrence of the two disorders. More recently, Debrabant et al. (2016) reported lower FA in the main sensory motor tracts (left retrolenticular limb of the internal capsule) in children with DCD compared to controls, which was predictive of poorer visual-motor performance on the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery & Beery, 2004). Taken together, findings from these DTI studies suggest that children with DCD show altered development of brain pathways associated with sensorimotor function, which also correlates with motor function. Many of the studies to date have been equivocal. It is possible that the discrepancies reflect the use of different DTI acquisition protocols and pre-processing methodologies. It is also possible that these discrepancies reflect bias in *a priori* hypotheses. A comprehensive pattern of white matter abnormality of the whole brain in children with DCD has yet to be established. This study addresses this issue by applying a method of analysis that looks at the whole brain. Whether there is a unique neural signature that characterizes DCD remains to be seen. If we conceptualize the brain as a holistic network of interacting pathways, it would be expected that in the current sample of children with DCD, white matter pathology would be widespread.

1.3.2 Application of TBSS to investigate developmental disorders

For this study, DTI data were analyzed with tract-based spatial statistics (TBSS). TBSS is an automated observer-independent approach for assessing diffusion parameters in the major white matter tracts on a voxel-wise basis across groups of participants (Smith et al., 2006). It has been applied to investigate diffusion parameters of white matter in the paediatric population, revealing group differences in conditions such as autism spectrum disorder (Bakhtiari et al., 2012), sensory processing disorder (Owen et al., 2013), and attention deficit hyperactivity disorder (Fitzgerald,

Gallagher, & McGrath, 2016; Langevin et al., 2014; Tamm, Barnea-Goraly, & Reiss, 2012); these studies suggest that findings from DTI-TBSS has the potential to be used as a surrogate biomarker for subsequent neurodevelopmental outcome.

Using DTI, this research project will add to the limited research in this field and apply TBSS to characterize diffusion parameters of white matter that will differentiate children with and without motor impairment between 8-12 years of age. Findings from this research will contribute essential information towards the knowledge gaps and theories discussed above by identifying white matter abnormalities of the whole brain in children with DCD that are associated with impaired motor function.

1.4 Research Hypotheses and Aims

The purpose of the study is to *characterize the neural correlates of white matter abnormalities in children with DCD using DTI-TBSS*. We collected DTI data to investigate differences in diffusion parameters of white matter of the whole brain of children between 8-12 years of age and compared these values to motor outcomes in children with and without DCD. Given that children with DCD experience more difficulties with attention compared to typically-developing children (Dewey, Cantell, & Crawford, 2002), with up to 50% of children with DCD meeting diagnostic criteria for ADHD (Kadesjo & Gillberg, 1999; Pitcher, Piek, & Hay, 2003), we controlled for attention in our analyses. We hypothesized that white matter in the corticospinal tract, posterior thalamic radiations, corpus callosum, and cerebellar pathways (frontal cortex to and from the cerebellum) would have lower FA indices in children with DCD compared to TD children. To test this hypothesis, our primary aim was to identify whole brain differences of diffusion parameters that would differentiate children with DCD and TD children.

We also hypothesized that there would be a relationship in diffusion indices and motor performance. To test this hypothesis, our secondary aim was to determine if there was a positive correlation in FA and motor performance. It was anticipated that findings from this study would identify neural correlates of white matter abnormalities in children with DCD, as well as provide the foundation to a larger research program that will investigate neural plastic changes in children with DCD following an intervention program.

Chapter 2: Study Methods

2.1 Participants

Thirty-one children (8-12 years) who met diagnostic criteria for DCD using the Diagnostic and Statistical Manual – 5th edition were recruited for this cross-sectional investigation (APA, 2013). The inclusion criteria for the DCD group were a score of $\leq 16^{\text{th}}$ percentile on the Movement Assessment Battery for Children-2 (MABC-2) (Henderson et al., 2007) and a score in the DCD or suspected DCD range (≤ 55 for 8 to 9:11 year olds; ≤ 57 for 10 to 15 year olds) on the Developmental Coordination Disorder Questionnaire (DCDQ) (Wilson, Kaplan & Crawford, 2007). We also recruited 30 TD children with no history of motor difficulties and who scored in the normal range on the MABC-2 ($> 25^{\text{th}}$ percentile) and DCDQ. Children were excluded if they had a medical condition that could explain their motor problem such as cerebral palsy, significant intellectual disability, or visual impairment. The recruitment process is shown in Figure 2.1.

Based on previous pilot data on DTI in this population (Zwicker et al., 2012b), a sample size of 30 per group was estimated to be large enough to detect a 3% difference in diffusion parameters.

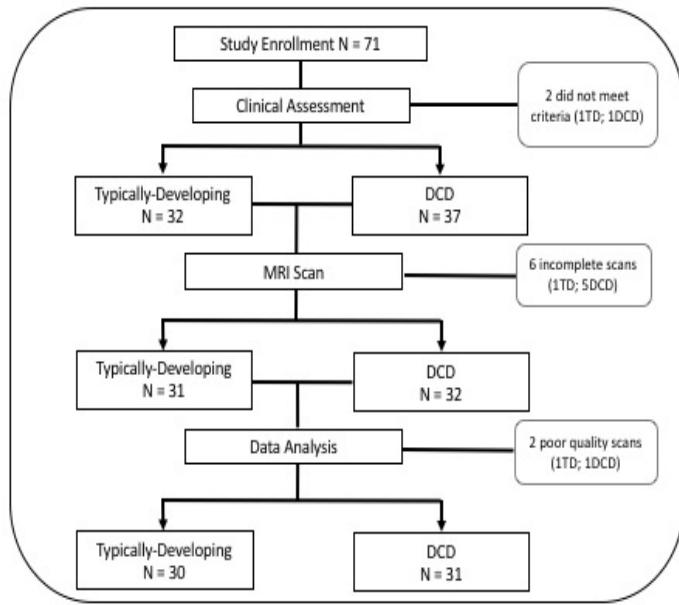


Figure 2.1 Recruitment flow chart

From the 71 participants that were enrolled in the study, 10 participants did not complete the study for the following reasons: 2 did not meet criteria, 6 incomplete scans were participants that dropped out of the study after the simulation session or scans that were stopped part way through due to too much movement or at the request of the study participant.

2.2 Research Design

The Children's & Women's Health Centre/University of British Columbia Clinical Research Ethics Board approved this project. Study participants with DCD were recruited from the DCD Clinic at Sunny Hill Health Centre for Children in Vancouver, BC, as well as from caseloads of occupational and/or physical therapists in the Greater Vancouver area. Families of children with DCD who responded to recruitment flyers also participated. TD children were recruited through advertisements in local schools and in the community or, by word of mouth.

Once parent consent and child assent were obtained, the family (study participant and a parent) were invited to participate in the study at BC Children's Hospital Research Institute. The initial study visit lasted approximately 2.5 hours, starting with a motor skills assessment using the MABC-2 (Henderson et al., 2007). During the MABC-2 assessment, parents completed the

DCDQ (Wilson et al., 2007), Connors 3 ADHD Index (Conners, 2000), and a demographic form. Children were screened for MRI safety and then experienced a session in a MR simulator before completing a 1 hour MR scan in a 3-Tesla MR scanner. From time to time, it was not possible that the family commit to a 2.5-hour study visit. In these situations, the assessment and questionnaires were completed on a different day than the MRI session, which was booked at a time more convenient for the family. Both the MR simulator session and MR scan were booked at the Child & Family Research Imaging Facility. This facility is onsite at BC Children's Hospital and is a scanner dedicated for paediatric research.

2.3 Clinical Measurements

The MABC-2 (Henderson et al., 2007) is the most commonly used assessment to identify children with DCD (Blank 2012); it has good reliability and validity. This scale provides an overall total score compiled from eight subtests across three domains of motor function: manual dexterity; aiming and catching; and balance. The Developmental Coordination Disorder Questionnaire (DCDQ: Wilson, Kaplan & Crawford, 2007) for a parent was used in conjunction with the MABC-2 in the identification of children with DCD. It has a high internal consistency (alpha = 0.94) and sensitivity (85%) (Wilson et al., 2009). A parent was also asked to fill out the Connors 3 ADHD Index. A T-score of 70 and greater is considered clinically significant of inattention and/or hyperactivity symptomatology (Conners, 2009). The Connors 3 has good predictive validity and ability to distinguish children with ADHD from those without a clinical diagnosis (Conners, 2009).

2.4 Neuroimaging Protocol and Analysis

All imaging was performed at the Child & Family Imaging Facility in Vancouver, BC, on a 3-Tesla GE Discovery MR 750 scanner, software version DV205_R02 and 32 channel head coil. Diffusion weighted data were acquired using the following parameters: TR: 7000 ms; TE: 64ms; FOV: 230; matrix: 128x128; slice thickness: 2mm; 32 directions; b=0 and 1000. Two sets of DTI data were collected. Raw diffusion files were converted to a file format that is compatible with the FMRIB software. To convert the raw files from dicom to nifti, mricron dcm2gui was used.

Preprocessing of diffusion data was subsequently completed using FSL brain imaging software (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), part of the FMRIB software library, Version 5.0.9 (www.fmrib.ox.ac.uk/fsl/fsl/download.html). Using FSLview, each dataset was visually inspected as part of the data quality protocol for image distortions, motion artifacts, and proper orientation of images. Diffusion-weighted images were corrected for motion and eddy currents using FDT (FMRIB's Diffusion Toolbox). All diffusion-weighted images were registered to the reference b = 0 volume to minimize image artifacts due to eddy current distortions. Of the two sets of DTI scans collected, the scan with the greatest number of good images was used. Diffusion images with artifacts and/or motion were removed. On average, 9 volumes were removed per scan and scans with more than 15 volumes identified as poor quality were excluded. Two participants were excluded due to poor quality. There was no group difference in the number of volumes removed ($p=0.49$). To conclude the pre-processing steps, the non-brain tissue (skull) was removed from the images using the Brain Extraction Tool (BET; <http://www.fmrib.ox.ac.uk/analysis/research/bet>) and the corresponding brain mask was applied to the fractional anisotropy maps (Smith, 2002).

After the pre-processing steps were completed, reconstruction of diffusion tensors was executed using the *DTIFIT* command that is part of the FMRIB’s Diffusion Toolbox. In this step, a target with the minimum mean warp displacement was selected and, then, each participant’s FA map was aligned in the target space. Following alignment to the target, a mean FA map was created. To ensure intra-rater reliability and consistency, random re-analysis of 30% of the scans was completed (ICC = 0.975; p<0.001).

A second set of registrations was then performed to register every individual FA map to the mean FA map. To characterize whole brain voxel-wise differences in FA between the groups, tract-based spatial statistics (TBSS) (Smith et al., 2006) was applied. TBSS is an automated observer-independent voxel-wise whole brain between group analysis. Using TBSS in FSL (Smith et al., 2006), FA maps from the study participants were aligned to the FA map of the “most representative subject” and then affine-transformed to the MNI152 space. This procedure is recommended for paediatric research because the standard FA template is derived from adults (Smith et al., 2006). The aligned images were then used to create a mean FA skeleton, which represents the centers of all tracts common to the group.

Clusters of the statistically significant results were created using the *FSL cluster command*. The *cluster command* in FSL is based on the idea of pixel connectivity in 3D (https://en.wikipedia.org/wiki/Pixel_connectivity) where 18-connected pixels are neighbors to every pixel that touches on of their faces or edges are clustered together.

Mean peak values of the diffusion indices of statistical significance were then extracted to determine anatomic location and later for correlation analyses with motor scores. For each statistically significant between-group cluster, the anatomic location was determined using the atlas tool in FSLView (<http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions>) and then labelled

using the Johns Hopkins University (JHU) ICBM-81 White-Matter Labels and White Matter Tractography Atlas (Mori, Wakana, Nagae-Poetscher & van Zijl, 2005; Mori et al., 2008).

The original nonlinear registration from the FA maps described above was then applied to investigate non-FA images, namely, the mean (MD), axial (AD), and radial diffusivity (RD) maps. Each subjects' aligned AD, RD, and MD data were projected onto the mean FA skeleton.

To quantify head motion in this study, a head motion index (sum of displacements) was obtained from every participant in the study. For each study participant, a $b = 0$ image was selected as a target image for co-registering the 32 $b = 1000$ images. Six motion parameters that include three translation and three rotation parameters in the x,y,z axes were estimated for each $b = 1000$ image using FSL script. For each parameter, the absolute displacement between adjacent images was averaged to assess the degree of head motion (Ling et al., 2012; Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014; Kong, 2014). The summation of the six motion assessments was used to denote the overall degree of head motion for each study participant. An independent two-sample t-test was conducted to verify whether there were significant differences between the two groups in movement during the MRI scan.

2.5 Statistical Analysis

For this study, statistical analyses were conducted using both FSL and SPSS software (SPSS 24). Assumptions of normality were examined by visual inspection of the data and confirmed using the Shapiro-Wilk test for all clinical variables. Independent t-tests were used to examine group differences in clinical measures, head motion parameters followed by diffusion metrics and Cohen's effect size calculated. To investigate between group differences in sex and age, Chi-square tests were run in SPSS.

Our primary analysis involved voxel-wise statistical analysis of FA data using TBSS that is part of FSL software (Smith et al., 2004; Smith et al., 2006). TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxel-wise cross-subject statistics. The FA skeleton threshold was set at 0.35, the maximum recommended setting to exclude peripheral tracts with high inter-subject variability and/or partial volume effects with gray matter (Barnea-Goraly, Lotspeich & Reiss, 2010). Each subject's aligned FA data were then projected onto this skeleton and the resulting data for each between-group analysis were fed into voxelwise cross-subject statistics ($p < 0.05$) using *randomize*, a permutation program used for inference (thresholding) on statistic maps when the null distribution is not known and is effective in controlling against false positives (Winkler, Ridgway, Webster, Smith & Nichols, 2014; Fitzgerald et al., 2016). Independent t-tests were run using *randomize* to examine between-group differences. A general linear model (GLM) was created to compare group differences in the diffusion parameters FA, AD, MD, and RD. Age and attention were included in the GLM as covariates. All analyses were corrected for multiple comparisons and family wise error; *threshold free cluster enhancement* (TFCE), a randomize output option was used to help find clusters in our data without having to define clusters in a binary way (Smith & Nichols, 2009) and run using 10000 permutations.

As a quality check to test the TBSS protocol described above and to rule out false positives, TBSS analysis was repeated in the TD group to investigate whether we would find any within group differences in FA.

Lastly, to investigate whether there was any relationship between significant diffusion parameters and motor performance on the MABC-2, Spearman's correlation coefficients were calculated. Significance was set at $p < 0.05$ and corrected for attention using Conner's T-score.

Chapter 3: Results

3.1 Cohort Characteristics

In this study, we recruited 61 study participants; 30 TD children and 31 children with DCD. Our sample was predominantly male, which is consistent with the higher prevalence of DCD in males (American Psychiatric Association, 2013). TD children and children with DCD did not differ in sex or age. As expected, the two groups differed in scores on the MABC-2 and the Conners 3 (Table 3.1). Furthermore, Cohen's effect size values for MABC-2 ($d=3.70$) and Conners 3 ($d=2.24$) suggest a large effect. Among the children with DCD, 15 were diagnosed with ADHD. Of the 16 children with DCD not diagnosed with ADHD, 11 of them scored in the ADHD range on the Conners 3.

Table 3.1: Cohort characteristics N = 61

Characteristics	TD N=30 Mean (SD) or N(%)	DCD N=31 Mean (SD) or N(%)	p-value
Male	21 (70)	26 (84)	0.20
Age (years)	9.9 (1.4)	10.1 (1.24)	0.24
MABC-2 (percentiles)	61.9 (22.4)	6.1 (7.8)	< 0.001
Conner's 3 ADHD Index (T-score)	54.2 (13.3)	83.4 (12.9)	<0.001

ADHD, attention deficit hyperactivity disorder; DCD, developmental coordination disorder; MABC-2, Movement Assessment Battery for Children- 2nd ed; TD, typically developing

3.2 Between-group Differences in Head Motion

Given that children with DCD tend to have greater attentional difficulties compared to TD children (Dewey et al., 2002), we expected children with DCD to have more head motion during the scan than their TD peers. In analyzing DTI data, head motion can potentially lead to an overestimation of diffusion results; therefore, it was important to test whether there were any group differences in head motion. We found no significant differences in head motion between the two groups in any of the three head motion parameters (Table 3.2). The effect size for the

analyses of total rotation, total translation, and head motion index ($d=0.01$; 0.03 ; 0.30) were found to meet Cohen's (1998) convention in the range of a small ($d<0.2$) effect size.

Table 3.2 Between group differences in head motion parameters

Head Motion Parameters	TD Mean (SD)	DCD Mean (SD)	p-value
Total Rotation	0.0044 (0.017)	0.0045 (0.019)	0.98
Total Translation	0.21 (0.35)	0.23 (0.49)	0.90
Head Motion Index	1.5 (0.34)	1.6 (0.31)	0.95

3.3 Research Aim 1: Group Differences in DTI parameters

Compared to TD children, children with DCD had significantly lower FA that was widespread across many white matter regions ($p < 0.05$). Lower FA was observed in white matter regions associated with the corticospinal motor tract (CST), the posterior thalamic radiation (PTR), the cerebellar pathways (CP), as well as regions associated with the attentional network (Table 3.3; Figure 3.1A). There were no regions where the DCD group had significantly higher FA compared to the TD children. The effect size for between group differences of FA analysis ($d=0.83$) was found to meet Cohen's (1998) convention for a large effect size ($d>0.8$).

Potential differences in MD, AD, and RD among children with DCD relative to TD children were explored. No statistically significant differences were found in MD and RD (all $p > 0.05$). Statistically significant differences in axial diffusivity (AD) (Table 3.4; Figure 3.1B) in white matter regions that overlap with our FA findings were found. The effect size for this analysis ($d=0.85$) was large. There were no regions where the DCD group had significantly higher AD values compared to the TD children. Further, from our within TD group TBSS analysis to test for false positives, no differences were found in FA within the TD group.

The FSL *cluster command* outputs were extracted for both FA and AD metrics to help identify the anatomical location of the mean peak FA (Table 3.3) and AD values (Table 3.4). Clusters that are 100 voxels or larger were reported.

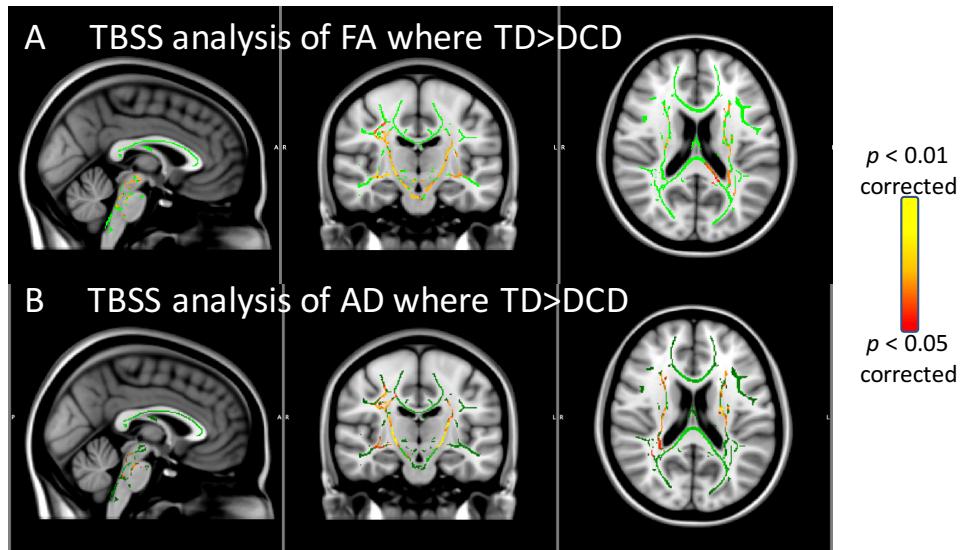


Figure 3.1A-B TBSS analysis of FA and AD

Lower FA (Figure 3.1A) and AD (Figure 3.1B) in the DCD group relative to TD group is shown in yellow and red representing significance. Images are displayed on the MNI 152-T1 template with the TBSS analysis overlaid on top of the group average skeleton in green. Images are displayed in radiological convention where right is left on the image.

Table 3.3 Between-group differences in TBSS analysis of FA

White matter regions	Right /Left	No. Voxels	X	Y	Z	TD		DCD		<i>p</i> -value
						Mean	SD	Mean	SD	
Corticospinal tract	R	1200	8	-22	-39	0.54	0.029	0.51	0.028	< 0.001
Cerebral peduncle	R	456	18	-39	-31	0.56	0.034	0.54	0.029	0.01
Posterior limb of the internal capsule	L	4314	-18	-10	7	0.56	0.023	0.54	0.022	< 0.001
Anterior corona radiata	L	167	-26	17	20	0.45	0.037	0.42	0.037	0.005
Posterior thalamic radiation	L	249	-38	-42	-2	0.55	0.031	0.53	0.032	0.03
Retrolenticular part of the internal capsule	L	180	-29	-32	10	0.57	0.034	0.55	0.035	0.18
Middle cerebellar peduncle	L	166	-12	-35	-28	0.66	0.051	0.63	0.035	0.02
Superior cerebellar peduncle	L	167	-6	-40	-27	0.49	0.050	0.46	0.033	0.03

White matter regions	Right /Left	No. Voxels	X	Y	Z	TD		DCD		<i>p-value</i>
						Mean	SD	Mean	SD	
Anterior limb of the internal capsule	L	149	-15	11	7	0.50	0.049	0.49	0.038	0.27
Superior longitudinal fasciculus	L	189	-30	-19	42	0.48	0.038	0.44	0.040	< 0.001
Inferior fronto-occipital fasciculus	R	4669	34	6	-17	0.55	0.022	0.525	0.020	< 0.001
Anterior thalamic radiation	L	155	-16	6	50	0.54	0.052	0.498	0.044	0.001
Splenium of the corpus callosum	L	416	-11	-36	21	0.76	0.026	0.735	0.032	0.002
External capsule	R	628	31	13	-2	0.49	0.032	0.464	0.024	< 0.001

Table 3.4 Between-group differences in TBSS analysis of AD

White matter regions	Right /Left	No. Voxels	X	Y	Z	TD		DCD		<i>p-value</i>
						Mean 10x2	SD 10x4	Mean 10x2	SD 10x4	
Corticospinal tract	R	325	9	-24	-28	0.13	0.98	0.12	0.46	0.01
Cerebral peduncle	R	682	12	-23	-11	0.14	0.74	0.13	0.40	0.004
Cerebral peduncle	L	2689	-15	-19	-7	0.30	0.45	0.13	0.36	< 0.001
Posterior corona radiata	R	362	28	-38	19	0.15	0.61	0.14	0.52	0.003
Superior corona radiata	R	2261	26	9	31	0.11	0.41	0.11	0.36	0.004
Posterior limb of the internal capsule	R	1430	18	-11	2	0.14	0.46	0.13	0.37	0.001
Retrolenticular part of the internal capsule	L	271	-28	-30	10	0.14	0.57	0.14	0.44	0.011
Superior cerebellar peduncle	L	137	-4	-36	-22	0.14	0.66	0.14	0.63	0.009
Anterior thalamic radiation	R	152	3	-31	-15	0.12	0.43	0.12	0.53	0.004
External capsule	R	470	34	-12	-7	0.13	0.65	0.13	0.51	0.002
Uncinate fasciculus	R	114	34	-1	-23	0.13	0.61	0.13	0.69	0.21
Uncinate fasciculus	L	411	-26	17	-8	0.12	0.68	0.12	0.49	0.004

3.4 Research Aim 2: Correlation Analysis of DTI Parameters and MABC-2 Scores

A correlational analysis was completed to explore the association with the clusters of significant diffusion parameters (FA and AD) and the degree of motor impairment. When we analyzed the correlation of FA split by TD ($r=-0.14$; $p=0.48$) and DCD ($r=0.06$; $p=0.75$) groups

and MABC-2 percentile scores, there was no statistically significant relationship. The FA clusters such as the CST, PTR and cerebellar pathways were also not statistically significant (all $p > 0.05$). We further explored the association between FA within the TD-only group by doing a median split of the MABC-2 percentile scores. No statistically significant relationship was found after correcting for multiple comparisons. However, when we examined FA in the whole cohort across a continuum of motor skills, significant relationships emerged. We found a significant positive linear relationship with white matter regions associated with the corticospinal tract motor pathway and MABC-2 scores ($r=0.38, p=0.003$), as well as the external capsule ($r=0.35, p=0.007$) and splenium of the corpus callosum ($r=0.26, p=0.05$) (Table 3.5). There was no relationship between motor scores and white matter regions associated with the posterior thalamic radiation ($r=0.22, p=0.10$) or the cerebellar motor pathways ($r=0.19, p=0.14$).

We also found that mean peak FA correlated with behaviour in brain regions associated with the attentional network. The regions were the superior longitudinal fasciculus ($r=0.41, p=0.001$) and the inferior fronto-occipital fasciculus ($r=0.39, p=0.002$).

Table 3.5 Correlation of FA and MABC-2 scores, controlling for attention

White Matter Pathways	Right/ Left	Brain regions	r	p-value
Corticospinal Motor Tract			0.38	0.003
	R	Corticospinal tract	0.38	0.003
	R	Cerebral peduncles	0.31	0.02
	L	Posterior limb of the internal capsule	0.35	0.007
	L	Anterior corona radiata	0.27	0.04
Posterior thalamic radiation			0.22	0.10
	L	Posterior thalamic radiation	0.24	0.06
	L	Posterior limb of the internal capsule	0.35	0.007
	L	Retrolenticular limb of the internal capsule	0.04	0.78
Cerebellar Pathways			0.19	0.14
	L	Middle cerebellar peduncle	0.14	0.30
	L	Superior cerebellar peduncle	0.24	0.10

White Matter Pathways	Right/Left	Brain regions	r	p-value
Other Regions				
	L	Anterior limb of the internal capsule	0.17	0.21
	R	Anterior thalamic radiation	0.23	0.08
	R	External capsule	0.35	0.007
	R	Inferior fronto-occipital fasciculus	0.39	0.002
	L	Splenium of the corpus callosum	0.26	0.05
	L	Superior longitudinal fasciculus	0.41	0.001

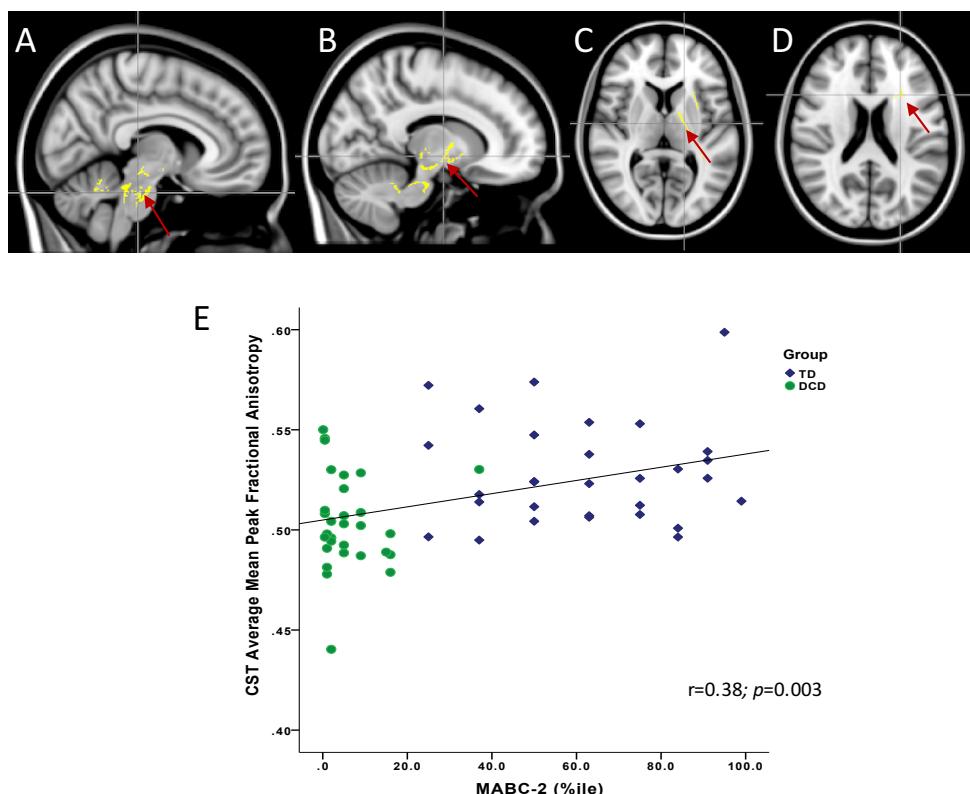


Figure 3.2A-E Correlation analysis between fractional anisotropy (FA) and motor performance. Figures 3.2A-D (CST; cerebral peduncle; posterior limb of the internal capsule; anterior corona radiata) are FA clusters that were significantly lower in children with DCD relative to typically-developing children. These clusters were put together to represent the CST tract and mean peak values averaged. Figure 3.2E shows the average mean peak values of white matter regions associated with the CST positively correlates with the MABC-2 ($r=0.38$, $p=0.003$).

Table 3.6 Correlation of AD and MABC-2 scores, controlling for attention

White Matter Pathways	Right/ Left	Brain regions	r	p-value
Corticospinal Motor Tract			0.46	< 0.001
	R	Corona radiata (superior)	0.38	0.003
	R	Corona radiata (posterior)	0.36	0.005
	R	Cerebral peduncle	0.40	0.002
	L	Cerebral peduncle	0.37	0.004
	R	Posterior limb of the internal capsule	0.42	0.001
	R	Corticospinal tract	0.37	0.004
Posterior thalamic radiation			0.40	0.002
	R	Posterior limb of the internal capsule	0.42	0.001
	L	Retrolenticular part of the internal capsule	0.31	0.02
Cerebellar Pathways	L	Superior cerebellar peduncle	0.27	0.04
Other Regions				
	R	Anterior thalamic radiation	0.34	0.009
	R	External capsule	0.33	0.01
	L	Uncinate fasciculus	0.40	0.002
	R	Uncinate fasciculus	0.25	0.06

Correcting for attention, there is a significant and positive linear relationship between AD in all the white matter regions (apart from the right uncinate fasciculus) and MABC-2 (Table 3.6; Figures 3.3; 3.4; 3.5).

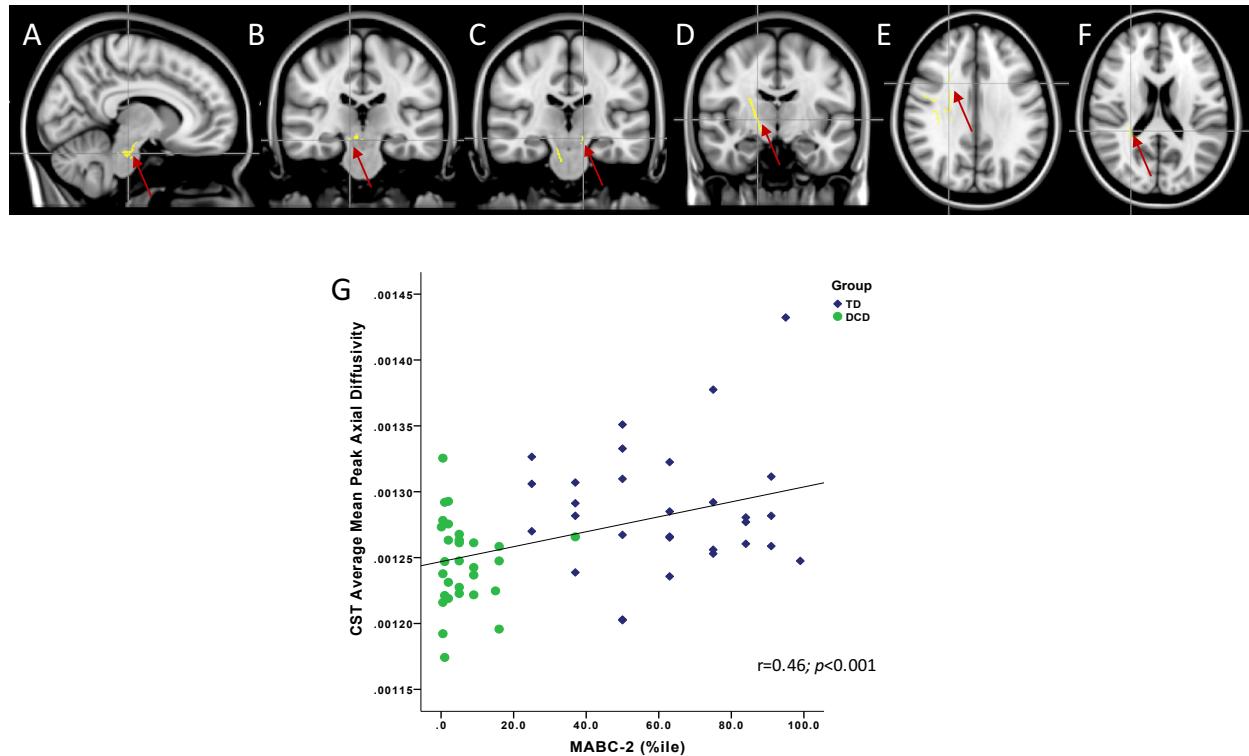


Figure 3.3A-F Correlation analysis between axial diffusivity (AD) of the CST and motor performance.

Figures 3.3A-F (CST, right and left cerebral peduncle, posterior limb of the internal capsule, and superior and posterior corona radiata) are AD clusters that were significantly lower in children with DCD relative to typically-developing children. These clusters were put together to represent white matter regions that are associated with the CST and mean peak values averaged. Figure 3.3G shows the average mean peak values of white matter regions associated with the CST positively correlates with the MABC-2 ($r=0.46$, $p<0.001$).

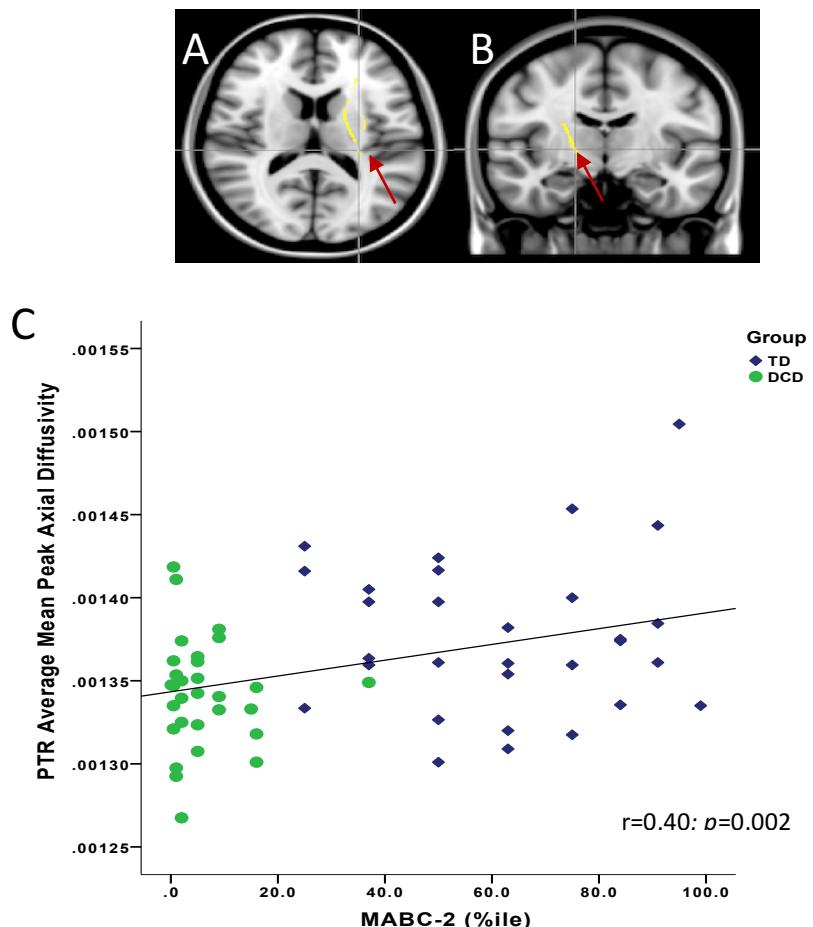


Figure 3.4 Correlation analysis between axial diffusivity (AD) of the PTR and motor performance. Figures 3.4A-C (posterior limb of the internal capsule, and retrolenticular part of the internal capsule) are AD clusters that were significantly lower in children with DCD relative to typically-developing children. These clusters were put together to represent white matter regions that are associated with the PTR and mean peak values averaged. Figure 3.4C shows the average mean peak values of white matter regions associated with the PTR positively correlates with the MABC-2 ($r=0.40, p=0.002$).

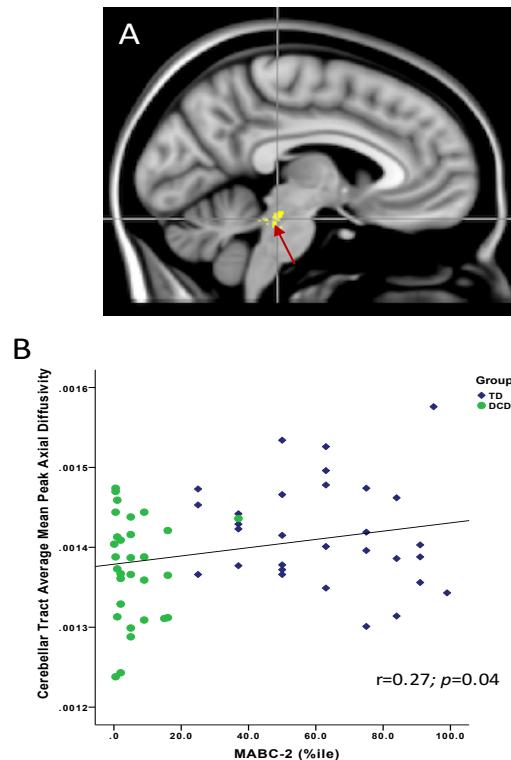


Figure 3.5 Correlation analysis between axial diffusivity (AD) of the cerebellar pathways and motor performance.

Figures 3.5A-B (superior cerebellar peduncle) is an AD cluster that was significantly lower in children with DCD relative to typically-developing children. This cluster is associated with the cerebellar motor tract. Figure 3.5B shows the mean peak values of the superior cerebellar peduncle as a part of the cerebellum motor tract positively correlates with the MABC-2 ($r=0.27, p=0.04$).

Chapter 4: Discussion

4.1 Tract-Based Spatial Statistics Reveal Diffuse White Matter Abnormalities in Children With DCD

This study investigated diffusion parameters of white matter in children with and without DCD. This is the first study to apply whole brain tract-based spatial statistics (TBSS) analysis in children with DCD. Our findings show that diffusion parameters of white matter are significantly different in children with DCD compared with typically-developing (TD) children; differences are widespread across the white matter pathways that were hypothesized to have lower fractional anisotropy (FA), including the corticospinal tract (CST), posterior thalamic radiation (PTR), and the cerebellar pathways (CP). Two diffusion metrics, fractional anisotropy (FA) and axial diffusivity (AD), were found to be significantly lower in children with DCD relative to TD children. In addition, we found that FA in the CST and AD in the CST, PTR and CP significantly correlated with motor performance. In this novel approach to investigate the neural correlates of DCD, our findings confirm our hypotheses as well as offer interesting findings that will help spring board exciting future research projects.

4.1.1 The corticospinal motor tract

The corticospinal tract (CST) is an extensive network of projection white matter pathways that connect the primary motor cortex through the corona radiata, posterior limb of the internal capsule, and cerebral peduncle to the spinal cord. The CST has a critical role in voluntary motor movement (Blumenfeld, 2002) and we hypothesized it to be implicated in the DCD. Previous studies found abnormal white matter in the CST pathway in children with cerebral palsy, a disorder of movement and posture secondary to injury to the developing brain (Yoshida et al.,

2010). They reported lower water diffusion along the length of their axons that was also significantly correlated with gross motor outcomes (Yoshida et al., 2010). The first study to investigate this motor pathway in children with DCD was in a pilot study by Zwicker et al. (2012b), who reported lower AD in the CST in children with DCD compared to TD children. Given the small sample size, our aim was to replicate these findings in a larger sample. As we hypothesized, the current study found altered white matter diffusion parameters in the CST in children with DCD as identified as lower FA and AD in the CST in children with DCD compared to TD peers.

4.1.2 The posterior thalamic radiation

The posterior thalamic radiation (PTR) is another network of projection white matter tracts that is associated with sensory and motor processing that we also hypothesized to be implicated in DCD. The PTR includes ascending and descending pathways, that involve the thalamus and project to the posterior thalamic peduncle to the retrolenticular part of the internal capsule, the posterior limb of the internal capsule, and eventually projects to the premotor cortex, as well as other parts of the cerebral white matter such as the occipital lobe and parietal lobes (Blumenfeld, 2002; Yao et al., 2015). Abnormal white matter in the PTR has been reported in studies investigating cerebral palsy (Yoshida et al., 2010; Debrabant et al., 2016). Again, using tractography seeds associated with the PTR in previous work (Zwicker et al., 2012b), we grouped the posterior thalamic radiation, the posterior limb of the internal capsule and the retrolenticular part of the internal capsule from our findings to be representative of the PTR. Our observations of decreased FA and AD in regions associated with the PTR among children with DCD is consistent with previous reports (Debrabant et al., 2016; Zwicker et al. 2012b). Our

findings suggest that altered processing of sensory information in DCD may be a factor that affects motor learning.

4.1.3 The cerebellar pathway

The cerebellum and cerebellar peduncle contains white matter fibers that we also hypothesized to be implicated in children with DCD (Zwicker, Missiuna, & Boyd, 2009). The tracts that run through the cerebellar peduncles project to and from the spinal cord, pons and cerebral cortex, and cerebellum. These pathways assist in refining motor movements, learning of new motor skills, and converting proprioceptive information into balance and posture (Keser et al., 2015). Our investigation found significantly lower FA and AD in children with DCD, particularly in the middle and superior cerebellar peduncles. The middle cerebellar peduncles are the main afferent pathway to the cerebellum via the pontine nuclei. The superior cerebellar peduncle contains efferent fibers that connects the cerebellum to the midbrain. Compromised white matter in the tracts that run through these structures, particularly the superior cerebellar peduncle, have been previously reported in fMRI studies that showed under-activation of the cerebellum and parietal regions in children with DCD relative to TD children (Kashiwagi et al., 2009; Zwicker et al., 2012b). The cerebellum is essential for motor corrections and motor control that is part of the internal model (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). Our findings support the role of impaired white matter pathways that project to and from the cerebellum in children with DCD.

4.1.4 Other white matter regions of significance – the attentional network

When compared to TD children, we found that children with DCD had significantly lower diffusion metrics in the superior longitudinal fasciculus and the inferior fronto-occipital fasciculus. Similar regions of impaired white matter had been reported in studies that investigate ADHD, ASD, and dyslexia – disorders that frequently co-occur with DCD. For example, the superior longitudinal fasciculus that is part of the fronto-striatal cerebellar tract regulates somatosensory perception along with attention, working memory, and motor behaviour (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013). Reductions in FA in the left superior longitudinal fasciculus (SLF) in children with DCD compared with controls demonstrated that motor and attention deficits are functionally and neurodevelopmentally distinct, yet share a common neurobiological substrate (Sasson et al., 2013). In our study, we report lower FA and AD in the left SLF among children with DCD compared to typically developing children after controlling for attention. Our findings are consistent with Langevin et al., 2014 who reported decrease in FA in the left SLF and the frontal region of the corpus callosum in children with DCD. Additionally, low FA accompanied with low AD in the SLF has been identified in ASD (Barnea-Goraly et al., 2010). Further, this pattern of low FA and low AD was also reported in children with dyslexia in the SLF, posterior limb of the internal capsule (PLIC) and inferior fronto-occipital fasciculus (IFOF). Taken together, this may suggest that the SLF may be a common neurobiological substrate in DCD, ADHD, ASD and dyslexia.

4.1.5 Atypical brain development theory of DCD

The benefit of doing a whole brain analysis is to investigate the extent of altered white matter in children with DCD over the entire brain. Our findings of low FA and low AD in the

cerebellum is consistent with previous reports on impaired internal model in DCD (Wilson et al., 2013; Desmurget & Sirigu, 2009; Zwicker et al., 2009; Zwicker et al., 2012a) that is part of a domain specific theory of motor development. Our findings of low FA and AD in white matter pathways, such as the SLF, PTR and the IFOF are reported to be associated with the attentional network and executive function (Barnea-Goraly et al., 2010; Langevine et al., 2014; Licari et al., 2015; McLeod et al., 2014; Querne et al., 2008). These findings support the domain general theory. Given that our findings identify widespread impaired white matter pathways that overlap with both the domain specific and domain general theories of DCD, we suggest that our findings support atypical brain development whereby widespread neurodevelopmental impairment affects both domain specific and domain general mechanisms. Perhaps the intricate interplay between these systems as a network that encompasses the whole brain may help explain the heterogeneous nature of DCD.

4.1.6 The role of the mirror neuron system theory in DCD

Recently, researchers have hypothesized and investigated the possibility that dysfunction of the MNS may be involved in motor difficulties experienced by children with DCD. In a review by Reynolds et al. (2015), several studies using functional MRI (fMRI) suggest dysfunction in brain regions among children with DCD that similarly describe brain regions that are part of the MNS. These studies propose that dysfunction in the fronto-parietal network, including the ventral premotor cortex and the inferior parietal lobule, regions that are part of the MNS (Rizzolatti & Craighero, 2004; Bernier, Aaronson, & McPartland, 2013), also underlie DCD (Werner et al., 2012). However, our analyses did not identify impaired white matter regions in children with DCD to be associated with the MNS.

4.2 Possible Mechanisms That Drive Low FA and AD

When compared to a baseline data such as a typically developing population, lower FA values is thought to reflect impaired white matter microstructure (Cascio et al., 2007). FA is a summary measure of white matter microstructure that is sensitive to changes over time but not to the specific type of change. Many factors may affect the FA of white matter including myelination, axon size, and density (Beaulieu, 2002; Mukherjee et al., 2002; Ciccarelli et al., 2008). In our study, we found that low FA values among children with DCD relative to TD children was accompanied by lower axial diffusivity without significant differences in radial diffusivity or mean diffusivity. It is generally believed that low axial diffusivity reflects alterations in axon structure (Soares, Marques, Alves, & Sousa, 2013; Song, 2003). This altered axon development could either be the intrinsic characteristics of axons or in the extra-axonal/extracellular space (Beaulieu, 2002). Further, given that we did not find any differences in RD or MD, we can likely rule out demyelination or dysmyelination (driven by RD changes) or membrane density (driven by MD) as potential factors in DCD. We suggest that the low FA and AD observed in children with DCD is potentially a manifestation of impaired microstructure associated with altered axonal development.

4.2.1 DCD risk factors

DCD is much more common in children born preterm compared to term-born children (Edwards et al., 2011); as such, risk factors associated with preterm birth may shed light on identifying possible reasons for altered brain development in DCD. For example, Zwicker, Yoon, et al. (2013) found that male sex, low birth weight, and postnatal steroid exposure were

associated with DCD. Postnatal steroids have been associated with altered cerebellar development in preterm infants (Tam et al., 2011), which may affect motor development consistent with DCD. Similarly, neonatal exposure to morphine has been associated with altered cerebellar development and poorer motor outcomes in preterm infants (Zwicker et al., 2016). Zwicker, Grunau et al. (2013) investigated the association of ante-natal, peri-natal, and post-natal predictors of DCD on the development of the corticospinal tract and reported that higher illness severity in the first days of life and greater exposure to painful procedures were associated with slower maturation of the corticospinal tract. These findings suggest that exposures during a period of rapid brain development may influence microstructural development of white matter pathways. Further evidence of altered white matter development in preterm infants who develop DCD has been reported by others (de Kieviet, Pouwels, & Lafeber, 2014).

4.3 Relationship Between FA and AD with Motor Performance

Understanding the associations between diffusion parameters that reflect white matter microstructure and motor scores may provide additional insight of clinical value. We found that low FA in regions associated with the CST pathway significantly correlated with low scores on the MABC-2. In addition, we found a strong relationship between FA and AD and MABC-2 in regions associated with the attentional network. Our findings suggest that these associations indicate a potential target for rehabilitation as well as for post-intervention studies that set out to investigate neuroplastic changes. As an example, our findings identified an association between low AD in the cerebellum with low motor performance. The impaired white matter regions of the cerebellum had previous been reported to be associated with dysfunction of the internal model hypothesis, whereby children with DCD experience difficulty with implicit motor learning

(Debrabant et al., 2013; Kashiwagi et al., 2009; Zwicker et al., 2010, 2011). It has been reported that task-specific cognitive approaches are effective for children with DCD (Smits-Engelsman et al., 2013), which suggests that the use compensatory strategies (explicit motor learning) can be used to work around deficits in forming or updating internal models of movement (implicit motor learning).

4.4 Limitations, Future Directions, Conclusion

There are several limitations in this study that should be mentioned. This is a cross-sectional study that provides only a snapshot of the neural correlates associated with DCD in children between 8-12 years old. Although the parameters derived from DTI infer microstructural differences in the white matter of children with DCD, a limitation of using DTI is that it is sensitive but not specific to telling us about the neuropathology or helping to identify risk factors. Another limitation is that some of the white matter tracts implicated in this study are observed in other neurodevelopmental disorders, such as ADHD. Our findings may not be specific to DCD per se and may reflect underlying brain differences in a range of neurodevelopmental disorders, such as ASD (Bakhtiari et al., 2012) or ADHD (Fitzgerald, Gallagher, & McGrath, 2016; Langevin et al., 2014; Tamm, Barnea-Goraly, & Reiss, 2012;). To address this, we excluded children with ASD and controlled for attention in our analyses to ascertain neural correlates of DCD. Another strength of our study is that we used TBSS, a user independent imaging technique, that to our knowledge has never been used before to study DCD to provide evidence of widespread impaired white matter pathways in children with DCD. Our findings help to shed some light on the neural correlates of DCD and provide a foundation for a larger research project that will investigate neural changes pre- and post-intervention. Finally, we

hope it will also spring board future projects that will continue the momentum of understanding the pathophysiology of DCD using neuroimaging techniques that will ultimately improve the outcome for children with this disorder.

To conclude, we used DTI-TBSS analysis to compare diffusion parameters that reflect white matter microstructure of the whole brain in children with DCD and TD children. As we had hypothesized, our results demonstrate that DCD is characterized by widespread impaired diffusion parameters of white matter in pathways associated with motor and sensory-motor processing, namely the corticospinal tract, posterior thalamic radiations, cerebellar pathways, and splenium of the corpus callosum. Differences were also noted non-motor regions of the brain that are associated with attentional network (i.e., superior longitudinal fasciculus, inferior fronto-occipital fasciculus). Of clinical significance is that lower FA in the corticospinal motor tract and low AD in many of the regions associated with both motor and sensory-motor processing correlated with motor performance. To build on these findings, future research could examine differences in brain morphometry in children with and without DCD to determine if differences exist at the macroscopic level, and if volume differences are associated with motor function. To extend the current study, research is underway to determine if a task-specific rehabilitation intervention changes brain structure and function and improves motor function in children with DCD.

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