Brain Imaging Correlates of Developmental Coordination Disorder and Associated Impairments

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Declaration

I, Alexandra Faye Bonthrone, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Contributions

I would like to acknowledge the following people for their contributions to this body of work:

Study Design:

Original study design and application for ethical approval were conducted by Dr Frederique Liegeois.

MRI sequences were designed by members of the Developmental Imaging and Biophysics section, UCLGOS Institute of Child Health.

Recruitment:

Information was distributed to participants from Royal Free Hospital by Betty Hutchon. Information was distributed to participants from Guys and St Thomas' NHS Foundation Trust by Katy Strudwick.

Assessment:

Georgia Pitts, Louise Weiss and Sarah Buck each assisted with assessments when siblings were seen concurrently.

MRI scans were conducted by Great Ormond Street radiographers: Tina Banks, Paul Xavier, Jessica Cooper, Nichola Sellers and Michelle Quigley

Scoring:

MSci student Andrea Nahum transcribed 40 CELF-4 formulated sentences recordings. I checked and corrected these and transcribed the remaining recordings. MSc student Kaila Ducret scored formulated sentences subtests using these transcriptions.

Professor Angela Morgan scored all VMPAC and Park Play videos.

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Finally, I owe this project to all the children and their families who took part in this study. This thesis is as much a product of their hard work, commitment and enthusiasm as mine.

Abstract

Aims Developmental Coordination Disorder (DCD) is a common developmental disorder characterised by an inability to learn age appropriate complex motor skills. The first aim of this thesis was to characterise additional cognitive impairments and their relationship with motor difficulties in school aged children with DCD. The second aim was to investigate grey and white matter neuroimaging correlates of motor and cognitive deficits identified.

Methods Thirty six children aged 8-10 years who met DSM-5 criteria for DCD and an age-matched typically developing group (N=17) underwent standardised assessments of motor, intellectual, attention, speech and language skills as well as structural and diffusion-weighted MRI scans. Grey matter correlates of impairments were identified using subcortical volumetrics and surface-based analyses of cortical morphology. White matter correlates were examined using tractography and fixel-based fibre morphology of the pyramidal tracts, corpus callosum and cerebellar peduncles.

Results Alongside impaired motor skills, children with DCD performed poorer than controls on several domains of executive function (attention and processing speed) and speech motor control. Motor skills did not correlate with impairments in other domains. Cortical thickness was significantly reduced in the left central sulcus in children with DCD compared to controls. Poor motor skills correlated with measures in left sensorimotor circuitry, posterior cingulate cortex and anterior insula. Poor speech motor control was associated with measures in the thalamus and corticobulbar tract. Poor sustained attention was linked to measures in the right superior cerebellar peduncle. Lower processing speed was associated with reduced mean cortical surface area.

Conclusions Children with DCD show co-occurring impairments in attention and speech motor control. DCD is associated with sensorimotor circuits as well as regions that form part of the default mode and salience networks. Disruption of subcortical circuits may underlie additional impairments. This study provides novel evidence of the neural correlates of DCD.

Impact Statement

This statement is adapted from Chapter Eight: Theoretical and Clinical Implications of this work

The neural correlates of DCD identified in this study were confined to sensorimotor regions and domain-general networks responsible for efficient cognitive functioning. Our theoretical understanding of the neurobiology of DCD may therefore need to be revised to account for the role of domain-general networks in the impairment. Our work also provides both behavioural and neuroimaging evidence that motor deficits in children with DCD are heterogeneous. Thus, it is unlikely that there is one region or pattern of regions that form an MRI marker for DCD. Instead DCD is likely a multivariate disorder characterised by structural changes in sensorimotor and domain-general regions where different patterns of structural changes are associated with different motor deficits but the same clinical diagnosis. This view provides a novel neuroanatomical explanation for the heterogeneous motor profiles of children with DCD.

From the behavioural characterisation reported in this thesis, it is clear that a high proportion of children with DCD display impairments in executive functions and speech/oromotor functions. The range of abilities in children with DCD and lack of a relationship between impairments identified in this work suggests independent axes of impairment rather than distinct subtypes or a singular spectrum of severity.

In current NHS clinical practice, children with suspected DCD are assessed by an occupational therapist or physiotherapist before a paediatrician makes a formal diagnosis. Our data suggest assessment by a multidisciplinary team including a clinical or educational psychologist and speech and language therapist is necessary to fully characterize the impairments in a child with DCD. Our findings should also be brought to the attention of teacher and parents so that educational support for executive functions and speech difficulties are also available to children. Based on the results of our research, further investigation is needed regarding the impact of additional impairments on motor intervention strategies. Refining our knowledge of the brain networks implicated in DCD may also help with the future development of targeted behavioural or pharmacological interventions.

Contents

List of Abbreviations

ADC	apparent diffusion coefficient
ADHD	Attention deficit/hyperactivity disorder
ADHD	Axial Diffusivity
ALSPAC	Avon Longitudinal Study of Parents and Children
ANCOVA	Analysis of co-variance
ASD	Autism spectrum disorder
ASHA	American speech-language-hearing association
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency- Second Edition
CAS	Childhood apraxia of speech
CBT	corticobulbar tract
CELF-4	Clinical Evaluation of Language Fundamentals, 4th Edition
CNV	Copy number variation
CO-OP	Cognitive Orientation to Daily Occupational Performance
CPT-2	Conner's continuous performance task- second edition
CSD	Constrained spherical deconvolution
CSF	cerebral-spinal fluid
CST	Corticospinal tract
DAMP	Deficits in attention, motor control and perception
DCD	developmental coordination disorder
DCD-Q	Developmental Coordination Disorder Questionnaire
DK	Desikan-Killiany
DLD	Developmental language disorder
DLSD	developmental speech and language disorder
DSM-4	Diagnostic and Statistical Manual of Mental Disorders- 4th edition

DSM-5	Diagnostic and Statistical Manual of Mental Disorders- 5th edition
DT	Dual task
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EACD	European Academy of Childhood Disability
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Examinations
FA	fractional anisotropy
FC	fibre cross-section
FD	Fibre density
FDC	Fibre Density modulated by cross-section
fMRI	functional magnetic resonance imaging
FOD	fibre orientation distribution
FSIQ	full scale IQ
fTCD	functional Transcranial Doppler Ultrasound
FWE	Family-wise error
FWHM	full width at half maximum
ICD-10	World Health Organisation's International Classification of Diseases- 10th edition
ICP	Inferior cerebellar peduncle
IMAGE	International Multicentre ADHD Genetics
IQ	Intelligence quotient
M-ABC	Movement Assessment Battery for Children
M-ABC2	Movement Assessment Battery for Children- Second edition
MANCOVA	multivariate analysis of co-variance
MCP	middle cerebellar peduncles
MD	Mean Diffusivity
MPRAGE	magnetisation prepared rapid gradient-echo

MRI	Magnetic resonance imaging
PRI	Perceptual reasoning index
RD	radial diffusivity
RF	radio frequency
ROI	region of interest
SCP	superior cerebellar peduncle
SD	Standard deviation
SDDMF	Specific Developmental Disorder of Motor Functions
SIFT	spherical-deconvolution informed filtering of tractograms
SLI	Specific Language Impairment
T	Tesla
TBSS	tract based spatial statistics
TE	Echo time
TEA-Ch	Test of Everyday Attention in Children
TIV	Total intracranial volume
TR	repetition time
TTS	total test score
VBM	voxel-based morphometry
VCI	verbal comprehension index
VMPAC	Verbal motor Production Assessment for Children
WASI-II	Wechsler Abbreviated Scale of Intelligence-Second Edition
WISC	Wechsler Intelligence Scale for Children
WISC-IV	Wechsler Intelligence Scale for Children-Fourth Edition

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Chapter One: Introduction to Developmental Coordination Disorder

The coordination of movement is a complex neural process necessary for many aspects of daily life. In healthy children the acquisition of coordinated motor skills occurs throughout preschool and school years. Some children have difficulty acquiring motor skills in the absence of known brain injury or genetic disorders. These children often have additional difficulties in other domains such as attention or language. The neural correlates of poor motor skills and the co-occurring deficits have not yet been elucidated. The first aim of this thesis is to understand the nature of co-occurring impairments in children with poor complex motor skills. The second aim of this thesis is to investigate the structural MRI correlates of motor difficulties and co-occurring impairments. The aim of this chapter is to introduce the condition investigated in this thesis, Developmental Coordination Disorder. I will summarise:

i) The definition and history of the disorder
ii) Current diagnostic criteria
iii) Prevalence
iv) Risk Factors for DCD
v) Theories of the underlying deficit in children with DCD and hypothesised neural correlates

1.1 Definition

Developmental Coordination Disorder (DCD) is a developmental disorder characterised by complex motor skills below levels expected for a person's age (APA 2013). Impaired skills can include dressing, using cutlery, handwriting or riding a bicycle. DCD is a non-progressive disorder that emerges in early childhood. Children with DCD have a motor impairment in the absence of any neurological conditions, brain lesions, abuse/neglect, or genetic disorders. The motor impairment is also not better explained by a global delay or impairment of development.

1.2 Brief History

In the early 19th century Collier coined the term 'congenital maladroitness' to describe children with coordination difficulties (Cermak 1985). In 1937 Orton first used the term clumsiness ((Orton 1937) as cited in (Kirby & Sugden 2007)) and in the 1960s and 1970s

scientific articles referring to 'clumsy children' were published describing cases of developmental movement difficulties of unknown aetiology in children with normal intellectual abilities (Walton et al. 1962; Gubbay et al. 1965; Gubbay 1975; Illingworth 1968). Clinicians in Scandinavia described children with a condition of combined deficits in attention, motor control and perception (DAMP). DAMP was diagnosed in children with co-occurring difficulties with attention and impulse control, perception and motor coordination (Gillberg & Gillberg 1988). Gillberg suggested diagnosing children with DAMP if they meet the Diagnostic and Statistical Manual of Mental Disorders- 4th edition (DSM-4, (APA 2000)) diagnostic criteria for both attention deficit/hyperactivity disorder (ADHD) and DCD (Gillberg 2003). Of note, the term DAMP does not exist in the current editions of the Diagnostic and Statistical Manual of Mental Disorders (APA 2013) or the World Health Organisation's International Classification of Diseases (ICD-10)(WHO 1992), nor is it utilised in the United Kingdom, partially because of the negative connotations of the term (Kirby & Sugden 2007; Blank et al. 2012). The high rate of co-occurrence between ADHD and DCD will be discussed in chapter two.

The term 'developmental dyspraxia' is commonly used in the United Kingdom to describe children with developmental movement difficulties. In 2012 the European Academy of Childhood Disability (EACD) published an expert consensus where this term was rejected in order to differentiate the condition from acquired dyspraxia caused by lesions in the parietal lobe (Blank et al. 2012). The name Developmental Dyspraxia is still used by some charities such as the Dyspraxia Foundation (UK), however this name has fallen out of favour in research.

Another concept that has emerged in recent years is 'ESSENCE' disorders: Early Symptomatic Syndromes Eliciting Neurodevelopmental Examinations (Gillberg 2010). ESSENCE acts as an umbrella term to describe impairments in different domains: general development, communication and language, social relations, motor coordination, attention, activity, behaviour, mood and sleep. Gillberg developed this framework for understanding co-occurring and overlapping learning and behavioural difficulties in children under 5 years of age. This concept is not currently used in clinical practice in the United Kingdom and the term is not regularly applied to children with DCD in research. This thesis will use the term DCD as recommended by the EACD expert consensus.

1.3 Current Terminology and Diagnostic Criteria

ICD-10 and Specific Developmental Disorder of Motor Functions

In countries that use the ICD-10, an alternate classification system, the condition is called Specific Developmental Disorder of Motor Functions (SDDMF)(WHO 1992). Of note, ICD-10 is currently is under revision and the 11th edition is likely to be published in the next year.

The diagnostic criteria for SDDMF are as follows:

1. Serious impairment in the developmental of motor coordination (fine or gross motor coordination)
2. Not solely explicable by general intellectual disability or any specific congenital or acquired neurological disorder
3. May show marked neurodevelopmental immaturities such as
    a. Choreiform movement of unsupported limbs
    b. Mirror movements

DSM-5 and Developmental Coordination Disorder

The EACD consensus determined that the name 'Developmental Coordination Disorder' was the most appropriate term for this disorder. This name comes from the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5 (APA 2013)), the classification system of mental disorders used by clinicians in the United States (APA 2013). The accepted diagnostic criteria for Developmental Coordination Disorder (DCD) were set out in DSM-5 and further refined in the EACD clinical practice guidelines (Blank et al. 2012; Smits-Engelsman et al. 2015):

> Criterion A: Motor abilities that are substantially poorer than expected given the child's age and opportunities for skill acquisition. Criterion A is typically assessed using a standardised motor skill assessment.
>
> Criterion B: The deficit described in criterion A has a significant effect on academic performance and activities of daily living. Criterion B is typically assessed through questionnaires or medical interview.
>
> Criterion C: The onset was in the early developmental period. Criterion C is assessed through a medical history.
>
> Criterion D: The motor skill deficit occurs in the absence of any underlying visual, congenital, neurological or severe psychosocial conditions. Children can have an

intellectual deficit however their motor abilities should be reduced below that expected based on their intellectual abilities. Criterion D is assessed through standardised assessments of intellectual functions, medical histories and further tests for a differential diagnosis such as cerebral palsy or muscular dystrophy.

Children with DCD may show delayed early motor milestones such as rolling, sitting, crawling and walking, but these delays are not a requirement for diagnosis (Blank et al. 2012). DCD is not typically diagnosed before five years of age because poor motor skills at this age may not reflect a persistent impairment (Darrah et al. 2003; Van Waelvelde et al. 2010). If a child between three and five years shows marked impairment on motor skills, a clinical diagnosis can be made based on at least two standardised assessments separated by at least three months (Blank et al. 2012).

1.3 Prevalence

The estimated prevalence of DCD in school aged children varies from 1.8 to 20% (Smits-Engelsman et al. 2015; Lingam et al. 2009; Kadesjö et al. 1999; Wright & Sugden 1996; Tsiotra et al. 2006). These variations in estimates are likely due to different criteria and diagnostic thresholds used to identify children with DCD. In particular, prevalence studies sometimes do not measure the impact of motor difficulties on activities of daily living (Criterion B of the DSM-5 criteria). Previous studies with higher prevalence estimates often used non-standardised neurological testing to characterise poor motor coordination. Lingam and colleagues (Lingam et al. 2009) used strict DSM-4 criteria, including a standardised motor assessment and an activities of daily living questionnaire in a the Avon Longitudinal Study of Parents and Children (ALSPAC) a regional population-based cohort of UK children aged 7-8 years. In this sample the prevalence of DCD was 4.9%, based on EACD guidelines recommending a cut off of at or below the 16th percentile on standardised motor assessments alongside impaired activities of daily living. Despite a UK prevalence of one in twenty school aged children, DCD is significantly under researched compared to other developmental disorders with similar prevalence and severity (Bishop 2010).

1.4 The persistence of DCD into adulthood

DCD is a developmental disorder that is characterised by childhood movement difficulties, yet difficulties may persist into adulthood (Kirby 2011). Adults with probable DCD (N=135) defined using a questionnaire reported impaired activities of daily living (Tal-Saban et al. 2012). Another study reported difficulties with motor skills and driving in 19 adults with DCD (Cousins & Smyth 2003). In a sample of 101 twenty-two year olds, those with DCD

and/or ADHD were more likely to be unemployed, have a criminal conviction, or suffer from substance abuse, psychiatric or personality disorders compared to a control group (Rasmussen & Gillberg 2000). There is emerging evidence that DCD can have a significant long-term impact on adult life however there is currently no literature regarding the prevalence of DCD in adulthood.

1.5 Risk Factors for DCD

Gender

Developmental coordination disorder is reported to be more common in boys than girls with ratios ranging from 2:1 to 7:1 (Blank et al. 2012). In Lingam's study described above, a ratio of 1.7 boys to 1 girl was present in the sample with DCD as categorised according to EACD guidelines (Lingam et al. 2009).

Genetic susceptibility

There is evidence that DCD is a heritable condition suggesting at least a partial genetic aetiology (Lichtenstein et al. 2010; Martin et al. 2006; Fliers et al. 2009). Mosca and colleagues (Mosca et al. 2016) examined children 82 children with DCD compared to 2988 European controls to identify copy number variations (CNVs) that may contribute to the aetiology of DCD. The authors identified an increased rate of rare CNVs in children with DCD particularly in genes previously implicated in other neurodevelopmental disorders. Another genome-wide association study in children with ADHD from the International Multicentre ADHD Genetics (IMAGE) cohort identified some association between motor coordination in ADHD and genes implicated in brain development and musculoskeletal function (Fliers et al. 2012). Of particular note was the identification of 15 single nucleotide polymorphisms significantly associated that were with low scores on a standardised questionnaire of motor coordination (Developmental Coordination Disorder Questionnaire, DCD-Q).

Premature Birth

A systematic review and meta-analysis published in 2011 found that children born very preterm (below 32 weeks gestation) and/or very low birthweight (below 1500 grams) were 6.29 times more likely to score below the 5th percentile on a standardised test of motor ability than the term-born populations (Edwards et al. 2011). In 7 year follow-up study of the Danish National Birth Cohort children born moderately preterm (32-36 weeks gestation) were 2.1 times more likely to fall in the impaired ranged on the DCD-Q (Faebo Larsen et al. 2013). Marlow and colleagues (Marlow et al. 2007) published a study of children born at or below 25 and 6 days without a diagnosis of cerebral palsy (assessed at

6 years of age). The children born prematurely scored lower on fine and gross motor tasks, sensorimotor and visuospatial functioning when compared to term-born classmates. These differences were not fully explained by differences in general cognitive ability.

1.6 The nature of motor impairments in children with DCD

In 2017 Wilson and colleagues conducted a review of all peer-reviewed behavioural literature published between 2011 and 2016. The authors identified evidence of impairments in a variety of motor skills including anticipatory motor control, motor learning, oculomotor control, balance, gait, handwriting and postural adaptation (Wilson et al. 2017). Children with DCD had a motor skill impairment rather than a simple motor execution deficit, with preserved performance on simple tasks but poor performance on tasks with increased complexity, less visual or sensory feedback, and those that required quick and precise movements.

1.7 Subtypes and Heterogeneity in DCD

DCD is not a homogenous disorder and children can present with varied deficits. Several studies have attempted to categorise children with DCD into subtypes (Green et al. 2008; Macnab et al. 2001; Vaivre-Douret et al. 2011). Consistent subtypes are difficult to identify due to differences in assessment tools. Nevertheless, results from cluster analyses have yielded some similar subtypes (Green G. 2005). Macnab and colleagues (Macnab et al. 2001) identified 5 subtypes in children with DCD similar to those previously identified by Hoare (Hoare 1994). These subtypes are:

1. Weak dynamic balance and kinesthesis
2. Weak kinesthesis but good visuomotor skills
3. Weak visuomotor skills
4. Weak static balance and visuomotor functions
5. Weak static and dynamic balance and manual dexterity

Green and colleagues (Green et al. 2008) identified 5 overlapping subtypes similar to those identified by MacNab and colleagues and Hoare based on a cluster analysis of motor and visuomotor assessments from 90 children which show some overlap with those described above (Figure 1.1). Of note there was significant overlap between clusters suggesting subtypes are not distinct. Thirty-three of the children in this study had diagnosed comorbidities or complex medical histories. The authors also note that some children's' cluster allocation changed as other comorbidities were included or excluded. Co-occurring

deficits were spread across the subtypes and different disorders were not confined to certain subtypes. There is good evidence for subtypes within DCD which raises the possibility of not one, but several neural correlates for different subtypes. To date no research has been published on whether subtypes could be identified from neuroimaging variables.

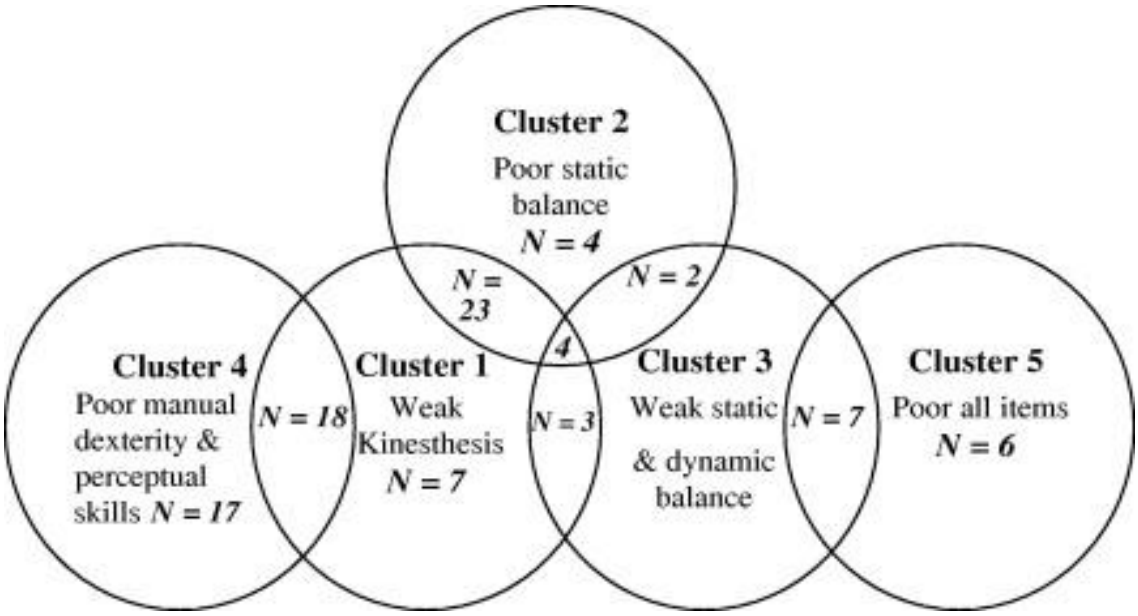

Figure 1.1 Subtypes of DCD identified by Green and colleagues using cluster analysis (Figure from Green et al. 2008)

1.8 Theories of the underlying deficit in DCD

The underlying deficit in DCD is currently unknown, but four hypotheses have emerged in the mainstream literature: i) atypical brain development (Gilger & Kaplan 2001); ii) an automatization deficit (Nicolson & Fawcett 2007), iii) an internal modelling deficit (Adams et al. 2014) and iv) the mirror neuron system (Reynolds, Thornton, et al. 2015). These theories differ regarding where in the motor learning and control systems the deficit occurs. An overview of the systems involved in motor learning and execution according to each theory is given below. As discussed in the section above entitled 'subtypes and heterogeneity in DCD', we cannot rule out that different deficits underlie subtypes of DCD.

Atypical brain development

The concept of atypical brain development/minimal brain dysfunction suggests that developmental coordination disorder and other developmental disorders are caused by disruption of brain development due to genetic, in-utero or perinatal factors (Gilger & Kaplan 2001). This manifests as impairments in motor, cognitive or behavioural function depending on the precise location of the disruption (Figure 2.2). This theory was revisited

in a paper in the Lancet in 2013 as 'Developmental Brain Dysfunction' (Moreno-De-Luca et al. 2013). The authors suggest that shared copy number variants and single gene mutations between developmental disorders indicate a common denominator. Proponents of this theory also suggest the high level of co-occurrence between DCD and other developmental disorders indicates that these disorders may have the same root cause ((Kaplan et al. 1998; Gilger & Kaplan 2001; Kaplan et al. 2006). This theory is difficult to test behaviourally, because it does not generate specific hypotheses of motor performance deficit nor does it generate specific hypotheses regarding neuroimaging findings (Wilson et al. 2013). Instead Atypical Brain Development may be viewed as a theory of aetiology rather than underlying deficit.

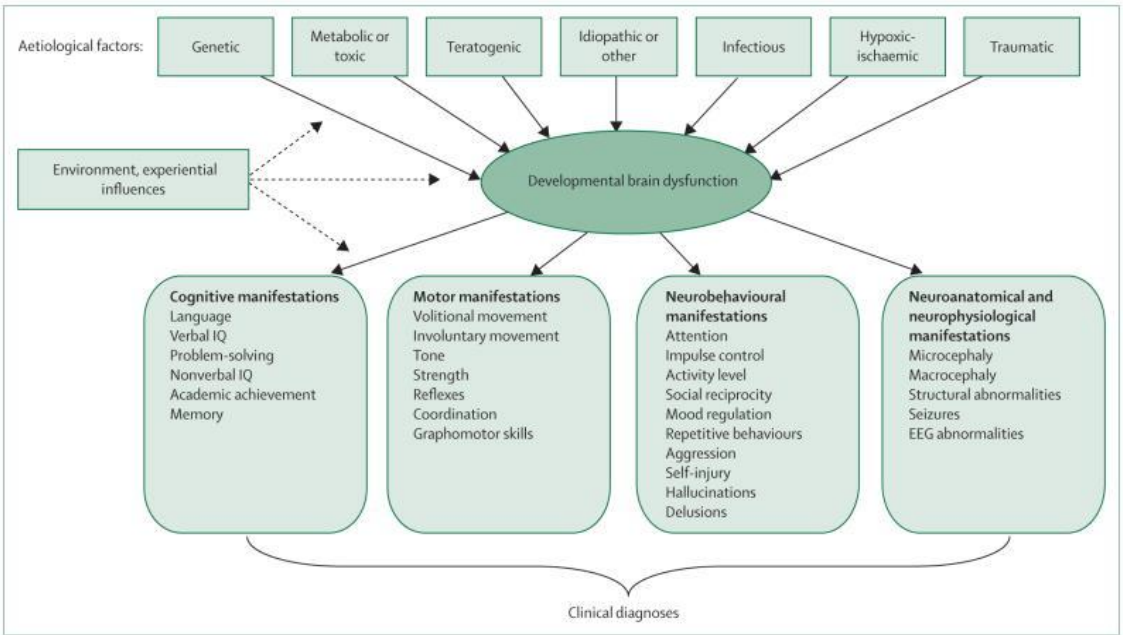

Figure 1.2 The cause of developmental disorders according to the theory of atypical brain development/developmental brain dysfunction (Figure from Moreno-De-Luca et al. 2013)

Procedural Learning and Automatization Deficit

Procedural Learning of a new motor skill consists of five stages (Doyon & Benali 2005; Doyon et al. 2018):

1. Fast Learning: online learning when task execution is improved over minutes
2. Slow Learning: when task performance is improved over hours
3. Consolidation: when incremental gains are made over practice sessions and with task rehearsal
4. Automatization: when a skill becomes fluent and over-learned so that it can be performed with minimal use of executive functions

5. Retention: when a skill is fully retained

Of particular interest for the study of DCD is automatization. Dual task paradigms, in which a participant has to perform a primary motor and cognitive distractor task at the same time, can be used to test whether a motor sequence has become automatized (Tsai et al. 2009). Alternatively, it can also be probed by comparing the execution of a particular motor skill between experts and novices (Doyon et al. 2009).

Brain Correlates of Procedural Learning and Automatization

There are several models which implicate cortical-cerebellar and cortical-basal ganglia loops in motor sequence learning (Shadmehr & Krakauer 2008; Doya 2000; Doyon et al. 2018). In the model of motor learning proposed by Doyon, the cortical motor regions, sensorimotor striatum (the putamen) and parietal cortices underlie automatization of learned motor sequences (Doyon et al. 2018) (Figure 1.3).

Doyon's review published in 2009 identified general decrease in fMRI activation in motor cortical, basal ganglia and cerebellar regions during automatized movements in healthy adults (Doyon et al. 2009). The authors suggest that this decrease indicates more efficient functioning during automatic skill performance. In the same review, an fMRI study on expert adult knitters executing an overlearned knitting stitch and a novel knitting stitch found activation in both cerebellar and basal ganglia regions during early learning of the novel stitch but no cerebellar activation when performing the automatized stitch (Doyon et al. 2009). Another fMRI study which examined finger sequencing during a dual task paradigm reported decreased activation of lateral prefrontal regions and the striatum (Poldrack et al. 2005). In a quantitative meta-analysis of fMRI research into adult motor learning, bilateral supplementary motor cortex, bilateral primary motor cortex, left dorsal premotor cortex, left primary somatosensory cortex, left superior parietal lobule, left thalamus, bilateral putamen and multiple clusters of the cerebellum were activated across testing paradigms (Hardwick et al. 2013). The authors of this review did not divide these results into stages of motor learning, so it is not possible to tell which regions are involved specifically in automatization.

It is important to note that these models are based on research on adults. It is not currently understood how motor skill learning develops in children and the corresponding neural correlates. This poses a challenge when hypothesising which neural networks could be disrupted in a developmental disorder which affects motor skill acquisition such as DCD.

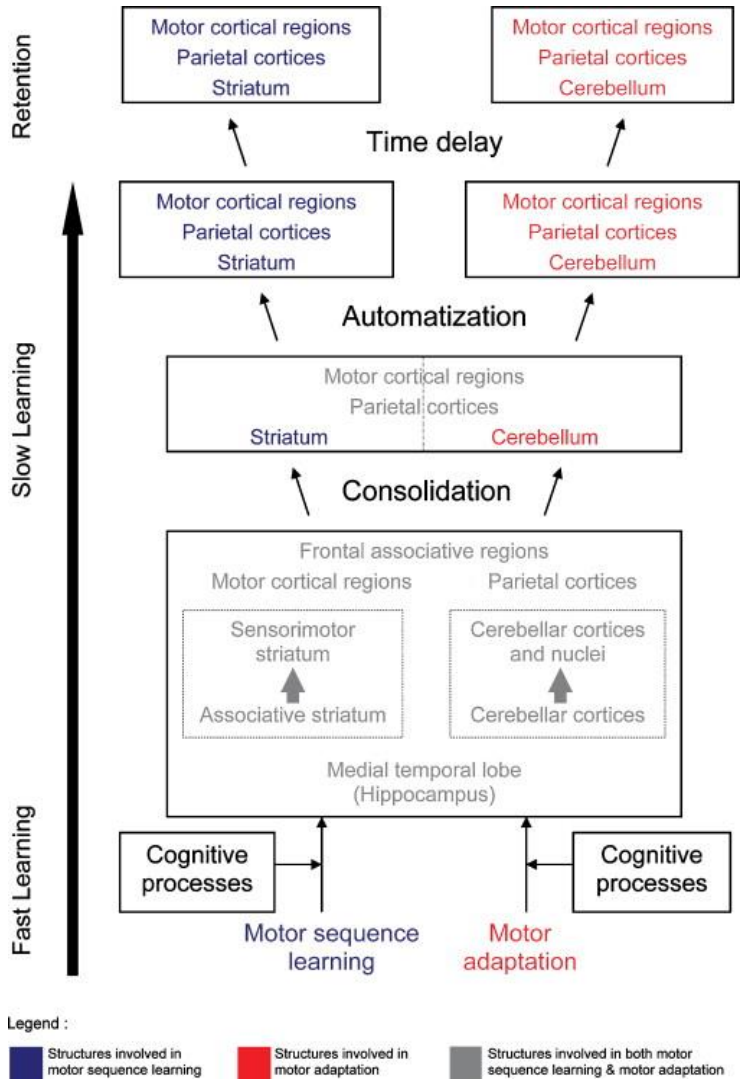

Figure 1.3 Doyon's Theory of motor learning. Automatization of motor sequences occurs in the striatum. Motor commands are stored in motor cortical regions, parietal cortex and either the cerebellum or Striatum (Blue=sequence learning; red=motor adaptation; Figure from Doyon et al. 2009)

The Procedural Learning and Automatization Deficit Hypothesis in DCD

Nicolson and Fawcett first hypothesised that the core deficit in developmental dyslexia is poor automatization of skills (Nicolson et al. 2001). They later expanded this theory to suggest all developmental disorders such as DCD, dyslexia, specific language impairment (SLI now called developmental language disorder (DLD)) and ADHD result from deficits in the procedural learning system (Nicolson & Fawcett 2007). This theory explains high rates of co-occurrence between developmental disorders by suggesting deficits in procedural learning are the underlying cause. The authors suggest that the nature of the developmental disorder is dictated by where in the procedural learning system the deficit occurs (Figure 1.4). They hypothesise that DCD is caused by impaired cortical-striatal procedural learning and automatization. Based on Doyon's theory in Figure 1.3, this

corresponds to poor automatization of motor sequences. This deficit suggests children with DCD need to consciously monitor motor sequence execution and will perform significantly worse on motor tasks when they are unable to monitor skill execution due to other cognitive demands.

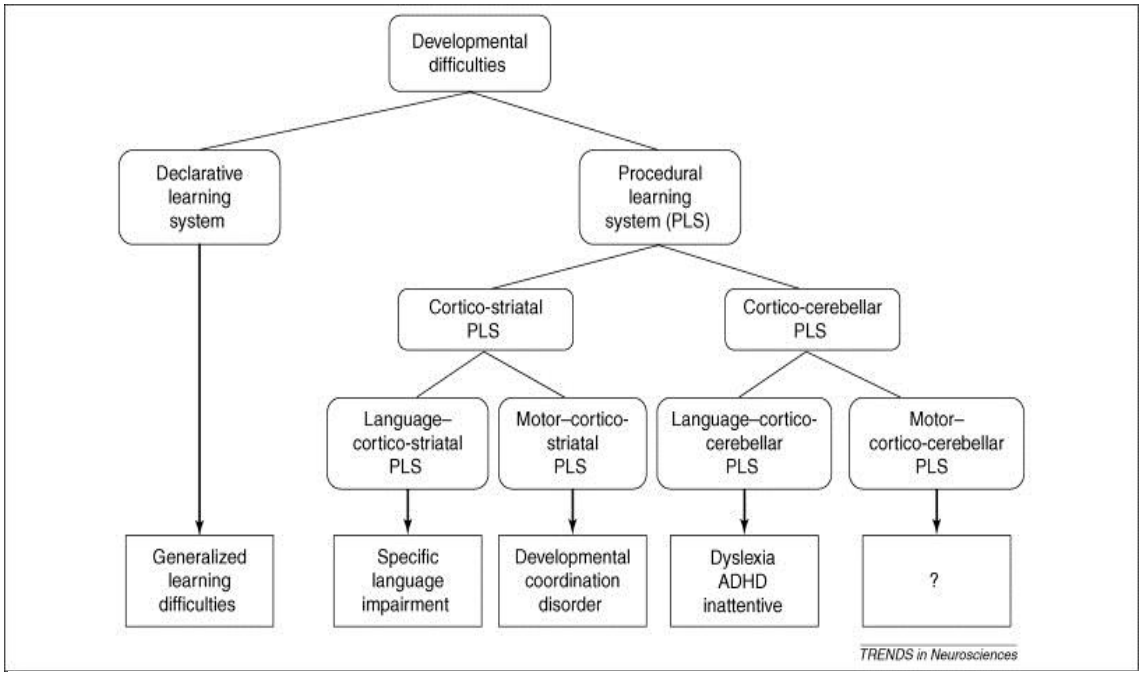

Figure 1.4 Nicolson and Fawcett's conceptualisation of procedural learning deficits in children with Developmental Disorders Including DCD (Figure from Nicholson & Fawcett 2007)

The behavioural literature regarding procedural learning and automatization in DCD is mixed. Tsai and colleagues (Tsai et al. 2009) found children with DCD and balance problems performed significantly worse than their typically developing peers on a balance task during certain dual task paradigms. Alternatively, Biotteau and colleagues (Biotteau et al. 2015) tested children with DCD and dyslexia on a finger tapping task before and after two weeks of practice and while completing a dual task. Their results showed children with DCD were able to perform the motor task well during the dual task, indicating automatization was intact. This study did not include a control group which means we cannot infer if motor learning as a whole was lower in children with DCD. Lejeune and colleagues (Lejeune et al. 2013) have also shown sequence learning is intact in children with DCD. A recent review found that task performance worsens in children with DCD as task difficulty increases suggesting automatization may only fail for highly complex motor skills such as those requiring multiple steps, high speed, precision or tasks with less sensory feedback (Wilson et al. 2017). Further investigation with experimental paradigms that assess (i) performance at all the stages of learning (ii) the effect of increasing task

difficulty and (iii) the different task parameters is required to fully understand the nature of automatization deficits in children with DCD.

Internal Modelling and Motor Control Deficit

It is suggested that two internal models underlie motor control. The 'forward model' uses a copy of a motor command sent to the musculoskeletal system to predict the sensory consequences of movement, while the 'inverse' model generates motor commands to achieve a desired outcome (Blakemore et al. 2002; Wolpert et al. 1995; Wolpert & Kawato 1998; Wolpert 2007; Wolpert 1997). The predicted effects and the sensory feedback of a movement are compared to update the forward model and optimise motor control. This process underlies fast motor learning. When the actual and predicted sensory feedback do not match, an error is generated which alters motor commands and corrects movement in real time, the internal model is also updated to improve the accuracy of future movement execution as part of motor learning (Shadmehr & Krakauer 2008; Wolpert 1997).

Brain Correlates of Internal Modelling

The cerebellum and parietal lobe are involved in predicting sensory outcomes of movement, updating internal models, adapting motor commands and online motor correction, however their differing roles are not yet clear (Blakemore & Sirigu 2003).

The cerebellum is heavily implicated in the forward modelling of motor commands to control movement. It is not yet clear whether the cerebellum stores internal models, combines the efference copy with sensory information to estimate the forward model or compares predicted and actual consequences of a movement to generate an error signal and update the internal model (Popa et al. 2016; Manto et al. 2012; Krakauer & Mazzoni 2011; Blakemore & Sirigu 2003; Argyropoulos 2015; Blakemore 2003). In healthy adults transcranial magnetic stimulation (TMS) of the lateral cerebellum induced reaching errors consistent with movements being planned with incorrect estimated hand positions, which suggests disruption of internal model input (Miall et al. 2007). Another study in healthy adults reported that transcranial direct current stimulation (TDCS) of the cerebellum improved adaptation to visuomotor transformation and reduced movement errors, which suggests online updating of the forward model was improved (Galea et al. 2011).

In their review, Blakemore and Sirigu (Blakemore & Sirigu 2003) found evidence that activation in the left posterior and inferior parietal lobe is higher in imagined than executed movement, which suggests the parietal lobe is particularly important for motor

imagery. Motor imagery tasks require execution of a forward model in the absence of sensory feedback to consciously simulate a movement. These results suggest that perhaps the parietal lobe is involved in the execution of the forward model. Shadmehr and Krakauer (Shadmehr & Krakauer 2008) hypothesise that the parietal lobe acts as the comparator by combining expected and actual sensory feedback to estimate the error. Doyon and colleagues suggest the long term retention of programs to execute motor sequences and adapt motor commands are distributed across parietal and sensorimotor cortices (Doyon et al. 2009; Doyon et al. 2018; Figure 1.3 retention phase).

Internal Modelling Deficit Hypothesis and DCD

i) The Forward Model

The most prominent hypothesis in the DCD research community is that a deficit in the forward internal model underlies motor skill problems in children with DCD (Figure 1.5, red box). Internal modelling has been tested in children with DCD using several paradigms including imagined or simulated pointing, mental rotation of limbs, predictive control of eye movements, anticipatory adjustments of posture or grip force and rapid online correction of reaching movements (Wilson et al. 2013; Wilson et al. 2017). A systematic review published in 2014 examined the behavioural evidence in favour of the internal modelling deficit hypothesis (Adams et al. 2014). This review identified 'moderate support' for deficits in the forward model in children with DCD across effector systems. The authors found that, in general, the difference was greater in tasks requiring more top-down or explicit control.

Motor imagery tasks are used to access the internal model behaviourally. In such tasks participants are required to perform imagined movements; this means the motor control system lacks sensory feedback and is thus solely reliant on the internally generated model of motor outcome (Adams et al. 2014). Fitts law (Fitts 1954) states that with movement execution, there is a speed/accuracy trade off. This law also applies to simulated movements in healthy individuals (Sirigu et al. 1996; Smits-Engelsman & Peter H. Wilson 2013). Studies have shown that executed movements in children with DCD follow Fitts Law, but that their imagined movements do not, which authors suggest indicates a deficient internal model of movement (Adams et al. 2014; Adams et al. 2017; Wilson et al. 2001; Reynolds, Licari, Elliott, et al. 2015; Williams et al. 2008).

ii) Sensorimotor Integration

A related hypothesis is that execution of motor programmes is highly variable in children with DCD due to noisy sensorimotor representations of motor skills (Bo et al. 2013; Gomez & Sirigu 2015). Every motor command executed has a slightly different outcome due to variability in environment or execution; this is the noise inherent to the motor system (Friston 2010). Smits-Engelsman and Wilson (Smits-Engelsman & Peter H Wilson 2013) have proposed that children with DCD may have too much noise in their sensorimotor system. This means that when comparing the predicted outcome of a motor command to actual sensory feedback children with DCD do not detect discrepancies unless they are large (Figure 1.5, orange box). As a result their internal models are not updated, execution is not refined and motor skills are not learned accurately.

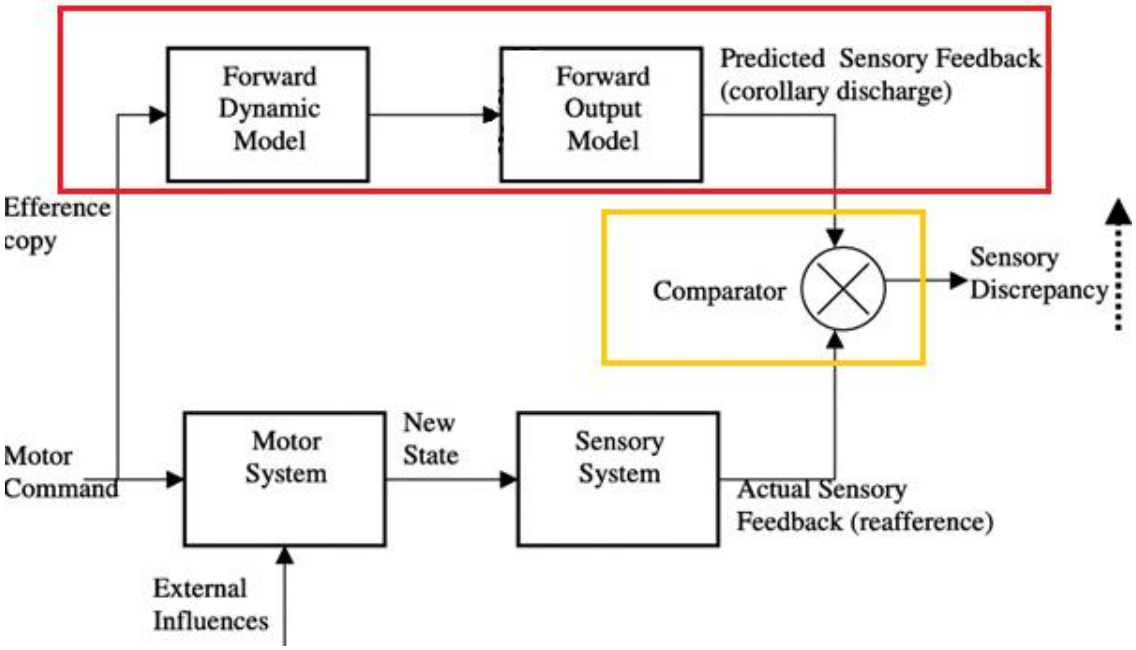

Figure 1.5 Model of motor control using internal models. DCD may be caused by a deficit in the forward model (red box), the comparison between estimated and actual sensory feedback (orange box) or both (Adapted from Blakemore 2003).

To test this hypothesis, studies have used paradigms where participants adapt movements to compensate for environmental changes created with prisms or computer interfaces (Bo & Lee 2013; Gomez & Sirigu 2015). These studies consist of three sets of trials: normal sensory feedback, sensory perturbation, and post perturbation trials where the sensory feedback returns to normal. Successful adaptation is measured by the presence of altered performance in the post perturbation trials. Kagerer and colleagues (Kagerer et al. 2006) found that children with DCD did not adapt well to gradual distortion of the environment because the distortion is within the noisy baseline sensory representation. The evidence for altered sensorimotor representations is limited, but Visser (Visser 2003) has suggested

that a subgroup of children with DCD might have a core deficit in sensorimotor representations. Of note, the internal modelling literature does not currently give any explanation of why children with DCD often show additional impairments in other domains.

Mirror Neuron System Dysfunction

A more recent hypothesis is that mirror neuron dysfunction underlies poor forward motor control in children with DCD.

The Mirror Neuron System

The Mirror Neuron System is formed of a type of neuron which fires when the subject observes and imitates the actions of another (Cattaneo & Rizzolatti 2009) and was first identified in monkeys (Gallese et al. 1996). The human mirror neuron system is thought to incorporate the inferior frontal gyrus (BA44), the adjacent ventral premotor cortex (BA6), the rostral inferior parietal lobule (BA40) and the superior temporal sulcus (STS)(Figure 1.6). The concept of the mirror neuron system in humans remains controversial (Hickok 2009; Kilner & Lemon 2013).

The Mirror Neuron System Deficit Hypothesis in DCD

Children with DCD are poor at imitating movements and many have noted the importance of learning motor skills through imitation (Reynolds, Thornton, et al. 2015). A review published in 2015 proposed that the human mirror neuron supports motor control and is disrupted in children with DCD (Reynolds, Thornton, et al. 2015). Reynolds and colleagues (Reynolds, Thornton, et al. 2015) hypothesise that the superior temporal sulcus codes for visual input during action observation and imitation, specifically goal-directed and meaningful actions. The STS then transfers this visual information to the inferior parietal lobule which specifically codes action kinesthesis. This information is then transferred to the inferior frontal gyrus to define the goal of action. Efference copies of the planned motor action are sent back to the superior temporal sulcus for matching with the observed action. The authors of this review acknowledge that, to date, the evidence for mirror neuron dysfunction in DCD is weak.

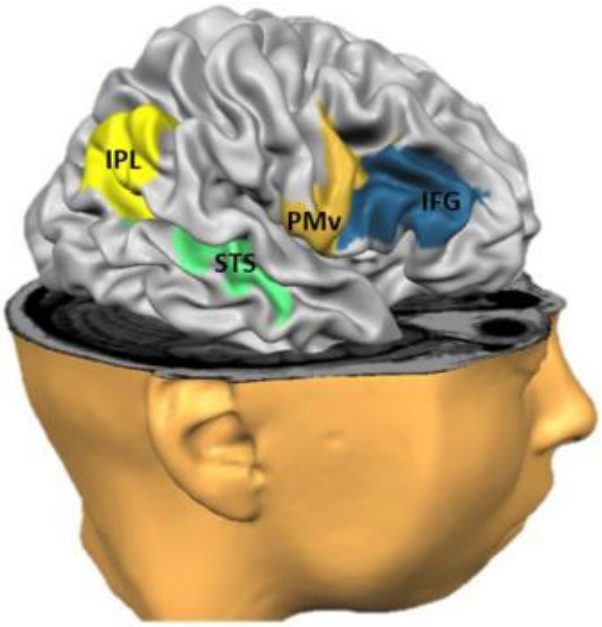

Figure 1.6 A lateral view of the proposed mirror neuron system. Note the proposed mirror neuron system is bilateral, not right lateralised. (Figure from Reynolds, Thornton, et al. 2015)

1.9 Summary

Developmental Coordination Disorder is a common developmental condition that is characterised by poor complex motor skills in the absence of any known genetic or neurological cause. The three theories that emerge from the literature on DCD and the hypothesised neural correlates are summarised in Table 1.1 and Figure 1.6. The literature on Atypical Brain Development does not yield any hypothesised neural correlates. The literature on automatization hypothesises the neural correlates of DCD may lie in the basal ganglia, parietal lobe or cortical motor regions such as the primary motor cortex, premotor cortex and supplementary motor cortex. The literature on internal modelling hypothesises the neural correlates may lie in the cerebellum, parietal lobe, mirror neuron system or cortical motor regions. In this chapter I have provided an overview of the nature of DCD, associated theories and hypothesised neural correlates. The following two chapters will expand on the nature of co-occurring deficits in children with DCD and then explore the current neuroimaging literature in children with DCD.

Table 1.1 Main theories of the underlying deficit in DCD and brain regions implicated

Theory of Deficit	**Brain Regions Implicated**
Atypical Brain Development	Not specified
Automatization Deficit	Putamen, Parietal lobe, cortical motor regions
Internal Modelling Deficit	Cerebellum, Parietal Lobe, cortical motor regions
Mirror Neuron System	Inferior Parietal Lobule, Superior temporal sulcus, ventral premotor cortex, inferior frontal gyrus

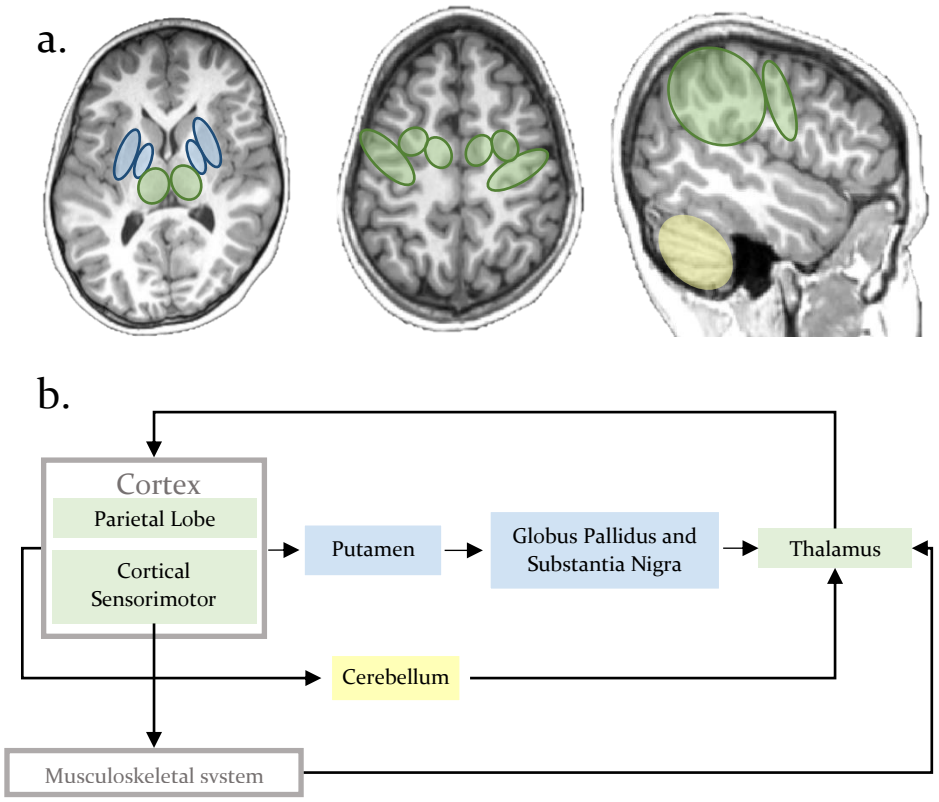

Figure 1.6 a. brain regions on MRI and b. the neuroanatomical model implicated in the automatization deficit hypothesis (blue), internal modelling deficit (yellow) and regions implicated by both hypotheses due to connections (green)

Chapter Two: Cognitive abilities and co-occurring impairments in children with DCD

2.1 Introduction

Neurodevelopmental disorders frequently co-occur and many children diagnosed with one disorder will display impairments in other domains (Crawford & Dewey 2008; Kaplan et al. 1998; Thapar et al. 2017) (Crawford et al 2008; Visser 2008; Kaplan et al 1998; Thapar et al 2017). The aim of this chapter is to review the literature describing co-occurring neurodevelopmental disorders and neuropsychological impairments in children with DCD, and motor skills in children with other developmental disorders. This literature will underpin the first aim of this thesis which is to:

i) describe the neuropsychological phenotype of children with DCD
ii) investigate the relationship between motor and cognitive abilities in children with DCD.

In particular, I will explore intellectual abilities, speech and language skills and attention abilities.

2.2 Intellectual Abilities

Intelligence and the Intelligence Quotient

Performances on different cognitive tasks are highly correlated in healthy people. Intelligence is a construct which attempts to quantify the general cognitive abilities that underpin performance on unrelated cognitive tasks. It may be viewed as a general factor, 'g factor', or as a composite of separate abilities such as visuospatial reasoning, vocabulary, processing speed and working memory. The Intelligence Quotient (IQ) was developed to approximate the 'g' factor through standardised testing. Standardised assessments such as the Wechsler scales were developed to approximate the intelligence quotient and the separate abilities that make up 'g' (Bodin et al. 2009; Deary 2011; Deary et al. 2010). Due to space limitations I will focus on Wechsler scales in this thesis but other scales exist such as the Kaufman (Naugle et al. 1993). These tests attempt to capture both raw reasoning and information processing ability and learned skills such as vocabulary and general knowledge utilising several different subtests. Scores on these subtests are summed and normalised to give an estimate of total or 'full scale' IQ relative to other individuals of the same age. Multiple subtest scores can also be summed to estimate subcomponents of IQ such as verbal comprehension/verbal IQ, perceptual reasoning/performance IQ, working

memory, and processing speed (Figure 1.1). Subcomponent scores allow clinicians to quantify specific strengths and weaknesses in cognition.

The definition of intelligence, and by extension the concept of an 'intelligence quotient', has remained controversial. Nevertheless IQ is consistent across the lifespan and correlates highly with performance on other neuropsychological tests in healthy people (Deary et al. 2013; Diaz-Asper et al. 2004). IQ scores are useful for quantifying general cognitive abilities and identifying specific learning difficulties in the context of general cognition. To date all studies specifically examining intellectual abilities in children with DCD have used Wechsler scales.

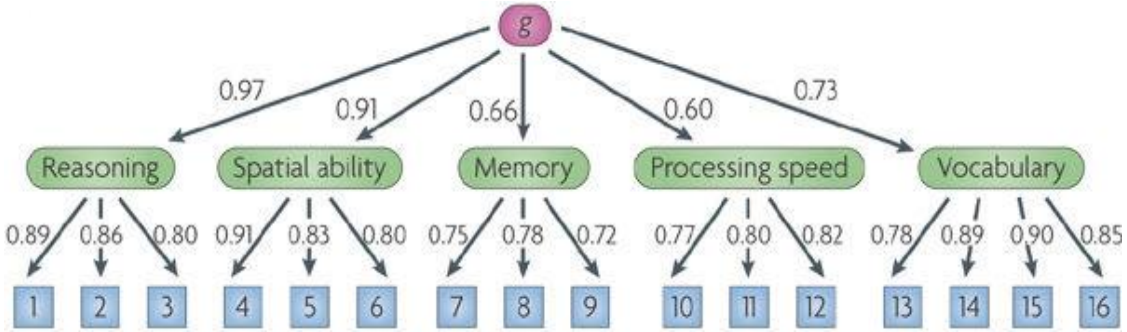

Figure 2.1 Structure of intelligence that underlies Wechsler Intelligence Scales. Blue boxes represent subtest which separate into 5 separate factors representing domains of intellectual ability which in turn load onto 'g' (Figure adapted from Deary et al. 2010).

The relationship between motor skills and IQ across all IQ scores

Although motor and intellectual abilities may be seen as independent from one another two studies have reported relationships between motor skills and IQ across the IQ range. In one study (Smits-Engelsman & Hill 2012), intellectual abilities explained 19% of the variance in total motor score percentile on the Movement Assessment Battery for Children (M-ABC) or Movement Assessment Battery for Children- Second Edition (M-ABC2) in 460 children aged 4-13 years with IQ scores ranging from 50 (exceptionally low) to 145 (exceptionally high), including those with and without known motor skill impairments. A decrease in one standard deviation of IQ (15 points on a Wechsler scale) predicted a mean loss of 10 percentile points on motor test. At a group level, children with low IQ were poorer on motor tests than those with an l IQ within the normal range. The authors acknowledge the large variability of motor performance, with 26.3% of children with IQ 84-71 (1-2 SD below average) and 11.5% of those with IQ 70 or below (2SD below average) performing in the normal range on motor tests.

Westendorp and colleagues (Westendorp et al. 2011) assessed gross motor skills using the Test of Gross Motor Development- 2nd edition, a standardised assessment of gross motor abilities, in 156 children with IQ scores ranging between 50 and 79 and who had no diagnosis of ADHD or autism spectrum disorder (ASD) and a typically developing comparison group. They determined that gross motor skills were poorer in children with IQ impairments compared to children with no known intellectual deficits or difficulties at school (n=255). This study did not assess IQ in either group: IQ scores for the low IQ group were taken from school reports and membership in the unimpaired group was based on parent and teacher reports. As a consequence it was not possible to determine how highly motor and IQ skills correlate.

IQ in children with DCD

Criterion D of the DSM-5 diagnostic criteria states that motor impairments cannot be better explained by an intellectual impairment. Despite this, only 30% of studies published in 2010-2014 included an IQ assessment according to a review published in 2015 (Smits-Engelsman et al. 2015). The literature on IQ profiles in children with DCD is mixed. Two studies examining working memory (Alloway 2007) and mathematical abilities (Gomez et al. 2015) have reported lower block design scores in children with DCD compared to typically developing children. Of note, these two studies did not include all the subtests used to calculate the full perceptual reasoning index. It is therefore not known whether the Block Design reduction is specific to this subtest. Loh and colleagues (Loh et al. 2011) reported lower Wechsler Intelligence Scale for Children (WISC) perceptual reasoning index (which includes the block design subtest) in children with DCD (N=11) and DCD+ADHD (N=11) compared to controls.

In contrast, a recent study of 52 children, aged 7-14, with DCD did not identify any impairment on block design or perceptual reasoning index compared to age matched controls (N=52)(Sumner, Pratt, et al. 2016). Instead, these authors reported poorer performance on working memory and processing speed indices, although the mean for the DCD group was still within the average range. The authors acknowledge the large variability in performance on IQ subdomains in children DCD, and that the motor component of the coding subtest could drive any impairments in processing speed (Sumner, Pratt, et al. 2016). A study of children with DCD alone, dyslexia alone, and co-occurring DCD and dyslexia reported that children with DCD and DCD+Dyslexia had lower processing speed compared to other indices of intelligence, although the mean was still within the average range (Biotteau, Albaret, et al. 2017). In this study, poorer

perceptual reasoning and processing speed indices were associated with poorer motor skills in children with DCD, but not in those with co-occurring DCD and Dyslexia or dyslexia alone. The authors did not include a control group so it is not clear whether children with DCD were significantly poorer than typically developing children. In contrast, the study conducted by Loh and colleagues (Loh et al. 2011) reported no difference between children with DCD alone, DCD+ADHD and control children on processing speed index.

To conclude, there is some evidence that children with DCD show impaired processing speed relative to controls and to other IQ indices. Subtests of the Wechsler processing speed indices involve rapid response on pen and paper, and can therefore be influenced by motor skills. Information processing should therefore be further investigated in children with DCD using tasks that do not rely on a motor response.

Relationship between IQ and motor skills in other disorders

IQ has been associated with motor skills in children where motor skills can be compromised such as those with ASD and those born prematurely. Preterm birth is associated with both low IQ and impaired motor skills in childhood ((Linsell et al. 2017) and see chapter one). A prospective follow-up study of 60 children born prematurely (25-33 weeks) reported abnormal 'general movements' up to 8 weeks post term age were associated with lower IQ scores at school age (7-11 years) (Bruggink et al. 2010). Another study of very preterm children aged 5 (N=81) found that lower full scale IQ was significantly associated with impaired motor skills as tested on the M-ABC2, independent of the effect of soft neurological signs (Van Hus et al. 2014). Additionally, the effect of preterm birth on manual dexterity scores was mediated by IQ, processing speed and symptoms of hyperactivity/attention measured with the strengths and difficulties questionnaire. ASD is a condition characterised by difficulties with social communication that frequently co-occurs with coordination difficulties (Dewey et al. 2007; Miller et al. 2014). Green and colleagues (Green et al. 2009) reported that children with ASD and intellectual impairments (IQ<70) were more likely to have motor impairments than those with ASD and IQ above 70.

2.3 Speech and Language Abilities

Language Abilities

Language is a set of complex cognitive skills including phonology, morphology, syntax, prosody, semantics and pragmatics. These aspects of language can be divided into three domains: language structure, language content and language use (Table 2.1). Language

skills can also be divided into expressive (the ability to produce grammatically accurate and meaningful words and sentences) and receptive language skills (the ability to understand words and sentences that are heard or read).

Table 2.1 The Components of Language

	Definition
Morphology	The structure and form of words
Syntax	The grammatical structure and form of sentences
Semantics	The meaning of words and sentences
Pragmatics	The social rules and conventions of using language to communicate

Children with DLD, previously known as SLI, show different patterns of impairment across these aspects of language (Figure 2.2)(Bishop et al. 2017; Norbury et al. 2004). Children with DLD may also show selective impairments in expressive (generating) or receptive (understanding) language.

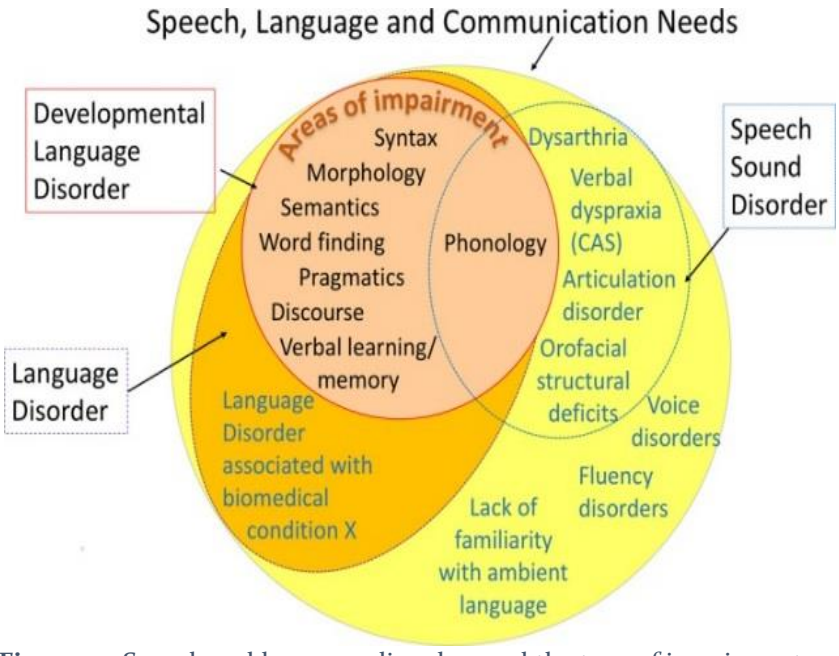

Figure 1.2 Speech and language disorders and the type of impairments associated with the conditions (Figure from Bishop et al 2017)

Speech and oromotor control

Motor speech involves planning and executing rapid movements of the tongue, face, larynx and diaphragm in coordination to produce speech sounds and sequences to form language (Guenther 2006) (Guenther 2006). It is distinct from oromotor control, which

typically refers to the production of non-speech movements (e.g. sticking tongue out, smiling, lip pursing). The components of speech motor and oromotor control and the impairments associated with them are summarised in Table 2.2.

Table 2.2 Components of motor speech and oromotor control and associated impairments

	Definition	**Impairment**
Speech Praxis (Dodd 2005) quoted in (Waring & Knight 2013)	Programming/planning sequences of rapid movements to produce accurate speech with correct prosody	Childhood apraxia of speech (CAS)
Orofacial Praxis (Bearzotti et al. 2007)	Planning and execution of rapid voluntary non-speech movements using the muscles of the face, mouth and throat	Orofacial dyspraxia
Phonology (Dodd 2005) quoted in (Waring and Knight 2013)	Discriminating and correctly using speech sounds	Phonological disorder
Articulation (Dodd 2005) quoted in (Waring and Knight 2013)	Accurately producing/pronouncing speech sounds	Articulation disorder
Speech Execution (Hayden & Square 1999)	Movement of muscles in the head, throat and diaphragm with adequate strength, control and range of movement	Dysarthria

Motor Skills in Children with Speech and Language Disorders

In a review of motor skills in children with speech and/or language disorders, between 40% and 90% of children also had some form of limb co-ordination difficulties (Hill 2001). Visscher and colleagues (Visscher et al. 2007) assessed 125 children aged 6-9 years with developmental speech and language disorders with the M-ABC. Fifty-one percent scored below the 16th percentile and thirty percent scored at or below the 5th percentile. Children with language disorders alone performed better than those with only speech or both speech and language disorders. Comparable rates were also reported in other samples of children with SLI (51% below 16th percentile and 32% below the 5th percentile in (Finlay & McPhillips 2013); 32% children meeting full DSM-4 criteria in (Flapper & Schoemaker 2013).

In a sample of children aged 5-7 years tested three years after intervention for speech/language impairments Gains and Missiuna (Gaines & Missiuna 2007) reported 12 out of 40 children met diagnostic criteria for DCD. Of those, 9 children had persistent speech/language deficits (3 with speech, two with language and 4 with both). Interestingly, only 3 children showed persistent speech/language impairments but no form of motor impairment. Overall this literature illustrates a significant co-occurrence between speech, language and motor impairments with around a third of children with developmental speech and language disorders also displaying motor impairments.

Motor skills in children with Speech Disorders

Tukel and colleagues (Tukel et al. 2015) examined motor abilities in 18 children with childhood apraxia of speech using the Bruininks-Oseretsky Test of Motor Proficiency-Second Edition (BOT-2). The authors report that as a group, children with CAS did not show motor skill impairments, however they displayed a wide range of scores and a range of impairments on different motor skills. There were no correlations between speech and motor variables. Further research is needed to understand whether children with motor speech disorders also display motor skill impairments.

Speech and language impairments in children with DCD

Speech and language impairments are frequently identified in children with DCD. Manual dexterity on the M-ABC was predictive of scores on several speech and language tests in a sample of 363 Taiwanese children at mainstream primary school aged 5-6 years (Cheng et al. 2009). Co-occurring developmental speech and language disorder (DLSD), as defined by performance <10th percentile on two out of three speech and language assessments, was found in 6 of 45 children (13%) who met criteria for DCD. The authors noted lower IQ scores in children with DLSD compared to those without. Children with 'mental insufficiency' based on an IQ test were excluded, but the authors did not define the cut off used. King-Dowling and colleagues (King-Dowling et al. 2014) reported children scoring or below the 16th percentile on the M-ABC2 (considered at risk of movement disorders) scored significantly worse on the preschool language scales when compared to typically developing children (M-ABC2 above 16th percentile). Of note, the "at risk" group still performed within the average range (70.5 percentile on total language).

Language abilities in children with DCD

Few studies have examined the nature of language impairments in children with DCD. Children with DCD (N=11) performed worse than typically developing controls (N=11) but better than those with SLI (N=11) on tests of vocabulary, grammar, sentence repetition,

articulation, story recall and non-word repetition (Archibald & Alloway 2008). Children with DCD showed more variability on these tests, with performance ranging from average to more than two standard deviations below the test mean. Many children with DCD showed impairments similar to those of the SLI group. This study included tests of language production but only a word-level language comprehension task. It is possible children with DCD may show additional receptive language impairments that differ from those found in SLI. In a UK regional population cohort study of seven year old children (ALSPAC) Lingam and colleagues (Lingam et al. 2010) reported probable DCD, as assessed based on the ALSPAC coordination test (a shortened M-ABC assessment) and questionnaire, was associated with difficulties in non-word repetition (odds ratio 1.83), reading (odds ratio 3.35) and spelling (odds ratio 2.81). By contrast, children with probable DCD were not impaired on expressive and receptive language once performance IQ, ADHD symptomatology and social communication skills were accounted for. Although the literature is limited, children with DCD are at increased risk of language difficulties and some children with DCD may show a profile of impairments similar to children with SLI.

Pragmatic language impairments are common in children ASD but are not part of the DSM-5 diagnostic criteria for ASD (Ramberg et al. 1996; Volden et al. 2009; Philofsky et al. 2007; Simms & Jin 2015; APA 2013). Although studies have identified difficulties with social interactions in children with DCD (Cummins et al. 2005; Dewey et al. 2002; Sumner, Leonard, et al. 2016), no study has specifically examined pragmatic language abilities in children with DCD.

Speech and oromotor control abilities in children with DCD

Three studies have examined the nature of speech and oromotor profiles in children with DCD. Farmer et al (Farmer et al. 2016) reported that 36% of children with DCD aged 4-18 had orofacial dyspraxia and 26% had verbal dyspraxia (also known as childhood apraxia of speech, see Table 2.2) based on examination by a neurologist and speech/language therapist. Of note, the authors of this study do not explain the diagnostic criteria or assessments used for speech and orofacial praxis. Consequently these labels may not meet international diagnostic thresholds. Another study identified impaired production of six orofacial gestures (whistle, cough, chew gum, smell a flower, drink from a straw, wink) in children aged 6-12 years of age with developmental motor problems (n=51) compared to controls (N=51) and that the type of errors produced were similar across orofacial and limb praxis tasks (Dewey 1993). Finally, a pilot study of speech and oromotor functions in 5

children with DCD and no history of speech disorders (9y9m-13y6m) showed atypical movement patterns during syllable sequence and sentence production, but normal patterns during non-verbal and single word movements (Ho & Wilmut 2010). Although more work needs to be done to accurately characterise speech and oromotor deficits in children with DCD, these studies nevertheless suggest that many children may show impairments in orofacial and speech sequencing. The studies previously published did not utilise standardised assessments of speech and oromotor control, which limits accurate determination of the type of speech and oromotor disorders seen in children with DCD.

2.4 Attention Abilities and ADHD

Attention Abilities

Attention skills fall under the umbrella of executive functions which are a set of abilities related to but are independent from intelligence that enable a person to plan and execute goal directed activities and support other cognitive abilities (Anderson 2002). Attention is a multidimensional concept and two main neuropsychological models of the components of attention have been proposed.

Posner and Petersen proposed a model of three separate modality-independent attention systems (Posner & Petersen 1990; Petersen & Posner 2012) (Figure 2.3a):

i) 'executive'- the ability to accurately switch between tasks
ii) 'orienting'- the ability to selectively orient attention to stimuli of interest
iii) 'alerting'- maintaining attention during a task

This model underpins the Test of Everyday Attention in Children (TEA-Ch), a standardised assessment of attention abilities in children (Manly et al. 2001)(Figure 2.3b).

Mirsky proposed a four domain construct of attention based on assessments of attention (Mirsky et al. 1991; Koziol et al. 2014)(Figure 2.4):

i) Encoding information: the ability to register information and hold it for utilisation, this overlaps with concepts of working memory
ii) Sustained attention: The ability to maintain attention of one item for a period of time
iii) Shifting Attention: The ability to move from one aspect of the environment to another
iv) Attentional Focus/executive control: The ability to allocate attention to a specific task and filter out unnecessary information. This ability overlaps with concepts of processing speed

Children may display selective impairments on individual domains of attention. Although there is some debate regarding the distinct domains of attention, all models encompass the distinct abilities to (i) remain alert; (ii) filter out unnecessary information; (iii) inhibit inappropriate responses and (iv) easily switch attentional focus (Strauss et al. 2000).

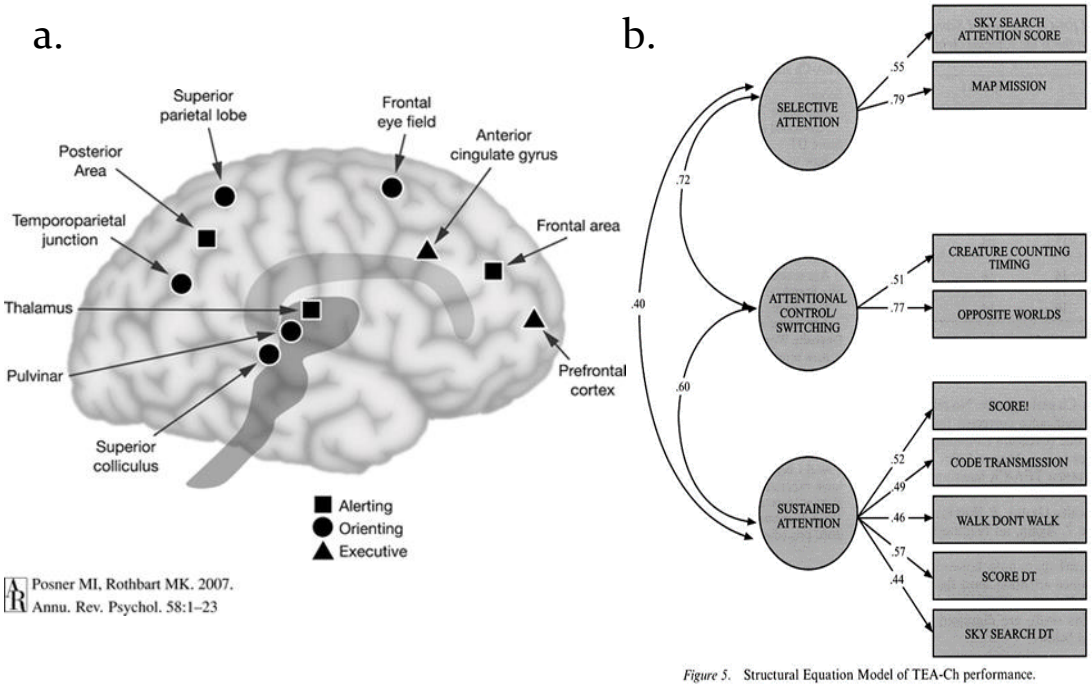

Figure 2.3 a. Posner's model of attention mapped onto brain regions (Figure from Strauss et al 2000) b. construct of the TEA-Ch based on Posner's model (Figure from Manly et al. 2001)

Attention abilities in Children with DCD

Assessments of sustained attention in children with DCD have yielded mixed results. Two studies reported that attention was not impaired in DCD excluding those with ADHD when measured using the Conner's continuous performance task- second edition (CPT-2). The CPT-2 (Conners & Sitarenios 2011) is a test of sustained attention and inhibition which gives metrics relating to impulsivity (pressing a button at the wrong time), inattentiveness (not pressing a button at the correct time) and speed of reaction. One study reported that children with DCD alone and those with DCD and dyslexia perform within normal limits on the CPT-II (Biotteau, Albaret, et al. 2017). Similarly, adolescents with DCD did not differ from their typically developing peers in CPT-II performance (Blais et al. 2017). Attention abilities measured using the Das-Naglieri Cognitive Assessment system in 5-6 year old children with DCD were significantly poorer than those of typically developing peers (Asonitou et al. 2012). In the latter study, attention scores did not

correlate with M-ABC subscales in children with DCD. Young adults with DCD aged 19-25 reported more attention and executive functioning impairments than healthy controls on self-report questionnaires (Tal Saban et al. 2014). Given the inconsistent evidence reported to date, further research on the types of attention problems common to children with DCD and how these relate to motor skills are necessary.

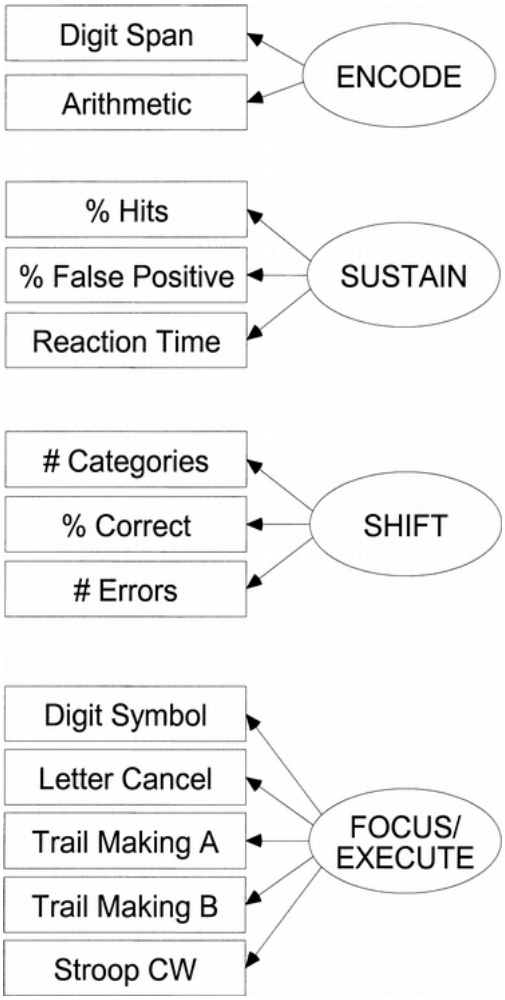

Figure 2.4 components of Mirsky's model of attention and tasks which can assess the components (figure from Strauss et al 2000)

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by persistent symptoms of hyperactivity, impulsivity and/or inattention that interfere with activities of daily life and are not the result of other psychiatric disorders or better explained by other impairments (Faraone et al. 2015). Subtypes of predominantly inattentive, hyperactive/impulsive or combined ADHD were used in DSM-4 (APA 2000). More recently, the DSM-5 has moved away from subtypes to describing 'presentations'

(APA 2013). Of note, ADHD is not diagnosed based on standardised tests of attention. Paton and colleagues (Paton et al. 2014) summarised the research on children with ADHD using the TEA-Ch and identified consistent impairments on the "code transmission" subtest of sustained attention (4/4 studies) and on the attentional control subtests (3/4 studies). ADHD is a behavioural disorder characterised by hyperactivity, impulsivity and/or inattention and children with ADHD may show impairments on standardised tests of everyday attention, in particular on sustained attention and attentional control.

ADHD in Children with DCD

The co-occurrence of DCD and ADHD is well studied with estimates of 35-50% (Kaplan et al. 1998; Pearsall-Jones et al. 2009; Sergeant et al. 2006; Martin et al. 2006; Ghanizadeh 2010; Goulardins et al. 2013; Kadesjo & Gillberg 2001). These estimates vary due to different assessment methods and clinical cut offs used for both DCD and ADHD categorisation. Of note, stimulant medications can improve motor skills performance in children with ADHD (see (Kaiser et al. 2015) for a review). In some children motor performance is improved into the average range (Bart et al. 2013; Bart et al. 2010; Kaiser et al. 2015). In the ALSPAC cohort severity of motor impairment was associated with increased risk of inattentive or hyperactive behaviours in children with DCD (Schoemaker et al. 2013). From the existing literature it is clear that there is significant overlap between ADHD and DCD.

Motor skills in children with ADHD

Kaiser's review of motor skills in children with ADHD without medication found that in studies utilising the M-ABC to assess motor skills, the number of children with probable DCD (below 15th percentile) was 51-73% (Kaiser et al. 2015). These authors also report some evidence of higher rates of motor impairment in children with ADHD-Inattentive and combined subtypes compared to ADHD-hyperactive. On simple motor reaction time tasks children with ADHD were not slower than controls however reaction times were impaired as task complexity increased. The authors also identified increased variability and inconsistency in motor performance in children with ADHD compared to typical controls. A recent review of motor performance in children with DCD identified increased variability and inconsistency in motor performance as well (Wilson et al. 2017). A significant proportion of children with ADHD also show motor impairments however these children may not all meet the full DSM-5 criteria for DCD and it is not yet clear whether a particular profile of ADHD is more likely to display motor impairments.

2.5 DCD and other impairments

Children with DCD can show impairments beyond speech and language and attentional domains. DCD can co-occur with reading disabilities (Alloway 2007; Cheng et al. 2011). Although estimates vary, more recent studies suggest 50-60% of children with dyslexia or poor reading skills have a motor impairment indicative of DCD (Iversen et al. 2005; Ramus et al. 2003; Fawcett & Nicolson 1999) and 70% of children with DCD have difficulty reading (O'Hare & Khalid 2002).

Children with DCD are also impaired on measures of verbal and visuospatial working memory compared to typically developing children (Tsai et al. 2012; Alloway & Archibald 2008; Alloway et al. 2006; Alloway & Archibald 2015; Alloway et al. 2009; Alloway 2007; Alloway 2011). In one study (Chen et al. 2013), Children with DCD showed impairments on everyday memory that were mediated by verbal IQ.

Many children with DCD also show traits of ASD. A study of motor skills in children with ASD found a movement impairment in 76% of the sample utilising the M-ABC and a questionnaire of activities of daily living (DCD-Q) (Green et al. 2009). Sumner and colleagues (Sumner, Leonard, et al. 2016) reported that children with ASD performed as poorly as those with DCD on some tests of fine and gross motor skills. As a group, children with ASD performed more poorly than controls but better than children with DCD on the M-ABC2, with 16 out of 30 children with ASD falling at or below the 16th percentile. Regression analysis revealed socialisation skills significantly predicted DCD vs control group membership. Many children with ASD also show a profile indicative of DCD but no studies have explored the specific relationship between pragmatic language skills and motor skills. Despite no diagnoses of ASD in the DCD group 5 out of 30 children (16%) displayed significant ASD symptomatology based on a parental questionnaire in Sumner and colleagues' study. Another study of children with DCD aged 7 (N=55) showed increased symptoms of Asperger's syndrome relative to controls across the group and four children met the diagnostic criteria (Kadesjo & Gillberg 1998). The main focus of this thesis is speech, language and attention deficits in children with DCD however children with DCD can show a wide range of additional disorders including reading disabilities, working memory difficulties and ASD.

2.6 Summary

Up to 50% of children with developmental disorders such as ADHD and speech/language disorders show motor impairments indicative of DCD. The literature describing intelligence, attention, language and speech functions in children with DCD and the rate

of impairment in these children is less extensive. The occurrence of ADHD in children with DCD is well studied, with estimates of 30-50%. To understand the relationship between ADHD and DCD further studies should examine the neuropsychiatric and motor phenotypes of both children with DCD and those with ADHD to understand the relationship between these disorders. More extensive study of attention, speech and language abilities in children with DCD beyond co-occurring disorders is needed in order to (i) better understand the type of impairments that occur and (ii) the relationship between difficulties in different domains. The first aim of this thesis is therefore to describe motor, IQ, speech, language and attention abilities in children with DCD. In chapter five I will examine:

i) To what extent attention, speech and language skills are impaired in children with DCD relative to typically developing children
ii) The relationship between motor skill deficits and impairments in other domains in children with DCD

Chapter Three: Literature review of neuroimaging in DCD

3.1 Introduction

Neuroimaging research into developmental coordination disorder has increased in recent years but remains limited. The first aim of this chapter is to summarise and critically appraise findings from neuroimaging research in people with DCD. The second aim is to assess the amount of evidence in the current literature for each hypothesised deficit of impairment in DCD. Nineteen Magnetic Resonance Imaging (MRI) studies have been published examining the neural correlates of DCD, four utilising T1-weighted structural imaging (Table 3.1), four utilising diffusion-weighted imaging (Table 3.2) and eleven functional MRI studies (Table 3.3). The tables are located at the end of the chapter. Results from MRI studies are discussed according to evidence of:

i) Cerebellar involvement
ii) Basal ganglia involvement
iii) Parietal lobe involvement
iv) Frontal Lobe involvement
v) Mirror neuron system involvement

In section 3.8 I will discuss the limited imaging research into co-occurring deficits in children with DCD. In section 3.9 I will explore the limitations of the current MRI literature. Finally, in section 3.10 I will briefly review the studies from other imaging modalities.

3.2 Evidence of Cerebellar involvement

The internal modelling deficit hypothesis suggests the cerebellum could be the locus for impairment in children with DCD as discussed in chapter one. Children with DCD may have difficulty predicting the sensory and motor consequences of a movement or detecting a discrepancy between the predicted and actual sensory consequences of a motor command. Of particular interest are lobules V, VI, VIIB and VIII which are implicated in sensorimotor tasks (Stoodley & Schmahmann 2009; Stoodley & Schmahmann 2010; Ramnani 2006)(See Figure 3.1 for cerebellar lobule diagram).

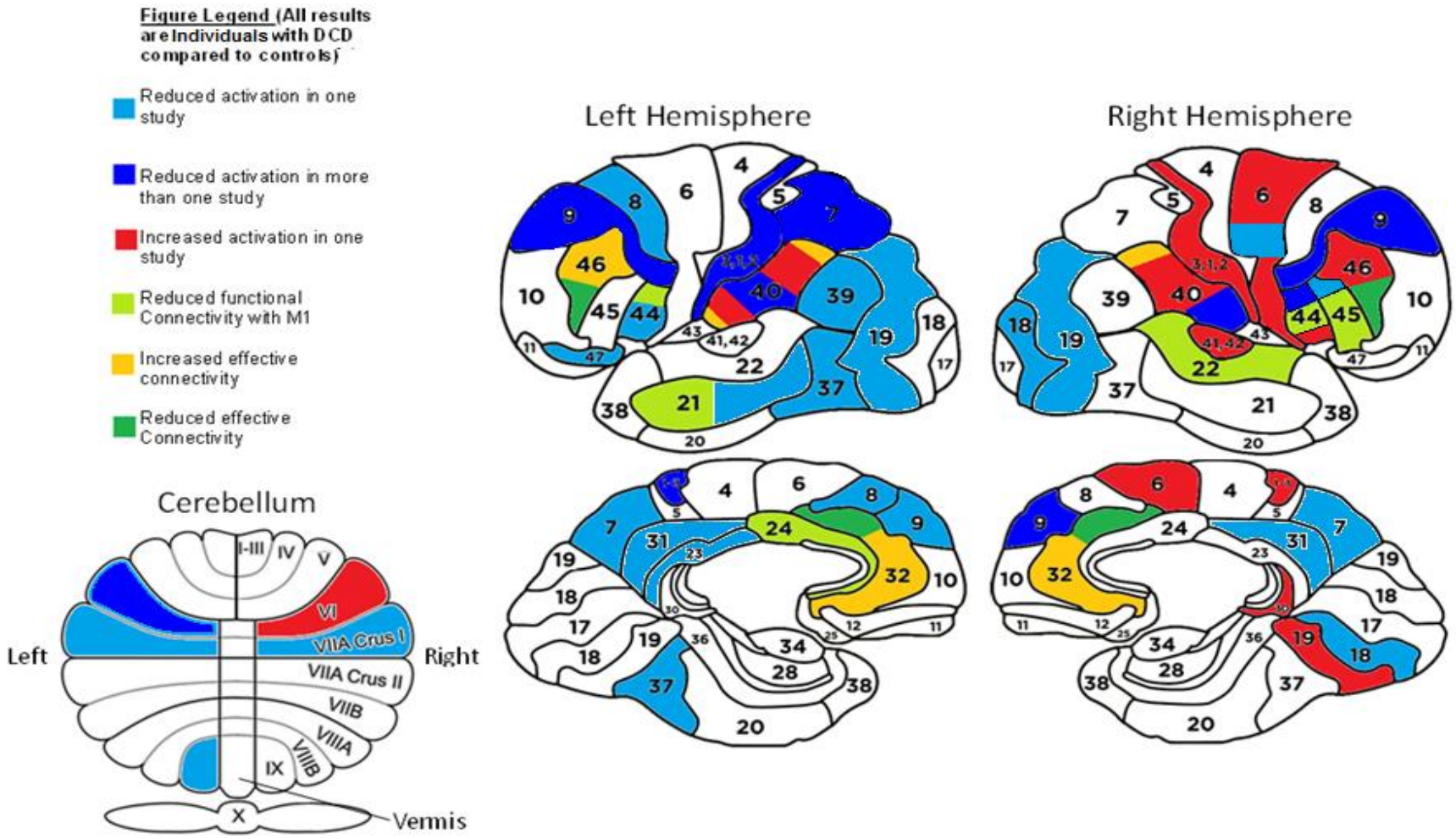

Figure 3.1 Summary of Cortical and cerebellar fMRI differences in participants with DCD. Biotteau and colleagues' study is not summarised here because they did not include a typically developing control group

Structural Evidence

Evidence for structural differences in the cerebellum in individuals with DCD is mixed. A factor made up of cerebellar lobule volumes (VIIA, VIIB, Crus II, V, VI, IX, vermis of V, VI, IX) predicted aiming and catching score from the M-ABC across a sample of over 100 children aged 4-17, including children with i) DCD ii) ADHD iii) DCD and ADHD and iv) no diagnoses (Shaw et al. 2016). In the same study, cerebellar volume was not reduced in children with DCD or DCD and ADHD relative to controls. A whole brain voxel-based morphometry (VBM) study revealed no cerebellar alterations in 22 children with DCD relative to 22 typically developing controls nor any correlation between cerebellar grey matter density and M-ABC2 percentile scores (Reynolds et al. 2017). In the diffusion MRI literature, a pilot tractography study did not find any differences in diffusion metrics in the middle cerebellar peduncles and no relationships between motor skill and diffusion metrics (Zwicker et al. 2012). This latter study had a small sample of only seven children with DCD and seven controls so it is not possible to determine whether this result is due to a lack of power or a true effect that would be replicated in a larger sample. Another study utilising graph theoretical analysis of DWI data found that nodal efficiency in the left cerebellum VI along with efficiency in the right superior parietal gyrus best discriminated between children with DCD and typically developing children (Debrabant et al. 2016).Overall there is evidence some that cerebellar volume is associated with the aiming and catching M-ABC score in children. There are no reported alterations in cerebellar structure in children with DCD compared to typically developing children however organisation of cortico-cerebellar structural networks may be altered.

Functional Evidence

Three functional MRI (fMRI) papers from two studies have reported reduced cerebellar activation in children with DCD when compared to controls; however, this reduction is not consistently reported in one region of the cerebellum (Figure 3.1). These studies report under activation in left crus 1 in a motor timing task (Debrabant et al. 2013) and right lobule VI during trail tracing (Zwicker et al. 2010). The percentage signal change associated with practice of the trail tracing task was significantly reduced in children with DCD in right crus 1, left lobule VI and left lobule IX compared to typically developing children (Zwicker et al. 2011). In another study, adults with probable DCD and those without were asked to determine if a pictured hand was the left or right by imagining their own hand rotating to match a picture given (Kashuk et al. 2017). Adults without impairments showed higher activation with increasing task difficulty than those with probable DCD. Finally, in a study with children with Dyslexia, DCD and DCD+Dyslexia, children with DCD show

reduced activation relative to dyslexic children in a region of the right anterior cerebellum (Biotteau, Péran, et al. 2017). In the absence of a control group in this study it is not possible to conclude whether children with DCD are showing activation that differs from a typical pattern. There is some evidence for altered cerebellar activation in children and adults with DCD however the literature does not converge on a particular lobule.

3.3 Evidence of Basal Ganglia and Thalamus involvement

As discussed in chapter one, the putamen and globus pallidus are implicated in motor sequence learning and the automatization of motor skills. As Doyon and colleagues report, the putamen has been implicated in the automatization of motor skills (Doyon et al. 2009; Doyon et al. 2018). The globus pallidus is the output structure of the basal ganglia and receives projections from the putamen. The automatization deficit hypothesis suggests impairment in the cortico-striatal circuit may underlie DCD.

Structural evidence

One study has examined basal ganglia and thalamus volumes in a large sample of children aged 4-17. Neither a factor containing volumes from basal ganglia nuclei nor a factor containing thalamic volumes explained any variance in subscales of the M-ABC across the whole sample, nor were there differences in between children with DCD, DCD+ADHD, ADHD and a typically developing group (Shaw et al. 2016). No differences between children with DCD and controls or correlations with M-ABC2 percentile were reported using whole brain VBM (Reynolds et al. 2017).

Functional evidence

There is inconclusive evidence from the fMRI literature of functional differences in the basal ganglia (Figure 3.2). One study specifically examined fMRI activation in children with DCD during execution of both automatized and novel finger sequences (Biotteau, Péran, et al. 2017). During execution of the automatized sequence, Activation was higher in the left thalamus and globus pallidus in children with DCD compared to Dyslexic children and to those with both DCD and Dyslexia. In children with DCD, activation during the novel sequence was also increased in the bilateral thalamus and right caudate compared to those with Dyslexia. Performance on both tasks did not differ across groups. This study did not include a typically developing comparison group so it is not possible to know which if any of the clinical groups displayed anomalous activation. On a finger sequence imitation task, activation in a cluster covering the left caudate, claustrum and anterior cingulate positively correlated with praxis across a sample of children with DCD and controls (Reynolds, Licari, Billington, et al. 2015).

Children with DCD and DCD+ADHD showed reduced resting state fMRI functional connectivity between left primary motor cortex and bilateral caudate relative to controls (McLeod et al. 2014). Reduced connectivity to the contralateral putamen and globus pallidus in children with DCD compared to controls was also reported in the same study. Children with DCD+ADHD showed reduced connectivity to the ipsilateral putamen and pallidum compared to controls. A later study on the same cohort reported connectivity between bilateral sensorimotor cortex and basal ganglia structures was limited in children with DCD however this was not tested statistically compared to a typically developing group (McLeod et al. 2016). Of note this cohort had a small sample of children with DCD alone (N=7) in comparison to the ADHD and DCD+ADHD groups so these results should be tested in a larger sample of children (see Table 3.3).

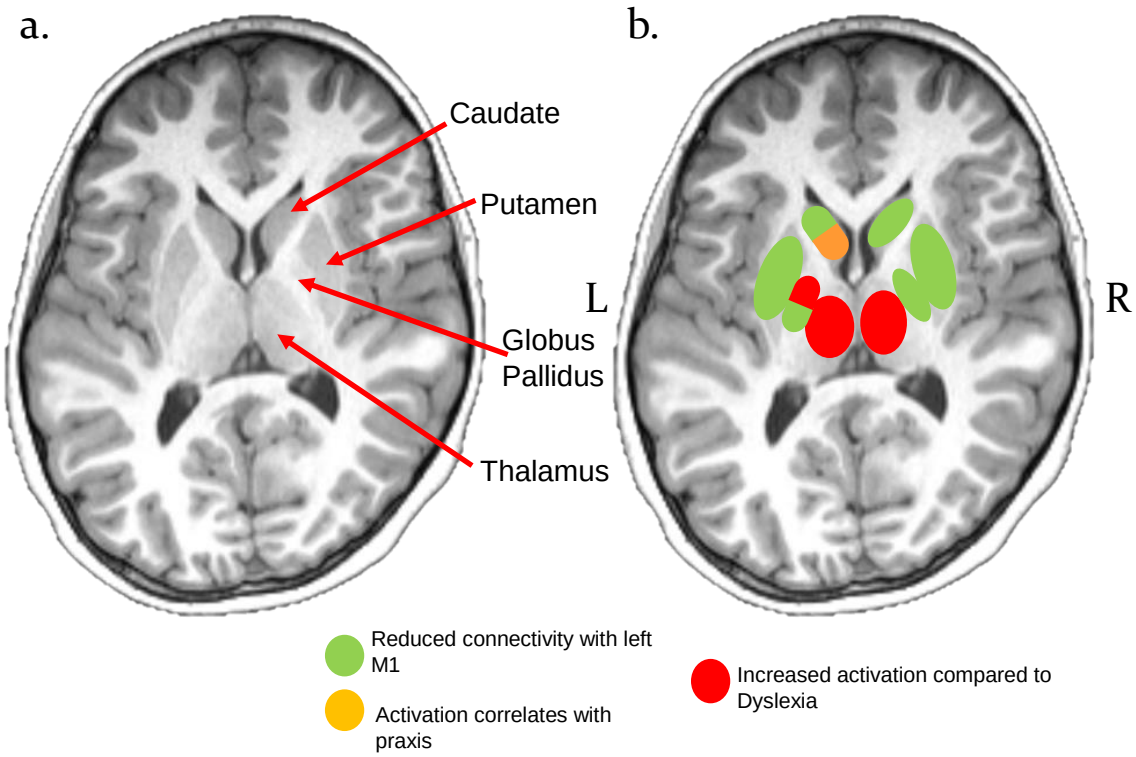

Figure 3.2 a. basal ganglia structures on T1-weighted MRI b. fMRI differences in the basal ganglia in children with DCD

3.4 Evidence of Parietal Lobe involvement

The internal modelling deficit hypothesis implicates the parietal lobe in the core deficit of DCD as discussed in chapter one.

Structural evidence

Three studies have reported structural differences or brain-behaviour relationships in the parietal lobe in children with DCD. Volume of a structural component encompassing

caudal frontal, parietal and posterior temporal cortices explained a significant proportion of variance in aiming and catching M-ABC scores in Shaw and colleagues' (Shaw et al. 2016) study mentioned in the cerebellar structural section. In the same study children with DCD, DCD+ADHD and ADHD all had reduced volume in this component when compared to controls but there were no significant differences between clinical groups. In a graph theoretical analysis of diffusion-weighted imaging (DWI) data, nodal efficiency in the right superior parietal gyrus together with the left cerebellum VI mentioned above discriminated between children with DCD and controls (Debrabant et al. 2016). This study utilised number of streamlines connecting each region to construct the connectome. Number of streamlines is not a measure of white matter microstructure therefore these results may not reflect a microstructural alteration (Jones et al. 2013; Sotiropoulos & Zalesky 2017). In Reynolds and colleagues' VBM study, grey matter concentration in a region spanning the left precuneus and posterior cingulate positively correlated with log-transformed M-ABC2 percentile scores across the whole sample (Reynolds et al. 2017). Of note, the authors did not state why log normalised percentile scores were utilised; statistically it would have been preferable to use scaled scores. Associations between the parietal lobe structure and DCD have been reported in bilateral parietal cortices, right superior parietal gyrus and left precuneus.

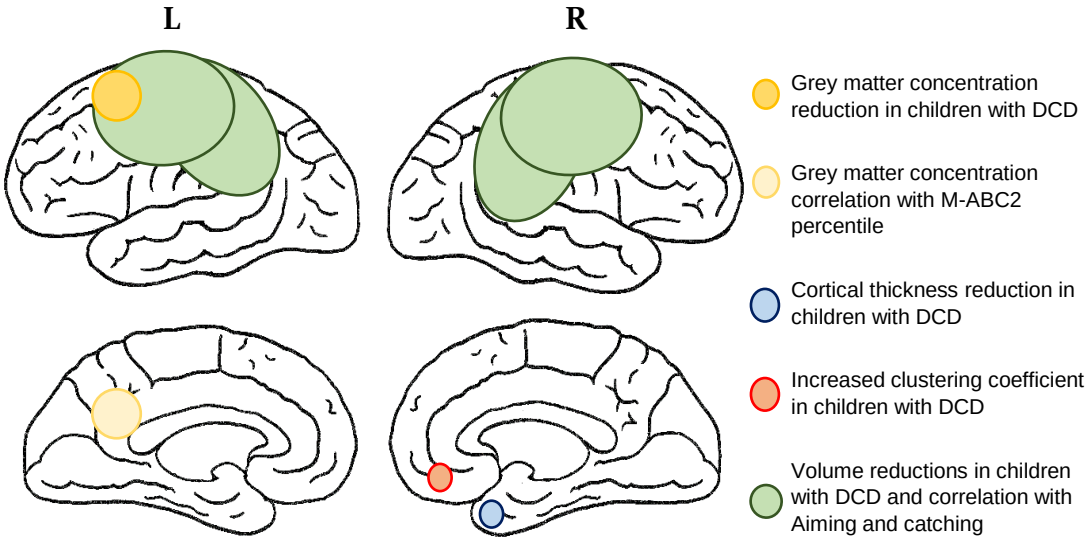

Figure 3.3 summary of cortical structural neuroimaging alterations reported in children with DCD

Functional evidence

The most commonly reported alteration in fMRI research in children with DCD is the inferior parietal lobe. Results have however been inconsistent regarding whether the activity is increased or decreased in children with DCD (Figure 3.1). Decreased activation

in the left inferior parietal lobe during a joystick tracking task was reported in one study (Kashiwagi et al. 2009) but the study using a flower tracing task mentioned above reported increased activation in the same region (Zwicker et al. 2010). Activation signal changes after tracing task practice were significantly lower in the right and left inferior parietal lobe and right lingual gyrus in children with DCD compared to control children (Zwicker et al. 2011). Debrabant and colleagues' timing study reported that when reacting to unpredictably timed stimuli vs predictably timed stimuli, children with DCD showed significantly lower activation in the right temporoparietal junction when compared to typically developing children (Debrabant et al. 2013). This activation was positively correlated to reaction time in both groups. The authors suggest this is an indicator of additional processing for unsuccessful anticipation in unpredictably timed stimuli possibly acting to update the forward model of the action. In the resting state fMRI literature, children with co-occurring DCD and ADHD show decreased connectivity between left motor cortex and bilateral supramarginal gyri (McLeod et al. 2014). Connectivity between the right sensorimotor cortex and bilateral angular gyri was negatively correlated with motor skills in the same cohort (McLeod et al. 2016). Finally, Querne's study of children performing a go/no-go task revealed that effective connectivity to bilateral inferior parietal lobes from the middle frontal and anterior cingulate gyri was increased in children with DCD relative to control children (Querne et al. 2008).

Alterations in the rest of the parietal lobe have also been reported in children with DCD, however these are not consistent across studies (Figure 3.1). In Boitteau's fMRI study, children with DCD showed increased activation compared to Dyslexic children and those with DCD and Dyslexia in bilateral temporal-parietal junction when executing the automatized task (Biotteau, Péran, et al. 2017). Resting state functional connectivity between the right SM1 and bilateral angular gyri was negatively correlated with a standardised score of motor skills in children with DCD and DCD+ADHD (McLeod et al. 2016). Lower activation in the right precuneus and left posterior cingulate has been reported in children with DCD compared to controls when executing a finger sequencing paradigm (Reynolds, Licari, Elliott, et al. 2015). In the same study, Praxis scores negatively correlated with activation in the cingulate and posterior insula during imitation of the same task. Another finger sequencing fMRI study did not report the same result; instead children with DCD showed increased right postcentral activation relative to controls which the authors suggest reflects an increased reliance on sensory feedback for motor control (Licari et al. 2015). Kashuk and colleagues reported higher increases in activation with increasing task difficulty in the left superior parietal lobe in adults with probable

DCD compared to those without (Kashuk et al. 2017). Overall there is extensive evidence of parietal dysfunction in children with DCD with converging evidence for dysfunction in the inferior parietal lobule.

3.5 Evidence of Frontal Lobe involvement

The frontal lobe contains premotor, supplementary motor and motor regions of the cortex that are necessary for movement (Scott 2012). Additionally, the frontal lobe contains regions of cortex involved in learning, information integration, decision making and cognitive control (Struppler et al. 2007; McGuire & Botvinick 2010; Ramnani 2012; Rushworth et al. 2011; Nogueira et al. 2017).

Structural evidence

Four studies have examined frontal lobe structure in children with DCD with little overlap in the results (Figure 3.3). Shaw and colleagues' results are not specific to the frontal lobe and are discussed in the previous section (Shaw et al. 2016). Children with DCD and co-occurring ADHD showed widespread reductions in cortical thickness across the frontal and parietal cortices when compared to controls (Langevin et al. 2015). By contrast, children with DCD alone only showed reductions in the right temporal pole. The differences found the co-occurring group were beyond the summation of alterations in DCD alone and ADHD alone, and suggests a separate neural signature for children with co-occurring motor and attention difficulties. The DCD alone group was small (N=9) compared to the others so the limited differences between this group and the control group may be due to a lack of power. There may also be errors in the cortical thickness reconstructions; the temporal and frontal poles are particularly vulnerable to this due to their proximity to the sinus cavity. It is also difficult to interpret a reduction in the temporal pole in a theoretical context as the temporal poles are not part of the motor control or learning system (Bonner & Price 2013).

Children with DCD showed reduced grey matter concentration using VBM in a region of the right superior and middle frontal gyrus compared to typically developing children (Reynolds et al. 2017). The authors also used data from two different MRI scanners; scanner was entered as a co-variate but without reporting the numbers on each scanner in each group. If the majority of children in one group were scanned on one scanner and the majority on another then entering this as a co-variate may have removed variance from the sample resulting in false negatives. Finally, children with DCD also showed increased clustering coefficient in the right orbitofrontal cortex compared to controls in a graph theoretical analysis of structural covariance based on cortical thickness, although the

authors state that as they did not correct for multiple comparisons their results should be considered exploratory (Caeyenberghs et al. 2016).

Functional evidence

Functional neuroimaging studies in children with DCD have shown alterations in activation in the frontal lobe (Figure 3.1). Four studies have reported altered activation in the middle frontal gyri, which contain premotor cortex, and dorsolateral prefrontal cortex. During the flower tracing task, increased activation in the right middle frontal gyrus but decreased activation in the left superior and inferior frontal gyri was found in children with DCD compared to typically-developing children (Zwicker et al. 2010). Upon examining percentage signal change after training on the task in the same cohort, children with DCD showed lower signal change in the right middle frontal gyrus compared to controls (Zwicker et al. 2011). In Kashuk et al (Kashuk et al. 2017)'s mental rotation task, adults without DCD showed increased activation in bilateral middle frontal gyri with increasing task difficulty when compared to adults with probable DCD who showed less increase. In Debrabant's motor timing paradigm comparing irregular and regular pacing of button presses, children with DCD showed reduced right dorsolateral prefrontal cortex activation when compared to controls (Debrabant et al. 2013).

During a finger sequencing task, decreased activation was found in regions of the left superior and inferior frontal gyri in children with DCD compared to controls (Licari et al. 2015). Reynolds and colleagues (Reynolds, Licari, Billington, et al. 2015) reported reduced activation in different regions of the right inferior frontal gyrus during observation, execution and imitation of a finger sequencing task when compared to controls. In Boitteau and colleagues' (Biotteau, Péran, et al. 2017) fMRI study, children with DCD showed increased activation in bilateral cingulate, insula, premotor and sensorimotor cortices compared to Dyslexic children when performing an automatized task. The activation in bilateral cingulate and primary motor cortices was also higher in children with DCD alone compared to those with DCD and Dyslexia.

Resting state connectivity between right sensorimotor cortex and bilateral frontal poles positively correlated with motor abilities children with DCD and DCD+ADHD (McLeod et al. 2016). The same score was negatively correlated with connectivity between right sensorimotor cortex and left anterior cingulate in the same study. Finally, a study of nine children with DCD performing a go/no go task reported no difference in activation in the frontal lobes, but when analysing effective connectivity using structural equation modelling the authors found higher path coefficients from inferior parietal cortex to

middle frontal cortex, and a strongly negative coefficient from the middle frontal cortex to inferior parietal cortex in children with DCD when compared to ten controls (Querne et al. 2008). This study suggests network based differences in the interaction between the frontal and parietal lobes may exist in children with DCD. Overall several studies have reported functional changes in bilateral regions of the middle frontal gyrus, dorsolateral prefrontal cortex and inferior frontal gyrus. Dysfunction has also been reported in the bilateral anterior cingulate and right sensorimotor cortex.

3.6 Cortical White Matter involvement

Four studies have examined microstructural properties of cortical white matter tract in individuals with DCD (Figure 3.4). The first study published was a pilot study of seven children with DCD and seven controls examining the corticospinal tract, posterior thalamic radiations and the middle cerebellar peduncles (Zwicker et al. 2012). Children with DCD showed reduced mean diffusivity (MD) in the corticospinal tract and posterior thalamic radiations averaged across hemispheres when compared to controls. The authors also reported a positive correlation between motor proficiency and axial diffusivity (AD) in both structures across the whole sample. The authors of this study acknowledge that the differences in MD are contrary to those reported in children with severe movement difficulties such as cerebral palsy where lower MD is associated with better motor function (Scheck et al. 2012). It should be noted that this study had a small sample size and the authors did not correct for multiple comparisons, consequently these results should be considered exploratory. Additionally, as the authors averaged track measures across hemispheres, it is not clear whether these reductions reflect bilateral differences or are driven by one tract.

Interestingly, another study has reported decreased MD in adults with DCD in a region of the anterior limb of the left internal capsule (Williams et al. 2017). The authors used tract based spatial statistics (TBSS) to examine voxel-wise differences in MD and fractional anisotropy (FA) across the whole brain between adults with probable DCD and those without. The results were examined, and regions with significant differences were used to create bilateral spherical regions of interest (ROIs). These were in the corticospinal tract, superior longitudinal fasciculus, anterior limb of the internal capsule and inferior longitudinal fasciculus. FA, MD, AD and radial diffusivity (RD) were extracted from each region and compared between groups. Adults with probable DCD showed reduced FA in the right corticospinal tract and left superior longitudinal fasciculus ROIs and reduced MD in the left anterior limb of the internal capsule and right inferior longitudinal

fasciculus ROIs. There were no differences in AD or RD. The values with significant differences also positively correlated with motor functioning across the sample, although examination of the plots suggests some of these correlations may be driven by group differences rather than a continuous distribution. Another methodological limitation of this study is that the authors did not correct for multiple comparisons in the TBSS or ROI analyses, increasing the chance of false-positives.

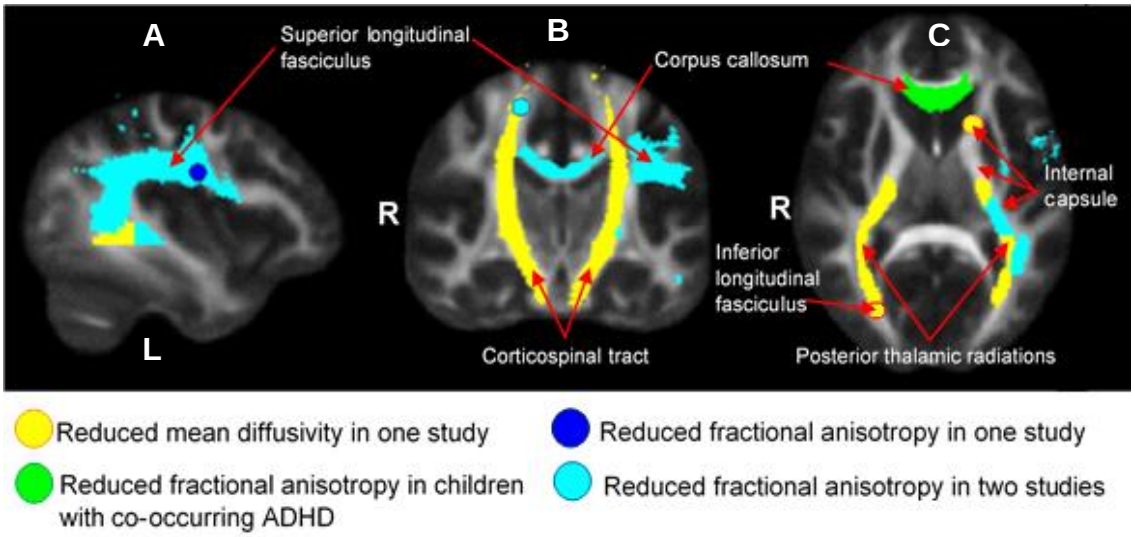

Figure 3.4 Summary of diffusion microstructural alterations in cortical white matter in children with DCD from a. sagittal, b. coronal and c. axial views

Langevin and colleagues (Langevin et al. 2014) used diffusion tensor imaging (DTI) to examine microstructural properties in the superior longitudinal fasciculus, cingulum bundle and corpus callosum in children with i) DCD alone, ii) ADHD alone iii) co-occurring DCD and ADHD and iv) typically developing children. FA in the body of the corpus callosum was reduced in children with DCD alone and DCD+ADHD. Children with DCD alone also had reduced FA in the third segment of the superior longitudinal fasciculus in the left hemisphere. Children with DCD+ADHD and ADHD alone had reduced FA in the anterior corpus callosum. The authors suggest a summation of callosal microstructural changes may underlie co-occurring motor and attention disorders in children. The corpus collosum segments in this study were large, in particular the middle section extended from the posterior genu to anterior splenium. It is therefore difficult to draw conclusions about which cortical regions have reduced interhemispheric connectivity. Additionally, the reconstructed superior longitudinal fasciculus track seems to incorporate fibres from the arcuate fasciculus. This structure is not implicated in motor or attention functions and is instead implicated in language functions (FJ Liegeois, Mahony, et al. 2013; Dick et al. 2014; Leclercq et al. 2010; Sarubbo et al. 2015). As a result,

incorporating FA from these fibres may have masked differences specific to the superior longitudinal fasciculus.

Finally, Debrabant and colleagues (Debrabant et al. 2016) reported that children with DCD have reduced FA and increased RD in the left retrolenticular limb of the internal capsule relative to controls, and that FA in this region correlated with visuomotor integration abilities across the whole sample. The retrolenticular limb of the internal capsule corresponds to the optic radiations, and the authors suggest this reflects altered visual perception. This region may also contain fibres that project from the thalamus to primary somatosensory cortex carrying sensory information from the body. As they did not utilise tractography to measure these fibres, it is not possible to know which anatomical connections are altered. In the graph theoretical analysis reported in the same study, children with DCD showed decreased mean clustering coefficient and global efficiency.

From a methodological viewpoint all previous diffusion MRI studies used the basic tensor to model the diffusion signal which does not accurately model signal in voxels where different fibre populations cross (Tournier et al. 2011). More complex models such as constrained spherical deconvolution (CSD) or ball-and-sticks may better characterise fibre populations, and as a result be more sensitive to subtle differences and brain-behaviour relationships in individuals with DCD. Previous studies nevertheless reported evidence that individuals with DCD have microstructural changes in the corticospinal tract, internal capsule, and superior longitudinal fasciculus, which are form part of circuits involved in motor control and execution. Additionally, there is some evidence of changes in the corpus callosum, inferior longitudinal fasciculus and posterior thalamic radiations.

3.7 Evidence of Mirror Neuron System involvement

A recent hypothesis to emerge is that dysfunction of the Mirror Neuron System underlies the impairments identified in children with DCD yet research to date is limited.

Structural evidence

The mirror neuron is a hypothesised system of neurons in cortex which are selectively activated during observation and imitation of an action as discussed in chapter one. One study reported reduced clustering coefficient in children with DCD and co-occurring ASD in the right pars opercularis compared to controls however this effect was not found in DCD alone (Caeyenberghs et al. 2016). Additionally, this reduction was not related to any metric of imitation or observation of action.

Functional evidence

A systematic review by Reynolds and colleagues (Reynolds, Thornton, et al. 2015) reported no neuroimaging studies that specifically investigated the function of the mirror neuron system, but differences between children with DCD and controls in associated regions, such as inferior frontal gyrus and inferior parietal lobule (Figure 3.1). One fMRI study by the same group specifically investigated mirror neuron system function in children with DCD compared to controls (Reynolds, Licari, Billington, et al. 2015). They found reduced activation in the right pars opercularis during observation of movements in children with DCD. In a region of interest analysis focused on the mirror neuron system, there was no effect of group on the changes in activation across baseline, execution, imitation and observation of finger sequencing movements. Overall, there is evidence for dysfunction in the inferior frontal gyrus and inferior parietal lobule which are part of the mirror neuron system however only one study has reported reduced activation in the inferior frontal gyrus during a task specifically related to mirror neuron function.

3.8 MRI Research into DCD and Co-occurring Deficits

Seven studies have examined the relationship between DCD and co-occurring deficits. Four neuroimaging studies from the same group have characterised co-occurring ADHD and DCD. Langevin and colleagues' (Langevin et al. 2014) study on the corpus callosum identified reduced FA in the genu and the middle section of the corpus callosum in ADHD and DCD respectively, and both reductions in the group with DCD and ADHD together, suggesting a summation of separate effects. By contrast, studies on the same cohort utilising resting state fMRI and cortical thickness indicated widespread differences in children with DCD+ADHD which are beyond the summation of effects seen in the single disorder groups (McLeod et al. 2016; McLeod et al. 2014; Langevin et al. 2015). One graph theory study examining co-occurring DCD and ASD reported little overlap in network differences between DCD, ASD and the co-occurring group which suggests a separate aetiology for co-occurring DCD and ASD (Caeyenberghs et al. 2016). Finally, Biotteau and colleagues (Biotteau, Péran, et al. 2017) examined activation patterns during an automatized finger sequence and novel finger sequence in children with i) DCD, ii) Dyslexia and iii) co-occurring DCD and Dyslexia. The authors didn't find any differences in task performance but found increased activation across the brain in both tasks in children with DCD alone compared to both those with Dyslexia and those with DCD+Dyslexia. As this study did not include a sample of typically developing children, it is not possible to know where these increases represent a significant deviation from typical function.

All studies examining co-occurring impairments in children with DCD have utilised co-occurring deficits to define subgroups of children, implying a binary presence or absence of additional impairments. This is despite the fact that children with all developmental disorders are likely to fall on the severe end of a spectrum of abilities found in children. If level of impairment or symptomatology exists on a continuous distribution, utilising group differences to understand co-occurring impairments may result in few significant results, or results driven by outliers. Correlating MRI measures with continuous measures of co-occurring impairment severity would help to better characterize the brain changes associated with additional impairments in DCD, this approach was used in the current thesis.

3.9 Limitations of previous MRI literature

There are methodological issues within the imaging literature currently published concerning DCD. Many of the previous studies in children with DCD have small sample sizes (below fifteen per group). Considering the heterogeneity of both motor impairments and co-occurring disorders in this condition, it is difficult to draw conclusions about the neural correlates of DCD from smaller samples. Many studies also do not correct for multiple comparisons in their analyses and do not define clear neural hypotheses. These two issues increase the chance of a false-positive result, particularly in regions not associated with motor function. Additionally, inconsistent results across fMRI studies may be due to different attentional and executive function loads between fMRI tasks. Indeed, authors often do not report or account for performance differences on fMRI tasks. Recent reviews on the neuroimaging research in DCD have discussed in detail the problem of task and sample differences (Adams et al. 2014; Biotteau et al. 2016). Studies often include participants from a large age range without controlling for the effect of age in analyses. They also do not control for intellectual abilities, which may differ between individuals with DCD and healthy volunteers. Given that functional and structural MRI metrics change with development and may change with IQ, not controlling for these effects can introduce false positive or negatives into results (Brito & Noble 2014; Pietschnig et al. 2015; Snook et al. 2005; Weiss-Croft & Baldeweg 2015).

Another major methodological limitation of previous neuroimaging studies relates to sample characterization. The majority of studies have either excluded children with co-occurring disorders, or not quantified their impairments. Given the high level of co-occurrence between other impairments and DCD it is possible the 'DCD only' groups in these studies contained participants with other developmental conditions either

undiagnosed or unquantified. If impairments are not quantified then we cannot rule out that results may be confounded by attention, language or social communication problems. This is of particular note in studies where whole-brain methods were used. Differences between children with DCD and controls may occur in regions associated with co-occurring deficits rather than the motor difficulty. Identifying relationships between behavioural scores and MRI measures allows us to better define the structures associated with specific impairments. If a sample does indeed contain only children with DCD alone, then the results may not be representative of the wider population of children with DCD considering the pervasiveness of co-occurring conditions in these children.

3.10 Evidence from other imaging modalities

The focus of this thesis is MRI correlates of DCD in children aged 8-10. Here I will briefly summarise the imaging research conducted in children with DCD utilising other modalities.

One study has examined the lateralisation of speech in adults with DCD utilising functional Transcranial Doppler Ultrasound (fTCD) to measure hemispheric blood flow(Hodgson & Hudson 2017). The authors hypothesised that altered motor speech lateralisation may accompany limb coordination difficulties and when performing a covert word generation task, cerebral blood flow was indeed less left-lateralised in adults with DCD compared to typical adults. Lateralisation did not correlate with motor scores. Word generation is an expressive language task which engages language cortices such as Broca's area and its right-sided homologue in healthy adults (Price 2012; John et al. 2011; Friedman et al. 1998). The altered hemispheric lateralisation may be driven by altered language laterality or a global alteration in lateralisation of functions. fMRI studies utilising a large battery of speech and language tasks would better characterise this effect.

Two studies have been published on individuals with DCD utilising SPECT. One case study of a 19 year old with DCD and cerebellar symptoms such as ataxia found reduced perfusion in the cerebellum, with larger effects on the right side compared to a group of healthy older adults (Mariën et al. 2010). These effects may be confounded by differences in age between the case (aged 19 years) and reference group (aged 45 to 70 years). A second study in children with ADHD and co-occurring DCD and ADHD alone found that children with DCD and ADHD had lower blood flow in the left cerebellum but higher in the right compared to those with ADHD alone (Yeh et al. 2012).

Three studies have examined electrophysiological differences in children with DCD. This literature has been reviewed elsewhere (see (Wilson et al. 2017)). Overall, alterations in motor and attention components measured over sensorimotor and parietal cortices during attention, working memory and motor tasks have been reported.

3.11 Summary

Neuroimaging research in children with DCD has increased in recent years but remains limited relative to other neurodevelopmental disorders such as Dyslexia or ADHD (Bishop 2010). Evidence has yet to converge on a consistent pattern of structural of functional changes or provide overwhelming support for one neural hypothesis. Fewer structural imaging studies using T1-weighted or diffusion-weighted MRI have been published compared to the fMRI literature. During fMRI tasks, differences are most commonly reported in the inferior parietal lobule. There is little overlap in results from the structural MRI literature and none of the structural literature has implicated the inferior parietal lobule in DCD. In both fMRI and structural imaging studies, alterations have been found across the cortex in both hypothesised regions involved in motor learning and motor control; and in non-hypothesised regions such as the temporal lobe and orbitofrontal cortex. In conclusion, further research is needed into the relationships between specific motor and cognitive measures which vary within children with DCD and MRI measures. Applying stringent statistical thresholds and controlling for confounding factors such as intellect, age or brain volumes will allow us to draw more robust conclusions regarding the neural correlates of DCD.

3.12 Tables

Table 3.1 T1-weighted MRI studies in children with DCD

Citation	Participants	DCD assessment and inclusion/exclusion criteria	Methods used	Key results	Comments
(Langevin et al. 2015)	8-17 years DCD– 14 (9y9m) ADHD– 19 (9y9m) DCD+ADHD– 10 (9y7m) Controls-14 (11y9m)	M-ABC2 <16th percentile Autism excluded ADHD included Gestation >35 weeks	T1-weighted imaging cortical thickness analysis in Freesurfer. Cortical thickness calculated in 28 cortical regions	Cortical thinning in right temporal pole in DCD alone and ADHD alone, Widespread thinning in frontal, parietal and temporal cortices in ADHD+DCD compared to controls	Widespread changes in co-occurring group beyond summation of two disorders. Unclear whether surface reconstructions were checked for quality
(Caeyenberghs et al. 2016)	8-12 years DCD– 11 (8.82y) DCD+ASD-8 (9.75y) ASD-15 (9.4y) Controls– 19 (9.68y)	MABC2 <16th percentile WISC-III Dutch Total IQ>75 ADHD excluded Birthweight >1500g	T1-weighted imaging cortical thickness graph theoretical analysis using Deskian/Killiany atlas in Freesurfer	No difference in global or small world properties in DCD. DCD>TD clustering coefficient in right lateral orbitofrontal. More widespread changes in DCD+ASD in paralimbic regions. Little overlap between DCD, ASD and DCD+ASD.	Widespread changes in co-occurring group separate from the summation of two disorders. No correction for multiple comparisons in regional analyses.

(Shaw et al. 2016)	4-16.9 years 226 children with MABC data DCD-22 (10.5y) ADHD-42 (8.8y) DCD+ADHD-41 (9.1y) Controls– 65 (9.4y) Uncategorised– 56 (unknown)	DCDQ in impaired range used to define DCD IQ>80 Psychiatric disorders besides ADHD, conduct disorder and oppositional defiant disorder excluded All children assessed on M-ABC	T1-weighted MRI volumes PCA and generation of 4 latent variables: Thalamus, cerebral cortex, basal ganglia, cerebellum ~30% of children excluded due to motion/segmentation errors Partial least squared pathway modelling used to predict subscales of M-ABC in whole sample Examination of Group differences	No significant predictors of manual dexterity or balance. Aiming and catching linked to cerebral cortex and cerebellum volume. No effect of ADHD diagnosis on relationship between variables. All clinical groups below controls on cerebral cortex volume. No difference between clinical groups.	Aiming and catching predicted by cerebellar and cortical structure. Number of children with scans per group is unclear. No correction for multiple comparisons. Didn't used M-ABC to define group with DCD so mean total score is in the average range (8.9 in DCD and 9.4 in DCD+ADHD)

(Reynolds et al. 2017)	7.8-12 years Right handed boys DCD-22 (9.9y) Controls-22 (9.7y)	MABC-2 <17th percentile and a clinician referral Autsim and ADHD excluded	T1-weighted MRI scans from 2 different 3T MRI scanners. VBM analysis co-varying for scanner, age and total intracranial volume. Group differences and correlation with M-ABC2 total test score. Cluster-level correction P<0.05 FWE	Controls>DCD in region of right middle and superior frontal gyrus. Lower Log_{10} transformed M-ABC2 percentile was associated with lower concentration in region of left precuneus/posterior cingulate	Unclear how many children from each group were scanned on each scanner. Cluster level correction used instead of peak-level scores which is not advised I VBM.

Table 3.2 Diffusion MRI studies in Children and adults with DCD

Citation	**Participants**	**DCD assessment and inclusion/exclusion criteria**	**Methods used**	**Key results**	**Comments**
(Zwicker et al. 2012)	aged 8-12 DCD 7 (10y10m) Controls 9 (10y4m)	≤16th percentile on M-ABC2 ADHD excluded	DTI tractography of the posterior thalamic radiations, corticospinal tract and middle cerebellar peduncles	TD>DCD mean diffusivity in corticospinal tract ($p<0.05$ uncorrected). Axial diffusivity in corticospinal tract and posterior thalamic radiations correlates with M-ABC2 percentile	This study had a small sample size and it is not known whether they excluded children born very preterm. No correction for multiple comparisons.
(Langevin et al. 2014)	Aged 8-17 DCD– 9 (12y3m) ADHD– 23 (11y9m) DCD+ADHD– 23 (11y4m) Controls –26 (11y7m)	<16th percentile on M-ABC2 Autism excluded	DTI tractography of the Corpus Callosum and superior longitudinal fasciculus	TD>DCD FA in body of corpus callosum and left SLF III ($P<0.05$; Tukey's HSD). TD>ADHD in genu of corpus callosum, both in DCD+ADHD. FA in body correlated with MAND score	Included children with DCD and co-occurring ADHD to understand the co-occurrence. No correction for age, small sample of children with DCD alone
(Debrabant et al. 2016)	Aged 8-10 DCD– 21 (9y2m) Controls– 20 (9y4m)	M-ABC2 <5th percentile and MABC2 checklist impaired WISC Total IQ>85	DTI metrics in ROIs in primary motor and sensory pathways; graph theoretical	Controls>DCD FA and DCD>control RD in left retrolenticular limb of internal capsule ($p<0.003$ bonferroni), FA correlates with BEERY VMI. Left	Retrolenticular limb of the internal capsule corresponds to the optic radiations. Number of

			analysis based on normalised number of streamlines	cerebellum VI and right superior parietal gyrus nodal efficiency discriminate DCD from controls (P<0.008 Bonferroni)	tracks used to generate connectome which does not correspond to microstructural properties of white matter.
(Williams et al. 2017)	18-40 DCD– 12 (24.5) Controls– 11 (26.7)	McCarron assessment of neuromuscular development (MAND) Neuromuscular Development Index <85 and history of childhood motor impairments ADHD, ASD and intellectual disabilities excluded	Whole brain FA, and MD TBSS group comparison. Regions of significant difference (P<0.05 uncorrected) used to generate bilateral ROIs in CST, SLF, anterior limb of internal capsule and ILF. Compared between groups and correlated with MAND.	Control>DCD in: FA– right CST, left SLF MD– right ILF and left anterior limb IC MAND score correlated with these results across whole group	No correction for age or multiple comparisons.

Table 3.3 fMRI studies in children and adults with DCD

Citation	Participants	DCD assessment and inclusion/exclusion criteria	Methods	Key results	Comments
(Querne et al. 2008)	8-13 DCD– 9 (9y11m) Control– 10 (10y0m)	Motor control deficits on clinical examination and NEPSY WISC-III VIQ >80 ADHD, Conduct disorder, Oppositional defiant disorder, depression excluded	fMRI during go/nogo task– structural equation modelling between bilateral middle frontal cortex, middle frontal cortex, anterior cingulate and Caudate/anterior putamen	Control>DCD right MFC to right ACC, right MFC to right IFC (positive in controls, negative in DCD), DCD>TD right ACC to right IPC. Same but bigger differences in left hemisphere, no differences in striatum connectivity	Examining attention networks in children with DCD. Altered connectivity in DCD with bigger differences in left hemisphere indicating less lateralisation. Corrected for multiple comparisons, didn't assess motor skills with M-ABC2 or BOT
(Kashiwagi et al. 2009)	9-12 DCD-12 (10y10m) Control–12 (10y5m)	M-ABC <15th percentile >3 soft neurological signs Parent identified impact on daily life WISC-III Full Scale IQ >89	fMRI activation patterns manual tracking compared to visual tracking of a target,	TD>DCD left hemisphere cluster spanning parietal lobe and postcentral gyrus (P<0.001 uncorrected peak level and P<0.05FWE cluster level). Performance on task negatively correlated with signal change in left inferior parietal lobe	Used cluster level correction for multiple comparisons. Signal change and left IPL correlation may be driven by an outlier

(Zwicker et al. 2010)	8-12 DCD-7 (10.8y) Control-7 (10.9y)	M-ABC2 ≤ 15th percentile Kaufman IQ >80 Asperger's syndrome Conners ADHD DSM-4 scale <70	fMRI activation during flower shape tracing task	DCD>TD left: inferior parietal lobe, right: middle frontal gyrus, supramarginal gyrus, lingual gyrus, parahippocampal gyrus, posterior cingulate, precentral, superior temporal, cerebellar lobule VI TD>DCD left: precuneus, superior frontal gyrus, inferior temporal gyrus, postcentral gyrus Right: superior temporal gyrus (p<0.01 corrected) DCD group– right middle frontal gyrus negatively correlated with number of tracing completed	No performance differences on task. Higher activation in regions of right hemisphere, lower activation in regions of left hemisphere in DCD. Small sample size.
(Zwicker et al. 2011)	8-12 DCD-7 (10.8y) Control-7(10.9y)	M-ABC2 ≤ 15th percentile Kaufman IQ >80 Asperger's syndrome Conners ADHD DSM-4 scale <70	fMRI activation during flower shape tracing task. Percentage signal change after 3 days task practice (4x2m per day)	TD>DCD interaction over time points right: inferior parietal lobule, lingual gyrus, middle frontal gyrus cerebellar crus I left: fusiform, inferior parietal lobule cerebellar lobule VI and X (P<0.001 corrected)	Changes in activation after task training. Same task and likely same sample as study above. No statistically significant difference in task performance after practice between groups

(Debrabant et al. 2013)	7-10 DCD– 17 (9.4y) Control– 17 (9.2y)	M-ABC2 ≤5th percentile WISC-III TIQ >84 ADHD and ASD excluded	fMRI activation during a button press timing irregular>regular timing contrast	TD>DCD right: dorsolateral prefrontal cortex, temporal-parietal junction, left: cerebellum crus I (P<0.001 corrected)	Corrected for multiple comparisons and has a small age range to minimise age effects. Did not control for performance differences in fMRI tasks
(Licari et al. 2015)	8-10 right handed boys DCD– 13(9.6y) Control-13 (9.3y)	M-ABC2 ≤5th percentile ADHD diagnostic parental rating scale used to exclude ADHD	fMRI sequential finger sequencing task	TD>DCD left: superior and inferior frontal gyrus DCD>TD right postcentral gyrus P<0.05 FDR corrected	Corrected for multiple comparisons and used a small age range
(Reynolds, Licari, Billington, et al. 2015)	7-12 Right handed boys DCD– 14 (10.08y) Control-12 (10.1y)	M-ABC2 ≤16th percentile No autism or ADHD diagnosis or indication on questionnaires	fMRI task observing, executing and imitating finger sequencing task. Activations compared whole brain and in ROIs in the mirror neuron system	TD>DCD execution contrast: left: middle temporal gyrus, posterior cingulate right: inferior frontal gyrus, precuneus TD> DCD imitation: right pars opercularis DCD>TD observation: right pars opercularis (P<0.001 uncorrected) Praxis task positively correlated with imitation activation in left cluster of	No correction for multiple comparisons used, small cluster extent threshold (5)- clusters in right inferior frontal gyrus, right precuneus and left middle temporal gyrus all below 15 voxels No control of performance differences between groups in imitation or execution tasks.

				caudate/anterior cingulate and negatively in cluster of posterior insula/cingulate No differences in Mirror neuron ROIs	
(Biotteau, Péran, et al. 2017)	7-13 DCD– 16 (9y6m) Dylexia– 16 (10y3m) DCD+Dyslexia-16 (9y9m)	M-ABC<5th percentile Exclude low IQ, specific language impairment, ADHD	fMRI executing finger tapping sequences– one overtrained (2x3m per day for 15 days) and one novel (P<0.05FWE andP<0.001 uncorrected cluster level)	No differences in learning and automatization of task DCD>dyslexia overtrained: bilateral: cingulate, primary sensorimotor, preomotor, temporoparietal, right: insula anterior cerebellum left: thalamus DCD>DCD+dyslexia overtrained: bilateral: primary motor, temparietal right: cingulate, cerebellum left: premotor, thalamus, globus pallidus DCD>dyslexia novel: bilateral: cingulate, thalamus right: caudate, claustrum DCD>DCD+dyslexia novel: right cingulate	Different activation patterns but no differences in performance. No control group included Unclear which results survive correction for multiple comparisons

(Kashuk et al. 2017)	18-40 DCD– 12 (24.5y) Controls– 11 (26.7y)	MAND total score <86 (15th percentile) No self-reported ADHD, autism, intellectual deficits	fMRI mental hand rotation task– view picture of hand and imagine rotating one's own hand into this position to determine if it's left or right Reaction time and accuracy recorded	No differences in reaction time or accuracy between groups, no interactions of group Control>DCD signal increases with increasing difficulty– left: superior parietal lobe,middle frontal gyrus, occipital lobe/cuneus, cerebellum lobule VI, right: middle frontal gyrus, occipital lobe/cuneus (P<0.05 FDR)	Corrected for multiple comparisons Block design used so contrast includes incorrect trials or ones where reaction time is too fast for accurate task performance
McLeod et al. 2014	8-17 DCD– 7 (13y) ADHD– 21 (12.5y) DCD+ADHD– 18 (11.5y) Controls– 23 (11.3y)	<16th percentile on M-ABC2 ADHD characterised autism excluded Low IQ, preterms and very low birth weight excluded	Resting state fMRI connectivity seed-to-voxel connectivity between left M1 and whole brain	Controls>DCD connectivity to bilateral inferior frontal/precentral gyrus, caudate, insula, superior temporal gyrus, right: frontal operculum, nucleus accumbens, globus pallidus, putamen Left: anterior cingulate Controls>DCD+ADHD Bilateral: postcentral gyrus left: globus pallidus, supramarginal gyrus, putamen, amygdala right: primary motor cortex	Corrected for multiple comparisons and age. Small numbers in the DCD alone group Larger differences in DCD alone than DCD+ADHD

				DCD+ADHD>controls left: lingual gyrus, frontal pole DCD+ADHD>DCD: bilateral: caudate, superior temporal right: inferior frontal, parietal operculum eft: premotor, postcentral, frontal pole (P<0.05 FWE)	
(McLeod et al 2016)	8-17 DCD– 6 (13y) ADHD–19 (12.4y) DCD+ADHD–14 (11.3y) Controls– 21 (11y)	<16th percentile on M-ABC2 ADHD characterised autism excluded Low IQ, <37 weeks gestation andvery low birth weight excluded	Resting state fMRI seed to voxel connectivity: seeds in left and right sensorimotor cortices	In children with DCD and DCD+ADHD MAND total score positively correlated with connectivity between right seed and bilateral anterior prefrontal cortex and negatively with bilateral angular gyrus and left anterior cingulate (P<0.05 FWE). DCD have few connections between left seed and basal ganglia and thalamus. Left and right seeds connect right cerebellum in clinical groups but left and right seeds to left cerebellum in controls.	Corrected for multiple comparisons. Large age range but no co-varying for age No direct statistical comparisons of connectivity between groups

Chapter Four: General methods

The aim of this chapter is to describe the methods employed in this study. Specific methods relevant to each individual chapter are also included throughout, such as the neuropsychology protocol (chapter five) and brain imaging analysis methods (chapters six and seven). This overarching methodological chapter will detail:

i) Recruitment methods
ii) Principles of MRI
iii) MRI acquisition
iv) Ethical approval

4.1 Recruitment methods

Inclusion criteria

Inclusion criteria are detailed in Table 4.1. Developmental Coordination Disorder is typically diagnosed in primary school. Children were recruited aged 8-10 years because this aligns with age band two of the movement assessment battery for children- second edition (Movement ABC-2) which is an assessment used clinically in the United Kingdom to assess for movement difficulties such as DCD (Henderson et al. 2007). A small age range was chosen to minimise the effect of age related changes on brain structure (Giedd et al. 1999; Houston et al. 2014). English as a primary language was required because our protocol included an assessment of speech and language abilities. Administering these tests in a language in which a child is not fluent would underestimate the child's abilities. Children included in the DCD group had either a diagnosis or a suspected diagnosis of DCD. Receiving a full clinical diagnosis requires appointments with several clinicians and can take several months so children were recruited even if their diagnosis hadn't yet been confirmed by a Paediatrician.

The aim of this study was to assess children with coordination difficulties without a known cause, therefore children with any history of neurological conditions or visible brain injury on clinical MRI scans were excluded. Preterm birth is associated with increased risk of DCD as discussed in chapter one. We excluded children born very or extremely preterm (<32 weeks gestation) because of increased risk of brain injury visible on clinical MRI in those born below 32 weeks gestation (Salmaso et al. 2014; Stoll et al. 2010; Vollmer et al. 2003). Children with hearing impairments and those with uncorrected visual impairments were also excluded. Hearing impairments can delay typical speech and language

development (Lieu 2004; Anne et al. 2017; Bobsin & Houston 2015). Children with uncorrected visual impairments are unable to complete the M-ABC-2 UK. Children were excluded if parents reported their children had claustrophobia or sensitivity to loud noises, as they were deemed unable to tolerate an MRI. Children were considered unsuitable for an MRI if they had metallic implants or objects present in their bodies or a history of swallowing metallic items. Children with metallic surgical implants were included if the parent could provide information about the implant to determine its MRI compatibility.

Table 4.1 Study Inclusion Criteria

	Inclusion criteria	**Exclusion criteria**
Children with DCD	· aged 8 to 10 · English as a primary language · Diagnosis or suspected diagnosis of DCD	· history of neurological conditions · hearing or uncorrected visual impairments · sleep disorder or severe psychiatric disorders
Typically developing children	· aged 8 to 10 · English as a primary language · No developmental disorders	· gestation <32 weeks · Visible lesion or other damage on clinical MRI scans · Unsuitable for or unable to tolerate an MRI scan

Recruitment Procedures

Children with a diagnosis or suspected diagnosis of Developmental Coordination Disorder were recruited through NHS clinics in London, schools, private occupational therapists and physiotherapists, and charity websites (Table 4.2). Typically developing children were recruited through staff advertisements and word of mouth. In total, 63 children aged 8-10 were recruited to the study.

Occupational therapists from NHS clinics sent information sheets to families who then contacted the research team to discuss the study. A consent form was then sent to them to sign. Families recruited through other means contacted me directly and I discussed the study with them before sending them the information sheets and consent form. The consent forms were returned by families. A telephone interview was then arranged to ensure children i) met inclusion criteria, ii) could safely have an MRI scan and iii) would tolerate an MRI scan. Recruitment methods are detailed below.

i) Schools

Over 200 schools in London and the surrounding counties were contacted in accordance with NHS ethics procedures. A letter was sent requesting the distribution of information to families. Schools were invited to contact us if they would consider sharing information with pupils in our age range.

ii) UCL and NHS staff members

Information about the study was distributed through staff newsletters for NHS trusts where I had an honorary contract and UCL Great Ormond Street Institute of Child Health emailing lists to recruit staff members.

iii) Charity Advertising

The Dyspraxia Foundation distributed an advertisement for our study on mailing lists and social media. The advertisement invited families to email me for further information.

iv) Advertising with private clinicians

Information about our research study was included in a paediatric occupational therapy newsletter and was sent to an emailing list for paediatric physiotherapists. Clinicians informed private clients of our study and families were invited to contact us directly.

v) NHS clinical advertisement

Occupational therapists at Guys and St Thomas's NHS Foundation Trust and The Royal Free Hospital identified children of the correct age and within our inclusion criteria who had visited their clinics. The occupational therapists sent study information to families who were invited to contact me directly if they were interested in participating.

vi) Siblings of participants

Siblings of children with DCD who met the inclusion criteria for the typically developing group were also recruited.

vii) Other

Information about the study was widely distributed and some families contacted the research team having heard about the study from our study website or word of mouth from other families who had participated.

Table 4.2 Number of children recruited from each recruitment method

	Children with DCD	Typically Developing
Schools	2	0
UCL/NHS staff	2	9
Dyspraxia Foundation	27	0
Private Clinicians	5	0
NHS clinics	6	0
Siblings of children with DCD	0	3
Study website/word of mouth	3	6
Total	**45**	**18**

4.2 Study Assessment

All participants underwent an assessment of motor and neuropsychological functions and also a short MRI scan. Where possible, cognitive and MRI assessments were carried out on the same day. If this was not possible then assessments were completed within two months of the initial visit. I assessed children at the UCL Great Ormond Street Institute of Child Health. Fifty eight children completed the neuropsychological assessment and MRI scan on the same day or on consecutive days. Four children completed the study across several appointments within two months of each other. One child attended an appointment at UCL, with a follow up assessment at home the following month to complete the study. The order of assessment administration was altered depending on MRI scanner availability. Parents were asked about their child's diagnoses and identified difficulties and this was used to alter the order of assessments to minimise tiredness and maximise compliance.

Four pairs of siblings participated in the study and were seen concurrently to minimise disruption for families. In these cases I administered half the protocol to both children and a colleague administered the other half. Colleagues who assisted with assessments are acknowledged at the beginning of this thesis. All colleagues had experience administering neuropsychological tests and were trained by me to administer assessments for this study.

4.3 Withdrawals

Withdrawals from the study are summarised in Table 4.3. Of 45 children with a diagnosis or suspected diagnosis of DCD, five children withdrew from the study before completion. Eighteen typically developing children were recruited. One child refused the MRI scan and withdrew from the study. 40 children with DCD and 17 typically developing children completed the study.

Table 4.3 Summary of Withdrawals from the study before completion

	Children with DCD	Typically Developing Children
Refused MRI scan	3	1
Refused to complete the neuropsychological assessment	1	0
Could not remain still during MRI scan	1	0
Total number of withdrawals before completion	5	1

4.4 Magnetic Resonance Imaging

What is Magnetic Resonance Imaging?

MRI systems generate images of the brain by measuring the response of hydrogen ions in water found within tissue to changing magnetic fields. The principles set out in sections 2.1 and 2.2 were informed by the following references (Hanson 2008; Gibby 2005; McRobbie et al. 2007).

Hydrogen ions are positively charged particles consisting of a single proton. These protons spin on an axis. In normal circumstances the spin axes are randomly oriented. When protons are placed in a magnetic field by entering an MRI scanner (Bo) the spin axes align either in the direction of the magnetic field or in the opposite orientation. As well as spinning the protons precess at Larmour frequency around the Bo axis (Figure 4.1). This alignment will reach a state called 'thermal equilibrium,' where the magnetic properties of the protons sum together to create a net magnetisation (M). The strength of Bo is measured in Teslas (T) and determines M.

During an MRI scan the magnetic field is disturbed by a short radio frequency (RF) pulse, a magnetic field oscillating at the Larmour frequency of the protons. This transfers energy to the protons and causes them to precess at a transverse axis to the magnetic field,

changing the direction of M. The strength of the pulse determines how much the orientation of M changes from Bo (the 'flip angle'). This high energy state magnetisation decays exponentially as proton spin axes return to thermal equilibrium and M realigns with Bo. This relaxation from high energy to low energy emits a radiofrequency signal which is the measured signal in Magnetic Resonance Imaging.

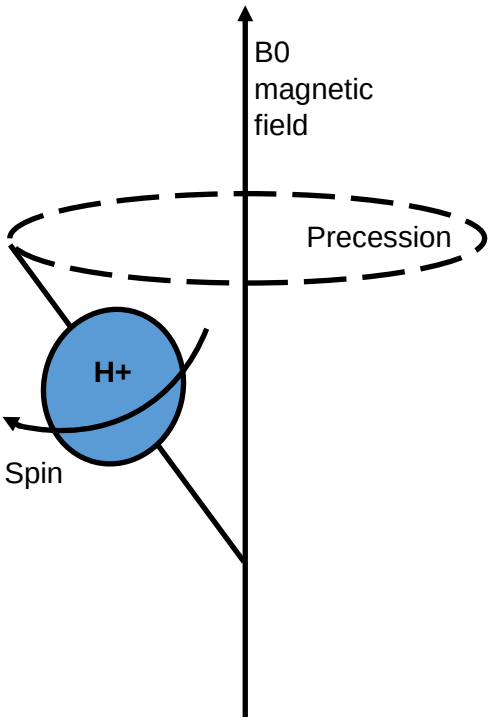

Figure 4.1 Proton spin and precession within the magnetic field generated by an MRI scanner

T1-weighted Magnetic Resonance Imaging

T1 relaxation is the relaxation of spins back into alignment with Bo as they lose energy absorbed from the RF pulse. The time it takes for spins to fully relax and return to equilibrium with Bo is different between tissues. T1-weighted MRI scans measure the increase in M along the Bo direction as spins relax back into thermal equilibrium. MRI scanning parameters are optimised to detect these differences by setting the time between RF pulses (repetition time, TR) and the time between the pulse and detection of signal (echo time, TE). Short TR (<500ms) and TE (<30ms) times create MRI scans sensitive to differences in T1 relaxation, known as T1-weighted imaging. Tissues that realign quickly appear bright on T1-weighted imaging because they emit a strong signal (e.g. white matter), tissues that realign more slowly appear dark because they emit a weak signal (e.g. cerebral-spinal fluid (CSF)).

T2-weighted Magnetic Resonance Imaging

T2 relaxation is the process of spins gradually dephasing from each other in the transverse plane. This is measured as a loss of magnetisation in the transverse plane. T2 relaxation forms the basis of Diffusion-weighted MRI (DWI).

Diffusion-weighted Magnetic Resonance Imaging

DWI relies on the concept of Brownian motion which states that water ions will move randomly from areas of low concentration to high concentration when unimpeded (Beaulieu 2002; Beaulieu et al. 1999). The diffusion of water in the brain is hindered by microscopic structures such as neuronal cell bodies, dendrites, axons, glial cells and myelin. Measuring the parameters of diffusion within tissue is thought to be sensitive to differences in these obstacles, the microstructure of the brain. In diffusion weighted images, we calculate the mobility of water in each voxel of the brain, the 'apparent diffusion coefficient' (ADC) (Jones et al. 2013; Feldman et al. 2014; Soares et al. 2013).

The hindrance of diffusion is different between tissues types. High diffusivity indicates little hindrance to diffusion, such as in ventricular spaces filled with CSF (Figure 4.2a). Low diffusivity indicates the presence of structures to limit displacement of ions, such as in grey matter (Figure 4.2b). Despite different levels of diffusivity, the net direction of diffusion in both these structures is 0 which means movement is uniform in all directions, called isotropic. White matter in the brain is primarily composed of axons; long tubular structures that output signals from the neuron. Axons are surrounded by a myelin sheath, a coating made up of protein and lipids which preserves cellular ionic gradients, retaining the electrical current within the cell and quickening information transfer. Myelin is a hydrophobic substance which means water molecules cannot travel across it. In white matter, water molecules will diffuse more in the direction of axonal structure but will diffuse less in the directions perpendicular to structures (Figure 4.2c). This principle is referred to as 'anisotropy' meaning diffusion is direction specific.

As mentioned above, DWI is a type of T2-weighted image. These images can be made sensitive to diffusion by adding direction-specific magnetic field gradients to the sequence. Random motion of hydrogen ions along the direction of the gradient results in signal loss. In white matter different levels of signal loss in different directions is used to infer the direction of the underlying microstructure (Jones et al. 2013). The b-value is the diffusion-weighting of an MRI sequence. It is set by altering the duration and strength of these gradients and is expressed in seconds per square millimetre. In an image with no diffusion-weighting, the value is 0s/mm^2 and in DWI sequences the value is usually set

between 1000s/mm² and 3000s/mm². By setting the b-value, gradient time and gradient strength we can estimate the motion of protons along the gradient direction.

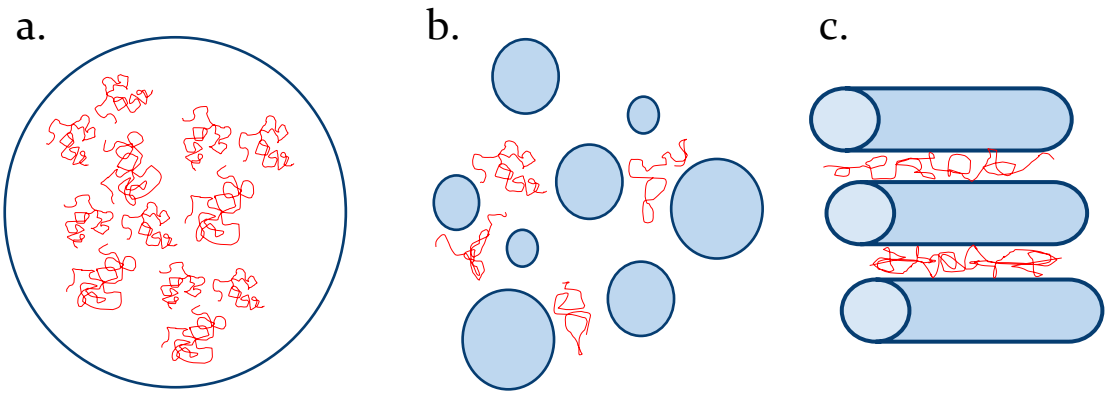

Figure 4.2 Diffusion characteristics in a. CSF b. grey matter c. white matter

Multi-shell Diffusion Weighted Imaging

In a basic DWI sequence several direction-specific gradients are applied to sample diffusion sensitivity in different directions at a certain diffusion weighting (b-value). This is referred to as a 'shell'. Previous advances in diffusion MRI technology have allowed for the acquisition of high numbers of directions on one shell in clinically-feasible imaging times; providing better sensitivity to angular differences in direction of diffusion. Recent advances in DWI technology mean that the direction-specific gradients can be applied at two different diffusion sensitivities (b-values). This is referred to as 'multi-shell' diffusion MRI and means one can apply more complex modelling to the DWI signal to infer properties of the underlying microstructure (Jeurissen et al. 2014).

Modelling the Diffusion Signal: Diffusion Tensor Imaging

Understanding the properties of white matter fibre microstructure utilising DWI requires modelling of the signal. DTI takes the signal from gradient pulses in different directions and models diffusion in three dimensional space (Wiegell et al. 2000). Within each voxel a 3D ellipsoid shape called a 'tensor' is generated. The tensor has three orthogonal directions (eigenvectors) and a diffusion coefficient value in each direction (eigenvalues). The tensor in a voxel of unimpeded random diffusion should be perfectly spherical (Figure 4.3a). If there are boundaries which selectively impede diffusion, the tensor becomes ellipsoid in shape (Figure 4.3b). The mean of the eigenvalues is the average displacement of water within the voxel (Mean Diffusivity, MD). This is equivalent to ADC determined from three directions. FA is calculated from the standard deviations of the three eigenvalues and reflects how high diffusion is in the highest direction relative to the other two (0 indicates isotropic to 1 indicates completely anisotropic) (Basser & Pierpaoli 2011;

Pierpaoli & Basser 1996; Pierpaoli et al. 1996). AD is the rate of diffusion along the highest eigenvector. RD is the average diffusion across the other two directions. High FA values are thought to reflect dense and well-organised white matter. A higher MD reflects lower microstructural density, less myelination or damage to white matter. AD and RD are used to further understand alterations in mean diffusivity. By comparing these properties between healthy people and clinical groups, or correlating these measures with behavioural or clinical variables we can infer changes in the underlying white matter microstructure that are associated with specific diseases or impairments (Feldman et al. 2014; Ciccarelli et al. 2008).

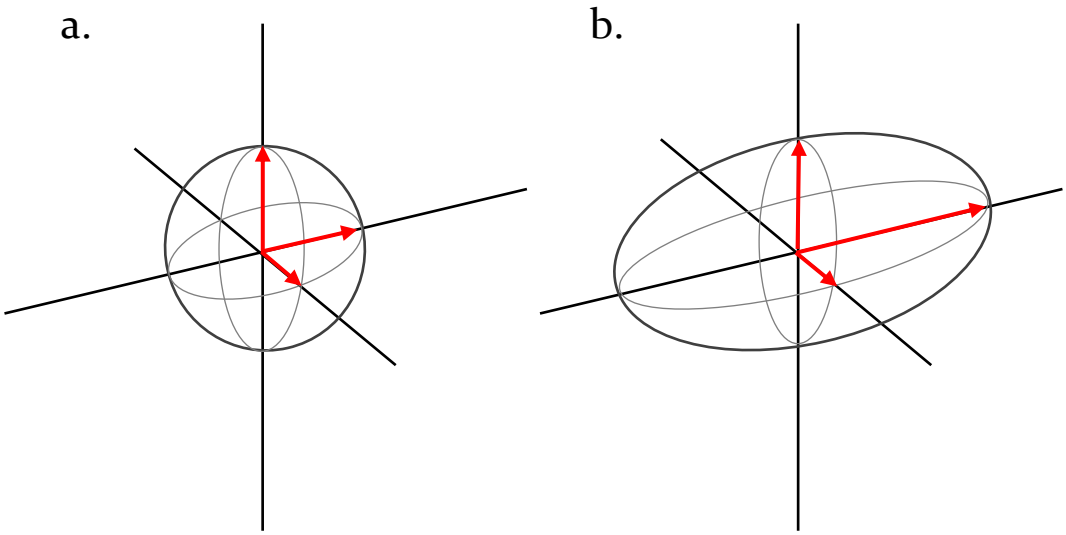

Figure 4.3 Tensor modelling of DWI signal to reflect a. isotropic and b. anisotropic diffusion (adapted from Wiegell et al. 2000).

Modelling the Diffusion Signal: More complex models

The diffusion tensor model oversimplifies the underlying structure of anatomy (Tournier et al. 2011). In particular the tensor will be spherical if there are multiple fibre populations with anisotropic diffusion properties in one voxel moving in different directions (''crossing fibres'') as occurs in up to 90% of white matter voxels in the human brain (Jeurissen et al. 2013). More complex mathematical models of the diffusion signal have been proposed over the last 20 years. Constrained spherical deconvolution is one such model that estimates the underlying fibre orientation distribution within a voxel by modelling the response function from the measured DWI signal (Tournier et al. 2008; Riffert et al. 2014).

Analysing metrics extracted from Diffusion Weighted MRI

Diffusion metrics can be compared between groups and correlated with behavioural or clinical variables. This can be done with voxel-wise methods such as TBSS which analyse relationships across a skeleton of voxels across the brain containing white matter (Smith et al. 2006). Analyses of diffusion metrics can also be done on measures from specific tracts within the brain. These tracts are reconstructed using tractography. In tractography the modelled diffusion signal in each voxel is used to identify continuous pathways of anisotropic diffusion through voxels. These are connected together to reconstruct fibre tracts within the brain (Ciccarelli et al. 2008). Advanced models of diffusion like constrained spherical deconvolution allow reliable reconstruction of fibres through regions of crossing fibres (Tournier et al. 2011). Diffusion metrics are averaged across each voxel within the reconstructed tract and then extracted for further analysis.

4.5 MRI data collection

Participants were scanned on a 3 Tesla Siemens Magnetom Prisma MRI scanner at Great Ormond Street Hospital with a 20 channel head coil. Participants underwent a T1-weighted magnetisation prepared rapid gradient-echo (MPRAGE) scan and a multi-shell diffusion MRI scan. Participants watched a DVD of their choice during the scan. Scans were conducted by a clinical radiographer. I supported the radiographer in the control room during the scan.

MRI Scan Preparation

Children with DCD rarely have MRI scans as part of clinical care; therefore the experience was novel for most participants. Previous studies have shown that scanner preparation procedures can significantly improve scan compliance and quality (Barnea-Goraly et al. 2014; Törnqvist et al. 2014; de Bie et al. 2010; Epstein et al. 2007). In preparation for the study, participants were referred to videos and sites with MRI sounds. Before the scan I discussed the experience of an MRI and the importance of remaining still with children. When possible participants were taken through a mock scanning scenario designed to improve participant compliance.

T1-weighted MRI sequence

T1 weighted MPRAGE scans were acquired for all participants (TE/TR=2.74ms/2300ms, voxel size 1mm isotropic, field of view= 256x256, flip angle= 8^{o}, coronal acquisition). Images were corrected for gradient linearity distortion by scanner software immediately after acquisition. Images were checked for motion artefacts at the end of the sequence,

and scans were rerun if artefacts were visible. Image acquisitions were repeated a maximum of three times.

Diffusion-weighted MRI sequence

High resolution multi-shell diffusion-weighted MRI images were acquired from all subjects (60 directions b=1000s/mm^2 and 60directions b=2200s/mm^2, TE/TR= 60ms/3050ms, voxel size 2mm isotropic, 13 b=0 images interspersed, phase encoding= anterior to posterior, 1 b=0 image with negative phase encoding). The slices from each directional pulse was displayed during the scan and examined for motion artefact. If there was evidence of movement the scan was restarted. Scans were repeated a maximum of three times.

Quality check

After acquisition all scans were visually inspected for artefacts associated with movement. Unacceptable T1-weighted image quality was defined as images with blurring of the grey-white matter boundary and boundaries between white matter and subcortical structures. T1-weighted images of acceptable quality were available from all participants. The DWI image quality was assessed after pre-processing to remove motion effects (see chapter six).

Clinical Image Review

The T1-weighted MRI scans from each participant were reviewed by Dr Kshitij Mankad, Consultant Clinical Neuroradiologist, to identify anything of clinical concern. If anything was identified families were informed, and their GP informed with their permission. Structural imaging was deemed normal by Dr Mankad if children did not have focal abnormalities which may relate to neurological impairment. Of note as we only acquired T1-weighted images for clinical image review it was not possible to do a comprehensive clinical imaging assessment. A very small grey matter heterotopia was identified in one child with DCD. Scans from all other children with DCD and typically developing children were reported to be normal.

One child displayed an atypical pattern of movement and speech characteristics, together with abnormalities on T1-weighted imaging. After informing the family and GP in accordance with ethically approved procedures, we received a letter from a Consultant Paediatric Neurologist informing us that the child did not have DCD and had been given a different diagnosis. This child no longer met our inclusion criteria and therefore was excluded.

4.6 Additional Participant Information

Years of maternal education post 14 years of age was used as a measure of socio-economic status as it has been shown to be predictive of school performance in children born prematurely (Gross et al. 2001). Mothers were asked for years of education post 14 years of age and to explain part-time learning, these were then collapsed into fulltime years of education. Handedness was determined by asking parents which hand the child writes with, as recommended in the M-ABC2. Parents also gave the child's week of birth and birth weight. Additional diagnoses were determined by asking parents if their child had a diagnosis of or investigations for: autism/ASD/Asperger's syndrome, ADHD/ADD/other attention difficulties, Arithmetic/number processing difficulties, reading/spelling difficulties, feeding problems, speech/language difficulties as well as any other learning/developmental problems or concerns raised at a parent's evening. On the day of assessment parents were asked about any medications the child was currently taking.

4.7 Ethical Approval and Funding

This PhD was completed as part of a grant from The Waterloo Foundation entitled 'White Matter Correlates of DCD and associated impairments'. This grant contained funding for equipment, participant travel and MRI scans for 40 children with DCD and 40 age-matched typically developing children. The PhD studentship was funded by the Child Health Research CIO. R&D approval was received from ICH and GOSH joint research office (13CN03). NHS Ethical Approval was obtained from Fulham ethics committee (14/LO/00059). Written informed consent was obtained from all parents/guardians and written informed assent was obtained from all participants.

4.8 Power Calculation

The research study was powered to detect a one standard deviation difference in diffusion microstructure as was reported by Zwicker and colleagues in the first DWI paper published (Zwicker et al. 2012). We aimed to recruit 18 participants in each group to detect a difference of one standard deviation with a power of 80% (α= 0.05). Additionally this study was designed to identify MRI predictors of impairments in children with DCD. We aimed to recruit 40 children with DCD so we could conduct multiple regression with four predictors and a power of 80% (α= 0.05, effect size=0.4).

4.9 Study Aims

The original aims of this study were to:

i) Characterise motor, IQ, attention, speech and language abilities in children with DCD aged 8-10 in comparison to typically developing children
ii) Determine the relationship between motor deficits and additional impairments in children with DCD. In particular, if more severe motor difficulties are associated with more severe additional deficits.
iii) Characterise the brain changes associated with DCD in comparison to typically developing children
iv) Describe the neural correlates of specific motor deficits in children with DCD
v) Determine the MRI predictors of additional impairments outside the motor domain in children with DCD

4.10 Analytical plan

In order to investigate aims i and ii discussed above I did the following:

i) Administered motor, IQ, attention, speech and language assessments to all participants
ii) Identified significant differences in all behavioural domains between children with DCD and those without
iii) Characterised relationships between motor skills and additional impairments within the sample of children with DCD

In order to investigate aims iii-v discussed above I did the following:

i) Collected T1-weighted and DWI-weighted MRI scans from all participants
ii) Measured structures in the subcortical and cortical circuits implicated in motor skills and additional impairments in a hypothesis driven manner
iii) Used whole brain analyses with stringent statistical correction to characterise both hypothesised regions and explore any results outside of the hypothesised circuits

Chapter Five: Cognitive and motor profiles in children with DCD

5.1 Introduction

Background

As discussed in chapter two, children with DCD often display co-occurring developmental disorders. Nevertheless impairments outside of the motor domain in children with DCD, regardless of co-occurring disorders, have yet to be studied. The relationship between motor impairments and deficits in other domains has not yet been fully characterised in children with DCD. There may be a spectrum of impairment where more severe motor difficulties are associated with increased co-occurring deficits, separate dimensions of impairment, or behaviourally distinguishable subtypes of DCD.

Study Aims

The aim of this study was to extensively characterize motor, IQ, attention, and speech and language abilities in children with DCD using standardised tests, and to describe the relationship between skills in children with DCD.

Hypotheses

Based on the existing literature summarised in chapter two, I hypothesized that:

1. Children with DCD would not be impaired on full scale IQ relative to age matched typically developing controls
2. Children with DCD would perform significantly poorer than controls on tests that assess:
    i) All motor skills
    ii) Processing speed
    iii) Attention skills
    iv) Speech sequencing
3. Amongst children with DCD, there would be a range of language abilities, with a proportion of children demonstrating impairments in language skills

5.2 Methods

I received training from an experienced paediatric occupational therapist to administer the motor assessment correctly. I received training from an experienced speech and language pathologist to administer the speech assessments correctly. I observed assistant

psychologists and experienced researchers conduct standardised IQ and language assessments in order to learn the correct administration methods for neuropsychological tests.

Motor Assessment

Standardised Assessment of Motor skills: Criterion A of the DSM-V diagnostic criteria

As mentioned in my general methods chapter, all children recruited to the DCD group had either a confirmed or suspected diagnosis of DCD. The second age band of the MABC-2 was used to assess motor abilities in all participants (Henderson et al. 2007). This test includes subscales of manual dexterity, aiming and catching skills and static and dynamic balance (Table 5.1). The raw scores on all subscales were summed and normalised to give a total test score. Raw scores for all subscales and the total test score were converted to scaled scores and percentiles using conversion tables included in the manual. This test is used clinically to screen for motor impairments indicative of DCD (Blank et al. 2012). All scaled scores on the M-ABC2 have a mean of ten and a standard deviation of three. This study will follow the EACD guidelines which suggest a cut off of at or below 15th percentile (total test score of seven or below on M-ABC2) on a standardised motor assessment reflecting a motor skill impairment to meet criterion A of the DSM-5 guidelines (Blank et al. 2012; APA. 2013). The M-ABC2 subscales and total test score show good test-retest reliability (r=0.73-0.84) and validity (Schulz et al. 2011)(Henderson et al. 2007).

Table 5.1 Subscales and subtests of the M-ABC2 Age Band Two

Sub scale	Subtest	Description
Manual Dexterity	Placing pegs	Placing 16 pegs into a board as quickly as possible using one hand
	Threading lace	Threading lace in and out of 6 holes on a board using both hands
	Trail tracing	Draw a continuous line between targets keeping within boundaries
Aiming and Catching	Catching with two hands	Throwing a ball at the wall and catching the rebound
	Throwing a beanbag	Throw a beanbag onto a target
Static and Dynamic Balance	Balance board	Balance on one leg on a balance board
	Heel-to-toe walking	Walking forwards along a line with heel touching the toe
	Hopping onto mats	Hopping on one leg along a series of coloured mats

Parental Questionnaires: Criterion B of the DSM-V diagnostic criteria

Parental Questionnaires were used to assess the impact of motor impairments on activities of daily living (criterion B of the DSM-5 criteria). Parents completed the M-ABC2 checklist and the DCD-Q questionnaire, two standardised checklists designed to detect developmental coordination disorder/motor skill impairments that affect daily life in school-aged children (Henderson et al. 2007; Wilson et al. 2009)(Table 5.2). Two questionnaires were used because confirmation of the impact of motor impairment on daily life is necessary to diagnose DCD based on the DSM-5 criteria. As some children who participated in our study had not yet had their diagnosis confirmed by a paediatrician we administered two parental questionnaires to assess the impact of coordination difficulties on daily life, in case parents omitted answers in one questionnaire. This occurred in four children with DCD (see appendix A).

The M-ABC2 checklist is made up of two subscales. Section A assesses movement in a static or predictable environment during self-care (five questions), in the classroom (five questions) and during physical education/recreation (five questions). Section B assesses movement in a dynamic or unpredictable environment during self-care (five questions), when playing with balls (five questions) and during physical education/recreation (five questions). On each item on the M-ABC-2 checklist, parents rated their child's abilities on a scale ranging from 0 (very well) to 3 (not close). These scores were summed into a total score and interpreted on a traffic light system based on age-specific normative data:

i) Red, a motor impairment is highly likely: Total score ≥13 for 8 year old children; ≥10 for 9 year old; ≥7 for 10 year old.
ii) Amber, at risk of motor impairment: 9-12 for 8 year old children; 6-9 for 9 year old; 4-6 for 10 year old
iii) Green, no movement difficulty detected: ≤8 for 8 year old children; ≤5 for 9 year old; ≤3 for 10 year old

The M-ABC2 checklist overlaps with the first edition of the checklist that showed acceptable test-retest reliability (r=0.77 in a UK sample) ((Sugden & Sugden 1991) quoted in Henderson et al. 2007). The M-ABC2 checklist also shows good content validity in children with DCD (Henderson et al. 2007).

On the DCD-Q, parents indicated how much a statement was like their child, ranging from 0 (not at all) to 5 (extremely)(Wilson et al. 2009). The DCD-Q consists of fifteen statements: six regarding control of movements, four about fine motor skill, and five about

general coordination and engagement. These responses were summed into a total score that was used to categorise children based on age specific normative data:

(i) 'indicative of DCD': score ≤ 55 for 8 and 9 year old children; ≤ 57 for 10 year old)

(ii) 'probably not DCD': score ≥56 for 8 and 9 year old children; ≥58 for 10 year old children).

Criterion B of the DSM-5 diagnostic criteria was met if children were categorised as 'indicative of DCD' or 'motor impairment is highly likely' on the DCD-Q or M-ABC2 checklist.

Table 5.2 Questionnaires on impact of motor impairment on activities of daily living

Questionnaire	Subscales	Description
M-ABC-2 Checklist (Henderson et al. 2007)	Movement in a predictable environment	Performance when the child is in control of their movements and not under time pressure
	Movement in an unpredictable environment	Performance when the child responds to a moving object or move within a changing environment
DCD-Q (Wilson et al. 2009)	Control during movement	Accurate and controlled performance of motor skills
	Fine motor	Fine motor skills such as writing and using scissors
	General coordination	Engagement in motor activities, motor learning and clumsiness

IQ Assessment

The Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) was administered to all participants to obtain a verbal comprehension index, perceptual reasoning index and full-scale IQ score (Wechsler 2011). The WASI-II is a standardised assessment of intellectual abilities for people aged 6-90 (Table 5.3). Raw scores for each subtest were converted to T-scores (mean of 50, standard deviation of 10) which were then summed into raw full scale IQ (FSIQ), perceptual reasoning (PRI) and verbal comprehension index (VCI) scores. These were then converted to a standard score with a mean of 100 and a standard deviation of 15. A cut-off of 80 (1.33 SD below the mean) was

used to categorise children as having low IQ based on the Wechsler standard score categorical ranges.

Table 5.3 Subscales of the WASI-II

Sub scale	Subtest	Description
Verbal comprehension index (VCI)	Vocabulary	Define words of increasing difficulty
	Similarities	Describe how two words are semantically similar
Perceptual reasoning index (PRI)	Block Design	Replicate a pattern using coloured blocks as quickly as possible
	Matrix Reasoning	Identify which of five images completes a given pattern

An abbreviated scale of intelligence was used to reduce the length of the assessment and therefore the burden on children. The behavioural testing was approximately 3-3.5 hours long excluding an assessment of IQ. The WASI-II FSIQ, PRI and VCI are each highly correlated with the corresponding measures in the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) discussed in chapter two (PRI corrected r^c=0.82, VCI corrected r^c=0.84, FSIQ corrected r^c=0.91). The WASI-II composite scores show good test-retest reliability in children aged 6-11 (PRI corrected r^a=0.87, VCI corrected r^a=0.96, FSIQ corrected r^a=0.93). The WASI-II subtests are moderately correlated with one another (r between 0.45 and 0.72) and factor analysis supports the separation of subtests into two composite indices indicating good test validity (Wechsler 2011).

Language Assessment

The Clinical Evaluation of Language Fundamentals, 4th Edition (CELF-4) UK edition is a standardised assessment of language abilities in children (Semel et al. 2006). All children were assessed using the CELF-4 to determine core, receptive and expressive language abilities. Core, receptive and expressive language indices were calculated for each participant based on the subtests described in Table 5.4. Children aged eight performed two additional subtests of the CELF-4, namely word structure and sentence structure subtests, to calculate these indices. Raw subtest scores were converted to scaled scores with a mean of ten and standard deviation of three. Scaled scores for the subtests in each index were summed and converted to a standard score with a mean of 100 and a standard deviation of 15.

The administration of the CELF-4 was modified by ignoring reversal rules in recalling sentences and formulated sentences subtests. Children aged 9-10 are required to start these subtests at a later point than the eight year olds. The administration instructions state that if the child fails to obtain a perfect score on the first item, the administrator must revert to the 8 year old starting point. This can add more than 15 minutes to the administration time and result in test failure due to lack of attention and motivation. The decision was taken with an understanding that expressive language indices might be slightly over estimated in some children.

Table 5.4 Subscales of the CELF-4

Sub scale	Subtests	Description
Core Language	Concepts and following directions	Point to a series of objects in response to increasingly complex oral instructions
	Recalling sentences	Verbally imitate sentences of increasing complexity
	Formulated sentences	Generate a grammatically correct sentence describing a pictured scene using a target word or phrase
	Word Classes 2-total (age 9-10 only)	Identify two semantically related words from a set of four and describe the relationship
	Word Structure (age 8 only)	Complete a given sentence with a grammatically and semantically correct word
Receptive Language	Concepts and following directions	As above
	Word Classes 2-receptive	Identify two semantically related words from four as described above
	Sentence Structure (age 8 only)	Point to a picture that illustrates an orally presented sentence
Expressive Language	Recalling sentences	As above
	Formulated sentences	As above
	Word Classes 2-expressive (age 9-10 only)	Explain the relationship between two words as described above
	Word Structure (age 8 only)	As above

The CELF-4 composite scores show good interrater reliability in our age range (corrected r^a=0.84-0.94). The CELF-4 subtests are moderately correlated with one another (r between

0.45 and 0.83) and structural equation modelling supports the separation of subtests into two composite indices indicating good test validity (Semel et al. 2006).

Attention Assessment

The Test of Everyday Attention in Children (TEA-Ch) was used to assess attention abilities in all participants (Manly et al. 2001). This standardised test was designed to examine different attentional capacities in children aged 6-16 years, using 9 subtests divided into three domains: selective attention, sustained attention and attentional control/switching (Figure 5.1)(see chapter two for further information). This three-factor model is based on Posner and Petersen's model of three separate modality-independent attention systems: attentional control, attentional selection and vigilance/readiness (Posner & Petersen 1990). Raw scores from each subtest are converted to gender-specific scaled scores with a mean of ten and standard deviation of three.

To identify attention impairments in children with coordination difficulties, five subtests that required minimal motor skill were chosen (Table 5.5).

Table 5.5 Domains of the TEA-Ch administered in this study

Domain	Subtest	Description
Selective attention	Sky Search	Selectively circle targets in a sheet filled with distractors.
Sustained Attention	Score!	Keep count of tonal sounds played with silences of varying lengths between them
	SkySearch DT	Execute Sky Search and Score! tasks simultaneously
Attentional Control/switching	Creature Counting	Switch between counting targets upwards (1 ,2, 3) and downwards (3, 2, 1)
	Opposite Worlds	Rapidly name a string of 1s and 2s using the correct names and incorrect names ("say 1 when you see 2, say 2 when you see 1")

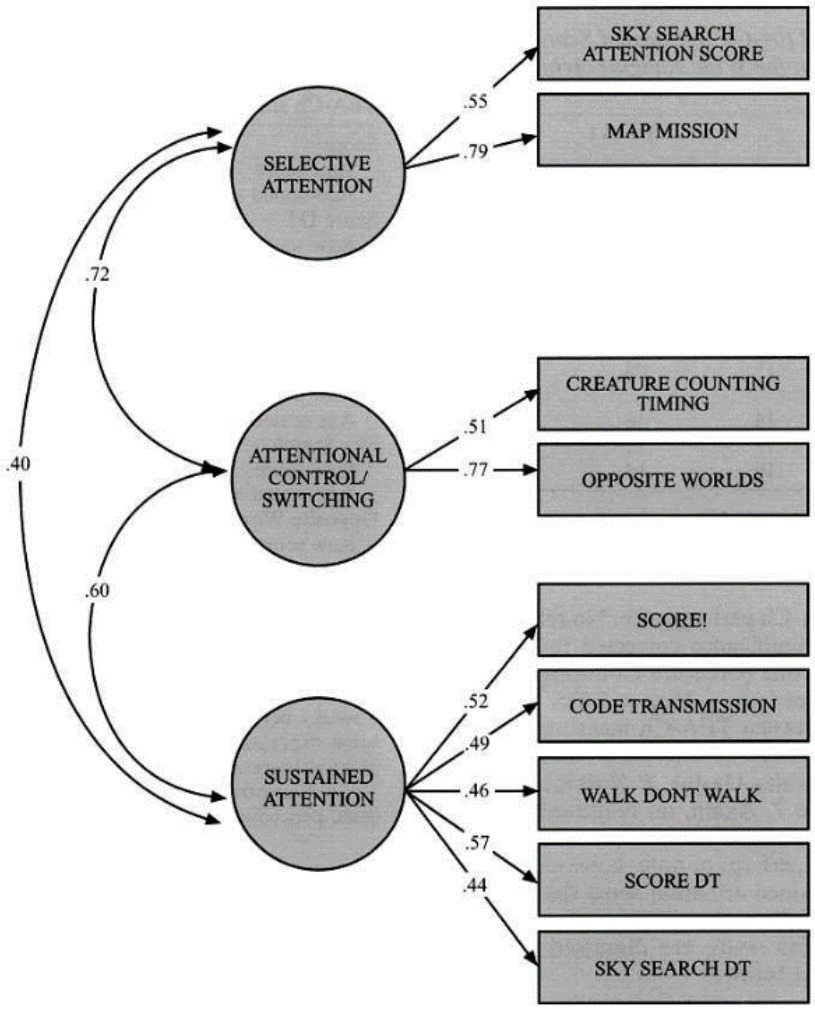

Figure 5.1 structure of the TEA-Ch (Figure from Manly et al. 2001)

Selective Attention

Selective attention was assessed using the Sky Search subtest. This test includes a motor component but motor speed is accounted for by subtracting time per target on circling targets without distractors from time per target during the test. This difference was converted to a standard score and used in subsequent analysis.

Sustained Attention

Sustained attentional abilities were assessed utilising the Score! and Sky Search Dual Task (DT) subtests of the TEA-Ch. During the Score! subtest children counted the number of tonal sounds heard over a period of time with varying lengths of silence between them. Scaled scores were generated based on number of correct total tones counted in ten trials.

The Sky Search DT subtest required children to perform another version of the sky search subtest while simultaneously performing the Score! subtest. Scaled scores were generated

based on the dual task increment (calculated by subtracting the sky search time per target score from the time per target on Sky Search DT adjusted for correct number of tones counted).

Attentional Control

The Creature Counting and opposite world subtests were administered to assess attentional control abilities. During Creature Counting children had to switch between counting figures on a page upwards (1,2,3) and downwards (3,2,1) several times per trial. Scaled scores were generated based on the number of times the final counting value was correct in seven trials.

During the opposite world subtest children rapidly named a string of printed ones and twos with the correct name (see 1 say 'one') and using the opposite name (see 1 say 'two'). In order to account for differences in naming speed, the difference between time taken on the opposite naming task and the correct name task was calculated. These values were converted to z-scores based on the mean and standard deviation of the control group. These z-scores were used for subsequent analysis.

Processing Speed

The WASI-II is an abbreviated scale of intelligence that does not include a processing speed index (Wechsler 2011). Time taken in the first trial of the same world task was used as a measure of processing speed as previously done by Mulder and colleagues (Mulder et al. 2011). The values were converted to z-scores according to the mean and standard deviation of the control group and used for subsequent analysis.

The TEA-Ch scores show good test-retest reliability (partial r=0.71-0.87). Structural equation modelling supports the separation of subtests into three domains of attention indicating good test validity (Manly et al. 2001).

ADHD Symptomatology Questionnaire

The Conners-3 full length parental questionnaire was completed by all parents to assess the presence of ADHD symptomatology (Conners 2008). The Conners-3 is a standardised questionnaire for children aged 6-18 designed to screen for symptoms of ADHD and related issues. For each question, parents answered how true a statement was for their child's behaviour in the past month ranging from not true (0) to very much true (3). The structure is summarised in Table 5.6. Questions are divided into 6 content scales and 4 symptom scales. Raw scores for each scale were converted into T-scores with a mean of 50

and a standard deviation of 10 using gender specific normative data. Parental responses were screened for inconsistency, positive, and negative response bias. Questionnaires with inconsistent or biased responses were excluded.

T-scores for the DSM-5 ADHD inattentive and hyperactive symptom scales were used to categorise children into ADHD symptom profile based on questionnaire guidelines:

i) No impairment: T-score<65 on inattentive and hyperactive symptom scales
ii) ADHD predominantly inattentive profile: T-score>64 on inattentive symptom scale
iii) ADHD predominantly hyperactive-impulsive profile: T-score>64 on hyperactive-impulsive scale
iv) ADHD combined type profile: T-score>64 on both symptom scales

Table 5.6 Structure of the Conners-3 parental questionnaire

Content Scales	Inattention
	Hyperactivity/Impulsivity
	Learning problems
	Executive functioning
	Deviance/Aggression
	Peer Relations
DSM-5 Symptom Scales	ADHD Predominantly Inattentive Presentation
	ADHD Predominantly Hyperactive-Impulsive Presentation
	Conduct Disorder
	Oppositional Defiant Disorder

There was no data included in the manual regarding validity and reliability of the DSM-5 symptom scales. The DSM-4 symptom scales show good test-retest (r=0.84-0.94) and inter-rater reliability (r=0.75-0.94). The scales are also good predictors of ADHD diagnosis, explaining 24-42% of the variance between children with ADHD and controls. The DSM-4 symptom scales also correlate with the BRIEF and BASC-2, two other parental rating scales sensitive to inattention and hyperactivity (r=0.41-0.92)(Conners 2008).

Assessment of Speech and Oromotor Control abilities

Speech and oromotor control were assessed using the Verbal motor Production Assessment for Children (VMPAC) (Hayden & Square 1999). The VMPAC is used by speech and language pathologists to test for the following motor speech disorders: dysarthria,

CAS and orofacial dyspraxia. Control and sequencing of face and tongue movements during speech and non-speech movements were assessed using the focal oromotor control and sequencing subscales of the VMPAC (Table 5.7). For each scale, raw scores were converted to percentage correct and children were classified based on level of impairment (normal, mild, moderate, severe). The VMPAC is standardised for children aged 3-12, with performance at ceiling expected from age seven. The raw scores were also converted to z-scores based on the control group mean and standard deviation.

The focal oromotor control and sequencing subscales of the VMPAC show good test-retest reliability (r=0.90 and r=0.88 respectively) and good inter-rater reliability (r=0.99 for both scales)(Hayden & Square 1999). The test also shows good validity with constructs of speech motor control.

The Park Play is a child friendly picture description task that was used to elicit a sample of spontaneous connected speech from all participants (Patel & Connaghan 2014). This speech sample was screened for symptoms of CAS using a checklist based on the American speech-language-hearing association (ASHA) diagnostic criteria (Fedorenko et al. 2016). Children were categorised into:

i) Speech within normal limits
ii) Features of CAS (some speech errors but do not meet full diagnostic criteria)
iii) Diagnosis of CAS (evidence of inconsistent errors, lengthened & disrupted co-articulatory transitions and inappropriate transitions)

The children with features of CAS and a diagnosis of CAS were combined into one group entitled 'indication/features of CAS' for statistical analysis. Both the VMPAC and Park Play tests were video-recorded. A speech and language pathologist with 20 years of experience in the differential diagnosis of motor speech disorders (Prof. A Morgan, MCRI, Melbourne) scored all videos blinded to group (DCD vs. control), previous diagnoses and other standardised test results.

Table 5.7 Structure of Speech Assessment

Assessment	Description
VMPAC	
Focal Oromotor Control	Control of movement in jaw, lips, face and tongue in single and combined movements
Example: Non-speech motor control	Example: 'show me how you smile'
Example: Speech motor control	Example: 'say m-u'
Sequencing	Accurate production of speech and non-speech movement sequences
Example: Non-speech sequencing	Example: 'show me how you kiss… and stick out your tongue'
Example: Speech sequencing	Example: 'say m-u, m-u, m-u, m-u'
PARK PLAY	Picture description task designed to elicit spontaneous connected speech

Summary of assessment battery

The behavioural testing battery for this study is summarised in Table 5.8. Overall this battery allowed me to measure motor, IQ, language, speech and attention skills in children with DCD and in controls.

Table 5.8 Summary of behavioural assessment battery

Test	**Measure**
Movement ABC 2 (M-ABC2)	Motor Skills i) Manual Dexterity ii) Aiming and Catching iii) Balance
Wechsler Abbreviated Scale of Intelligence II (WASI-II)	Intelligence Quotient (IQ) i) Full scale IQ ii) Verbal comprehension index iii) Perceptual reasoning index
Clinical Evaluation of Language Fundamentals 4 (CELF-4)	Language Abilities i) Core Language ii) Receptive Language iii) expressive language
Test of Everyday Attention in Children (TEA-ch)	Attention abilities i) Selective Attention ii) Sustained Attention iii) Attentional Control and Switching iv) processing speed
Verbal motor production assessment for children (VMPAC) and Park Play	Speech and oromotor functions i) oromotor control ii) sequencing iii) Symptoms of childhood apraxia of speech.

Statistical Analyses

Statistical analyses were performed using IBM statistical package for the social sciences (SPSS) version 24.

Normality testing

All data were tested for normality using Kruskal-wallis tests and skewness/kurtosis values. The residuals from regressions were tested for normality and examined for outliers. Non-parametric tests were used for non-normally distributed data. Data transformation was

attempted but none of the possible transformations rendered all data normally distributed.

The processing speed z-score values were highly positively skewed. In order to utilise regression methods, children were also categorised into unimpaired (within 1.5 standard deviations of the control group mean), mildly impaired (1.5-2.5 SD from the control group mean) and severely impaired (>2.5SD from the control group mean). Non-parametric tests were also used to analyse the continuous z-scores.

Differences between children with DCD and typically developing children

Differences between groups in continuous variables were assessed using student's t-test for normally distributed data and Mann-Whitney U test for non-interval or non-normally distributed data. One sample t-tests were used to examine differences between the children with DCD and standardised test means when the control group mean was above average and the data were normally distributed. Analysis of co-variance (ANCOVA) was run for each significant result to determine whether differences between groups remained once full scale IQ and maternal education were controlled for. Perceptual reasoning index was used in place of full scale IQ in language test ANCOVAs as there is overlap between the VCI and CELF tests.

Group differences in categorical variables were tested using Chi-Square. In cross-tables where the expected count in each cell was below 5 the Fishers Exact test was used. In cross tables larger than 2x2 that violated assumptions for a Chi-Square test impairment categories were collapsed into one group before utilising a Fisher's exact. Finally, a forward Wald logistic regression was conducted to determine significant neuropsychological predictors of DCD or typically developing group membership. Motor tests were excluded from this regression as these were used to classify the children.

Relationships between behavioural variables in children with DCD

Parametric (Pearson) and non-parametric (Spearman) correlations were run to test for significant relationships between variables. Where significant correlations between multiple scores were identified, multiple linear regressions were used to identify significant predictors of neuropsychological scores in the children with DCD.

Correction for multiple comparisons

Bonferroni correction was used to control the type 1 statistical error. The significance threshold of 0.05 was divided by the number of comparisons performed in each analysis.

Confirmatory factor analysis

Within the sample of children with DCD, linear regression was run to remove the effect of Perceptual reasoning index from all variables. The residuals from variables with significant correlations between them were entered into a principle axis factor analysis with varimax rotation and eigenvalues greater than1.

Missing data

Any participants with missing data were excluded from analyses in a pair-wise manner. Missing data for each test is summarised in appendix A.

Confirmation of group membership

Results from behavioural assessments were used to ensure children with DCD met the full criteria for DCD and typically developing children did not. For purposes of this study children were categorised as having DCD if they met the diagnostic criteria from DSM-5 in accordance with EACD guidelines (Blank et al. 2012)(Table 5.9). The DSM-5 Criteria are:

i) Criterion A: Motor abilities that are substantially below expected levels given age, intelligence and opportunities for skill acquisition.

Two children with TTS scored above 16th centile but a manual dexterity score below five were included in accordance with EACD guidelines.

ii) Criterion B: The disturbance described in criterion A has a significant effect on academic performance and activities of daily living.

Criterion B was assessed using the M-ABC-2 checklist and DCD-Q.

iii) Criterion C: onset of motor deficit was in the early developmental period

Criterion C (onset in the early developmental period) was determined using a telephone interview before participation as discussed in the previous chapter.

iv) Criterion D: Motor impairments cannot better be explained by underlying congenital, neurological or severe psychosocial conditions or by a global developmental or intellectual impairment.

Table 5.9 Summary of diagnostic criteria used to categorise children with DCD

Diagnostic criteria	Assessment used
A	MABC-2 total test score <16th percentile (standard score of 7) or subscale ≤5th percentile (standard score of 5)
B	Categorised as impaired on the M-ABC2 checklist or DCD-Q
C	Telephone interview was used to discuss onset of difficulties
D	IQ above 80 or ≥1SD difference between IQ and TTS

Assessment for presence of intellectual impairment in Criterion D

Criterion D was met if a child had a FSIQ score above 80, considered in the normal range. Twenty-eight children who met criteria A and B for DCD had a full scale IQ score above 80. Nine children had a FSIQ below 80 and M-ABC2 TTS below 16th centile. For these children, the discrepancy between motor and IQ scores was further examined. Any children with a low IQ (FSIQ<80) were expected to have motor skills more than one standard deviation below their IQ to meet criterion D. FSIQ is not considered valid in a clinical setting if there is more than one standard deviation difference between performance and Verbal comprehension index scores, in cases of a >1 standard deviation (SD) discrepancy the higher subscale was subsequently used to examine the discrepancy between IQ and motor skills.

IQ standard scores were converted to scaled scores (mean=10, SD=3) using a standard conversion table available with standardised assessments to make them directly comparable to the M-ABC2 total test score (TTS). IQ and M-ABC TTS were then converted to z-scores. Criterion D was met if M-ABC2 TTS fell more than one z-score below the highest IQ score (Figure 5.2).

Eight children with IQ<80 were included in this sample because they meet full criteria for DCD however I will co-vary for IQ in the following sections to control for the effect of general cognition.

Children excluded from further analysis

Two children with suspected DCD did not meet criterion A or B based on the study assessment. These children were not referred to the study through a clinical pathway so it was impossible to verify the diagnosis. It was not possible to rule out compensatory mechanisms or alternative impairments that affect schooling. These children were subsequently excluded.

One child with a full scale IQ below 80 did not show a significant discrepancy between motor and FSI, PRI and VCI scores and was subsequently excluded (Figure 5.2, highlighted in orange).

Two typically developing children had M-ABC2 total test score below seven and another had a manual dexterity score below five however none of these children met criterion B. These children remained in the control group.

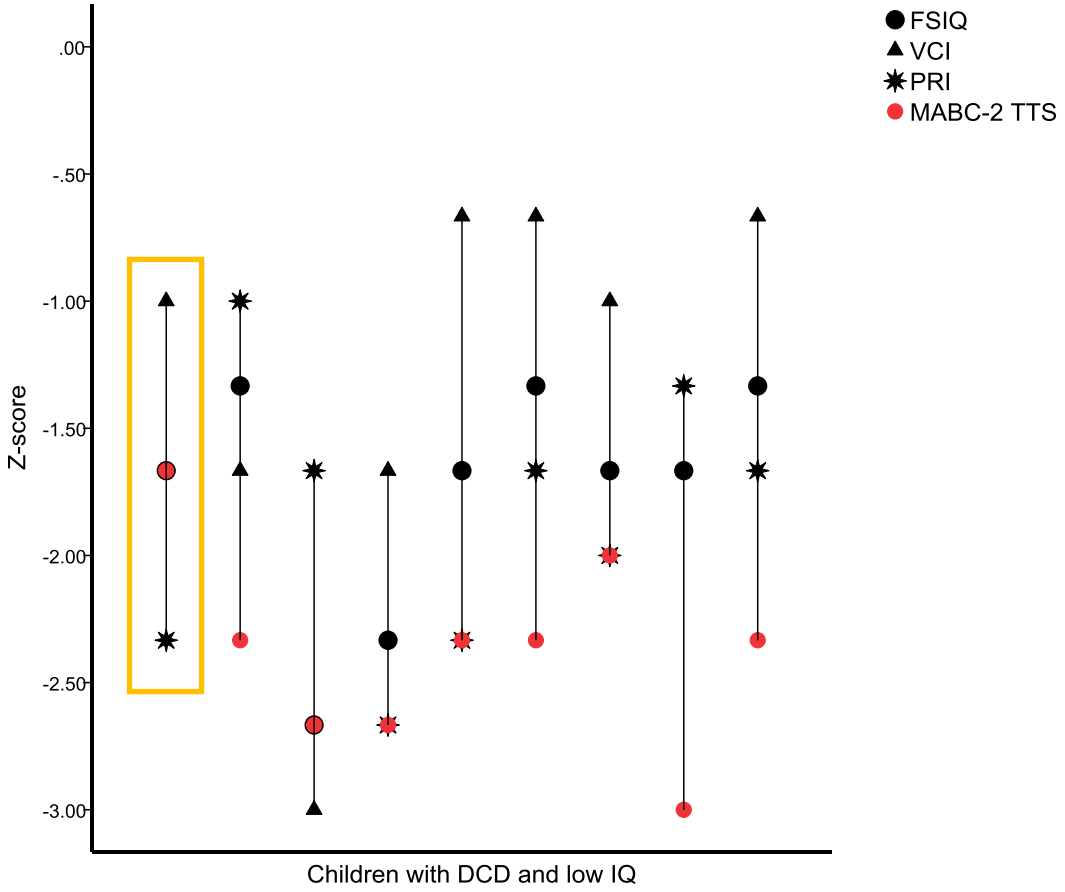

Figure 5.2 Discrepancy between IQ and motor skill in children with motor impairments and low IQ. The child highlighted in orange was excluded from further analysis.

5.3 Results

Final Sample Characteristics

Demographics

Thirty-nine children with DCD and seventeen typically developing children completed the research study. Three children with DCD were subsequently excluded because they did not meet our criteria for DCD (as described above). The final sample included thirty-six children with confirmed DCD and seventeen typically developing children. The groups did not differ on age, gender or handedness (Table 5.10). There was a significant difference

in maternal education. Maternal education was entered as a co-variate in subsequent analyses. Four children in the DCD group were born prematurely, two children at 36 weeks (normal birth weight >2500g), one child at 33 weeks (birth weight approx. 1928g) and one child at 32 weeks (birth weight approx. 1956g). One typically developing child was born at 37 weeks and weighed 2495 grams. This child was a twin of a child with DCD recruited to the study. Three parents could not provide accurate birth weights for their children but their approximations were within the normal range. Three children with DCD were taking oral medications to treat ADHD: one child was taking atomoxetine, one child was taking methylphenidate and one child was taking methylphenidate and prolonged release melatonin.

Table 5.10 Demographic information for study participants

	DCD group (N=36)	**Control Group (N=17)**	**Group comparison (Statistic and p Value)**
Age in months mean (SD)	114.53 (9.32)	112.50 (11.26)	t(50)= 0.679, p=0.501
Gender male (female)	28 (8)	10 (7)	Fisher's exact p=0.197
Handedness Right (left)	32(4)	12(5)	Fisher's exact p=0.126
Maternal years of education beyond 14 Median (IQR)	7(2.25-11.75)	8(5-11)	U=192.5, p=0.028

Previous diagnoses in children with DCD

Many children with DCD had additional diagnoses or suspected diagnoses currently under investigation (Table 5.11). Co-occurring diagnoses/suspected diagnoses are summarised in Table 5.12.

Table 5.11 Summary of number of children with additional diagnoses or suspected

Number of additional diagnoses reported in screening	Number of children with DCD
0	13
1	14
2	2
3	4
4	3

Table 5.12 Summary of additional diagnoses/suspected diagnoses in children with DCD

Diagnosis or Suspected Diagnosis	Number reported in screening
ADHD	10
Autism/ASD traits	6
Language Impairments	5
Developmental/Intellectual delay/disability	2
Speech/articulation disorders	5
Reading disabilities	10
Other Impairments	4

Motor Skills in children with DCD

Children with DCD scored significantly poorer than controls across all measures of motor skill. All domains of motor skill remain impaired after co-varying for maternal education and full scale IQ (Table 5.13).

Table 15.13 Motor abilities in children with DCD and controls

M-ABC2 scaled score	**Children with DCD**	**Typically developing children**	**DCD vs control group**	**DCD vs controls co-varying for maternal Education and FSIQ**
Total test score Median (IQR)	4 (1-7)	8.5 (5.75-11.25)	**U=18 p<0.001**	**F(1,47)=68.168 p<0.001**
Manual dexterity Median (IQR)	4 (1.25-6.75)	8 (5-11)	**U=76 p<0.001**	**F(1,49)=20.729 p<0.001**
Aiming and catching Mean (SD)	6.64 (3)	9.75 (2.11)	**t(51)=3.711 p=0.001**	**F(1,48)=12.509 p=0.001**
Balance Median (IQR)	5 (3-7)	9 (6-12)	**U=57 p<0.001**	**F(1,48)=35.38 p<0.001**

Results in bold follow Bonferroni correction for multiple comparisons (p<0.0125)

Relationships between Motor Abilities in children with DCD

Children with DCD showed variable profiles of deficits within motor domains and M-ABC2 subscale scores did not correlate with one another in either participant group (Table 5.14).

Table 5.14 Correlations between M-ABC2 subscales in children with DCD and controls

Group	**Manual Dexterity and Aiming and catching**	**Manual Dexterity and Balance**	**Aiming and catching and Balance**
DCD	Rho= -0.063 p=0.716	Rho=0.155 p=0.373	Rho=0.137 p=0.431
Controls	Rho=-0.318 p=0.230	Rho=-0.062 p=0.813	Rho=-0.185 p=0.493

Thirty-one children with DCD had a TTS at or below the 5th percentile on the M-ABC2 and two children had a M-ABC2 TTS between the 6th and 15th percentile. Two children with DCD scores above the 16th percentile, these children showed a selective deficit in manual dexterity (Table 5.15).

Table 5.15 M-ABC2 total test score categories in children with DCD

≤5th percentile	6th-15th percentile	16th-25th percentile	26th-100th percentile
31 (88.6%)	2 (5.7%)	2 (5.7%)	0 (0%)

Differences between children with DCD and typically developing children

Intellectual abilities

Children with DCD scored significantly lower than control children on full scale IQ, verbal comprehension index, and perceptual reasoning index. There were no significant differences between groups once maternal education was entered as a co-variate (Table 5.16; Figure 5.3). Differences in full scale IQ are driven by high scores in the control group rather than low scores in children with DCD and were eliminated by correction for maternal education. This likely reflects a difference in socioeconomic status between groups. Comparisons between the children with DCD and the test mean revealed no significant differences. Children with DCD did not display a larger discrepancy between verbal and perceptual reasoning index scores than controls.

Table 5.16 Intellectual abilities in children with DCD and controls

IQ Scale	**Children with DCD**	**Typically developing children**	**DCD vs test mean**	**DCD vs control group**	**DCD vs controls co-varying for maternal Education**
FSIQ Mean (SD)	98.03 (19.1)	111.12 (9.39)	t(35)=-0.620 p=0.539	**t(50.85)=3.35 p= 0.002**	F(1,50)=2.049 p=0.159
VCI Mean (SD)	102.5 (19.58)	115.12 (13.58)	t(35)=-0.766 p=0.449	t(51)=2.393 p=0.02	F(1,50)=1.626 p=0.208
PRI Mean (SD)	93.75 (19.23)	104.35 (13.68)	t(35)=-1.950 p=0.059	t(51)=2.038 p=0.047	F(1,50)=0.781 p=0.381
Discrepancy between VCI and PRI	8.75 (17.5)	10.76 (21.93)	-	t(51)=0.360 p=0.720	-

Results in bold survive correction for multiple comparisons (p<0.01)

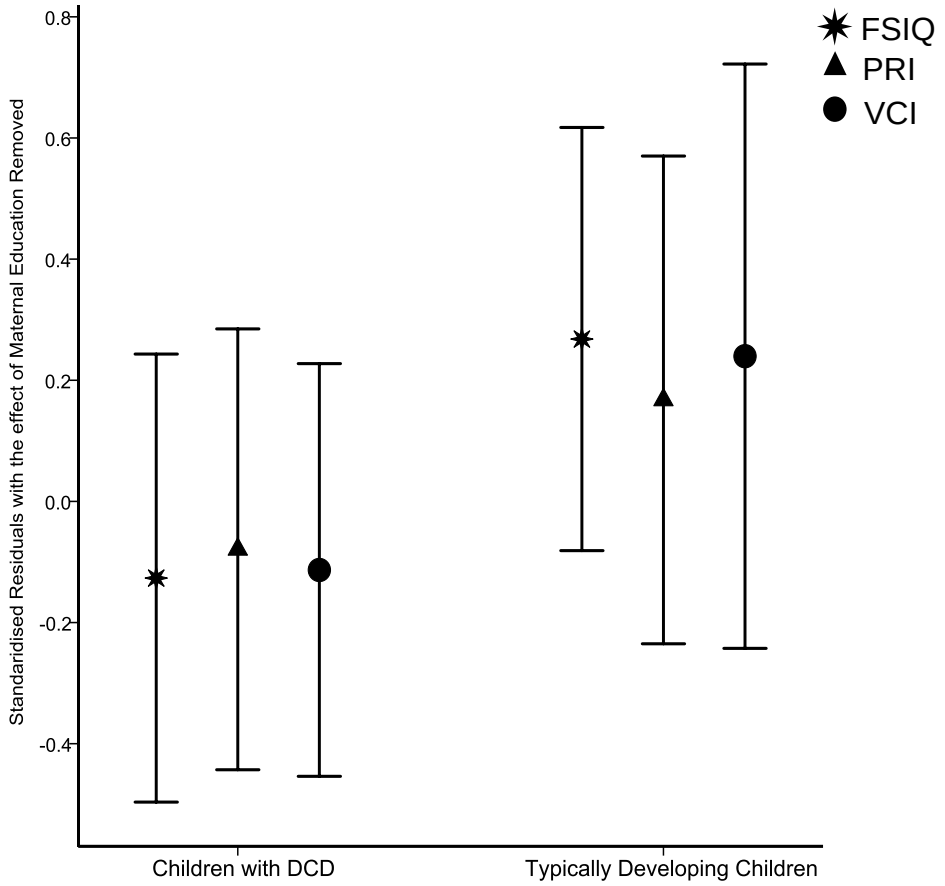

Figure 5.3 IQ scores in children with DCD and typically developing children (mean and 95% confidence intervals displayed)

Processing Speed

Children with DCD showed significant impairments in processing speed relative to controls. Twenty-two children with DCD (62.8%) fell more than 1.5 SD below the control mean. The raw data shows that median patient time taken was nearly four seconds slower than controls (Table 5.17 Figure 5.4).

Table 5.17 Processing speed in children with DCD and controls

	Raw score (s) Median (IQR)	**Z-score Mean (SD)**	**>2SD below control mean N (%)**	**DCD vs control group**
DCD	14.35 (10.53-18.17)	2.26 (1.81)	22 (62.8%)	χ^2= 13.479
Controls	10.82 (9.3-12.34)	0 (1)	1 (6.7%)	p=0.001

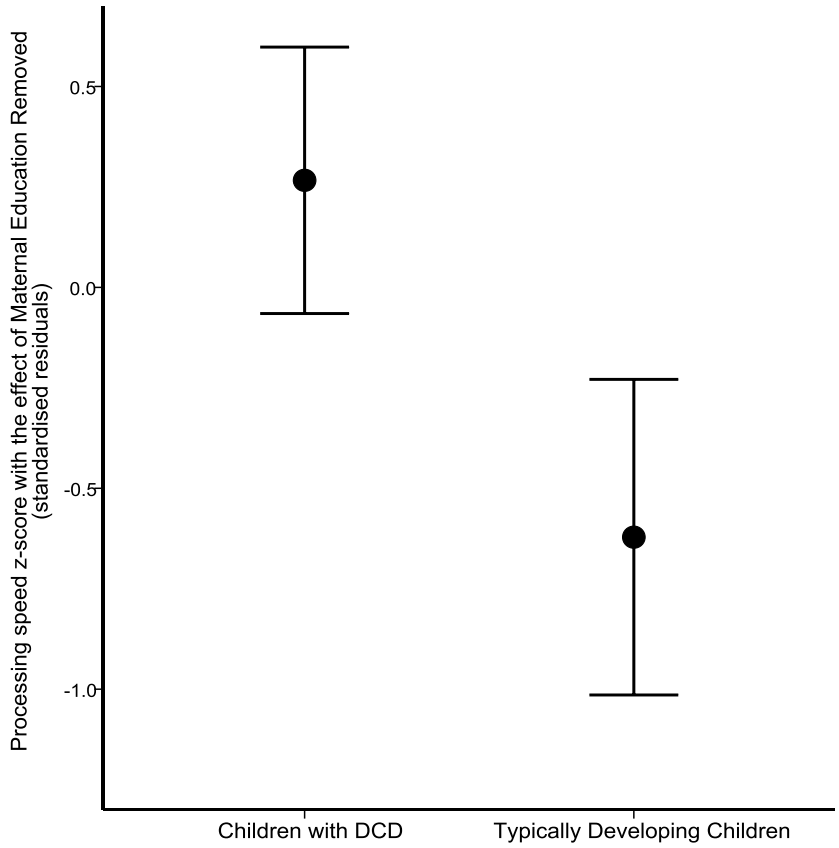

Figure 5.4 Processing speed in children with DCD and typically developing children (mean and 95% confidence intervals displayed)

Language Abilities

Children with DCD were significantly poorer than the control group on core language and receptive language scales. When perceptual reasoning index and maternal education were entered as co-variates there were no longer any significant differences between groups. There were no differences between the test mean and language indices in children with DCD after correcting for multiple comparisons (Table 5.18; Figure 5.5).

Table 5.18 Language abilities in children with DCD and controls

Language Index	**Children with DCD**	**Typically developing children**	**DCD vs test mean**	**DCD vs control group**	**DCD vs controls co-varying for maternal Education and PRI**
Core Mean (SD)	92.47 (18.05)	106.19 (11.86)	t(35)=2.5 p=0.017	**t(51)=2.777 p=0.002**	F(1,48)=2.649 p=0.11
Receptive Mean (SD)	94.33 (18.98)	110.81 (14.33)	t(35)=1.79 1 p=0.082	**t(51)=3.096 p=0.001**	F(1,48)=3.891 p=0.054
Expressive Mean (SD)	94.72(17.24)	106.25 (11.66)	t(35)=1.83 7 p=0.075	t(51)=2.433 p=0.019	F(1,48)=0.1.656 p=0.204
Results in bold survive correction for multiple comparisons (p<0.017)					

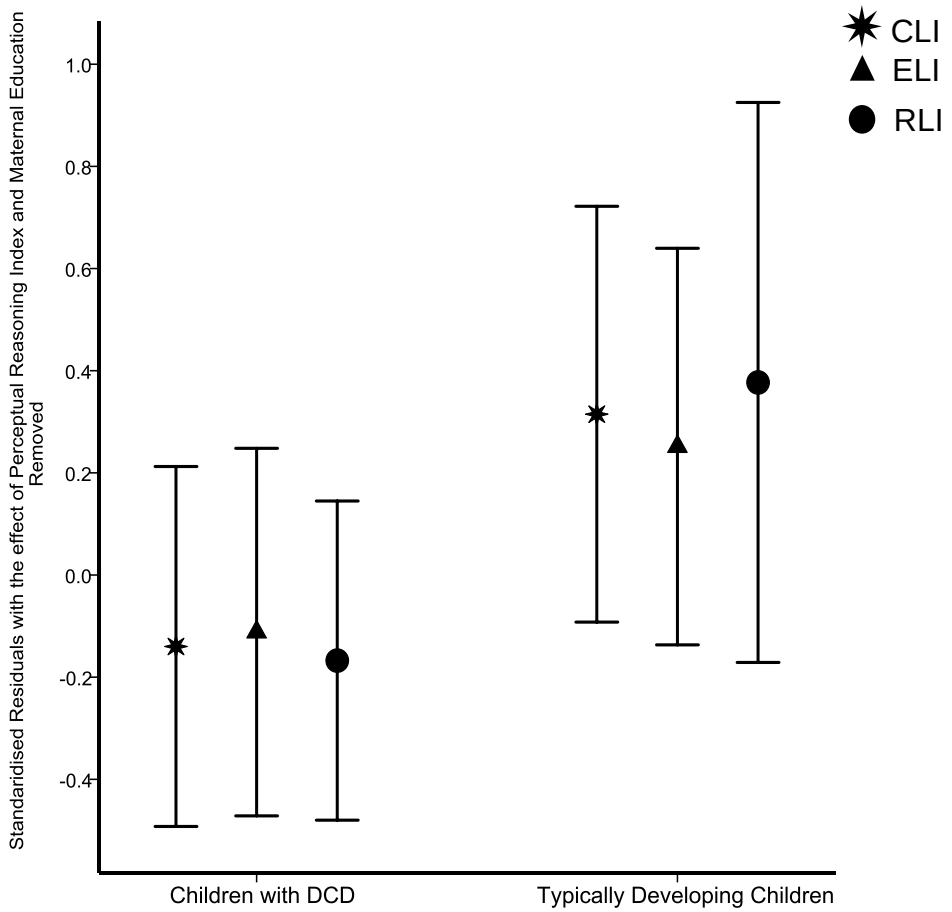

Figure 5.5 Language abilities in children with DCD and typically developing children (mean and 95% confidence intervals displayed)

Speech and oromotor control abilities

Children with DCD showed impairments on focal oromotor (42.4%) and sequencing (23.5%) subtests (Table 5.19). Comparing z-scores between groups revealed the DCD scored significantly lower than the typically developing group on both subscales (focal oromotor control U=95.5 p=0.001; sequencing U=134 p=0.009). Seven out of eight children with DCD who scored in the impaired range on the sequencing subscale also scored in the impaired range on focal oromotor control.

Table 5.19 VMPAC results in children with DCD and controls

subscale		**Normal**	**Mild**	**Moderate**	**Severe**
Focal Oromotor Control	DCD	19 (57.6%)	3 (9.1%)	1 (3%)	10 (30.3%)
	Controls	13 (86.7%)	1 (6.7%)	0	1 (6.7%)
Sequencing	DCD	26 (76.5%)	0	3 (8.8%)	5 (14.8%)
	Controls	15 (100%)	0	0	0

The CAS checklist indicated that 20.6% of children with DCD displayed features of CAS and one child had moderate CAS (Table 5.20). The speech features indicative of CAS according to the consensus criteria identified in each child with DCD and features/diagnosis of CAS are summarised in Table 5.21. All children with features/diagnosis of CAS displayed lengthened and disrupted co-articulatory transitions. Of those children with diagnosis/features of CAS: five were impaired on both subtests of the VMPAC, one had a focal oromotor control deficit and two were not impaired on the VMPAC.

Table 5.20 Indication of CAS in children with DCD and controls

	Normal	**Features**	**Diagnosis**
DCD	25 (73.5%)	7 (20.6%)	1 (2.9%)
Controls	14 (93.3%)	1 (6.7%)	0 (0%)

Table 5.21 CAS Diagnostic criteria and speech features in children with DCD and features/indication of CAS (adapted from Fedorenko et al 2016)

CAS Diagnostic Criteria	Speech Features Associated with CAS diagnostic criteria	C 1	F1	F2	F3	F4	F5	F6	F7
Inconsistent Errors	Same word/syllable different on repetitions								
	Same consonant/vowel different across different words	✓							
Lengthened and disrupted co-articulatory transitions	Speech motor behaviours, including groping during sound production							✓	
	Difficulty sequencing phonemes and syllables	✓	✓	✓		✓		✓	✓
	Voicing errors	✓							
	Errors increase with word length and phonological complexity	✓							
	Syllable segregation	✓		✓	✓				
	Difficulty achieving initial articulatory configurations or transitory movement gestures	✓		✓		✓	✓		✓
	Difficulty maintaining syllable integrity	✓		✓	✓	✓	✓		✓
	Repetitions of sounds and syllables					✓	✓		
	Epenthesis/intrusive schwa	✓							
	Metathesis								
	Addition errors	✓	✓						
	Frequent omissions (>10)	✓							
	Prolongation errors			✓		✓			
	Nonphonemic productions/distorted substitutions								
	Hypernasality/nasal emissions								

	Slowed and disrupted DDK sequence	✓	✓						
Inappropriate Prosody	Equal stress or lexical stress errors	✓		✓	✓	✓			
	Altered suprasegmental features	✓				✓	✓		✓
	Prolongation errors			✓					✓
Number of features		**13**	**3**	**7**	**3**	**7**	**4**	**2**	**5**
Number of diagnostic criteria met		**3**	**1**	**2**	**2**	**2**	**2**	**1**	**2**

C1= child with DCD and an indication of moderate CAS F1-7= children with DCD and features of CAS

Attention Skills

Children with DCD differed from controls on all subtests of the TEA-Ch except the Opposite Worlds dual task z-score. Co-varying for Full scale IQ left significant differences on the Score! (sustained attention), and Creature Counting (attentional control and set switching) subtests (Table 5.22, Figure 5.6). Running these comparisons without children with DCD and a co-occurring diagnosis of ADHD did not alter the result.

Table 5.22 Attention abilities in children with DCD and controls

TEA-Ch subtest	**Children with DCD**	**Typically developing children**	**DCD vs control group**	**DCD vs controls co-varying for maternal Education and FSIQ**
Sky Search Median (IQR)	8 (5-11)	11 (8-14)	**U=159 p=0.004**	F(1,49)=3.851 p=0.055
Score! Median (IQR)	6 (-1-13)	10 (5-15)	**U=125 p<0.001**	**F(1,49)=8.65 p=0.005**
Creature Counting Median (IQR)	5.5 (-0.5-11.5)	12 (6.5-17.5)	**U=73 p<0.001**	**F(1,49)=23.154 p<0.001**
Sky Search DT Median (IQR)	7 (-1-15)	8 (4-12)	**U=159.5 P=0.008**	F(1,47)=3.469 p=0.069
Opposite World z-score Median (IQR)	0.519 (-2.86-3.9)	-0.062 (-1.24-1.118)	U=205.5 p=0.232	-
Results in bold survive correction for multiple comparisons (p<0.01)				

Parental Questionnaire of ADHD symptomatology

26 Twenty-six children with DCD (77.8%) and no children in the control group displayed a profile indicative of ADHD based on the Conners-3 questionnaire (Table 5.23).

Table 5.23 ADHD indication based on the Conners-3 parental questionnaire

group	**Normal**	**Inattentive**	**Hyperactive**	**Combined**	**Chi-Square**
DCD	8 (22.2%)	2 (5.6%)	5 (13.9%)	19 (52.8%)	$X^2=25.52$
Controls	17 (100%)	0 (0%)	0 (0%)	0 (0%)	P<0.001

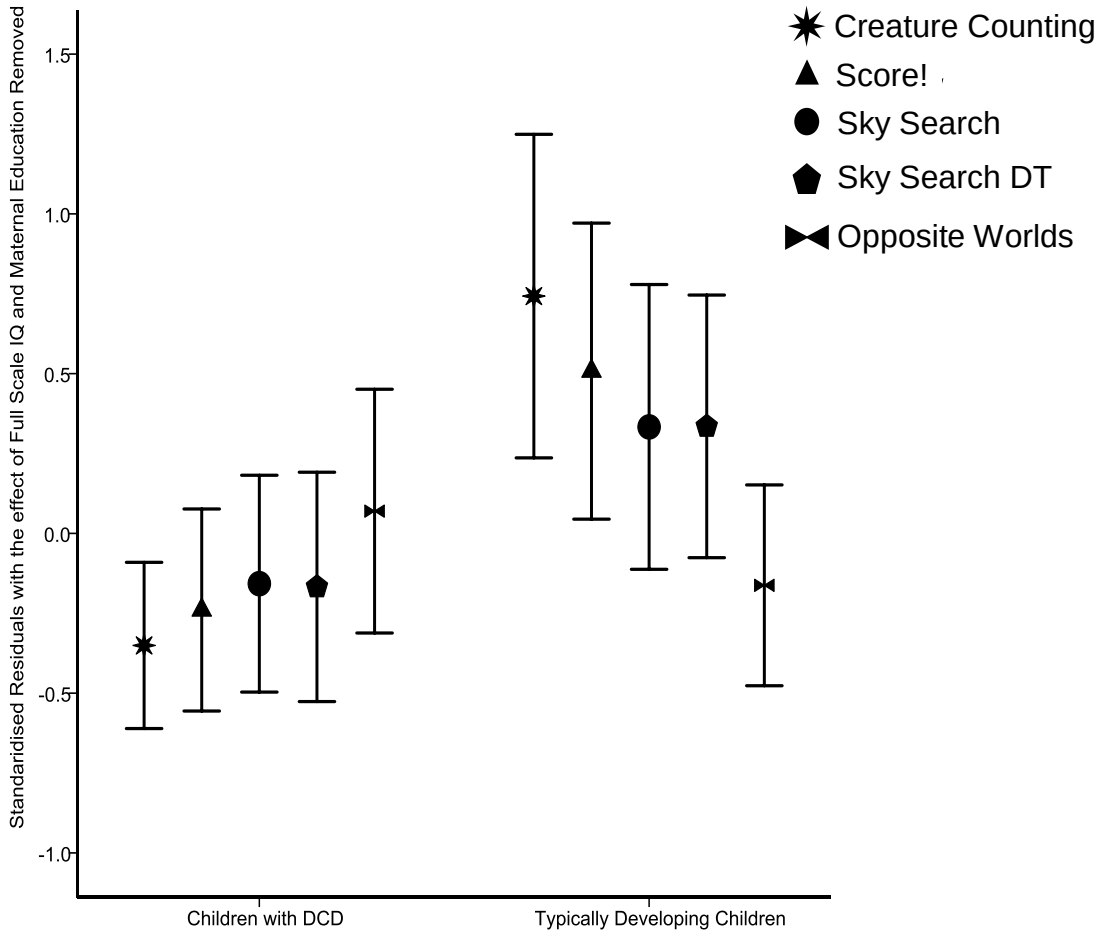

Figure 5.6 Attention abilities is children with DCD and typically developing children (mean and 95% confidence intervals)

Predictors of DCD or control group membership

Full scale IQ, Score!, Creature Counting, processing speed categorisation and diagnosis/indication of CAS were entered into a logistic regression to determine significant predictors of group membership. Creature counting was the only significant predictor of group membership (sensitivity=84.4% specificity= 64%)(Table 5.24).

Table 5.24 Predictors of group membership (DCD vs Control group)

	B (SE)	Exp(B)	Significance	Chi-Square
Step 1 (final model)				
Creature counting	0.459 (0.133)	1.583	0.001	19.606 p<0.0001

Relationships between impairments in children with DCD

Relationship between motor skills and neuropsychological variables

Aiming and catching and manual dexterity did not correlate with IQ, language, attention

or speech motor control scores (Table 5.25). Balance was significantly correlated with full scale IQ and core language skills. Post hoc correlations reveal this effect is significant in both IQ subscales (PRI Rho=0.375, p=0.026; VCI Rho=0.419, p=0.012) and both receptive (rho=0.639, p=0.000036) and expressive language indices (rho=0.631 p=0.000048). The association between balance skills and language abilities remains when excluding those children with full scale IQ below 80 (Core language Rho=0.514 p=0.006; Receptive Rho=0.480 p=0.011; Expressive Rho=0.465 p=0.014). The relationship between balance skills and IQ does not remain (Full scale IQ Rho=0.223 p=0.263).

Table 5.25 Correlations between standardised assessments and motor skills in DCD

	Manual Dexterity	**Aiming &Catching**	**Balance**
Full Scale IQ	Rho=0.361 p=0.031	r=-0.078 p=0.652	**Rho=0.481 p=0.003**
Core Language Index	Rho=0.301 p=0.074	r=0.084 p=0.626	**Rho=0.668 p=0.000012**
Sky Search (divided attention)	Rho=0.137 p=0.425	Rho=0.181 p=0.290	Rho=0.384 p=0.023
Score! (sustained attention)	Rho=0.302 p=0.073	Rho=-0.234 p=0.170	Rho=0.333 p=0.050
Sky Search DT (sustained attention)	Rho=0.061 p=0.733	Rho=0.118 p=0.505	Rho=0.273 p=0.124
Creature counting (attentional control)	Rho=0.416 p=0.012	Rho=-0.013 p=0.941	Rho=0.417 p=0.013
Opposite word z-score (attentional control)	Rho=-0.069 p=0.695	Rho=-0.328 p=0.054	Rho=0.305 p=0.079
Processing speed z-score	Rho=-0.299 p=0.081	Rho=-0.138 p=0.429	Rho=-0.208 p=0.239
Focal Oromotor control z-score	Rho=0.188 p=0.319	Rho=0.333 p=0.072	Rho=0.090 p=0.642
Sequencing z-score	Rho=0.205 p=0.268	Rho=-0.291 p=0.112	Rho=0.295 p=0.114

Results in bold survive correction for multiple comparisons (p<0.005)

Core language and Perceptual reasoning index were entered into a multiple linear regression to predict balance score based on the correlations in Table 5.25. Core language skills explained approximately 38.6% of variance in balance skills in children with DCD, independent of Perceptual reasoning index ($F(2,32)=10.043$, $p=0.001$)(Table 5.26; Figure 5.7).

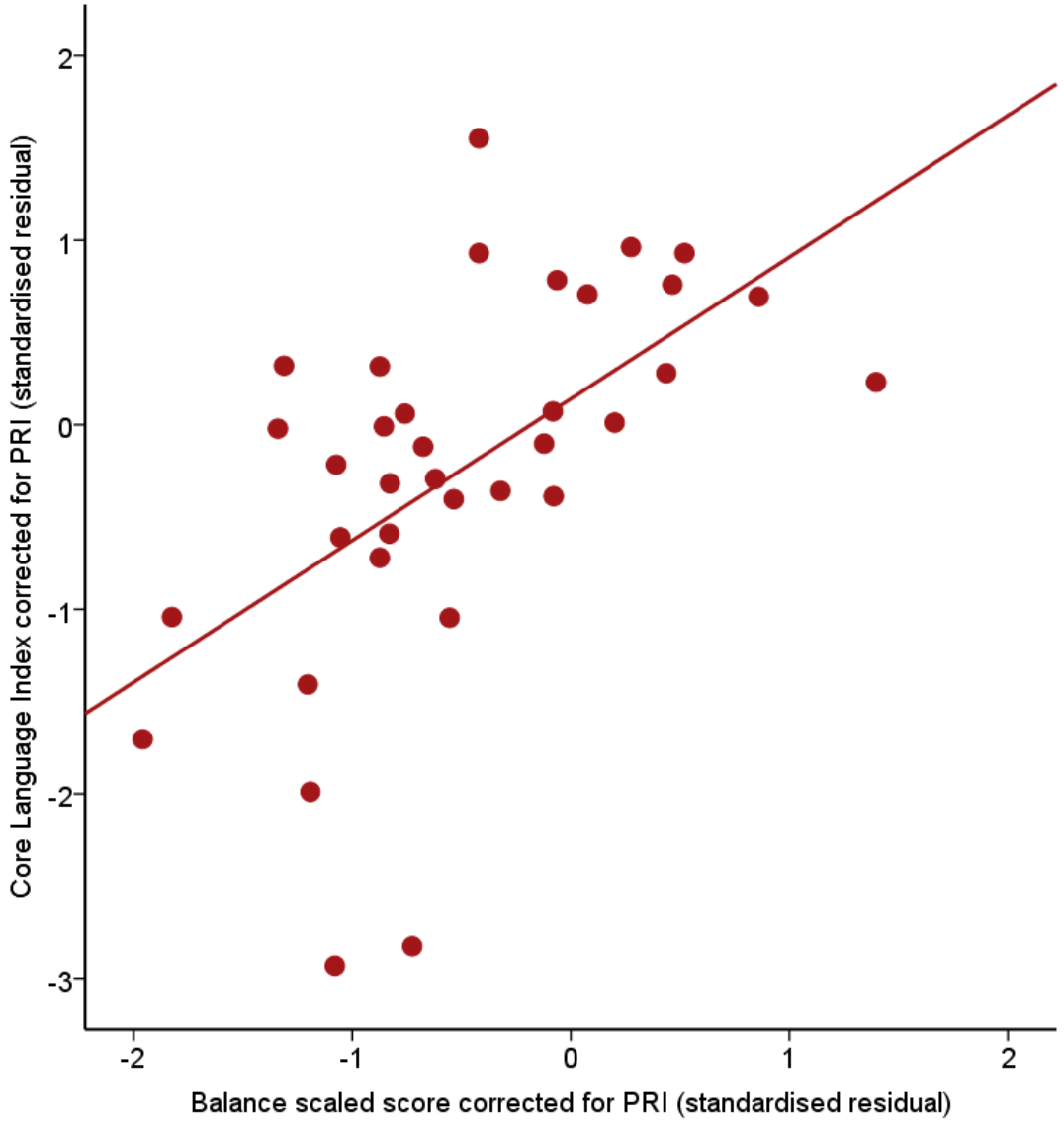

Figure 5.7 Relationship between language skills and balance in children with DCD corrected for perceptual reasoning index

Table 5.26 Predictors of balance score in children with DCD

Predictors	**B (SE)**	**Beta**	**Significance**	**R^2(Adjusted R^2)**
PRI	0 (0.021)	0.001	0.994	0.386 (0.347)
Core language index	0.085(0.023)	0.620	0.001	

After excluding children with full scale IQ scores below 80, the same model remained significant (F(2,26)=4.309, p=0.025)(Table 5.27).

Table 5.27. Predictors of balance score in children with DCD excluding those with low IQ (FSIQ<80)

Predictors	**B (SE)**	**Beta**	**Significance**	**R^2 (Adjusted R^2)**
PRI	0-0.01 (0.025)	-0.077	0.994	0.264(0.203)
Core language index	0.113(0.04)	0.539	0.009	

Relationship between processing speed difficulties and other abilities

Children with and without processing speed difficulties did not differ on motor or IQ tests. Poorer processing speed was significantly associated with poorer performance on creature counting (attentional control) (Table 5.28, Figure 5.8).

Table 5.28 Correlations between processing speed and neuropsychological variables in DCD

	Processing speed
FSIQ	Rho=-0.363 p=0.032
Core Language Index	Rho=-0.396 p=0.018
Sky Search	Rho=-0.429 p=0.010
Score!	Rho=-0.355 p=0.073
Creature counting	**Rho=-0.501 p=0.002**
Sky Search DT	Rho=-0.214 p=0.232
Opposite word z-score	Rho=-0.055 p=0.752
Results in bold survive correction for multiple comparisons (p<0.00625)	

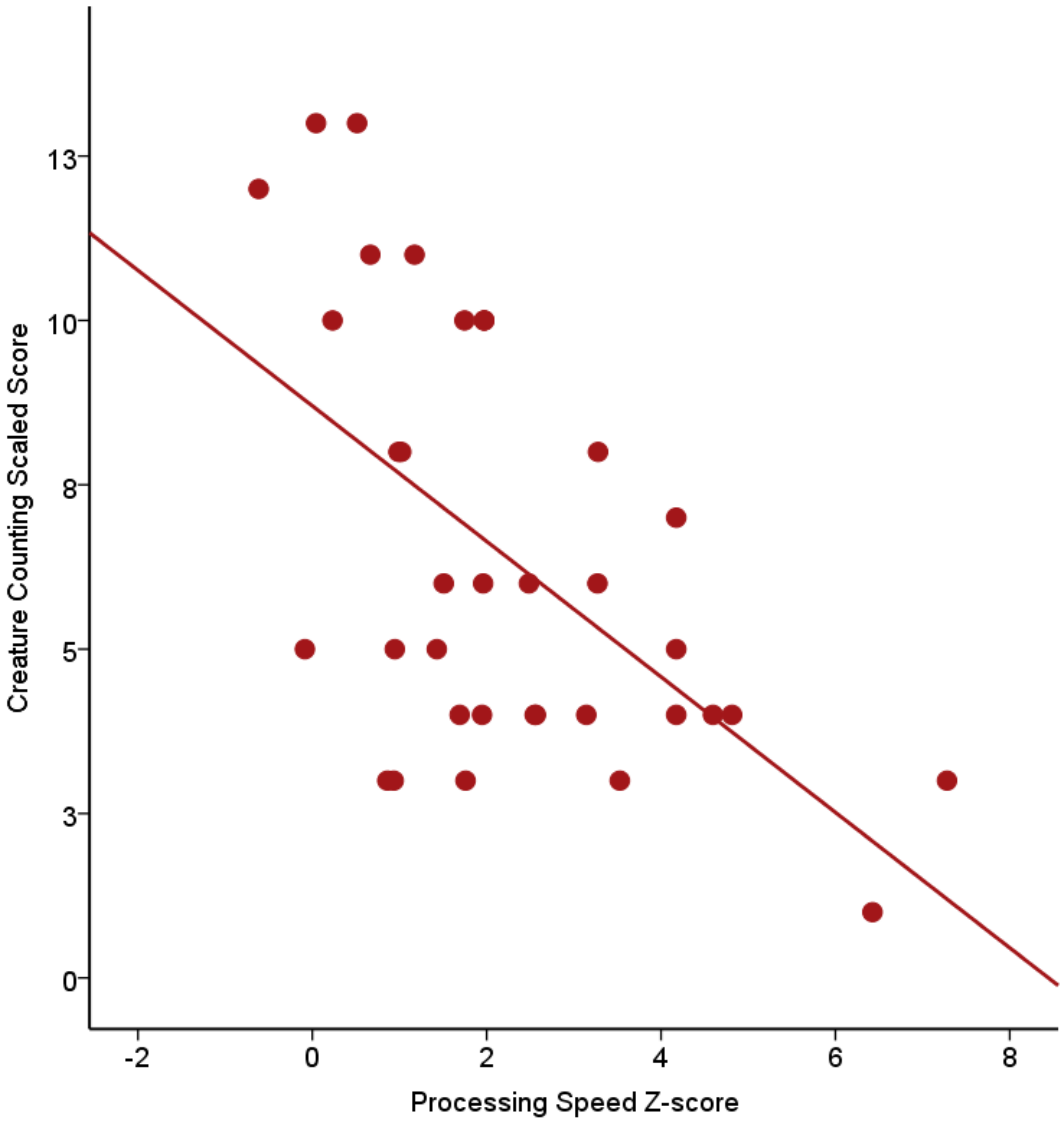

Figure 5.8 Relationship between creature counting scaled score and processing speed z-score in children with DCD

Language Abilities in DCD

As discussed above, once IQ and maternal education were accounted for, children with DCD did not perform more poorly than controls on the CELF-4 however some children did display poor language skills. Children who scored 1.33 standard deviations below the standardised test mean (<80) were classified as impaired on receptive or expressive language. Eight out of 36 children with DCD were classified as impaired on receptive and/or expressive language indices (Table 5.29). Perceptual reasoning index in children with DCD and language impairments (median= 74, IQR=13.5) was significantly lower than in those with DCD and no language difficulties (median=98.5, IQR=23.5) (U= 15; p<0.001).

Table 5.29 Number of children with DCD and co-occurring language impairments

Language Score <80	**Unimpaired**	**Receptive Only**	**Expressive Only**	**Both receptive and expressive language**
DCD	28 (77.8%)	3 (8.3%)	1 (2.8%)	4 (11.1%)
Controls	16 (100%)	0 (0%)	0 (0%)	0 (0%)

Attention Abilities in children with DCD

As shown in the previous section, children with DCD showed a heterogeneous pattern of impairments on measures of attention with significant deficits on Score! and Creature Counting. Scores on Score! and Creature Counting subtests was highly correlated (Rho=0.562 p=0.00036)(Figure 5.9). Removing the children with DCD and co-occurring ADHD does not alter this result. Performance on these subtests was also highly correlated with full scale IQ (Score! Rho=0.512 p=0.002; Creature Counting Rho=729 p<0.0001). Regression analysis revealed that these scores remained highly related with Full Scale IQ entered as a covariate (F(2,33)=8.724, p=0.001) (Table 5.30).

Table 5.30 Multiple linear regression predicting Score! Subtest in children with DCD

Predictors	**B (SE)**	**Beta**	**Significance**	**Adjusted R^2**
FSIQ	0.030 (0.037)	0.164	0.415	0.306
Creature Counting	0.496 (0.213)	0.461	0.026	

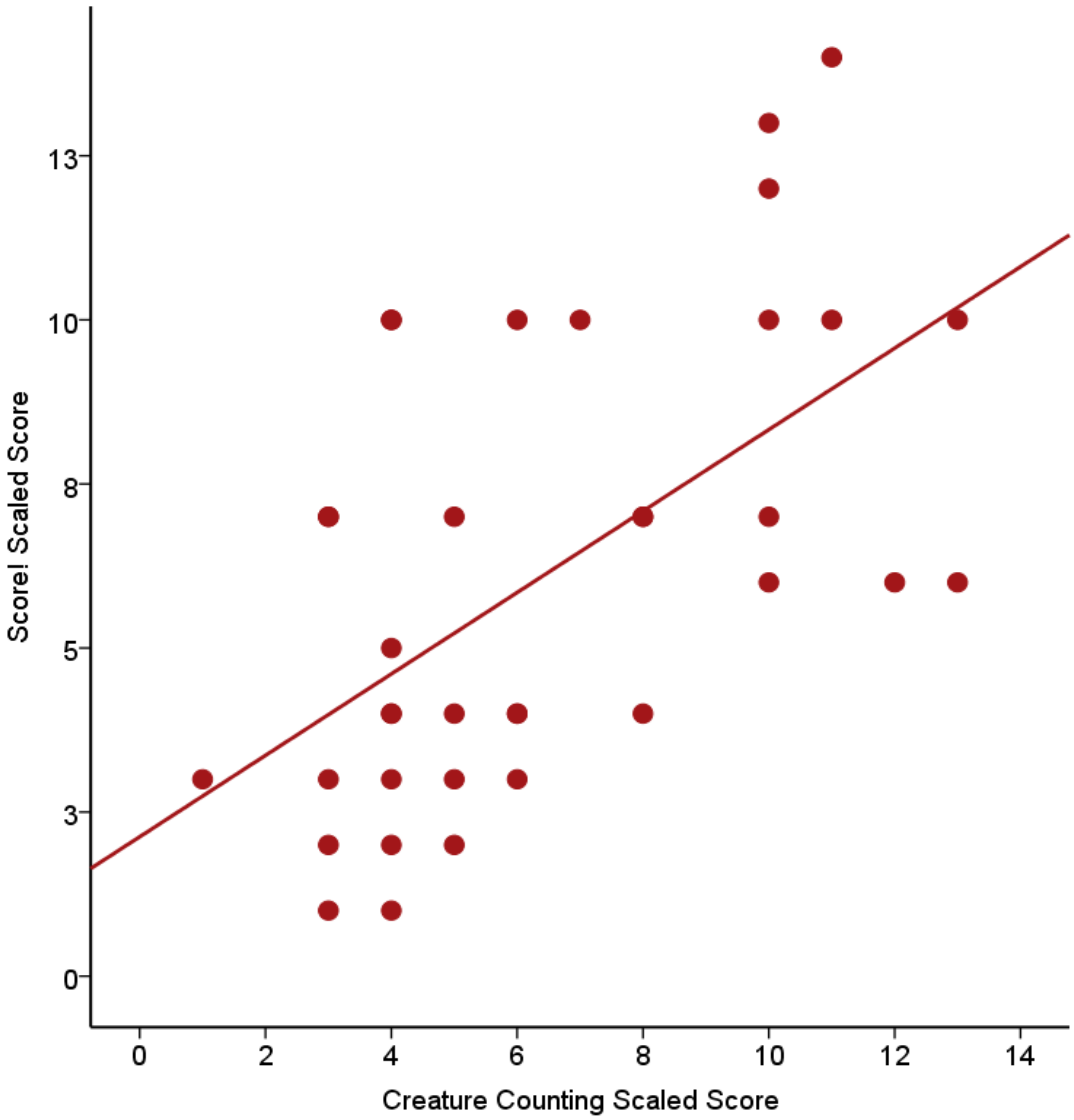

Figure 5.9 Relationship between attention abilities in children with DCD with the effect of IQ removed

ADHD symptomatology in DCD

There were no significant differences in attention, motor or cognitive abilities between children DCD with and without an indication of ADHD based on a questionnaire (Table 5.31). These comparisons were not run between the normal and inattentive group because the inattentive group consisted of only two children.

T**able 5.31** Differences between children with normal (n=8) and impaired profiles on the Conners-3 within the DCD group

	Hyperactive-impulsive ADHD (n=5)	**Combined type ADHD (n=19)**
FSIQ	U=19 p=0.943	U=48.5 p=0.150
Manual Dexterity	U=16.5 p=0.634	U=58 p=0.344
Aiming and Catching	U=18.5 p=0.859	U=67.5 p=0.663
Balance	U=19 p=0.938	U=69.5 p=0.897
Sky Search	U=16.5 p=0.667	U=71.5 p=0.821
Score!	U=10 p=0.155	U=40 p=0.056
Creature Counting	U=18 p=0.832	U=41.5 p=0.068
Sky Search– DT	U=19 p=0.919	U=66.5 p=0.775
Opposite worlds dual task increment	U=15 p=0.755	U=49.5 p=0.340
Processing speed	U=14.5 p=0.335	U=55 p=0.533

Speech and oromotor control abilities in Children with DCD

Focal oromotor control and sequencing abilities were highly correlated in children with DCD (Rho=0.671 p<0.0001). Sequencing and focal oromotor control were significantly poorer in children with features of childhood apraxia of speech compared to those without (Table 5.32). As reported previously, focal oromotor control and sequencing did not correlate with any motor subscales from the M-ABC-2. Sequencing z-score was significantly correlated with full scale IQ and performance on the creature counting test of attention (Table 5.33). Creature counting and FSIQ were entered into a logistic regression to predict CAS categorisation in children with DCD. Full scale IQ was the only significant predictor of group membership indicating the relationship between creature counting and sequencing impairment was no longer significant once FSIQ was taken into account (sensitivity=75% specificity=96%)(Table 5.34). Presence of CAS features/diagnosis and focal oromotor control score were not significantly associated with any cognitive or attention skills.

Table 5.32 Differences in IQ, language, attention and motor skills between children with DCD and features/diagnosis of CAS and those without

FSIQ	U=59.5 p=0.091
Core Language Index	U=49.5 p=0.032
Manual Dexterity	U=73 p=0.264
Aiming and catching	U=68.5 p=0.190
Balance	U=52 p=0.057
Score!	U=72 p=0.244
Creature counting	U=66.5 p=0.164
Processing speed	U=91 p=0.848
Focal oromotor control z-score	**U=20.5 p=0.007**
Sequencing z-score	**U=20.5 p=0.005**
Results in bold survive correction for multiple comparisons p<0.005	

Table 5.33 Correlations between speech abilities and neuropsychological variables in the DCD group

	Focal Oromotor Control	**Sequencing**
FSIQ	Rho=0.421 p=0.020	**Rho=0.591 p<0.001**
Core Language Index	Rho= 0.280 p=0.134	Rho=0.392 p=0.029
Score!	Rho=0.112 p=0.557	Rho=0.347p=0.056
Creature Counting	Rho=0.236 p=0.209	**Rho=0.531 p=0.002**
Processing speed	Rho=-0.086 p=0.657	Rho=-0.340 p=0.066
Results in bold survive correction for multiple comparisons p<0.01		

Table 5.34 Predictors of speech sequencing impairment in children with DCD

	B (SE)	**Exp(B)**	**Significance**	**Chi-Square**
Step 1 (final model)				
Full scale IQ	-0.120 (0.058)	0.887	0.039	12.368 p<0.002
Creature counting	0.070 (0.242)	1.072	0.773	

Confirmatory factor analysis

A factor analysis was run to determine which behavioural variables merge together into factors in children with DCD. Linear regression was used to remove the effect of PRI from balance, core language index, score! and creature counting scores. The residuals from

these were entered into the model. Processing speed, focal oro-motor impairment and features/diagnosis of CAS were entered as categorical variables. Manual dexterity and Aiming and catching were not entered into the model as these did not correlate with any other behavioural variables. VMPAC sequencing z-score was not included as it was highly correlated with focal oromotor control.

Kaiser-Meyer-Olkin measure of adequacy was 0.592. Bartlett's test of sphericity was significant (approximate χ^2 = 42.05, df=21, p=0.004). Three factors were extracted which accounted for 52.79% of the variance (Table 5.35). The first factor was a composite of balance and language skills. The second factor was a composite of processing speed and measures of attention. As expected, the third factor contained CAS and focal oromotor control impairment.

Table 5.35 Factors extracted from confirmatory factory analysis

	Eigenvalue	**variance explained**	**Behavioural variables in factor**
1	1.298	18.54%	Balance (residual removing PRI)
			Core language index (residual removing PRI)
2	1.269	18.13%	Score! (residual removing PRI)
			Creature counting (residual removing PRI)
			Processing speed categorisation
3	1.128	16.1%	Focal oromotor control impairment (yes/no)
			CAS features/diagnosis (yes/no)

5.4 Discussion

Summary

In the present study, children with DCD showed impairments on: all motor skills, sustained attention, attentional control and processing speed compared to control children once IQ was accounted for. A subset of children displayed impairments on focal oromotor control and speech/oromotor sequencing. Eight out of thirty-three children with DCD who completed the speech assessment showed features/diagnosis of CAS. Within children with DCD, manual dexterity and aiming and catching were independent domains which did not correlate with any other behavioural measures. Three composite domains were identified with a factor analysis:

i) Balance and language abilities

ii) Processing speed, attentional control (creature counting), sustained attention (score!)

iii) Focal oromotor control impairment and childhood apraxia of speech features

Motor Profiles of children with DCD

As predicted, children with DCD were impaired on all motor skills relative to controls. Interestingly these motor skills did not correlate with each other. This is not unexpected as the normative sample of school aged children from the M-ABC2 (N=1172) demonstrated small/moderate correlations between subtests (r=0.25-0.36)(Henderson et al. 2007).

Poorer motor skills were not associated with poorer executive functions or speech in children with DCD. Language impairments were associated with particularly poor balance skills in children with DCD. This is the first evidence that balance skills are significantly associated with language abilities skills independent of the effect of non-verbal IQ in children with DCD. A relationship between language and balance skills was not hypothesised and requires further replication in a larger sample. It may be that this relationship is mediated by a third behavioural factor not tested in this study such as working memory. Language impairments are associated with poor motor skills but no studies have identified a relationship between language impairment and balance impairment in children with DCD or SLI (Hill 2001; Müürsepp et al. 2011; Muursepp et al. 2014). Previous studies have reported a relationship between impaired balance and dyslexia (Rochelle & Talcott 2006). In contrast, a more recent study failed to identify a relationship between balance difficulties and reading ability or IQ in young adults (Loras et al. 2014). This relationship may point to a shared neural substrate for balance and language impairments in children with DCD. Nicolson and Fawcett (Nicolson & Fawcett 2007) have proposed a shared cortico-striatal impairment underlies developmental language and motor deficits. MRI studies have implicated the basal ganglia in developmental language impairments and balance skills (Liegeois et al. 2014; Karim et al. 2014; Ferraye et al. 2014). In addition, fMRI research has implicated the cerebellum in both language and balance tasks (Argyropoulos 2015; Stoodley & Schmahmann 2009; Karim et al. 2014; Ferraye et al. 2014). Investigation of the relationship between basal ganglia and cerebellar structures and balance and language skills in children with DCD will test the hypothesis of a shared neurobiological substrate for balance and language skills in DCD.

Intellectual abilities in children with DCD

As hypothesised, children with DCD did not differ from controls on IQ measures once maternal education was taken into account. There was a subset of children with DCD that had IQ scores in the impaired range. These children with low IQ still met our criteria for DCD. IQ scores correlated with attention, language and balance abilities in children with DCD. Previous studies have excluded children with intellectual impairments which may eliminate those most severely affected across these domains. Our data showed no evidence for reduced perceptual reasoning index relative to verbal comprehension index in children with DCD.

Children with DCD showed impairments on a measure of processing speed, as measured using the same world subtest on the TEA-Ch. This is in line with previous studies utilising Wechsler processing speed indices (Sumner, Pratt, et al. 2016; Biotteau, Albaret, et al. 2017). Importantly, unlike these indices our measure of processing speed did not have a motor component and instead required rapid naming. Slower information processing has been reported in children with DCD in experimental studies (Wilson & McKenzie 1998; Piek et al. 2007). Processing speed impairments have been identified in Dyslexia (de Oliveira et al. 2014), ASD (Travers et al. 2014) and children born preterm (Mulder et al. 2011). Our results and those of other studies suggest information processing deficits may be common across many developmental disorders.

Attention Profiles in children with DCD

Children with DCD were impaired on a test of attentional control but not an inhibitory control task possibly indicating impaired cognitive planning and switching but intact response suppression. Three studies have reported children with ADHD are significantly impaired on the creature counting subtest of the TEA-Ch ((Heaton et al. 2002; West et al. 2002; Lemiere et al. 2010) as reported in Paton et al. 2014). Heaton and colleagues (Heaton et al. 2002) also reported a deficit in the opposite worlds subtest in children with ADHD, by contrast Lemiere and colleagues (Lemiere et al.2014) reported no impairment relative to the control group.

Children with DCD had lower sustained attention relative to controls and this score correlated with ADHD-inattentive symptom scale in children with DCD. As the data were not normally distributed it was not possible to determine whether performance was significantly below the test mean. Two studies utilising a different assessment method did not report lower sustained attention in children with DCD (Biotteau, Albaret, et al. 2017; Blais et al. 2017). Results from studies examining performance on the score! subtest in

ADHD are mixed. Two studies have reported an impairment (Manly et al. 2001; Heaton et al. 2002) compared to three non-significant results ((Chan et al. 2008; Lemiere et al. 2010; West et al. 2002) see Paton et al 2014 for a summary). It is possible that children with DCD have an overlapping pattern of everyday attention impairment compared to children with ADHD.

The impairments in processing speed and cognitive control indicate that children with DCD display impairments in executive functions (Anderson 2002). Previous questionnaire studies and experimental work have identified impairments in executive functions in children with DCD (see Wilson et al. 2017 for a review). Additionally, previous literature has described widespread deficits in working memory, another component of executive functions, in children with DCD (Tsai et al. 2012; Alloway & Archibald 2008; Alloway 2011; Alloway et al. 2009; Alloway 2007). Our data in a carefully selected sample of children with DCD therefore supports the existing literature showing that children with DCD have impaired executive functions. Adele Diamond characterises working memory, inhibitory control and cognitive control as lower order executive functions that underpin planning, reasoning and problem solving (Diamond 2013). Anderson's construct of executive functions also suggests attentional control, information processing and cognitive flexibility develop before planning and goal setting in young children (Anderson 2002). There is a growing body of evidence from several sources to suggest all lower order executive functions are impaired in children with DCD. Although in our sample children with DCD were not impaired on non-verbal IQ, it is possible that poor executive functions affect the development of motor planning as well as cognitive planning, reasoning and problem solving skills. This may also account for poor compensation for motor impairments in children with DCD leading to a significant impact on daily living. Longitudinal research in infants at risk for DCD and assessing school-aged children with a wider executive functions assessment battery would test the hypothesis.

The Conners-3 questionnaire gave an indication of ADHD in nearly 80% of our sample, with over 50% categorised as ADHD-combined type. This rate is far higher than the 30-50% reported in the previous literature discussed in chapter two. The majority of participants in this study did not attend through NHS clinics, which may have biased recruitment towards children with additional difficulties. The Conners-3 is also not utilised for diagnosing ADHD (NICE Guidance 2008) and therefore it was not possible to determine whether all of these children would meet clinical thresholds for a diagnosis of ADHD. Given only ten children in our sample had a diagnosis or suspected diagnosis of

ADHD parents may have overestimated behavioural deficits. Additionally there is no data available regarding the sensitivity and specificity of the Conners-3 to ADHD in children with other developmental disorders. A recent review suggested DCD is more common in children with inattentive and combined-type profile ADHD rather than hyperactive-impulsive (Kaiser et al. 2015). This aligns with our results in children with DCD. A study utilising diagnostic criteria to identify ADHD in children with DCD would give better information on the profile of ADHD common in this condition. Interestingly children with DCD and an indication of ADHD did not differ from those with no indication on measures of attention however it is not possible to determine whether this represents a separation of attention and ADHD because of the caveats discussed above.

Language Profiles in children with DCD

Eight children with DCD in our sample (33%) showed some form of language impairment. This is the first evidence that the rate of language impairments in DCD is similar to the rate of motor impairments reported in SLI (32%). Language skills were highly correlated with general cognitive abilities, and language impaired children also showed cognitive impairments. Discrepancies between language and general cognition are no longer part of the diagnostic criteria for developmental language disorder (DLD, previously known as SLI)(Bishop et al. 2017). These results indicate that some children with DCD demonstrate a more general deficit that impacts language rather than specific difficulties with language.

Speech and Oromotor Abilities in children with DCD

Fourteen (42.4%) children with DCD had difficulties with orofacial control and eight children (23.5%) had difficulties with sequencing of movements on the VMPAC. These rates were not significantly different from controls, however this could be because of a small sample size in the control group. These rates are higher than those reported in adolescents born preterm assessed on the same test (31% and 12% respectively (Northam et al. 2012). Previous studies have reported impairments on verbal and orofacial praxis in children with DCD (Farmer et al. 2016; Dewey 1993; Ho & Wilmut 2010). This is the first evidence from standardised testing that a high proportion of children with DCD show impaired orofacial and speech motor control.

Children with DCD displayed impairments of execution and control of oromotor movements as well as motor sequencing. This profile indicates children with DCD have difficulties with precise individual movements of orofacial structures as well as accurate production of motor sequences. The high level of impairment in oromotor control was unexpected as no participants had brain lesions from radiological MRI reports, or a history

of brain injury. All but one child with sequencing impairments also displayed orofacial control impairments and scores between the two subtests were highly correlated in children with DCD. Speech impairments were not correlated with any motor variables which aligns with work by Tukel and colleagues (Tukel et al. 2015) who did not find any correlations between motor abilities and VMPAC scores in children with CAS.

Seven children with DCD showed features of childhood apraxia of speech and one child met the criteria for CAS with moderate severity. This rate is significantly higher than that reported in children referred to speech and language clinics (Shriberg et al. 1997) (1-2 per 1,000). All children with features/diagnosis of CAS had lengthened and disrupted co-articulatory transitions suggesting switching from one motor command to another is impaired. One typically developing child showed features of CAS. This child was a sibling of a child with DCD who also displayed speech and oromotor impairments. Speech proficiency is a highly heritable characteristic and impairment can aggregate in families (Deriziotis & Fisher 2013; Hayiou-thomas 2008; Tosto et al. 2017). Genetic factors may account for the co-occurrence of speech pathology in this family.

Relationship between motor impairments and additional deficits

The factor analysis suggests a five dimension structure of impairment in children with DCD:

Two factors which are associated with general cognition:

i) 'Attention and executive functions' containing processing speed, set switching and sustained attention
ii) 'Balance and language skills'

Three motor factors that are not related to general cognition:

i) Aiming and catching
ii) Manual dexterity
iii) Speech and oromotor functions

A cluster analysis of 90 children with DCD based on measures of motor and perceptual skills suggested 5 overlapping subtypes of DCD (Green et al. 2008). The overlap between subtypes suggests independent factors of impairment exist in DCD but do not form completely distinct subtypes. Recent work in developmental disorders also supports a dimensional conceptualisation of impairment rather than binary or subtype models (Bathelt et al. 2017; Ousley & Cermak 2014; Ramus et al. 2013). We found little evidence

that more severe motor impairments were associated with more severe co-occurring deficits.

Future directions

Children with DCD display neuropsychological impairments that are independent of motor skill impairment however in this study we did not utilise diagnostic thresholds to identify co-occurring disorders. Further research utilising more complete diagnostic tests for ADHD and ASD symptomatology in children with DCD would give a better indication of the nature of co-occurrence. Additionally while we have extensively characterised speech and language and attention deficits we have not characterised additional impairments such as reading, social communication and working memory. Further research utilising standardised assessments of these neuropsychological domains is needed to complement this work.

We have identified a possible subgroup of DCD characterised by low balance, poor language and IQ impairments. Further work utilising targeted recruitment would test this hypothesis.

The M-ABC2 serves as a screening test for motor impairments. Assessing children with DCD on more complete battery of motor tests as well as neuropsychological tests would indicate whether additional impairments are related to other aspects of motor functioning or are truly independent from severity or nature of motor impairments in children with DCD.

5.5 Conclusions

This study provides novel extensive characterisation of motor, language, speech, oral motor and attention impairments in children with DCD. Within a group of children with DCD who have no evidence of visible damage on MRI or very preterm birth, the results suggest five factors of impairment that are independent but interrelated, namely (i)-manual dexterity; (ii) aiming & catching (iii) balance & cognition (iv) executive functions, and (v) speech motor functions.

Chapter Six: T1-weighted structural imaging correlates of DCD and associated impairments

6.1 Introduction

Background

As discussed in chapter two, neuroimaging research in children with DCD is still in its infancy. Four studies have utilised structural neuroimaging methods to describe brain changes in children with DCD relative to controls, three discussing structural alterations and one examining structural connectivity. These studies are discussed in depth in chapter three but summarised again in Figure 6.1. One VBM study reported grey matter concentration in the posterior cingulate/precuneus positively correlated with M-ABC percentile (Reynolds et al. 2017). Volume across pretmotor/motor cortex and superior cerebellar lobules significantly predicated aiming and catching score across 226 children including typically developing children and those with ADHD and DCD (Shaw et al. 2016). Reduced cortical thickness in the temporal pole (Langevin et al. 2015) and increased clustering coefficient in the medial orbitofrontal cortex (Caeyenberghs et al. 2016) have also been reported in children with DCD. More anatomical specificity is required in the structural imaging literature. Additionally results in the medial orbitofrontal cortex and temporal pole may have been driven by differences in data quality between children with DCD and controls.

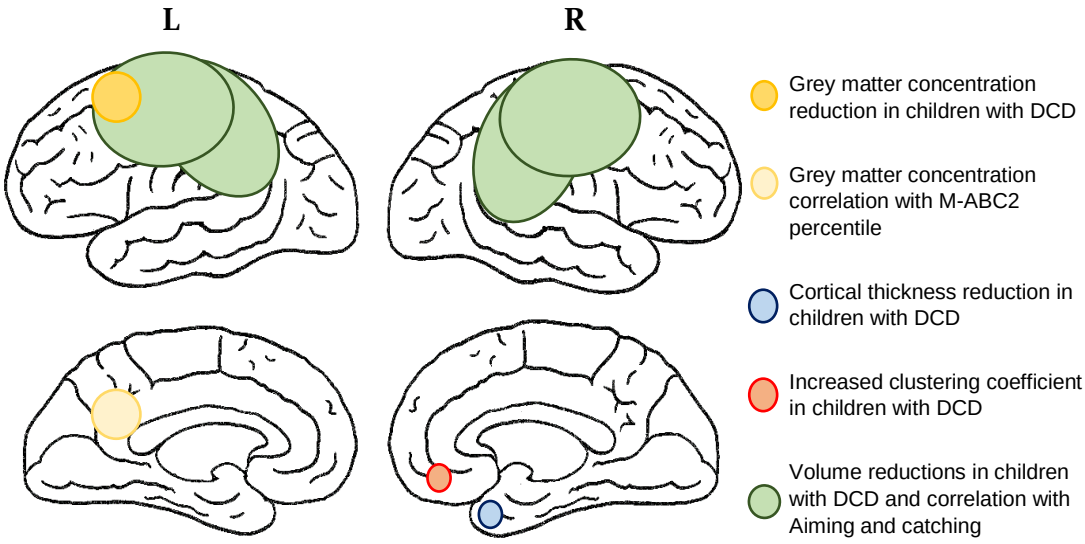

Figure 6.1 summary of cortical structural neuroimaging alterations reported in children with DCD, as seen in chapter three.

Cortical Morphology

As discussed in chapter one, regions of sensorimotor and parietal cortex are implicated in motor learning, motor control and sensorimotor representations which may underlie DCD. Cortical thickness and surface area are metrics of cortical structure which are genetically independent but which both influence grey matter volume measures (Panizzon et al. 2009; Winkler et al. 2010) (Figure 6.2). Altered cortical morphology have been identified in various developmental disorders. Decreased cortical thickness and surface area in regions of the frontal lobe have been reported in children with ADHD (Kasparek et al. 2015; Ambrosino et al. 2017). Point-wise analyses of cortical thickness and surface area across the whole brain in children with Dyslexia have identified both increases and decreases relative to controls (Ramus et al. 2017). One region of interest study has reported increased cortical thickness in a left supramarginal gyrus in treatment naïve children with CAS (Kadis et al. 2014). Cortical thickness and surface area have also been related to general cognitive abilities in adults and children (Schnack et al. 2015). Cortical thickness and surface area can be quantified across the brain using computerised tools such as Freesurfer. These measures can be extracted from hypothesised regions of interest or using point-wise comparisons across the whole brain.

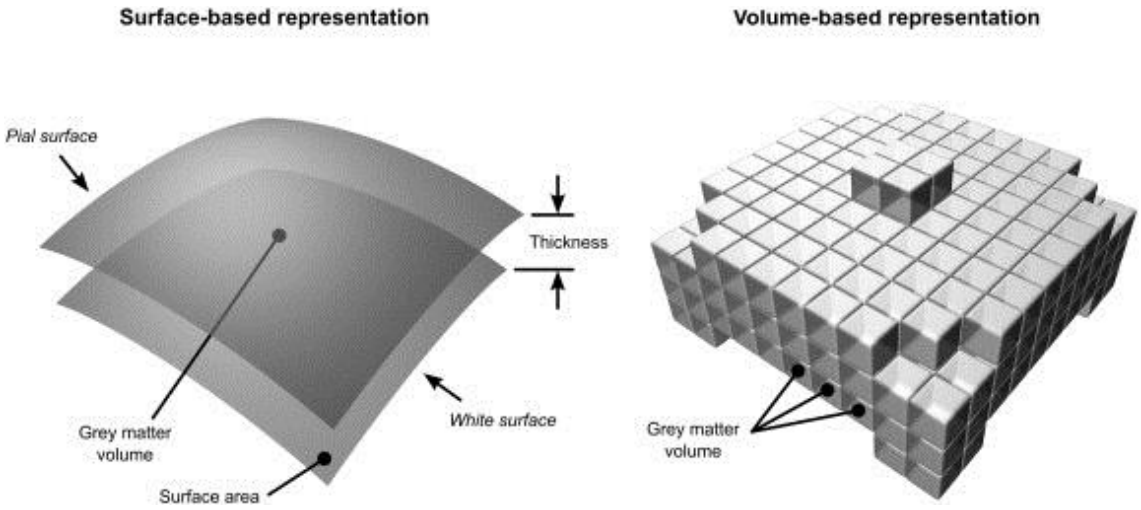

Figure 6.2 Surface based representations vs volume based representations of cortical structure (figure from Winkler et al 2010)

Subcortical Volumes

As discussed in chapter one, the procedural learning deficit hypothesis suggests children with DCD will primarily show alterations in basal ganglia circuits. The internal modelling deficit hypothesis implicates the cerebellum. These structures form subcortical networks involved in motor learning and control (Patel et al. 2014)(Figure 6.3). The cerebellum, thalamus and basal ganglia nuclei can be measured on T1-weighted MRI scans using

automated methods. Reduced volumes of the caudate, putamen and cerebellum have been reported in individuals with ADHD (Hoogman et al. 2017; Kasparek et al. 2015). Additionally, Nicolson and Fawcett (Nicolson & Fawcett 2007) hypothesise that disruption of cortico-cerebellar circuits underlies attention difficulties in developmental disorders such as ADHD.

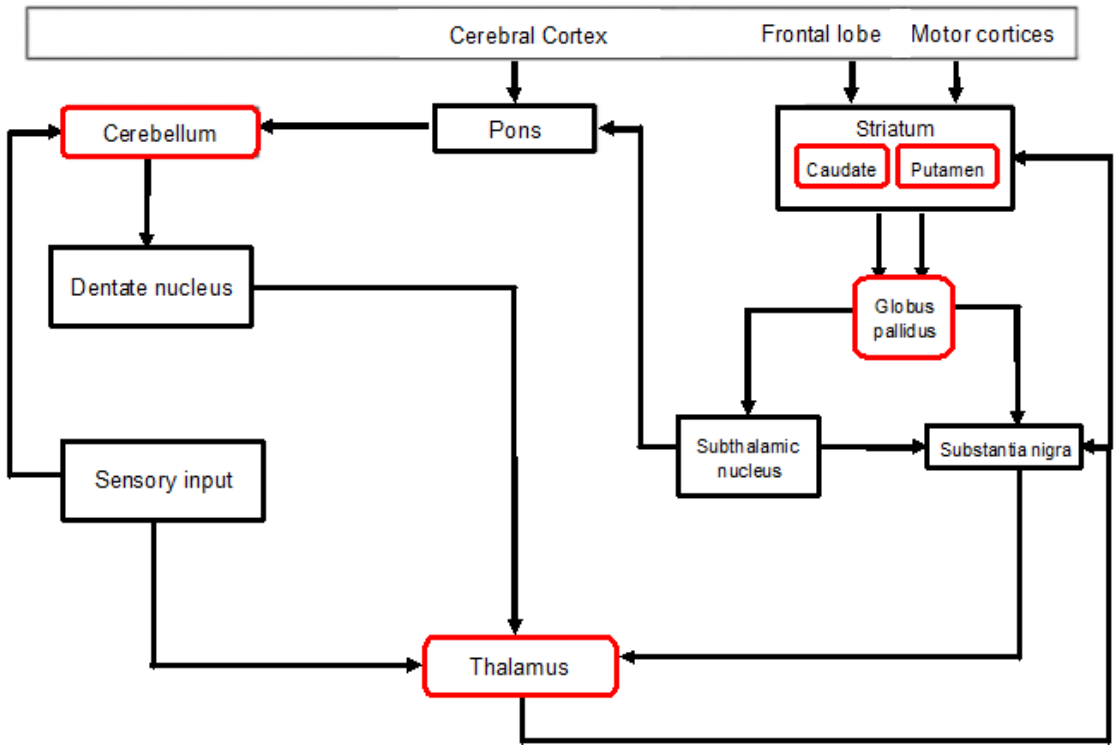

Figure 6.3 Cortical-basal and cortical-cerebellar networks involved in motor control (Figure adapted from Patel et al 2014). Structures in red can be measured automatically or semi-automatically from T1-weighted images.

Study Aims

The first aim of this study was to investigate group differences between children with DCD and age matched control children in:

i. cortical thickness and surface area across the brain
ii. basal ganglia and cerebellar volumes

The second aim of this study was to report brain-behaviour relationships between these metrics and motor, attention and speech motor control abilities. Children with DCD are behaviourally heterogeneous as illustrated in both the published literature and this thesis. It is likely that the multivariate nature of behavioural impairments is mirrored in brain structure.

Briefly, children with DCD showed impairments across three uncorrelated domains of motor skill (manual dexterity, Aiming & catching and balance), speech sequencing and oromotor control and executive functions (processing speed, auditory attention (Score!) and set-switching (creature counting)).

Cortical Hypotheses

i) Children with DCD will show bilateral alterations in cortical thickness and surface area in sensorimotor cortex and the parietal lobe when compared to controls
ii) Cortical thickness and surface area in bilateral regions of sensorimotor cortex and the parietal lobes will correlate motor skills
iii) Cortical morphology in right frontal and parietal regions will correlate with the measure of sustained attention, cortical morphology in the frontal lobe will correlate with the measure of attentional control
iv) Cortical thickness in left premotor, motor and parietal regions will correlate with speech motor control variables
v) Children with features/diagnosis of CAS will show increased cortical thickness in the left superior parietal lobe/supramarginal gyrus
vi) Poorer processing speed will be associated with lower average cortical thickness and total surface area across the brain in children with DCD

Basal Ganglia Hypotheses

i) Children with DCD will show reductions in putamen, globus pallidus and thalamus volume relative to controls
ii) Putamen, globus pallidus and thalamus volume will positively correlate with balance, aiming/catching and manual dexterity in children with DCD and across the whole group
iii) Caudate and putamen volume will positively correlate with attention measures in children with DCD
iv) Focal oromotor control and sequencing z-score will positively correlate with bilateral caudate, globus pallidus and thalamus volume
v) Children with features of CAS will display reduced volume in the caudate, globus pallidus and thalamus relative to their unaffected clinical peers.

Cerebellar Hypotheses

i) Children with DCD will show reduced cerebellar volume relative to controls

ii) Manual Dexterity, Aiming/catching, Balance and full scale IQ will positively correlate with cerebellar volumes in children with DCD and across the whole group
iii) Score! and creature counting will positively correlate with cerebellar volume

6.2 Methods

As previously discussed T1 weighted structural MRI were collected and analysed for each child.

Whole brain volumes

Images for each participant were segmented into grey matter, white matter and csf using the spm12 unified segmentation algorithm (Figure 6.4). Due to maturational changes in grey matter and white matter concentration, age appropriate tissue probability maps were generated using template-o-matic 8 toolbox (Wilke et al. 2008) in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Volumes of grey matter, white matter and CSF were estimated in mm^3 using these segmentations. These values were summed to estimate total intracranial volume (TIV). TIV and grey matter volume were entered as co-variates in subsequent analyses to control for gross anatomical differences.

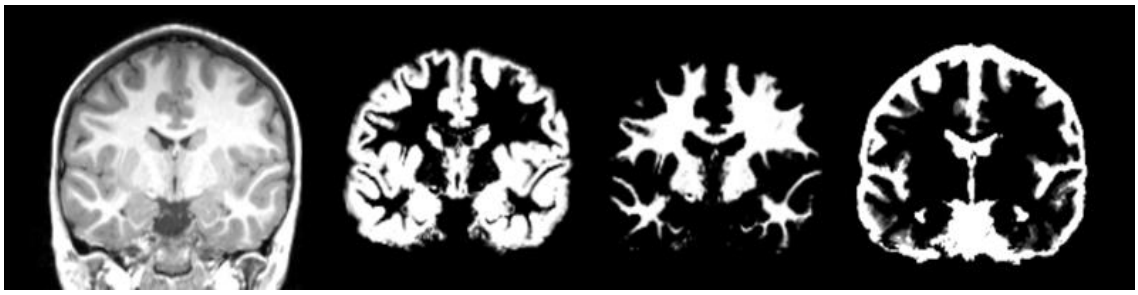

Figure 6.4 Example of a T1-weighted scan segmented into grey matter, white matter and CSF respectively using SPM12

Cortical thickness and surface area

FreeSurfer is a software package utilised for surface based analysis of cortical morphology including cortical thickness and surface area using MRI scans (Dale et al. 1999; Fischl & Dale 2000; Fischl et al. 1999). The grey-white matter boundary and the pial surface of the brain were transformed into triangular meshes made up of points, known as 'vertices'. These vertices were matched point-by-point on each surface. At each vertex the cortex was 'inflated' from the grey-white matter boundary to the pial surface to reconstruct cortical grey matter (Figure 6.5a).

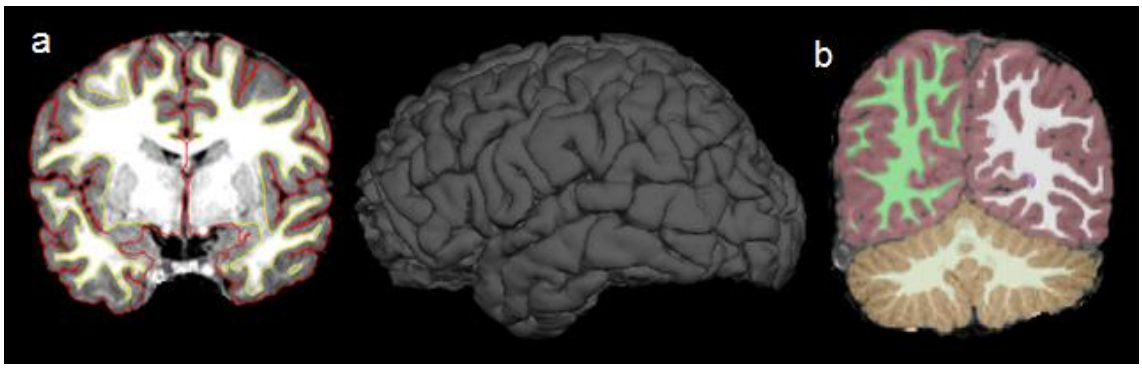

Figure 6.5 a. Example of FreeSurfer grey/white matter boundary and reconstructed cortical surface b. example of cerebellar volume segmentation

Cortical thickness and surface area were extracted from these reconstructions. FreeSurfer software v5.3 was used to generate reconstructions of the cortex. Freesurfer normalised intensity and RF-bias field inhomogeneities across images and then stripped them of non-brain structures (skull, neck tissue, eyes)(Segonne et al. 2004). Mesh representations of the grey-white matter boundary and pial surface were generated for each hemisphere separately with approximately 150,000 vertices each. Cortical thickness was calculated as the mean minimum distance between each vertex on the surfaces. Surface area was the relative expansion or compression of the space between vertices on the pial surface. The FreeSurfer pipeline takes approximately 20 hours per subject and was run using the Legion High Performance Computing Facility (Legion@UCL). All reconstructions were checked for inaccuracies in estimation of the grey-white matter boundary and incorrect inclusion of non-brain structures on the pial surface (often skull/dura at the ocular orbits or interhemispheric fissure). Minor inaccuracies were manually corrected. One child with DCD was excluded due to numerous large inaccuracies in the reconstructed pial and white matter surfaces which could not be corrected manually; these were likely caused by movement artefacts in the scan.

Total surface area and mean cortical thickness were extracted for each hemisphere and combined to give total brain surface area and mean whole brain cortical thickness. For whole brain vertex wise analysis the FreeSurfer estimations of vertex-wise surface area and cortical thickness underwent the following preprocessing and normalisation procedure:

1) Smoothing using a 20mm full width at half maximum (FWHM) Gaussian smoothing kernel to detect differences in cortical thickness of up to 0.25 mm across cortex (Pardoe et al. 2013).

2) Vertex-wise normalisation using a within-subject z-score transformation to adjust for inter-individual differences in mean and standard deviation of thickness and surface area

3) Registering each subject surface to an average subject template that forms part of the FreeSurfer software package

4) Vertex-wise normalisation using between-subject z-score transformation where each feature per vertex was normalised by the mean and standard deviation of the healthy control group. This adjusts for inter-regional differences in the mean and standard deviation.

This procedure was based on that used by Adler and colleagues (Adler et al. 2017), whose code is available at the following website (https://github.com/kwagstyl/FCDdetection).

Cerebellar Volume

FreeSurfer also estimates the volume of subcortical structures including the cerebellum (Figure 6.5b). Mean grey and white matter volume of the left and right hemispheres of the cerebellum were extracted for each subject. These values were also combined to give a measure of total cerebellar volume and expressed as a percentage of total brain volume ((volume/total intracranial volume from SPM12)*100).

Basal Ganglia Volumes

Volume of bilateral caudate, putamen, globus pallidus and thalamus were calculated using the FSL FIRST pipeline (Patenaude et al. 2011). This subcortical segmentation pipeline provides robust automated segmentation of subcortical structures (Figure 6.6). These segmentations were compared to the output of FreeSurfer parcellations of the basal ganglia and upon visual inspection the FSL FIRST segmentations were deemed more accurate and used for further analysis.

FSL FIRST gives the number of voxels and the volume in mm^3 for each structure. Due to the proximity of the caudate to the lateral ventricle the volume can be underestimated. Each caudate segmentation was manually edited in FSLVIEW based on a previously described tracing paradigm (Looi et al. 2008). Volumes were expressed as a percentage of total grey matter volume ((volume/grey matter volume from SPM12)*100) to correct for differences in total brain size.

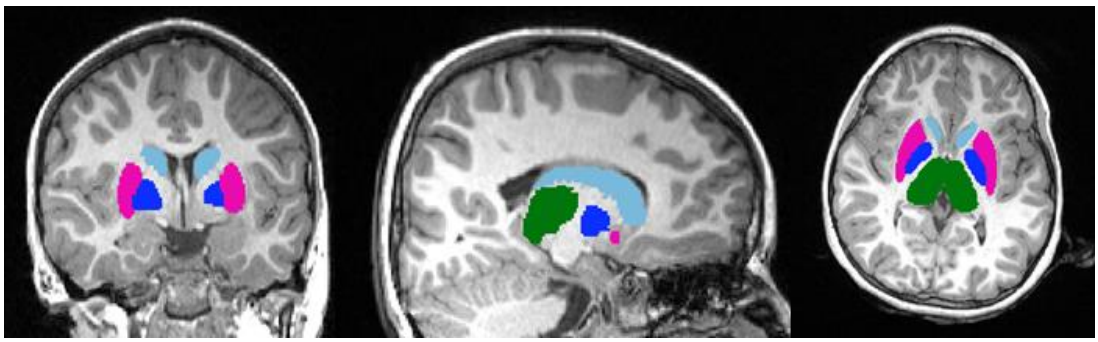

Figure 6.6 Example of FSL FIRST subcortical segmentations

Statistics

Whole-brain vertex-wise cortical features

Vertex wise cortical thickness and surface area analysis was performed in SurfStat for Matlab (http://www.math.mcgill.ca/keith/surfstat/)(Worsley et al. 2009). This software utilises general linear models to perform statistical comparisons across the cortex. Handedness, total intracranial volume and FSIQ were entered as covariates for each model.

The statistical threshold for defining clusters was set at 0.01 as previously used by Liu and colleagues (Liu et al. 2016). Results were corrected for type-1 error using random field theory for non-isotropic images (Worsley et al. 1999; Hayasaka et al. 2004). The following models of cortical thickness and surface area were examined:

i) Increases and decreases in children with DCD relative to controls
ii) Correlation between cortical features and motor scores (Manual Dexterity, Aiming and Catching, Balance) both within the DCD group and across the whole sample
iii) Correlations between cortical features and focal oromotor control z-score, speech sequencing z-score, sustained attention scaled score (Score!) and set-switching scaled score (Creature Counting) within the DCD group.

The family-wise error (FWE) rate was set at below 0.002 to control for number of models run. Speech/oromotor feature models were not run across the whole sample because control children reach ceiling performance on these measures leaving poor statistical power. Models of attention features were not run across the whole group because the co-occurring motor impairment could result in correlations between attention and cortical features driven by the difference in motor abilities. Data from each significant cluster was examined and any results driven by outliers were ignored.

Whole brain features, basal ganglia and cerebellar volumes

Group differences in basal ganglia and cerebellar volumes were estimated with mixed model ANOVAs co-varying for FSIQ and handedness. Correlations were run between brain features and behavioural measures. Multiple linear regressions were used to determine whether relationships between behavioural measures and imaging features remained when handedness and FSIQ are included in the model.

6.3 Results

Differences between children with DCD and typically developing children

Whole brain and cerebellar analyses

Multivariate analysis of covariance (MANCOVA) revealed no significant differences between groups on total white matter volume (F=0.001 p=0.976 partial eta squared=0.00002), mean cortical thickness (F=0.049 p=0.826 partial eta squared=0.001) and surface area (F=0.545 p=0.464 partial eta squared=0.012). There were no differences in cerebellar volume between groups (F(1,48)=1.092 p=0.301).

Vertex-wise cortical thickness and surface area

Children with DCD show reduced cortical thickness in the left central sulcus compared to controls (T=3.286 pFWE<0.0001)(Figure 6.7).

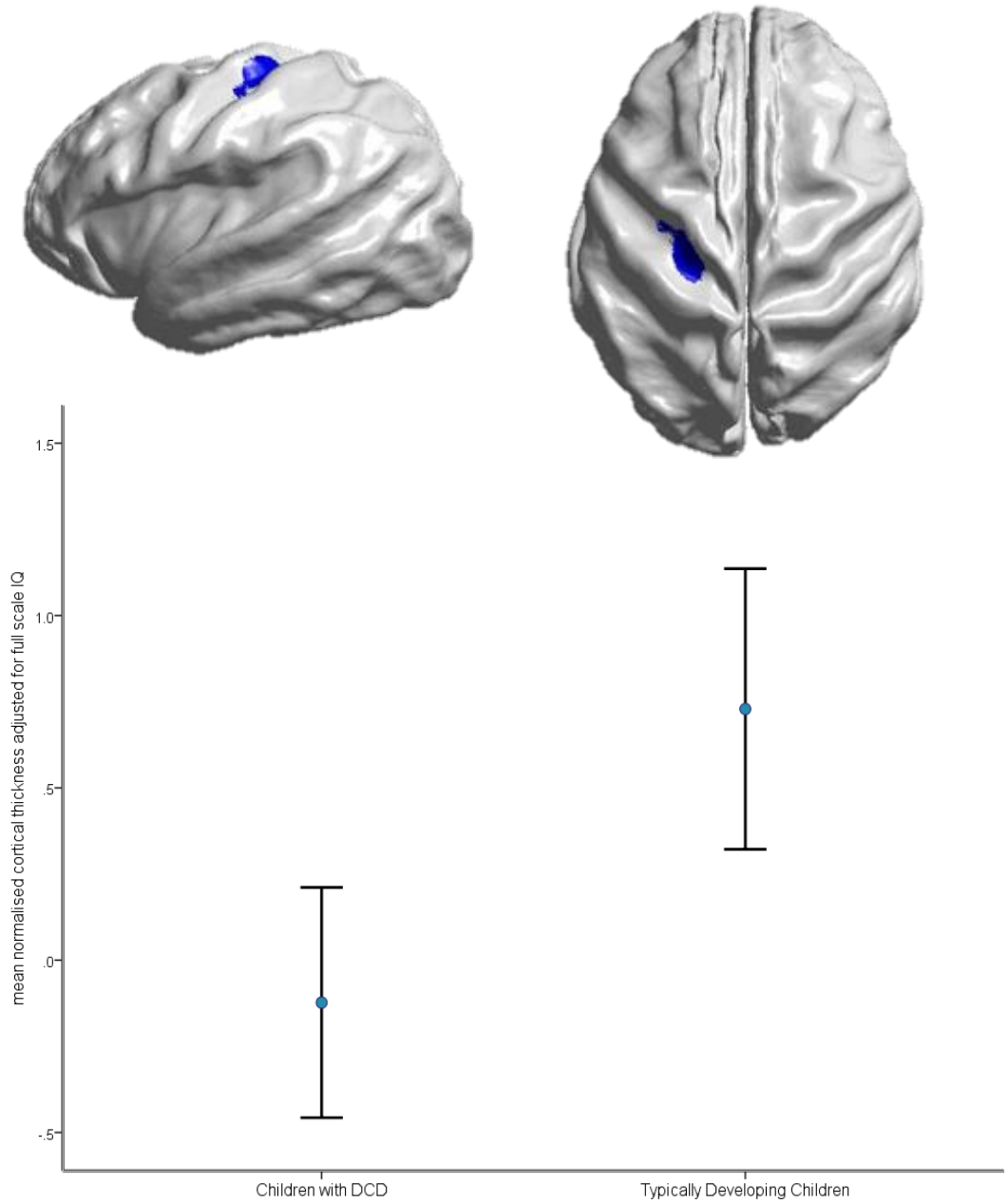

Figure 6.7 Cortical thickness reduction in children with DCD relative to controls (mean and 95% confidence intervals)

Basal Ganglia Volumes

There were no group differences in basal ganglia volumes. There was a significant interaction of hemisphere and group in putamen volume $F(1,49)=4.529$, $p=0.038$ (Figure 6.8a).

Posthoc comparisons of left and right putamen volumes did not differ between groups (Table 6.1). In order to further investigate the interaction of hemisphere and putamen a laterality index (lh-rh/lh+rh) was calculated. This indicated that children with DCD have

more left lateralised putamen volumes when compared to typically developing controls (t(51)=2.251 p=0.029; 95%CI 0.0013-0.023; Cohen's d= 0.63) (Figure 8b).

Table 6.1 Putamen volume differences between children with DCD and controls

	Without covariates	With covariates
Left Putamen	U=296 p=0.858	U=279 p=0.617
Right Putamen	U=267 p=0.467	U=286 p=0.713

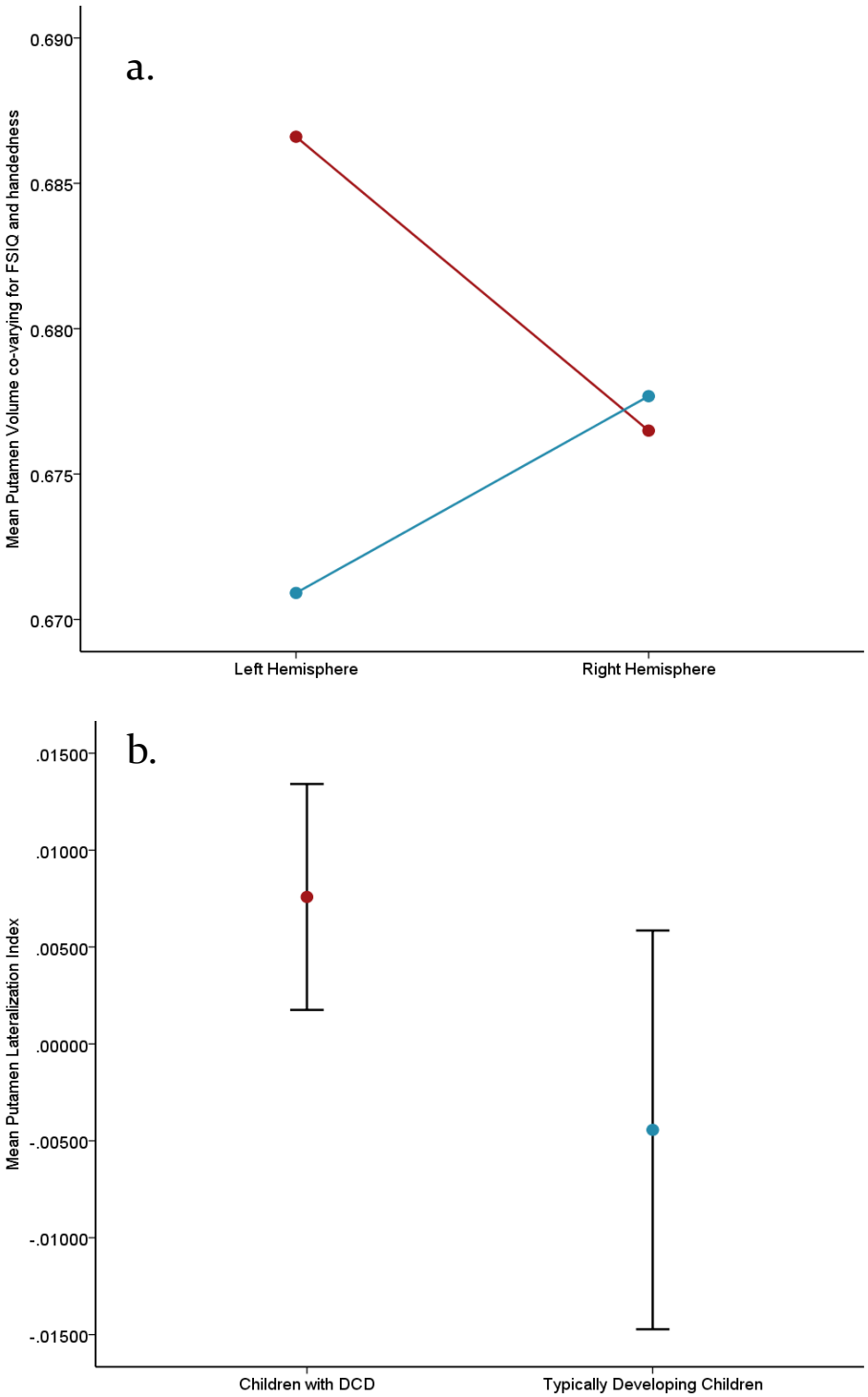

Figure 6.8 a. significant interaction between group and hemisphere in the putamen b. Putamen volume lateralisation index (Blue= typically developing children; Red=children with DCD)

MRI correlates of motor scores

Cerebellar and basal ganglia volumes

Cerebellar and basal ganglia volumes did not correlate with balance, aiming/catching or Manual Dexterity (Table 6.2). Co-varying for full scale IQ and handedness did not alter the results.

Table 6.2 Correlations between motor skills and subcortical brain volumes

	Manual Dexterity		**Aiming and Catching**		**Balance**	
	Whole group	*DCD group*	*Whole group*	*DCD group*	*Whole group*	*DCD group*
left putamen	Rho=0.054 p=0.702	Rho=0.040 p=0.817	r=-0.055 p=0.698	r=0.026 p=0.880	Rho=-0.105 p=0.459	Rho=-0.201 p=0.246
right putamen	Rho=0.170 p=0.225	Rho=0.195 p=0.254	Rho=-0.002 p=0.988	Rho=-0.073 p=0.672	Rho=0.007 p=0.960	Rho=-0.104 p=0.554
left globus pallidus	Rho=0.080 p=0.568	Rho=0.180 p=0.295	r=-0.058 p=0.685	r=0.045 p=0.753	Rho=0.002 p=0.960	Rho=0.036 p=0.836
right globus pallidus	Rho=0.129 p=0.359	Rho=0.147 p=0.392	r=0.138 p=0.328	r=0.244 p=0.152	Rho=0.083 p=0.557	Rho=0.170 p=0.330
left thalamus	Rho=0.001 p=0.996	Rho=0.020 p=0.909	r=0.064 p=0.654	r=0.171 p=0.319	Rho=0.032 p=0.823	Rho=-0.037 p=0.834
right thalamus	Rho=0.012 p=0.934	Rho=0.095 p=0.582	r=0.014 p=0.924	r=0.126 p=0.464	Rho=0.021 p=0.885	Rho=0.003 p=0.987
cerebellum	Rho=-0.085 p=0.551	Rho=0.073 p=0.678	r=-0.099 p=0.491	r=0.041 p=0.816	Rho=0.037 p=0.795	Rho=0.112 p=0.528

Vertex-wise associations between Cortical Morphology and Manual Dexterity

Associations between cortical morphology and motor skills are summarised in Table 6.3.

Poorer manual dexterity was associated with reduced cortical thickness in the left central sulcus across the whole sample (Figure 6.9a). This cluster overlaps with the area of reduced cortical thickness identified in the previous section (Figure 6.7). Poorer manual dexterity was also associated with increased surface area in a cluster that extends across left primary motor cortex, central sulcus and primary sensory cortex (Figure 6.9b). Plots reveal the relationships are stronger in the group with DCD.

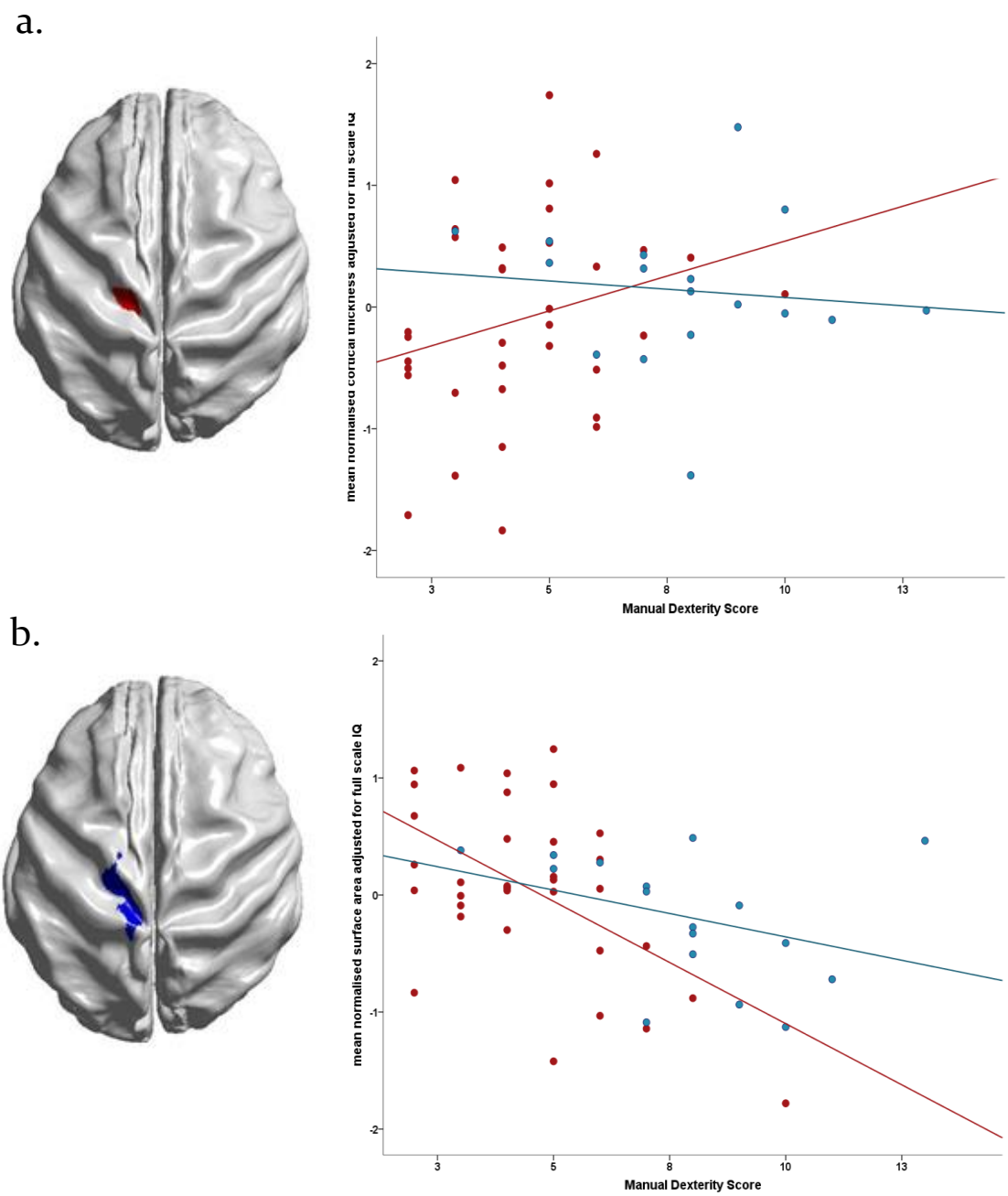

Figure 6.9 a. cortical thickness and b. surface area associations with manual dexterity across the whole sample (Blue dots= typically developing children; Red dots=children with DCD)

Vertex-wise associations between Cortical Morphology and Aiming/Catching

Poorer aiming and catching skills were associated with increased cortical thickness in left posterior cingulate cortex (figure 10a) across the whole group. Smaller surface area across left primary motor cortex was associated with better aiming/catching skills in children with DCD (figure 10b).

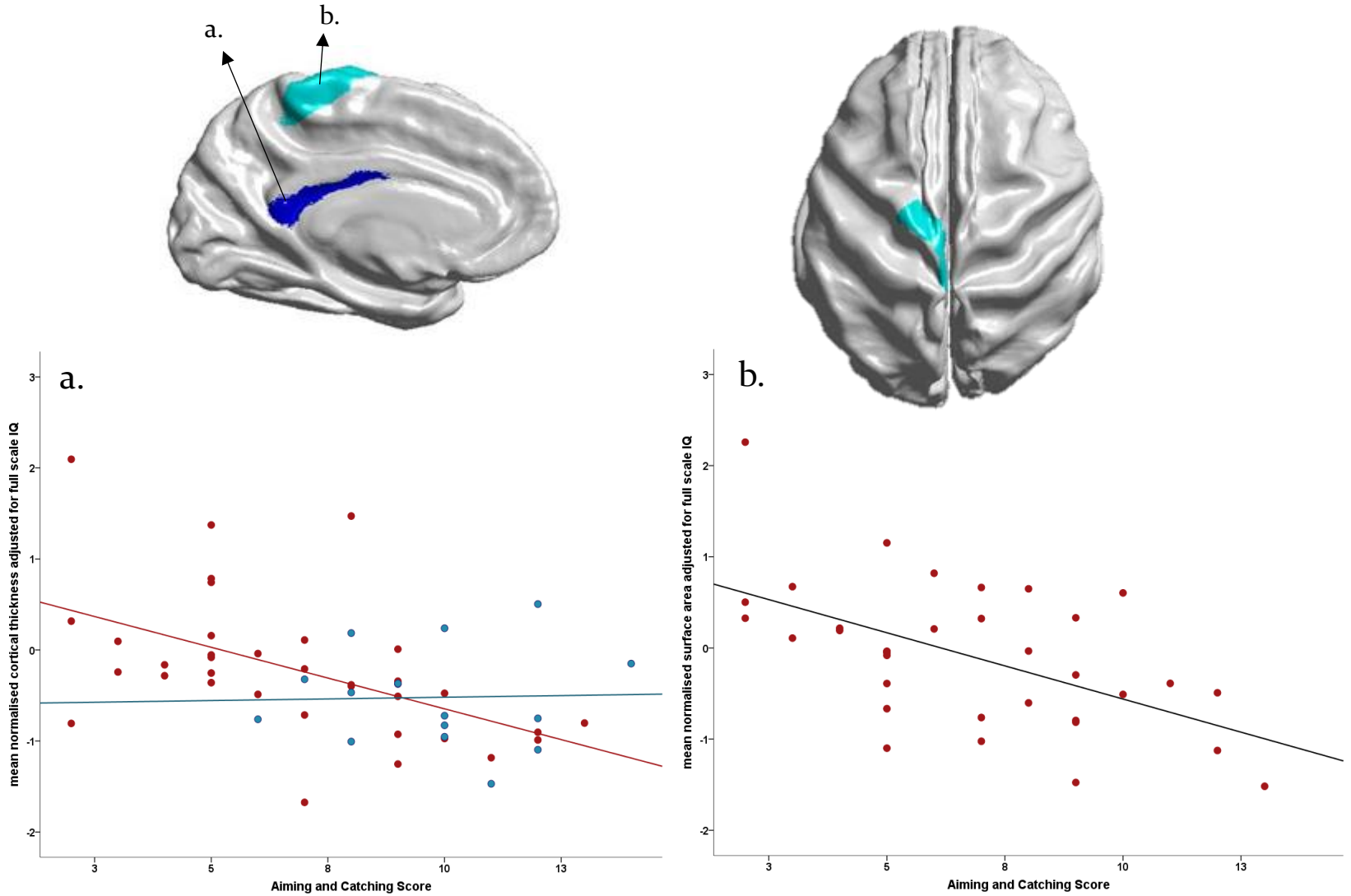

Figure 6.10 a. cortical thickness and b. surface area associations with aiming and catching score (Blue dots= controls; Red dots=children with DCD)

Vertex-wise associations between Cortical Morphology and Balance

There were no significant relationships between balance score and cortical morphology across the whole group. Within children with DCD better balance skills were associated with higher cortical thickness in the left anterior insula (figure 6.11).

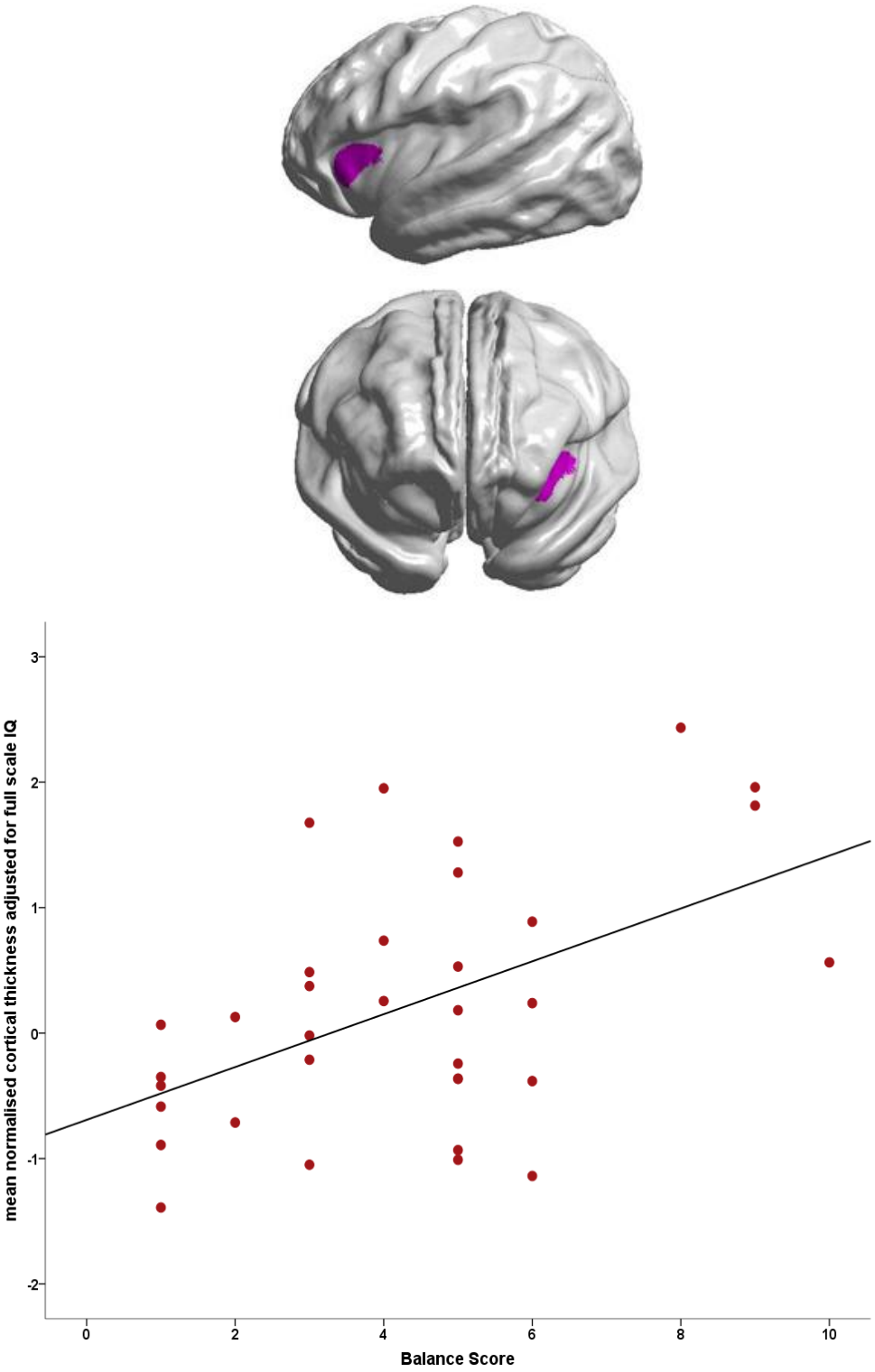

Figure 6.11 Association between cortical thickness and balance scores in children with DCD

Table 6.3 Summary of vertex-wise relationships between cortical morphology and motor skills

	Sample	Motor Skill	Direction of relationship	region	Statistic
Cortical Thickness	DCD and controls	Manual Dexterity	Positive	Left Central sulcus	T=2.88 p<0.00033
		Aiming & catching	Negative	Left Posterior cingulate	T=2.80 p<0.0001
	DCD only	Balance	Positive	Left anterior insula	T=2.90 p<0.002
Surface Area	DCD and controls	Manual Dexterity	Negative	Left primary motor, and primary sensory cortex	T=2.83 P<0.0012
	DCD only	Aiming & catching	Negative	Left primary superior motor cortex/paracentral gyrus	T=3.02 P<0.00037

MRI correlates of additional impairments in children with DCD

Intelligence

FSIQ did not correlate with whole brain thickness, surface area, cerebellar or white matter volume in children with DCD (Table 6.4).

Table 6.4 Correlations between brain measures and FSIQ

	FSIQ
Mean cortical thickness	r=0.128 p=0.463
Total surface area	r=0.325 p=0.056
White matter volume	r=0.203 p=0.235
Cerebellum volume	r=0.096 p=0.582

Attention

There were no significant associations between score! (sustained attention) or creature counting (attentional control) and cortical morphology in children with DCD. There were also no significant relationships between attention standard scores and subcortical volumes in children with DCD that survive correction for multiple comparisons (Table 6.5).

Table 6.5 Correlations between subcortical volumes and attention scores

	Sustained attention (Score!)	**Attentional control (creature counting)**
Left putamen	Rho=0.237 p=0.163	Rho=-0.012 p=0.942
Right putamen	Rho=0.282 p=0.095	Rho=0.104 p=0.547
Left caudate	Rho=0.067 p=0.698	Rho=-0.154 p=0.371
Right caudate	Rho=0.275 p=0.104	Rho=0.072 p=0.676
Cerebellum	Rho=-0.029 p=0.870	Rho=0.066 p=0.707

Processing Speed

Processing speed was negatively correlated with cortical surface area in children with DCD (Table 6.6; Figure 6.12). Processing speed was measured as a z-score of time taken so higher scores indicated poorer performance.

Table 6.6 Correlations between brain measures and full scale IQ

	Processing speed
Mean cortical thickness	Rho=0.033 p=0.855
Total surface area	**Rho=-0.392 p=0.022**

Results in bold survive correction for multiple comparisons (p<0.025)

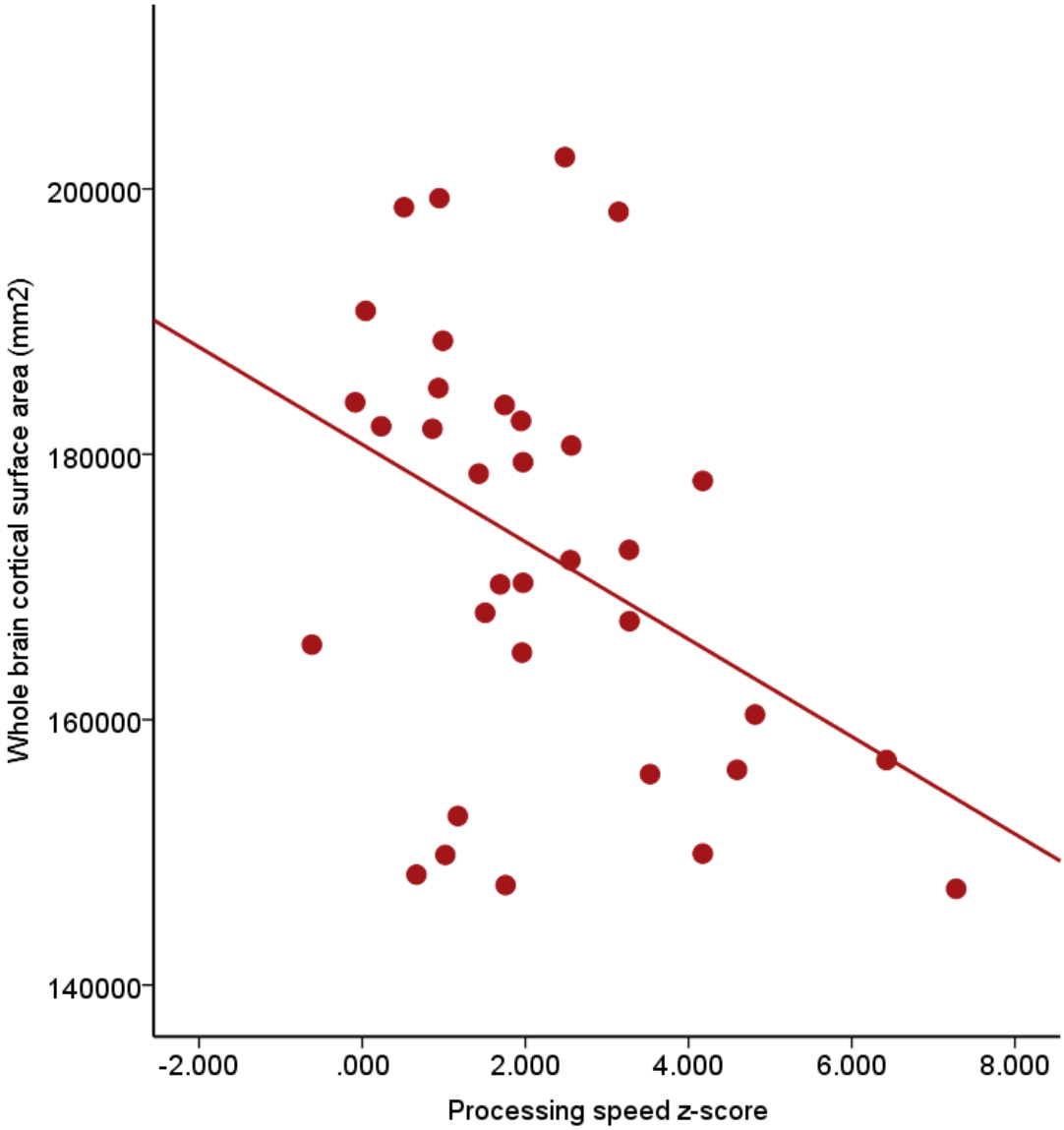

Figure 6.12 Correlation between processing speed Z score and total white matter surface area in children with DCD

Speech and ormotor control

There were no significant vertex-wise relationships between cortical morphology and VMPAC z-scores. There were also no significant differences in cortical morphology between children with DCD and features of CAS and those without.

Results of relationships between speech pathology and subcortical volumes are summarised in Table 6.7. Focal oromotor control score was positively correlated with bilateral thalamus volume in children with DCD (Figure 6.13). One child was an extreme outlier with severe focal oromotor and speech sequencing impairments as well as moderate CAS, the correlations remained significant with this child removed (Left

Rho=0.574 p=0.001; Right Rho=0.541 p=0.002). Focal oromotor control did not correlate with caudate or globus pallidus volume. Sequencing correlated with thalamus and globus pallidus volumes however these did not survive correction for multiple comparisons. Children with DCD and features/diagnosis of CAS did not show any reductions on subcortical volumes compared to children with DCD and no features of CAS. The results did not change if the effect of full scale IQ and handedness were taken into account. Thalamus volumes were summed and entered into a logistic regression which revealed bilateral volume is a significant predictor of presence of focal oromotor control impairment in children with DCD (Table 6.8; sensitivity=50% specificity 73.7%).

Table 6.7 Relationships between speech and oromotor control impairments and subcortical volume

	Focal Oromotor Control	**Sequencing**	**Features/diagnosis of CAS**
left caudate	Rho=0.093 p=0.625	Rho=0.092 p=0.624	U=92 p=0.757
right caudate	Rho=0.145 p=0.445	Rho=0.324 p=0.075	U=90 p=0.696
left globus pallidus	Rho=0.341 p=0.065	Rho=0.425 p=0.017	U=78 p=0.374
right globus pallidus	Rho=0.378 p=0.040	Rho=0.421 p=0.021	U=90 p=0.696
left thalamus	**Rho=0.593 p=0.001**	Rho=0.372 p=0.039	U=79 p=0.397
right thalamus	**Rho=0.534 p=0.002**	Rho=0.379 p=0.035	U=86 p=0.578

Results in bold survive correction for multiple comparisons (p<0.007)

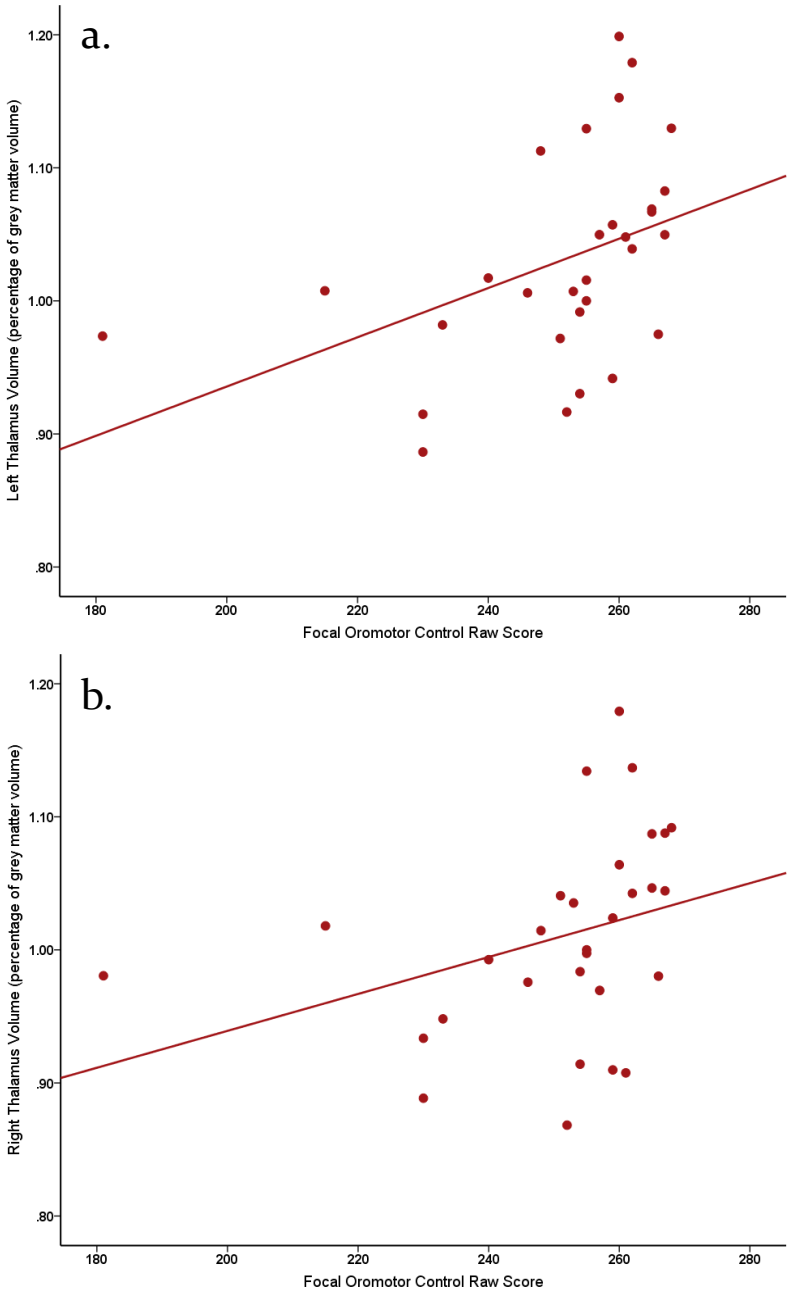

Figure 6.13 Correlation between a. left and b. right thalamus volume and focal oromotor control raw score in children with DCD

Table 6.8 Predictors of focal oromotor control impairment in children with DCD

	B (SE)	Exp(B)	Significance	Chi-Square
Final Model				
Bilateral Thalamus Volume	-7.751 (3.447)	0	0.026	6.637 p=0.009

6.4 Discussion

This study revealed reduced cortical thickness in the central sulcus in children with DCD when compared to typically developing children. There were also associations between motor scores and cortical morphology in left premotor, primary motor and primary sensory cortices, posterior cingulate and anterior insula (Figure 6.14). There was little evidence of basal ganglia or cerebellar structural correlates in children with DCD.

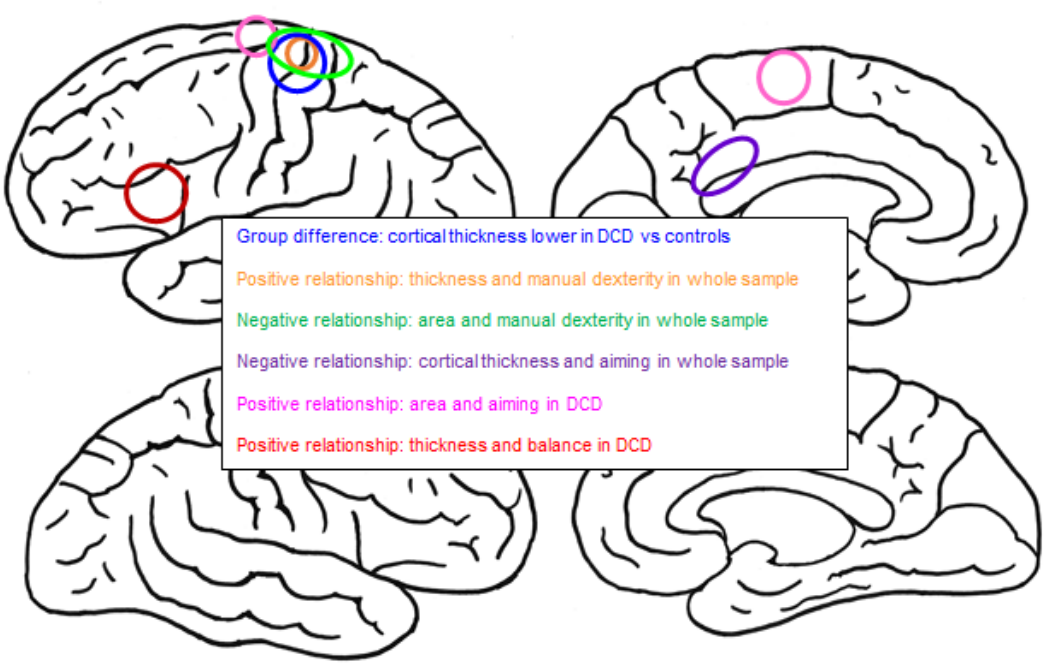

Figure 6.14 Summary of cortical differences and relationships between cortical morphology and motor skills

Evidence of cortical correlates in sensorimotor regions

As hypothesised, DCD was associated with anomalies in cortical sensorimotor regions of the brain.

The Central Sulcus

Children with DCD show reduced cortical thickness in the left central sulcus relative to controls. Lower cortical thickness and increased surface area in this region was associated with poor manual dexterity skills across the whole sample. The central sulcus divides primary motor and primary sensory cortex. Cytoarchitectonic and stimulation studies of the sulcus reveals a combination of Brodmann area 4 (primary motor) and area 3 (primary sensory cortex)(White et al. 1997). Studies have suggested the central sulcus also contains much of the somatotopic hand area of primary motor cortex (Sastre-Janer et al. 1998; Boling et al. 1999). The cortical thickness reductions and correlations with manual dexterity identified here might reflect variance in this hand region.

Alterations in the central sulcus may also be consistent with impaired internal modelling of motor commands in children with DCD. Efferent copies of motor command create feed-forward predictions of the outcome of motor commands, these predictions are compared to sensory input to generate error signals which are used to alter motor execution. It is currently unclear where in the brain this comparison takes place. The cortex is a layered structure and computational research suggests this error detection occurs in layers 1-3, known as supragranular layers (Bastos et al. 2012; Bastos et al. 2015). Wagstyl and colleagues (Wagstyl et al. 2016) recently developed a set of morphological measures designed to detect selective thinning in these supragranular layers of cortex on t1-weighted MRI scans: disproportionate thinning in the sulci relative to gyri, changes in intrinsic curvature, more cortical thinning in regions with large supragranular layers and steeper gradients of thickness across sensory hierarchies. These measures have been validated with post mortem imaging. Thinning in the central sulcus may indicate supragranular thinning in primary sensory and motor cortex leading to poor feedforward modelling and impaired error detecton. Examination of Wagstyl and colleagues' additional features would test this hypothesis however postmortem data is not available from individuals with DCD so it is not possible to determine histologically if supragranular thinning in the primary somatosensory cortices occurs in children with DCD.

Few studies have implicated the central sulcus in developmental disorders. One study examined bilateral morphology of the central sulcus in children with ADHD (Li et al. 2015). Contrary to our results the authors report increased cortical thickness in ADHD relative to control children. This study did not exclude children with motor/coordination impairments or specifically measure motor skill; as such the authors may have included children with co-occurring DCD. The authors suggest this morphometry is related to poor motor inhibition which manifests as hyperactivity. Another study reported widespread reductions in cortical thickness in adolescents born prematurely including regions around the central sulcus (Nagy et al. 2011).

Surface area in primary motor and primary sensory cortex

Reduced surface area in primary motor and medial primary sensory was associated with better aiming and catching skills in children with DCD. Increased surface area in a region of primary sensory cortex was associated with better manual dexterity scores. The culmination of motor planning, initiation and motor control processes are commands sent from primary motor cortex to limbs through the corticospinal tract and spinal cord. Altered structure in this region may be a consequence of poor internal modelling or reflect

poor final integration of motor planning into commands sent to the peripheral nervous system. Somatosensory information that enters the brain through the spinothalamic tract is first processed in primary sensory cortex. Alterations in this region may result in poor sensorimotor representation and integration of sensory information into motor control. The correlations of different directions suggest dysfunction of these regions is intrinsic to DCD; however there is considerable variation in the pattern of changes which may occur.

Evidence of cortical correlates in regions outside of the motor network

Correlates of DCD were also reported in regions that I did not hypothesise based on the existing literature and therefore these results should be considered exploratory.

Aiming/catching skills and the anterior cingulate cortex

Aiming skills was negatively correlated with thickness in the posterior cingulate across the whole sample. One VBM study in children with DCD found that decreased grey matter concentration in the posterior cingulate/precuneus was also associated with poorer motor skills (Reynolds et al. 2017). Grey matter concentration is a product of both cortical thickness and surface area so these results are not directly comparable however they do point to changes in the posterior cingulate in children with DCD. The inverse correlation identified here might reflect a compensational mechanism or an abnormal increase. The precise role of the posterior cingulate is still under investigation however it is part of the default mode network which mediates attentional focus and cognitive control (Zhou et al. 2017). Leech and Sharp (Leech & Sharp 2014) conducted a review of literature in different disorders that identified alterations in posterior cingulate cortex. They report increased posterior cingulate cortex grey matter concentration in individuals with ADHD in a voxel-based meta-analysis (Nakao et al. 2011) and reduced task-based deactivation and connectivity in posterior cingulate cortex in individuals with autism. One theory of ADHD suggests altered function of the default mode network may underlie the disorder (Faraone et al. 2015). The default mode network may be impaired in children with DCD and requires further analysis with functional imaging methods.

Balance skills and the anterior insula

Poor balance skills were associated with reduced cortical thickness in the left anterior insula in children with DCD. The anterior insula has been implicated in multiple motor and non-motor functions. Bilateral anterior insula cortices form part of the salience network which works to coordinate neural resources and respond to relevant external stimuli (Uddin 2015). The anterior insula is also part of the body representation system

responsible for neural representations of structure and spatial positioning of the body (Fontan et al. 2017). The anterior insula is activated in motor imagery based balance fMRI tasks in healthy adults (Taube et al. 2015; Ferraye et al. 2014). Altered activation and connectivity in the anterior insula have been identified in children with Autism (Uddin et al. 2013). One study has also identified bilateral reductions in anterior insula volume in adolescents with ADHD relative to controls (Lopez-Larson et al. 2012). Given that balance was highly correlated with cognition and language in children with DCD alterations in the anterior insula may disrupt both sensorimotor representations of the body and functioning of the salience network.

Left Lateralisation of cortical correlates

Cortical changes and correlations were confined to the left hemisphere. This may reflect the increased need for precise motor control of the dominant right hand (controlled by the left hemisphere) resulting in higher effect sizes for this hemisphere. Alternatively, there could be impaired lateralisation of functions to the left hemisphere for precise motor control. One research study on resting state fMRI functional connectivity found different patterns of connectivity between left sensorimotor cortex and the rest of the brain in children with DCD (McLeod et al. 2014). The body of fMRI literature in children with DCD provides some evidence of reduced activation in frontal-parietal regions of the left hemisphere and increased activation in the right hemisphere compared to controls (see chapter three, Figure 3.1).

Processing speed and total surface area

Poorer processing speed was moderately correlated with reduced total cortical surface area in children with DCD. In healthy children aged ten, higher total cortical surface area was associated with higher IQ (Schnack et al. 2015). Processing speed measures form part of many standardised IQ tests. As our metric of processing speed was not standardised and typically developing children reached peak performance on the task, it was not possible to determine whether this relationship is specific to children with DCD or not.

Evidence of Basal Ganglia Correlates

Contrary to our hypotheses we did not report differences in basal ganglia volumes in children with DCD compared to controls however Children with DCD show a moderate increase in left lateralisation of putamen volumes compared to controls (Cohen's d= 0.63). This may reflect an increase in left putamen volume in children with DCD that greater statistical power than available here would render significant. Alternatively this may be driven by a significant increase within a subsection of the left putamen. Putamen volume

asymmetry has not been identified in DCD or other developmental disorders however one study has reported increased left lateralisation of FA in white matter connecting the putamen to the ventrolateral prefrontal cortex in children with ADHD (Silk et al. 2015). Another study reported increased left>right volume asymmetry of the caudate and globus pallidus in children with ADHD (Uhlikova et al. 2007). The basal ganglia are involved in procedural learning and initiation of movement and the putamen receives input from the sensorimotor cortex. Taken together with the results from the cortical morphology analysis this may reflect altered input from these structures in the left cortical-striatal motor loop.

Bilateral thalamus volume and focal oromotor control

Poor focal oromotor control was associated with bilateral thalamic volume reductions in children with DCD. Reductions in bilateral thalamus volume were reported in a child with severe speech and oralfacial praxis impairments caused by a mutation in the FOXP2 gene (Liegeois, Hildebrand, et al. 2016). The thalamus serves as a relay system within the brain, receiving input from subcortical structures, sensory systems and the cerebellum and projecting to regions throughout the cortex. Reduced thalamic volume is likely to reflect reductions in the ventral nuclei which transfer information from the basal ganglia, cerebellum and sensory cranial nerves to the premotor, primary motor and primary sensory cortex (Patel et al. 2014; Johansen-Berg et al. 2005). Reductions in thalamus volumes have not been reported in idiopathic speech and language disorders (Morgan et al. 2016; Liegeois et al. 2014), Dyslexia (Ramus et al. 2017) or ADHD (Hoogman et al. 2017; Kasparek et al. 2015) (Hoogman et al 2017). One study reported preserved whole volume in children with ADHD but regional volumes within the thalamus correlated with ADHD symptom severity (Ivanov et al. 2010).

Evidence of Cerebellar correlates

Contrary to our hypotheses we did not find any evidence of group differences in cerebellar volume or relationships with motor or cognitive scores in children with DCD. The cerebellum is made up of distinct lobules which are part of separable brain networks that underpin different cognitive functions (Buckner et al. 2011; Stoodley & Schmahmann 2010; Keren-Happuch et al. 2014; Stoodley & Schmahmann 2009; Becker et al. 2013). As discussed in chapter three, fMRI studies in children with DCD have reported reduced activation in bilateral Crus I, left lobule VI and IX and increased activation in right lobule VI compared to controls. Significant reductions in volume of these lobules may not be detected in whole cerebellum volume particularly in a sample with heterogenous behavioural profiles.

Future Directions

Cortical Morphology

This study examined two metrics of cortical structure: surface area and cortical thickness. Investigation of other metrics of cortical morphology such as intrinsic curvature and sulcal depth would give a more complete picture of cortical structural correlates related to DCD (Ronan et al. 2011; White et al. 2010; Auzias et al. 2014; Auzias et al. 2015).

Cortical morphology develops throughout childhood and adolescence. Some debate exists on the trajectory of development; however it is known that cortical features are continuously changing (Walhovd, Krogsrud, et al. 2016; Walhovd, Fjell, et al. 2016). Longitudinal scanning and examination of cortical structure in individuals with DCD across a large age range would reveal whether the cortical correlates described here represent a delay or deviance in normal cortical development and whether these are specific to cortical structure at age 8-10 or remain consistent across development.

Functional correlates of structural imaging results

The default mode, salience and sensorimotor networks have been elucidated on resting state functional MRI (Damoiseaux et al. 2006; Barkhof et al. 2014; Pool et al. 2015; Lee et al. 2013; Patriat et al. 2013). These functional networks must be studied in children with DCD to determine whether structural correlates outside of the sensorimotor networks are accompanied with domain-general functional network impairments.

Basal Ganglia and Thalamus

Parcellation of basal ganglia nuclei and the thalamus is possible using tractography between voxels within these structures and cortical target regions (Draganski et al. 2008; Novak et al. 2015; Johansen-Berg et al. 2005). Parcellation of the putamen and thalamus using tractography between voxels in these structures and cortical target regions would identify:

1. Altered connectivity between left putamen/bilateral thalami and sensorimotor cortex in children with DCD
2. Alterations in regional volume within the thalamus and putamen and correlations between subsection volume and behavioural measures

Cerebellum

Structural correlates may exist in children with DCD that are not detectable in the whole cerebellum. SUIT cerebellar toolbox is a tool for cerebellar specific voxel-based

morphometry and lobule volumetric analysis (Diedrichsen 2006). Studying cerebellar structure in children with DCD with these methods would detect group differences and brain-behaviour relationships at the lobule and voxel level.

Children with DCD may show microstructural alterations in white matter connections between the cerebellum and the rest of the brain. One diffusion tensor study on seven children with DCD reported no alterations in the superior/middle cerebellar peduncles (Zwicker et al. 2012) however the small sample size means that changes in cerebellar microstructure cannot be discounted. Chapter seven of this thesis will examine the cerebellar peduncles using diffusion-weighted imaging techniques sensitive to alterations in white matter microstructure to test this hypothesis.

6.5 Conclusions

Structural MRI analyses in this chapter identified alterations in left cortical sensorimotor brain regions when comparing children with DCD to controls and through brain-behaviour relationships with motor skills. There was some evidence of altered putamen volume lateralisation in children with DCD which may reflect a disrupted sensorimotor network. There was also evidence of correlations between motor skills and cortical morphology in domain-general brain regions of the default mode and salience networks. There was limited evidence of subcortical or cerebellar structural correlates in children with DCD. DCD may be primarily driven by altered cortical development in sensorimotor structures and domain-general regions related to cognitive efficiency rather than subcortical or cerebellar structures.

Chapter Seven: Diffusion-weighted imaging correlates of DCD and associated impairments

7.1 Introduction

Background

Four studies have been published investigating the neural correlates of DCD using DWI. This literature is reviewed and appraised in chapter three, and diffusion microstructural correlates of DCD are again summarised here in Figure 7.1. Briefly, reduced FA has been reported in the body of the corpus callosum, internal capsule and superior longitudinal fasciculus in children and adults with DCD. Individuals with DCD also show reduced mean diffusivity in the internal capsule, corticospinal tract, inferior longitudinal fasciculus and posterior thalamic radiations. Children with co-occurring DCD and ADHD are characterised by reduced FA in the genu of the corpus callosum. On graph theoretical measures, nodal efficiency in the left cerebellar and right superior parietal gyrus best differentiated children with DCD from controls (Debrabant et al. 2016).

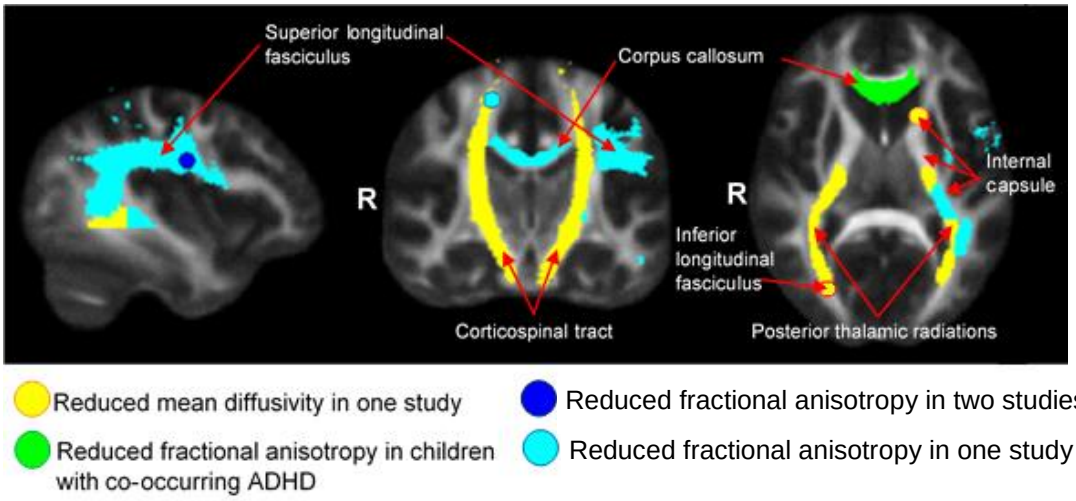

Figure 7.1 Summary of diffusion microstructural alterations in cortical white matter in children and adults with DCD, as seen in chapter three.

Pyramidal tracts

The pyramidal tracts are bilateral structures that carry efferent fibres from primary motor cortex to the spinal cord in order to control the musculoskeletal system. The pyramidal tracts contain the corticospinal and corticobulbar tract. The corticospinal tract (CST) descends from motor cortex to the spinal cord and is involved in voluntary limb movement (Jaspers et al. 2016). The corticobulbar tract (CBT) projects from face, lips and tongue regions of motor cortex to cranial nerve nuclei located in the brain stem and is responsible

for voluntary control of structures in the head, face and neck including the articulators. The Corticobulbar tract can be further split into a dorsal tract broadly corresponding to the cortical representation of the lips and layrnx, and a ventral tract broadly corresponding to the tongue representation (Brown et al. 2008; Takai et al. 2010).

There is some evidence for alterations in the CST in individuals with DCD, as well as in those with other developmental and motor disorders. MD was reduced in the CST averaged across hemispheres in seven children with DCD compared to seven control children (Zwicker et al. 2012). AD in the CST positively correlated with M-ABC2 percentile across the whole sample in this study although it is difficult to draw conclusions due to the small sample size and lack of correction for multiple comparisons. This finding is contrary to that in children with cerebral palsy, a more severe motor disorder, who show increased mean diffusivity compared to controls (Scheck et al. 2012). In a sample of adults with probable DCD, FA was reduced in a superior region of the right CST (Kashuck et al. 2017). Reduced FA in the CST has been consistently reported in children with cerebral palsy and FA positively correlates with motor functioning in this group (Scheck et al. 2012). Children with ASD show increased MD and RD in bilateral CST compared to typically developing controls (Carper et al. 2015), although the authors did not relate this to a measure of motor function. Differences in the corticospinal tract have been reported in cerebral palsy, ASD as well as DCD however in the developmental disorders this has not been consistently linked with motor performance.

As discussed in chapter five, many children with DCD show impaired focal oromotor control. To date, the neural correlates of impaired speech and oromotor control have not been studied in children with DCD. In adolescents born preterm (Northam et al. 2012) and children with traumatic brain injury (F Liegeois et al. 2013) FA in the left dorsal corticobulbar tract predicted impairment in focal oromotor control. Of particular interest is the adolescents born preterm, who showed impairments in focal oromotor control and microstructural alterations in the corticobulbar tract in the absence of dysarthria. There is emerging evidence of a relationship between microstructure of the CBT and oromotor abilities in children with neurological conditions however to date no literature has explored this relationship in children with developmental oromotor control impairments.

Corpus Callosum

The corpus callosum is a white matter structure in the brain that connects the cerebral hemispheres. Tractography of the corpus callosum can be conducted across the whole structure, in subdivisions based on anatomical landmarks, or between regions of interest

in each hemisphere. The corpus callosum is implicated in motor control and bimanual coordination (Takeuchi et al. 2012; Gooijers & Swinnen 2014). In healthy children aged 9-18 years, increased mean diffusivity in the callosal fibres between dorsolateral prefrontal cortices is associated with poorer motor control (Corporaal et al. 2017). FA in the splenium of the corpus callosum significantly predicted performance on a bimanual coordination task in children and young adults aged 9-24 years (Muetzel et al. 2008).

One diffusion MRI study has identified alterations in the corpus callosum in children with DCD. Langevin and colleagues (Langevin et al. 2014) investigated three segments of the corpus callosum using tractography in children with i) DCD, ii) ADHD and iii) DCD+ADHD compared to typically developing children. Children with DCD showed reduced FA the body of the corpus callosum compared to typically developing children. Children with ADHD showed reduced FA in the genu of the corpus callosum. Children with DCD+ADHD showed reductions in both segments. The corpus callosum was divided into large subsections in this study therefore it was not possible to specify which regions of the brain had reduced connectivity.

Microstructural alterations in the corpus callosum have also been implicated in other motor and developmental disorders. In a meta-analysis of TBSS studies FA was reduced in the splenium of the corpus callosum in individuals with ADHD compared to controls (Chen et al. 2016). In males with ASD, FA in the anterior corpus callosum follows a different developmental trajectory compared to typically developing children (Travers et al. 2015). FA in callosal fibres connecting motor cortices was reduced in children with bilateral spastic cerebral palsy (Koerte et al. 2011). Microstructural integrity of the corpus callosum has been associated with motor skills in typically developing children and differences have been reported in paediatric motor, attention and social communication disorders.

Cerebellar peduncles

The cerebellum is implicated in the internal modelling deficit hypothesis of DCD. The cerebellar peduncles are white matter structures that connect the cerebellum to the rest of the brain and spinal cord. The inferior (ICP) and middle cerebellar peduncles (MCP) are predominately made up of input fibres to the cerebellum. The superior cerebellar peduncles (SCP) consist of mainly output fibres that project to the red nucleus and thalamus (van Baarsen et al. 2016). One study has reported no alterations in the MCP in seven children with DCD (Zwicker et al. 2012). As this was a small pilot study it is not possible to draw conclusions from this work alone.

Alterations in the cerebellar peduncles have been reported in children born prematurely and those with developmental disorders. Children born prematurely with periventricular leukomalacia had reduced FA in the bilateral CST, SCP and MCP (Wang et al. 2014). In the same study, FA in these tracts negatively correlated with gross motor function classification system scores. Children with ASD have also sown microstructural alterations in the SCP (Catani et al. 2008; Sivaswamy et al. 2010; Hanaie et al. 2013). Hanaie and colleagues (Hanaie et al. 2013) reported not only that FA was reduced in the right SCP but also that FA positively correlated with M-ABC2 total test score in children with ASD. Reduced FA in the MCP has been reported in children with ADHD compared to controls (Ashtari et al. 2005; Bechtel et al. 2009). In healthy adults, performance on a test of sustained attention was positively correlated with FA in fibres passing through the left SCP (Ge et al. 2013). Microstructure in the superior and middle cerebellar peduncles has been associated with motor skill in cerebral palsy and ASD, additionally integrity of the SCP is associated with sustained attention in healthy adults.

Tractography

As discussed in chapter four, white matter pathways of interest can be reconstructed from diffusion MRI data using tractography (Farquharson et al. 2013; Feldman et al. 2014). Mean values of FA, MD, AD and RD can be extracted from these reconstructions, known as 'tracks', and used as outcome measures for analyses.

Fixel-Based Fibre Morphology

Advances in signal modelling allow us to apply more complex models to DWI datasets in order to estimate the underlying characteristics of a white matter pathway. Fixel-based fibre morphology is a recently developed method for analysing features of fibre populations within a voxel, called a 'fixel' (Raffelt et al. 2017). Fibre density (FD) corresponds to the number of fibres per fixel and is derived from the amplitude of a lobe of fibre orientation distribution (FOD) function calculated within a voxel (Figure 7.2a)(Raffelt et al. 2012). Fibre cross-section (FC) corresponds to the number of fixels the fibre bundle occupies perpendicular to the fixel orientation (Figure 7.2b). Fibre Density modulated by cross-section (FDC) is a feature that accounts for both alterations simultaneously and is obtained by multiplying the FD and FC to give a more comprehensive measure of intra-axonal volume (Figure 7.2c).These features (subsequently referred to as morphology) can be analysed at each fixel across the whole brain or within a subset of tracts similar to a voxel-wise comparison such as TBSS (subsequently referred to as a fixel-by-fixel analysis). Additionally, mean values can be extracted and analysed

from a tract of interest. Two studies employing this technique have been published. Increased fibre density in the splenium of the corpus callosum was associated with pubertal onset in healthy children (Genc et al. 2017). Adults with hippocampal sclerosis and temporal lobe epilepsy showed reductions in FDC across temporal and extra-temporal white matter tracts (Vaughan et al. 2017).

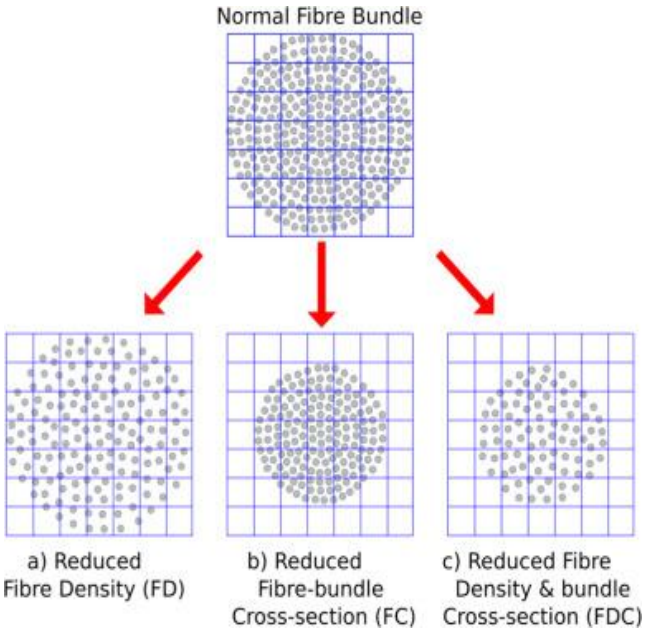

Figure 7.2 Fixel-based fibre morphology alterations in a. fibre density b. fibre cross-section c. fibre density and cross-section (figure from Raffelt et al. 2017)

Study Aims

The first aim of this study was to investigate differences in FA, AD and RD between children with DCD and age-matched control children in:

i) Corticospinal Tract
ii) Dorsal and Ventral Corticobulbar Tract
iii) Corpus Callosum
    a. Whole structure
    b. Subsections connecting specific regions of cortex
iv) Middle Cerebellar peduncles
v) Superior cerebellar peduncles

The inferior cerebellar peduncles were not investigated in this study due to differences in level of brainstem captured in the DWI images.

The second aim was to investigate differences in FD, FC and FDC between children with DCD and control children across the:

i) whole brain
ii) pyramidal tracts
iii) corpus callosum
iv) middle cerebellar peduncles

It was not possible to analyse the superior cerebellar peduncle data utilising this technique due to time constraints.

The third aim of this study was to report relationships between these white matter features and behavioural variables impaired in children with DCD as reported in chapter five: motor skills, speech and oromotor functions, and attention abilities.

Hypotheses

Pyramidal tract hypotheses

Compared to typically developing children, children with DCD will show:

i) reduced FA and increased RD in the corticospinal and corticobulbar tract
ii) reduced fibre morphology in the corticospinal and corticobulbar tract

MABC-2 scores will positively correlate with FA and features of fibre morphology in the corticospinal tract. Focal oromotor control z-score will positively correlate with bilateral dorsal CBT FA and negatively correlate with bilateral dorsal CBT RD.

Corpus Callosum Hypotheses

Children with DCD will show reduced FA and fibre morphology and increased RD in regions of the corpus callosum connecting sensorimotor cortex and dorsolateral prefrontal cortex compared to typically developing children.

FA and fibre morphology in sensorimotor regions of the corpus callosum will positively correlate with M-ABC2 scores. FA and fibre morphology in frontal and parietal regions of the corpus callosum will positively correlate with attention scores in children with DCD.

Cerebellar peduncle Hypotheses

Children with DCD will show reduced FA and fibre morphology and increased RD in the middle cerebellar peduncles and superior cerebellar peduncles. Motor scores will correlate with FA and fibre morphology in both the middle and superior cerebellar peduncles. Given

the association between focal oromotor control and bilateral thalamus volume, FA and fibre morphology in the cerebellar peduncles may correlate with speech motor control scores. Sustained attention scores will correlate with superior cerebellar peduncle FA and RD.

7.2 Methods

As previously discussed, diffusion weighted MRI scans were collected and analysed for each child (DCD N=36; Control N=17).

Image Pre-processing

All diffusion-weighted images were analysed using MRtrix3 software package (www.mrtrix.org). Images were pre-processed using a standard pipeline in MRtrix3 that utilises a combination of internal scripts and imaging tools from other packages. All images underwent the following procedures:

i) Thermal noise correction to improve signal to noise ratio (Veraart, Fieremans, et al. 2016; Veraart, Novikov, et al. 2016)
ii) Correction for susceptibility induced distortions using TOPUP in FSL (Andersson & Sotiropoulos 2016; Andersson et al. 2003; Smith et al. 2004)
iii) Motion correction using an outlier replacement strategy and eddy current correction using EDDY in FSL (Andersson et al. 2016; Andersson & Sotiropoulos 2016)
iv) Correction for Bias field inhomogeneities using ANTS N4 tools (Tustison et al. 2010)
v) Global intensity normalisation

Images were visually inspected for signal dropout caused by motion during acquisition of the sequence. Images were checked both before and after pre-processing. Datasets were excluded from further analysis if they showed either:

i) motion artefact in more than 10% (12 out of 120) of the diffusion-weighted volumes before pre-processing (a 10% threshold was recommended on the MRtrix3 community forum)
ii) motion artefact visible after pre-processing

Three DWI datasets from children with DCD were subsequently excluded due to motion artefact in more than 10% of volumes before pre-processing. No datasets from typically developing children were excluded. The final sample included in subsequent analyses was 33 children with DCD and 17 typically developing children.

Tractography

Probabilistic tractography using multi-tissue constrained spherical deconvolution in Mrtrix3 was conducted as follows:

i) Whole brain mask automatically derived, manually checked, and edited if needed
ii) Multi-tissue CSD response functions estimated for grey matter, white matter and CSF tissue (Dhollander et al. 2016)
iii) Fibre Orientation Distribution functions estimated using multi-tissue constrained Spherical Deconvolution (Jeurissen et al. 2014)
iv) FA, AD, RD and Red-Green-Blue (RGB) eigenvector maps estimated

Pyramidal tracts

CST and CBT seeds for tractography were identified axially on FA maps using Liegeois and colleagues' method (FJ Liegeois, Tournier, et al. 2013). The hand representation was identified from the omega sign and a 7-mm sphere was placed in the adjacent white matter to identify the CST. A 7mm seed was placed 15mm lower than the hand hook, in a region reported to correspond to the lips and larynx (Pan et al. 2012) to identify the dorsal CBT. A second 7mm seed was placed 15mm lower than the dorsal CBT seed, in a region that corresponds with the tongue representation, to identify the ventral CBT. It was not possible to accurately delineate the ventral CBT seed in more than half of this sample and therefore tractography was not conducted. An inclusion region was placed in the pons delineated on the RGB eigenvector map on an axial slice where the pyramidal tract was descending (coloured blue) and the transverse pontine fibres (coloured red) and middle cerebellar peduncle (coloured green) were visible. Tractography was terminated once fibres transversed this pons region (Figure 7.3). The maximum number of streamlines was set at 10,000 and a maximum of 1,000 streamlines were retained Tractography of the CST was possible in all cases. Tractography of the CBT was not possible in one child with DCD.

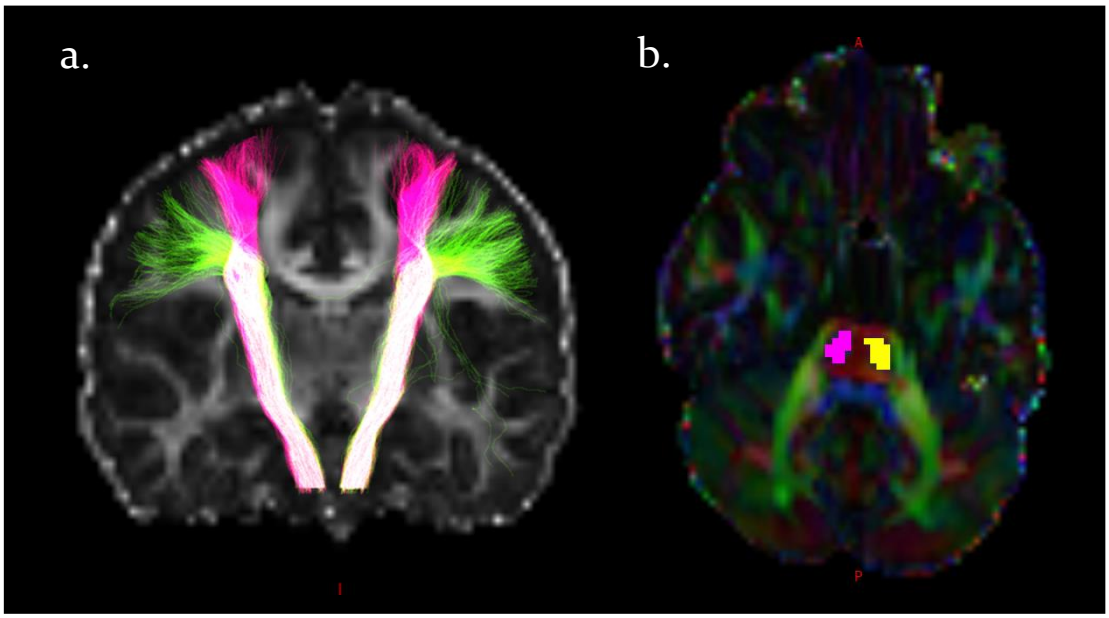

Figure 7.3 a. Reconstructions of the corticospinal track (pink) and corticobulbar track (green) from one child our sample b. axial view of inclusion regions after which tracking was terminated

Corpus Callosum

a. Whole corpus callosum

The entire corpus callosum was tracked based on Liegeois and colleagues (FJ Liegeois, Mahony, et al. 2013) methods. A single seed region was delineated on the mid-sagittal slice (coloured red) and extended to three slices thick (Figure 7.4). For some participants, the head was tilted during acquisition to such a degree that it was not possible to accurately delineate the corpus callosum on three slices. In these cases, the seed region remained three slices thick but was drawn across more than three slices to accurately track the corpus callosum. The maximum number of streamlines was set at 10,000 and a maximum of 3,000 streamlines were retained. Tractography was possible in all participants. Tractography was initially directed along the x-axis to reduce the number of spurious fibres.

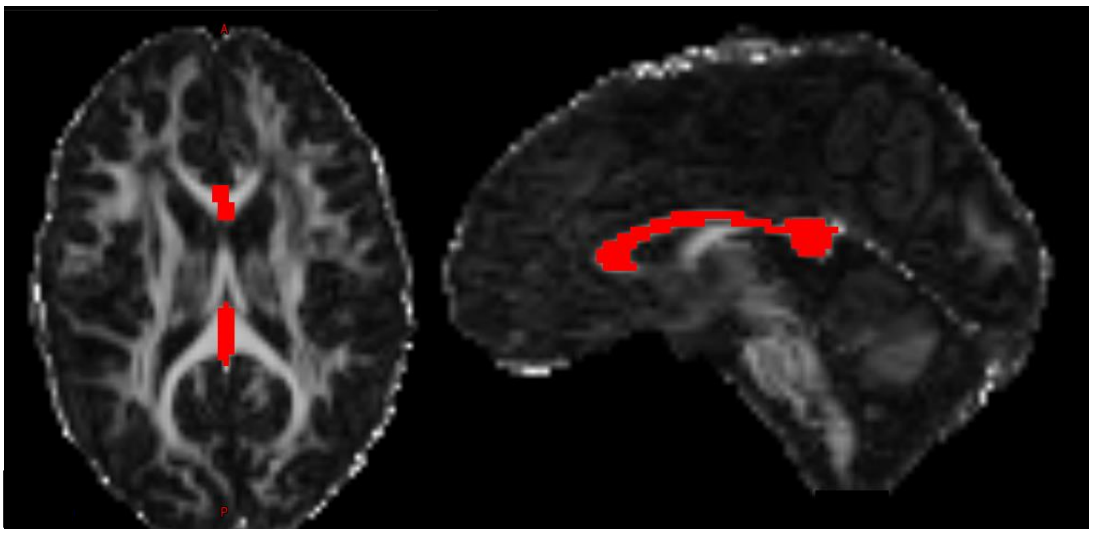

Figure 7.4 Axial and sagittal views of the corpus callosum ROI in one participant

b. Corpus Callosum Subsections

In the standard Freesurfer pre-processing pipeline (described in chapter six) T1-weighted MRI scans are automatically parcellated into 34 gyral based regions of interest in each hemisphere according to the Desikan-Killiany (DK) labelling protocol (Desikan et al. 2006; Fischl et al. 2004). Bilateral superior frontal, caudal middle frontal, rostral middle frontal, postcentral, superior parietal, inferior parietal, pars opercularis, pars triangularis, pars orbitalis and supramarginal DK labels for each participant were converted to binary volumetric masks. A rigid-body boundary-based cost function (Greve & Fischl 2009) was used to align a bo image from the diffusion-weighted sequence to the T1-weighted image and the resulting transformation matrix was converted to MRtrix format. The inverse linear transformation was then applied to move the DK atlas volumetric masks into alignment with the diffusion weighted sequence (Figure 7.5a). The superior parietal, inferior parietal and supramarginal volume masks were combined into one mask to conduct tractography of the parietal connections. The pars opercularis, pars triangularis and pars orbitalis masks were combined into one mask to conduct tractography between the inferior frontal gyri. The whole corpus callosum seed region was used to seed tractography and the DK atlas masks were used as bilateral inclusion regions to track the subsections (Figure 5b). The 7mm spherical seeds described for the CBT and CST tractography were used to track trans-callosal fibres in hand and lip regions of primary motor cortex.

For each subsection, the maximum number of streamlines generated was set at 10,000 and a maximum of 1,000 streamlines were retained. Tractography of connections between inferior frontal gyri did not generate more than 100 streamlines in many participants. This

was deemed an unreliable track and not included in subsequent analysis. Tractography of all other subsections was possible in each participant. Tractography was initially directed along the x-axis from the mid-sagittal seed to reduce the number of spurious fibres.

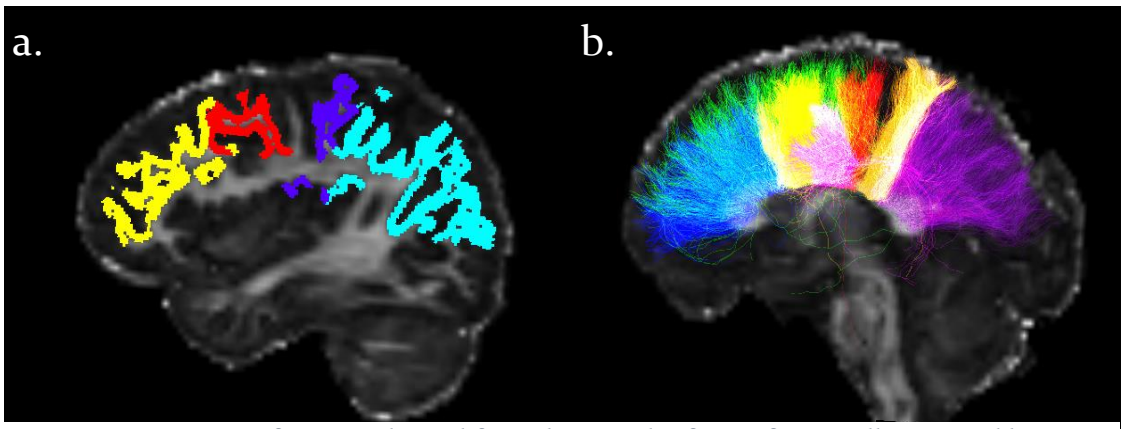

Figure 7.5 a. regions of interest derived from the DK atlas freesurfer parcellations and b. corpus callosum track subsection reconstruction

Cerebellar peduncles

Tractography of the left and right ICP was not performed due to different levels of coverage of the cerebellum and inferior brainstem in each participant.

a. Middle Cerebellar Peduncles

The MCP were identified on the RGB eigenvector map. In the coronal view the MCP were identified in green. When the pons was no longer visible bilateral ROIs were placed on the middle cerebellar peduncles (Figure 7.6). If the brain was tilted ROIs were placed in adjacent slices. Tractgraphy was conducted from left to right ROIs. As many participants had tilted heads it was not possible to accurately split the middle cerebellar peduncles into left and right structures. Tractography of the MCP was not possible in one child with DCD due to poor coverage of the inferior cerebellum in the DWI image.

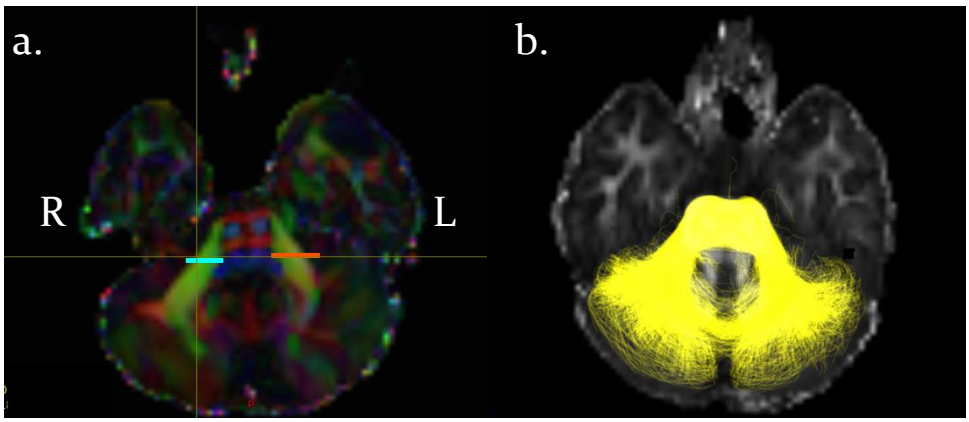

Figure 7.6 a. Regions of interest in the left and right middle cerebellar peduncles placed in adjacent slices due to tilting of the head b. a reconstruction of the middle cerebellar peduncles in our sample

b. Superior Cerebellar Peduncles

Tractography of the left and right SCP was performed using a procedure based on Wakana and colleagues (2004) and Leitner and colleagues (2016). Tractography seeds were placed using the RGB eigenvector map. A seed region was placed on the axial plane at the level of the decussation of the SCP (visible as a small red region between ascending blue fibres)(Figure 7.7a). Left and right inclusion regions were placed in cyan coloured voxels identified on two coronal slices in the cerebellum (Figure 7.7b). The pons regions of interest drawn for the pyramidal tractography were used as exclusion regions. Tractography was conducted unidirectionally from the decussation seed to prevent fibres from ascending into the cortex. A maximum of 10,000 streamlines were generated and a maximum of 1,000 streamlines were selected (Figure 7.7c and 7.7d).

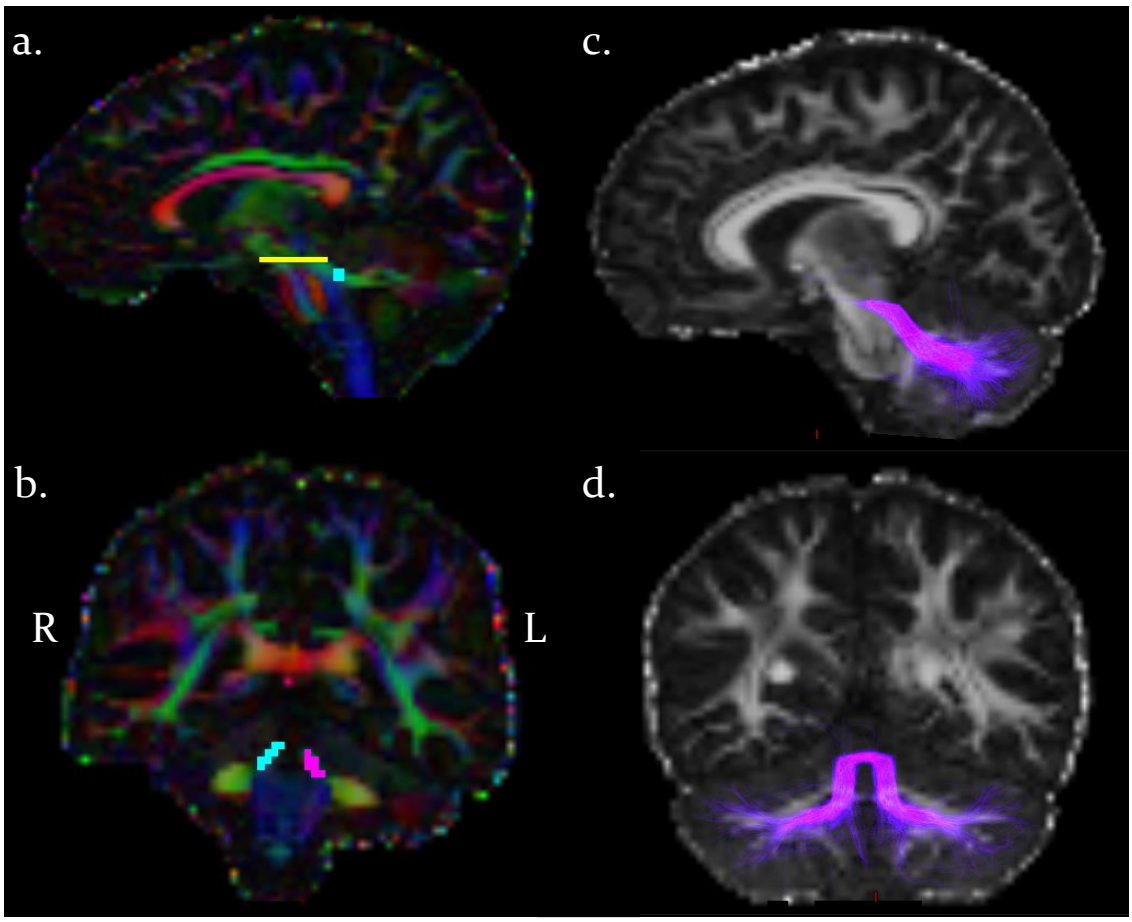

Figure 7.7 a. sagittal and b. coronal views of decussation seed (yellow) and inclusion regions (pink and blue) for the left and right superior cerebellar peduncles (tracked separately) c. sagittal and d. coronal views of reconstructed superior cerebellar peduncles

Extraction of microstructural measures

All generated tracks were checked for accuracy and regions of interest were altered as necessary. Final tracks were then transformed into track-weighted masks. In order to avoid including spurious fibres in the extraction of microstructural measures all voxels containing fewer than ten streamlines were excluded. Mean FA, AD and RD values for each tract were extracted from each participant.

Fixel-based fibre morphology

Fixel-based analysis of fibre morphology was performed according to the recommended pipeline available on the MRtrix3 website (Raffelt et al. 2017) http://mrtrix.readthedocs.io/en/latest/fixel_based_analysis/mt_fibre_density_cross-section.html). The DWI images were up-sampled to a voxel size of 1.25mm isotropic. FODs were estimated for each participant using a group average response function. An unbiased study-specific FOD template was created from sixteen randomly chosen children with DCD and sixteen control children. FODs for each participant were registered to the

template and images were then masked to ensure analysis is restricted to voxels containing white matter and those which contain data from all subjects. FODs were warped to the template and then segmented into separate lobes to identify the number and orientations of fixels in each voxel. Whole brain tractography was performed on the FOD to generate 20 million tracts and spherical-deconvolution informed filtering of tractograms (SIFT) was used to filter this to 2 million tracts the density of which corresponds to the fibre density in the data (Smith et al. 2013). FC values were log-transformed as recommended by the MRtrix3 pipeline available on the website.

Fixel masks were built for the corpus callosum, dorsal CBT, CST, cerebellum and brain stem, and MCP by selecting appropriate streamlines from the whole brain tractogram. Bilateral CST and CBT tracts were combined into one mask, and one mask encompassing the cerebellum and brainstem was used for fixel-by-fixel analyses to reduce the number of comparisons. Fixel-by-fixel analyses of fibre morphology were run across the whole brain and within masks of the pyramidal tracts, corpus callosum and cerebellum and brain stem. In addition, mean FD, FC and FDC values for left and right CST, left and right CBT, corpus callosum and MCP were also extracted for each participant.

Statistical Analysis

Tractography and mean fixel-based fibre morphology measures

Group differences in tractography-based and fixel-based measures in the CST, CBT and superior cerebellar peduncles were estimated with mixed model ANOVAs. Group differences in tractography-based and fixel-based measures in the whole corpus callosum, corpus callosum subsections and middle cerebellar peduncles were calculated with multivariate analysis of covariance (MANCOVA). Handedness and full scale IQ were entered as covariates for all models. Spearman correlations were run between track measures and behavioural measures. Correlations were run with FA in the first instance to reduce the number of comparisons. For any significant correlations, RD from the same track was then correlated with the corresponding behavioural measure. As fibre morphology measures are novel (FD, FC and FDC) all features were used for correlations. In cases where FD or FC and FDC were significantly correlated with a behavioural measure the FDC result was utilised in subsequent regression analyses.

Bonferroni correction was used to correct for multiple comparisons. As Bonferroni is a very conservative correction which may results in inflated false-negatives, the critical p-value for each section was divided by the number of independent track measures examined rather than all analyses run. Measures were not considered independent when

i) there is an expected relationship between variables (e.g. FD and FC or FA and RD within a track) ii) when one measure is contained within another (e.g. whole corpus callosum FA and corpus callosum subsection FA or FD and FDC within a track). Multiple linear regressions were also used to examine the relationship between white matter features and behavioural variables, removing the effect of handedness and full scale IQ. Stepwise multiple linear regressions were used to examine DWI predictors of behavioural measures. Forward Wald logistic regression was used to identify DWI predictors of presence/absence of speech and oromotor impairment instead of linear regression, as the z-scores for the speech and oromotor measures were not normally distributed (As discussed in chapter five).

Fixel-by-fixel analyses

General linear models were computed to examine fixel-by-fixel comparisons of FD, FC and FDC features between groups and association between morphological features and behavioural variables. Handedness and full scale IQ were entered as covariates for each model. Morphological features were examined using connectivity-based fixel enhancement in Mrtrix3 (Raffelt et al. 2015)). Results were generated using streamlines from the template tractogram (smoothing 10mm FWHM, 5000 permutations). The following models of fibre morphological features were run across the whole brain and within bilateral pyramidal tracts, cerebellum and brainstem, and corpus callosum:

i) Increases and decreases in children with DCD relative to controls
ii) Correlation between features and motor scores (Manual Dexterity, Aiming and Catching, Balance) both within the DCD group and across the whole sample
iii) Correlations between features and focal oromotor control z-score, speech sequencing z-score, sustained attention scaled score (Score!) and set-switching scaled score (Creature Counting) within the DCD group.
iv) Increases and decreases in children with DCD and CAS features relative to children with DCD without CAS features

The FWE rate was set to be below 0.002 to control for the number of models run. As before, attention, speech and oromotor control models were only tested within the children with DCD.

7.3 Results

Differences between children with DCD and typically developing children

Tractography

a. Pyramidal Tracts

There was a group by hemisphere interaction in microstructure features in the corticobulbar tract (Table 7.1, Figure 7.8 a-c). Post-hoc calculations reveal that children with DCD have significantly lower FA and AD and significantly higher RD than controls in the right CBT (Table 7.2, figure 7.8 d-f). There were no differences between children with DCD and controls in the CST (Table 7.1).

Table 7.1 Pyramidal tract microstructural differences between children with DCD and controls

	FA	AD	RD
Left CBT	F(1,45)=0.571 p=0.454	p=0.848 F(1,45)=0.636 p=0.429	p=1.000 F(1,45)=0.831 p=0.367
Right CBT	**F(1,45)=9.444 p=0.004**	**F(1,45)=4.975 p=0.031**	**F(1,45)=5.124 p=0.028**

Results in bold are significant

Table 7.2 Corticobulbar tract microstructural differences between children with DCD and controls

		FA	AD	RD
CBT	Main effect of group	F(1,45)=1.308 p=0.259	F(1,45)=0.795 p=0.377	F(1,45)=0.795 p=0.377
	Hemisphere * group	**F(1,45)=7.370 p=0.009**	**F(1,45)=5.501 p=0.023**	**F(1,45)=6.785 p=0.012**

Results in bold survive correction for multiple comparisons (p<0.025)

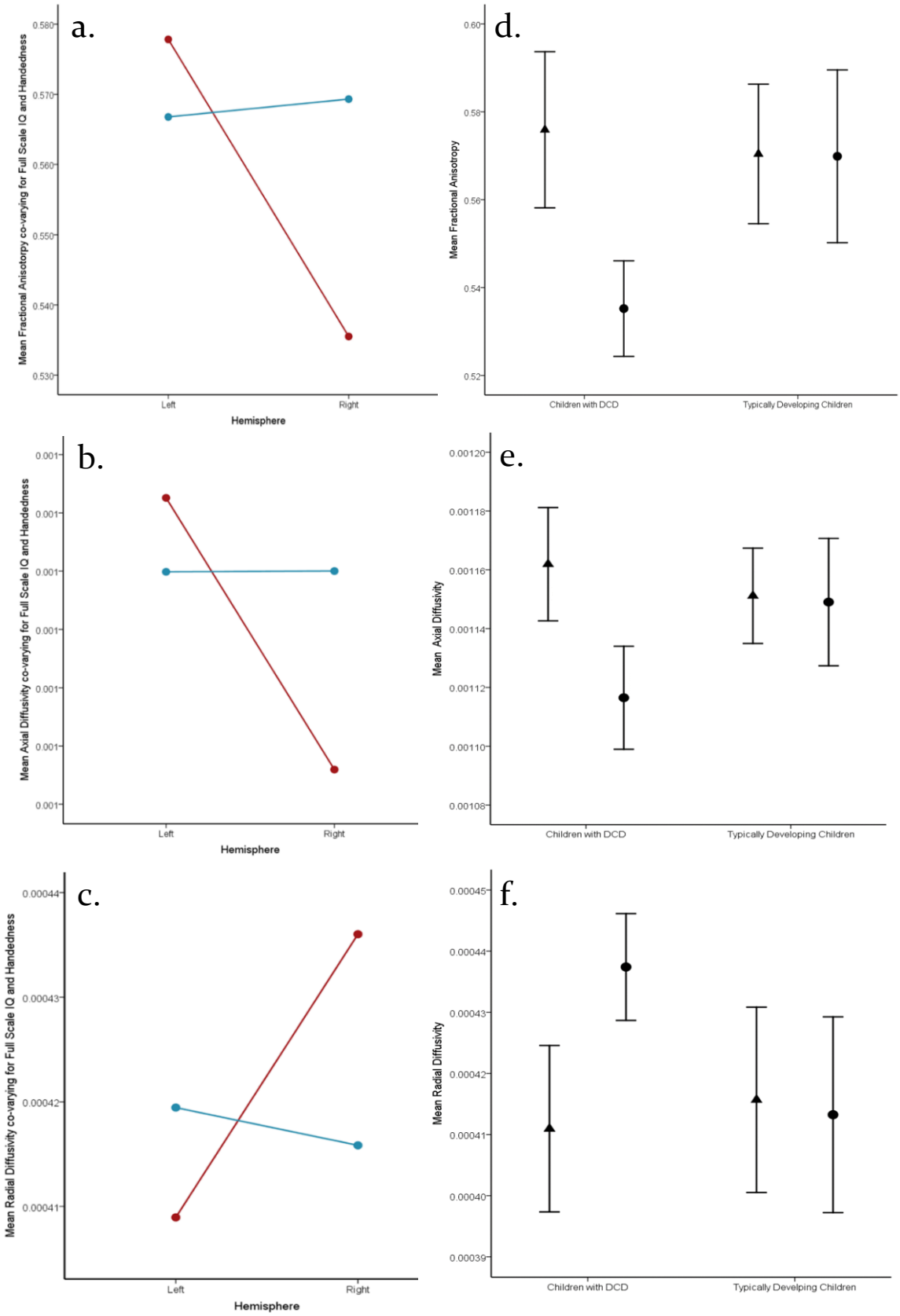

Figure 7.8 a-c. Group by hemisphere interactions of microstructural features in the CBT (controls=blue; DCD=red) d-f. Mean and 95% confidence intervals of CBT microstructural features in each group (left=triangle right=circle) Note: d-f displays the data without correcting for handedness or full scale IQ

b. Corpus Callosum

Children with DCD did not show any microstructural differences the callosum (Table 7.3). There was a significant difference in AD in the corpus callosum connecting the postcentral gyri however this result does not survive correction for multiple comparisons.

Table 7.3 Whole corpus callosum and subsections microstructural differences between children with DCD and controls

	FA	**AD**	**RD**
Whole Corpus Callosum	F(1,46)=0.086 p=0.770	F(1,46)=2.247 p=0.141	F(1,46)=0.075 p=0.786
Hand fibres	F(1,46)=0.941 p=0.337	F(1,46)=0.951 p=0.335	F(1,46)=0.00 p=1.00
Face fibres	F(1,46)=1.946 p=0.170	F(1,46)=0.027 p=0.869	F(1,46)=1.555 p=0.219
Caudal middle frontal fibres	F(1,46)=0.003 p=0.960	F(1,46)=0.80 p=0.376	F(1,46)=0.438 p=0.511
Postcentral fibres	F(1,46)=1.56 p=0.218	F(1,46)=4.247 p=0.045	F(1,46)=0.019 p=0.892
Parietal fibres	F(1,46)=2.037 p=0.160	F(1,46)=2.809 p=0.101	F(1,46)=0.517 p=0.476

Results in bold survive correction for multiple comparisons (p<0.0083)

c. Cerebellar Peduncles

There were no differences in the middle or superior cerebellar peduncle microstructure in children with DCD compared to controls (Table 7.4).

Table 7.4 Cerebellar Peduncle microstructural differences between children with DCD and controls

MCP		F(1,46)=0.018 p=0.893	F(1,46)=0.043 p=0.837	F(1,46)=0.00 p=1.000
SCP	Main effect of group	F(1,46)=0.000 p=0.994	F(1,46)=0.378 p=0.542	F(1,46)=0.115 p=0.736
	Hemisphere * group	F(1,46)=3.357 p=0.073	F(1,46)=0.03 p=0.863	F(1,46)=0.630 p=0.431

Fixel Based Fibre Morphology

There were no significant fixel-by-fixel differences in fibre morphology between children with DCD and typically developing children across the whole brain or within the hypothesised track masks. There were also no differences in mean fibre morphology extracted from tracts of interest (Table 7.5)

Table 7.5 Differences in fibre morphology between children with DCD and controls

		FD	**FC**	**FDC**
Corpus Callosum	MANCOVA	F(1,46)=0.004 p=0.952	F(1,46)=1.076 p=0.305	F(1,46)=0.447 p=0.507
MCP	MANCOVA	F(1,46)=1.314 p=0.258	F(1,46)=0.901 p=0.348	F(1,46)=0.212 p=0.647
CST	Main effect of group	F(1,46)=0.306 p=0.583	F(1,46)=0.068 p=0.796	F(1,46)=0.054 p=0.817
	Hemisphere *group	F(1,46)=0.065 p-0.800	F(1,46)=0.0001 p=0.991	F(1,46)=0.136 p=0.714
CBT	Main effect of group	F(1,46)=0.180 p=0.673	F(1,46)=0.010 p=0.920	F(1,46)=0.010 p=0.920
	Hemisphere *group	F(1,46)=0.015 p=0.903	F(1,46)=0.0002 p=0.987	F(1,46)=0.013 p=0.908

White matter correlates of motor scores

a. Corticospinal Tract

There were no correlations between motor skills and FA in the corticospinal tract (Table 7. 6).

Table 7.6 Correlation between motor scores and FA in the corticospinal tract

	Manual Dexterity		**Aiming and Catching**		**Balance**	
	Whole group	DCD group	Whole group	DCD group	Whole group	DCD group
Left CST FA	Rho=-0.062 p=0.670	Rho=-0.121 p=0.504	Rho=0.207 p=0.154	Rho=0.222 p=0.214	Rho=-0.066 p=0.651	Rho=-0.056 p=0.760
Right CST FA	Rho=0.020 p=0.888	Rho=-0.052 p=0.774	Rho=0.260 p=0.071	Rho=0.139 p=0.442	Rho=0.035 p=0.809	Rho=0.006 p=0.972

b. Corpus Callosum

FA within the whole corpus callosum correlated positively with Aiming and Catching score in the whole group (Table 7.7). This effect was most significant in postcentral and parietal segments of the corpus callosum. Stepwise linear regression revealed FA in the fibres of the corpus callosum connecting postcentral gyri best predicted aiming and catching score ($F(1,46)=9.716$ $p=0.003$). This remained significant when IQ and handedness are included in the model ($F(3,46)=3.551$ $p=0.022$) (Table 7.8; Figure 7.9)). Aiming and catching scores also correlated with radial diffusivity in the corpus callosum across the whole group however this did not survive correction for multiple comparisons. There were no correlation between corpus callosum microstructure and manual dexterity or balance scores in children with DCD or across the whole group.

Table 7.7 Correlation between motor scores and diffusion features in whole Corpus Callosum and segments

	Manual Dexterity		Aiming and Catching		Balance	
	Whole group	DCD group	Whole group	DCD group	Whole group	DCD group
Whole Corpus Callosum FA	Rho=-0.047 p=0.748	Rho=-0.073 p=0.687	**Rho=0.394 p=0.005**	Rho=0.357 p=0.041	Rho=0.101 p=0.488	Rho=0.041 p=0.822
Whole Corpus Callosum RD	not hypothesised	not hypothesised	Rho=-0.286 p=0.046	Rho=-0.326 p=0.064	not hypothesised	not hypothesised
Rostral middle frontal fibres FA	not hypothesised	not hypothesised	Rho=0.299 p=0.037	Rho=0.341 p=0.052	not hypothesised	not hypothesised
Caudal middle frontal fibres FA	Rho=0.106 p=0.465	Rho=0.130 p=0.470	Rho=0.127 p=0.383	Rho=0.213 p=0.233	Rho=-0.008 p=0.956	Rho=-0.052 p=0.780
Superior frontal fibres FA	not hypothesised	not hypothesised	Rho=0.354 p=0.013	Rho=0.367 p=0.036	not hypothesised	not hypothesised
Hand fibres FA	Rho=-0.003 p=0.981	*Rho=-0.123 p=0.495*	Rho=0.216 p=0.136	Rho=0.284 p=0.109	Rho=0.112 p=0.442	Rho=-0.025 p=0.891
Postcentral fibres FA	Rho=0.094 p=0.523	Rho=0.108 p=0.555	**Rho=0.376 p=0.008**	Rho=0.390 p=0.027	Rho=0.032 p=0.837	Rho=0.018 p=0.922
Parietal fibres FA	Rho=-0.090 p=0.535	Rho=-0.127 p=0.482	**Rho=0.392 p=0.005**	Rho=0.365 p=0.037	Rho=0.055 p=0.708	Rho=-0.137 p=0.456

Results in bold survive correction for multiple comparisons (p<0.0083)

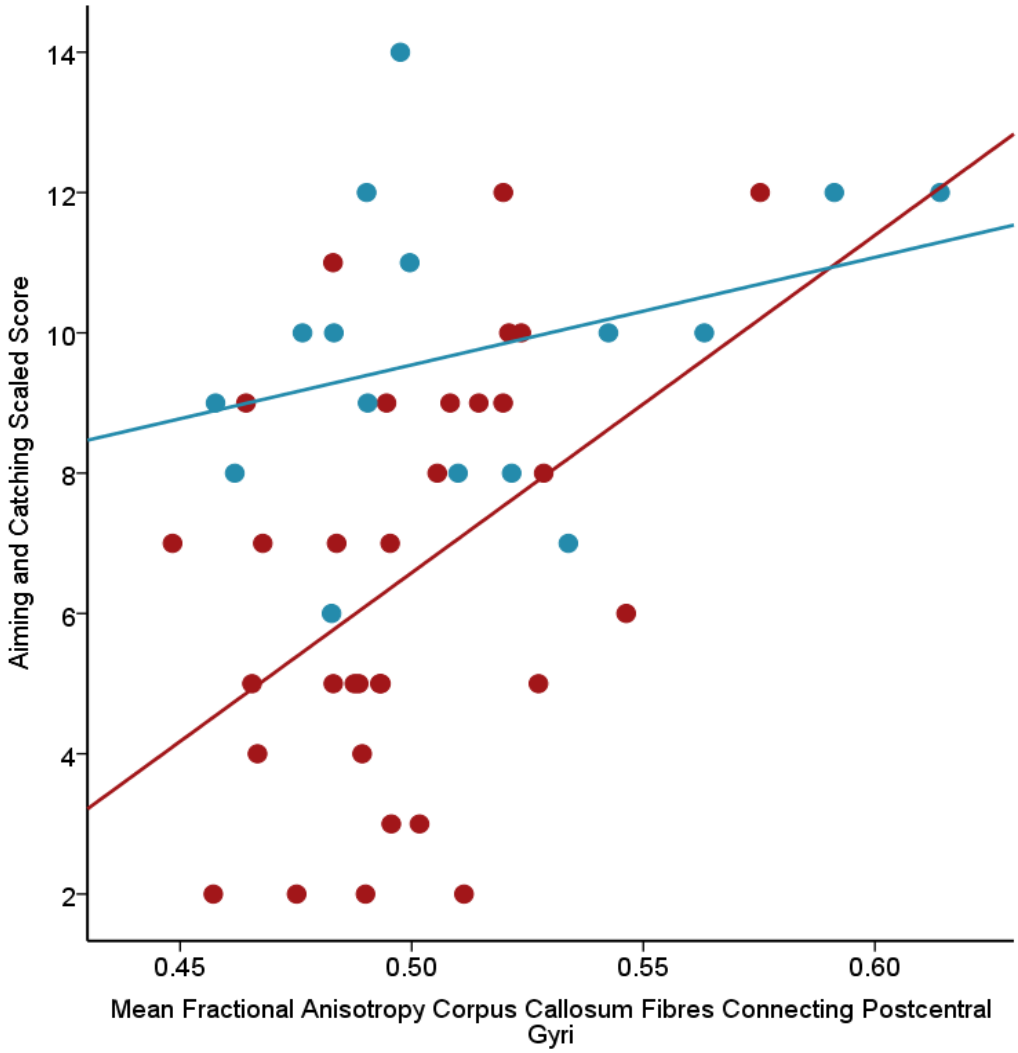

Figure 7.9 Correlation between Fractional Anisotropy in postcentral corpus callosum fibres and aiming and catching score (Red=children with DCD; Blue=Controls)

Table 7.8 Linear regression predicting aiming and catching from FA in corpus callosum fibres connecting postcentral gyri with handedness and full scale IQ taken into account

	B (SE)	Beta	Significance	R^2(Adjusted R^2)
Model 1				
Postcentral fibres FA	37.818 (12.132)	0.418	0.003	0.174 (0.156)
Model 2				
Postcentral fibres FA	36.657 (12.338)	0.405	0.005	0.195 (0.140)
Handedness	0.652 (1.080)	0.082	0.549	
Full Scale IQ	0.0 (0.024)	0.124	0.367	

c. Cerebellar Peduncles

FA in the middle cerebellar peduncles correlated with aiming and catching score both in children with DCD and across the sample (Table 7.9). Linear regression revealed that FA in the middle cerebellar peduncles was no longer associated with aiming and catching across the whole sample once IQ is taken into account (Table 7.10). There were no correlations between cerebellar peduncle microstructure and manual dexterity or balance scores in children with DCD or across the whole group.

Table 7.9 Correlation between motor scores and FA in Cerebellar Peduncles

	Manual Dexterity		**Aiming and Catching**		**Balance**	
	Whole group	DCD group	Whole group	DCD group	Whole group	DCD group
MCP FA	Rho=0.115 p=0.431	Rho=0.202 p=0.268	**Rho=0.355 p=0.013**	**Rho=0.432 p=0.014**	Rho=0.139 p=0.341	Rho=0.049 p=0.791
MCP RD	not hypothesised	not hypothesised	Rho=-0.099 p=0.504	Rho=0.053 p=0.774	not hypothesised	not hypothesised
Left SCP FA	Rho=0.014 p=0.921	Rho=0.058 p=0.748	Rho=0.217 p=0.134	Rho=0.084 p=0.642	Rho=0.136 p=0.351	Rho=0.111 p=0.546
Right SCP FA	Rho=-0.006 p=0.967	Rho=0.145 p=0.422	Rho=0.108 p=0.461	Rho=0.073 p=0.686	Rho=0.048 p=0.743	Rho=0.116 p=0.526

Results in bold survive correction for multiple comparisons (p<0.017)

Table 7.10 Linear regression predicting aiming and catching from MCP FA across the

whole group with handedness and IQ taken into account

Predictors	**B (SE)**	**Beta**	**Significance**	**R^2 (Adjusted R^2)**
Handedness	0.765 (1.132)	0.098	0.503	0.106 (0.046)
Full Scale IQ	0.004 (0.026)	0.020	0.893	
MCP FA	56.7 (28.9)	0.293	0.056	

Fibre-based fibre morphology

Aiming and catching correlated with FDC and FC in the corpus callosum and left CST across the whole sample and within children with DCD (Table 7.11). Within children with DCD only left CST FC and corpus callosum FDC remained significant after correcting for multiple comparisons. Across the whole sample, the relationship between Aiming and catching and FDC in both tracks remained significant once controlling for full scale IQ and handedness (Table 7.12; Figure 7.10). There were no correlation between fibre morphology and manual dexterity or balance scores in children with DCD or across the whole group. There were no significant regions in the fixel-by-fixel analysis.

Table 7.11 Correlation between motor scores and fixel-based measures of fibre morphology in tracks of interest

	Manual Dexterity		*Aiming and Catching*		*Balance*	
	Whole group	DCD group	Whole group	DCD group	Whole group	DCD group
Left CST FD	Rho=-0.215 p=0.136	Rho=-0.341 p=0.052	Rho=0.149 p=0.306	Rho=0.130 p=0.470	Rho=0.050 p=0.833	Rho=-0.117 p=0.523
Left CST FC	Rho=-0.116 p=0.421	Rho=-0.123 p=0.495	**Rho=0.421 p=0.003**	**Rho=0.449 p=0.009**	Rho=0.124 p=0.395	Rho=0.156 p=0.394
Left CST FDC	Rho=-0.169 p=0.240	Rho=-0.213 p=0.234	**Rho=0.401 p=0.004**	Rho=0.418 p=0.015	Rho=0.101 p=0.490	Rho=0.065 p=0.722
Right CST FD	Rho=-0.195 p=0.174	Rho=-0.325 p=0.065	Rho=0.161 p=0.270	Rho=0.262 p=0.141	Rho=0.037 p=0.799	Rho=-0.078 p=0.672
Right CST FC	Rho=-0.137 p=0.344	Rho=-0.145 p=0.421	Rho=0.323 p=0.023	Rho=0.257 p=0.149	Rho=0.141 p=0.334	Rho=0.178 p=0.330
Right CST FDC	Rho=-0.214 p=0.136	Rho=-0.262 p=0.140	Rho=0.313 p=0.029	Rho=0.346 p=0.049	Rho=0.104 p=0.471	Rho=0.118 p=0.521
Corpus Callosum FD	Rho=-0.187 p=0.193	Rho=-0.357 p=0.051	Rho=0.262 p=0.068	Rho=0.205 p=0.252	Rho=0.092 p=0.530	Rho=0.008 p=0.964
Corpus Callosum FC	Rho=-0.132 p=0.361	Rho=-0.141 p=0.434	**Rho=0.397 p=0.005**	Rho=0.426 p=0.013	Rho=0.075 p=0.611	Rho=0.107 p=0.558
Corpus Callosum FDC	Rho=-0.160 p=0.268	Rho=-0.186 p=0.300	**Rho=0.421 p=0.003**	**Rho=0.435 p=0.011**	Rho=0.053 p=0.716	Rho=0.045 p=0.806

MCP FD	Rho=-0.094 p=0.517	Rho=-0.270 p=0.129	Rho=0.064 p=0.662	Rho=-0.001 p=0.997	Rho=0.143 p=0.328	Rho=-0.055 p=0.763
MCP FC	Rho=-0.105 p=0.467	Rho=0.044 p=0.810	Rho=0.247 p=0.088	Rho=0.361 p=0.039	Rho=0.078 p=0.593	Rho=0.085 p=0.644
MCP FDC	Rho=-0.113 p=0.434	Rho=-0.070 p=0.701	Rho=0.207 p=0.153	Rho=261 p=0.142	Rho=0.161 p=0.270	Rho=0.119 p=0.517
Results in bold survive correction for multiple comparisons (p<0.0125)						

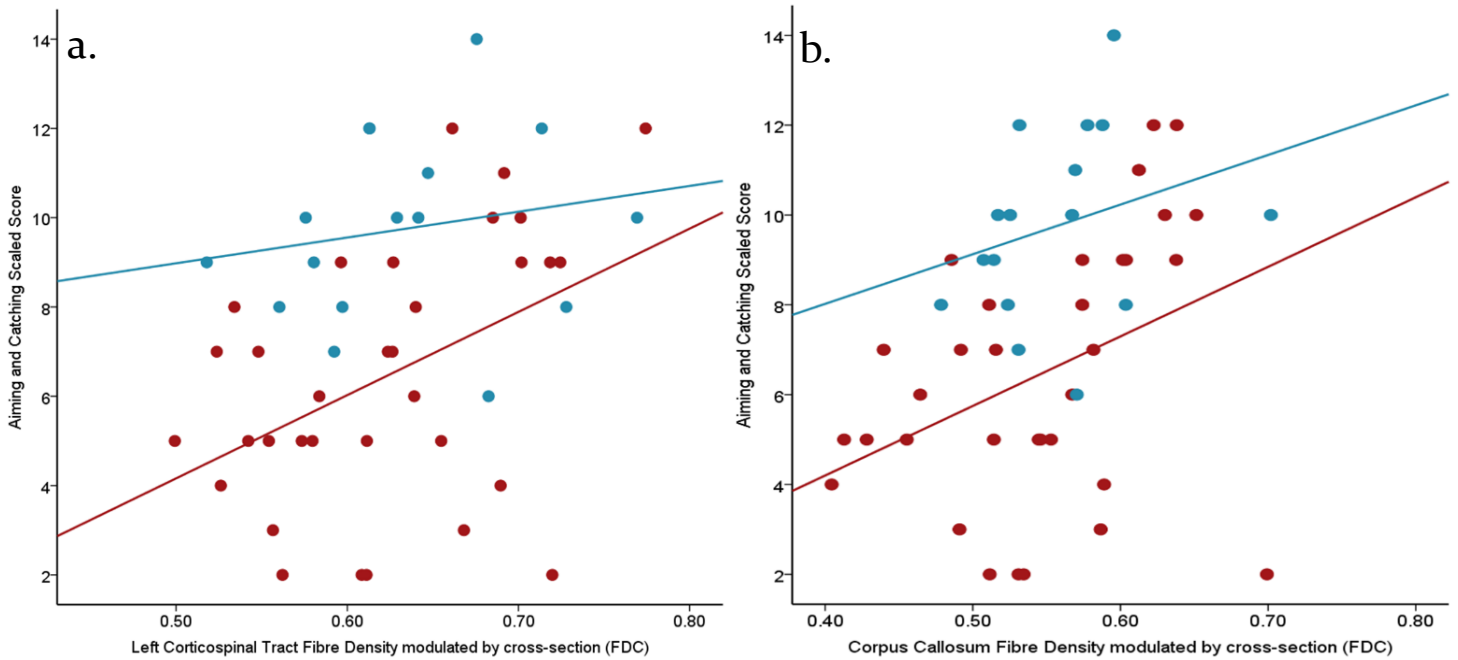

Figure 7.10 Correlation between aiming and catching score and FDC in a. left CST and b. whole corpus callosum (controls=blue; DCD=red)

Table 7.12 Association between fibre morphology and aiming and catching once handedness and full scale IQ is taken into account

Aiming and catching and left corticospinal tract FDC				
	B (SE)	**Beta**	**Significance**	**Adjusted R^2**
FSIQ	0.011 (0.024)	0.062	0.656	0.107
Handedness	1.354 (1.088)	0.171	0.220	
Left CST FDC	16.720 (6.323)	0.370	0.011	
Aiming and catching and corpus callosum FDC				
	B (SE)	**Beta**	**Significance**	**Adjusted R^2**
Full Scale IQ	0.015 (0.024)	0.088	0.529	0.096
Handedness	1.142 (1.090)	0.144	0.300	
Corpus Callosum FDC	16.057 (6.367)	0.349	0.015	

Predictors of Aiming and Catching

Left CST FDC, whole corpus callosum FDC and corpus callosum postcentral fibres FA were entered into a stepwise linear regression to predict aiming and catching score across the whole group. A significant equation was found ($F(2,46)=7.344$ $p=0.002$) with left CST FDC and FA in fibres connecting the postcentral gyri included as significant predictors of aiming and catching and explaining 24.6% of the variance in scaled scores (Table 7.13).

Table 7.13 Diffusion MRI predictors of aiming and catching score across the whole group

Predictors	**B (SE)**	**Beta**	**Significance**	**R^2 (Adjusted R^2)**
Model 1				
Postcentral fibres FA	37.818(12.132)	0.418	0.003	0.174 (0.156)
Model 2				
Postcentral fibres FA	31.991(12.056)	0.353	0.011	0.246 (0.213)
Left CST FDC	12.479(6.033)	0.275	0.044	

White matter correlates of attention scores in children with DCD

Tractography

Fractional anisotropy in the right superior cerebellar peduncle correlated with Score! scaled score in children with DCD (Table 7.14; Figure 7.11). This remained significant when handedness and FSIQ were controlled for with the model explaining 32% of the variance in Score! (Table 7.15). There was no correlation between creature counting score and diffusion microstructure.

Table 7.14 Correlations between track microstructure and attention scores in children with DCD

	Sustained attention (Score!)	**Attentional Control (creature counting)**
MCP FA	Rho=0.080 p=0.662	Rho=0.284 p=0.116
Left SCP FA	Rho=0.308 p=0.081	Rho=0.113 p=0.530
Right SCP FA	**Rho=0.435 p=0.011**	Rho=0.313 p=0.077
Right SCP RD	Rho=-0.125 p=0.490	-
Whole Corpus Callosum FA	Rho=0.042 p=0.815	Rho=0.117 p-=0.518
Superior frontal fibres FA	Rho=0.138 p=0.443	Rho=0.265 p=0.136
Rostral middle frontal fibres FA	Rho=0.080 p=0.659	Rho=0.121 p=0.501
Parietal fibres FA	Rho=-0.115 p=0.524	Rho=0.064 p=0.725

Results in bold survive correction for multiple comparisons (p<0.017)

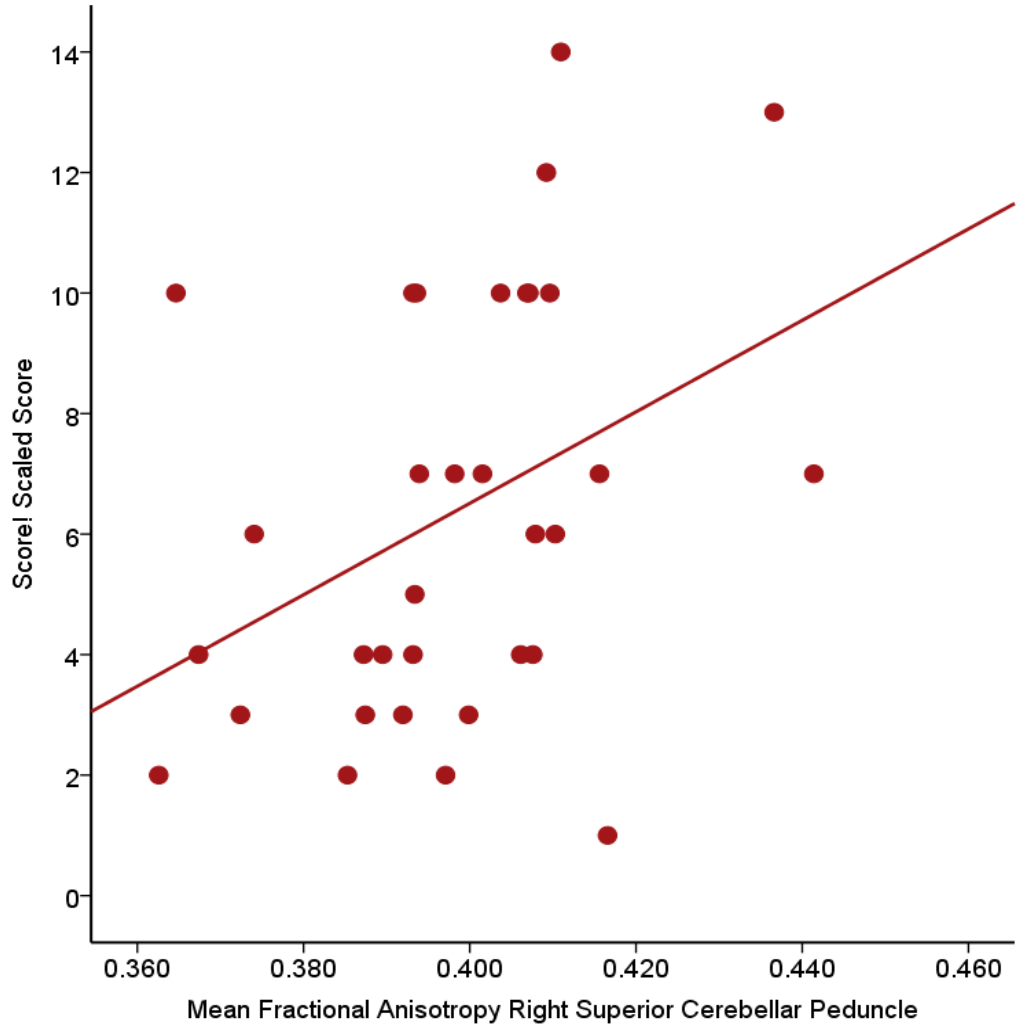

Figure 7.11 Correlation between Score! scaled score and FA in the right superior cerebellar peduncle in children with DCD

Table 7.15 Predictors of Score! scaled score in children with DCD

	B (SE)	Beta	Significance	R^2 (Adjusted R^2)
Handedness	0.915 (1.728)	0.086	p=0.600	0.324 (0.254)
FSIQ	0.081(0.03)	0.443	p=0.011	
Right SCP FA	63.189 (30.71)	0.321	p=0.049	

Fixel-based Fibre Morphology

There were no significant relationships between fibre morphology in the corpus callosum or middle cerebellar peduncles and attention scores (Table 7.16). There were also no significant regions in the fixel-by-fixel analysis.

Table 7.16 Correlations between measures of fibre morphology and attention scores in children with DCD

	Sustained attention (Score!)	Attentional control (Creature Counting)
Corpus Callosum FD	Rho=0.004 p=0.982	Rho=-0.071 p=0.693
Corpus Callosum FC	Rho=0.015 p=0.935	Rho=0.072 p=0.690
Corpus Callosum FDC	Rho=0.020 p=0.911	Rho=0.009 p=0.962
MCP FD	Rho=0.240 p=0.178	Rho=0.052 p=0.774
MCP FC	Rho=-0.099 p=0.584	Rho=0.054 p=0.767
MCP FDC	Rho=0.054 p=0.767	Rho=0.214 p=0.233

White matter correlates of speech and oromotor control in children with DCD

Tractography

Correlations were run between FA, AD and RD in bilateral CBT and focal oromotor control z-score because of the significant group difference identified in the section above. Focal oromotor control z-score was negatively correlated with RD in the right CBT (Table 7.17; Figure 7.12). One child had severe focal oromotor impairment (score of 181), with this child excluded the correlation remained significant (Rho=-0.494 p=0.009). Speech sequencing and focal oromotor control z-score also correlated with MCP FA however logistic regression revealed this effect was no longer significant once FSIQ and handedness were taken into account (Table 7.18).

Table 7.17 Correlations between microstructural measures and speech motor control in children with DCD

	Oromotor control	*Sequencing speech*
Left CBT FA	Rho=0.260 p=0.182	-
Left CBT AD	Rho=-0.018 p=0.929	-
Left CBT RD	Rho=-0.387 p=0.042	-
Right CBT FA	Rho=0.360 p=0.060	-
Right CBT AD	Rho=-0.05 p=0.801	-
Right CBT RD	**Rho=-0.533 p=0.003**	-
MCP FA	**Rho=-0.560 p=0.002**	**Rho=0.442 p=0.018**
MCP RD	Rho=-0.201 p=0.305	Rho=-0.218 p=0.266
Left SCP FA	Rho=0.256 p=0.181	Rho=0.321 p=0.090
Right SCP FA	Rho=0.368 p=0.050	Rho=0.411 p=0.027

Results in bold survive correction for multiple comparisons (p<0.0125)

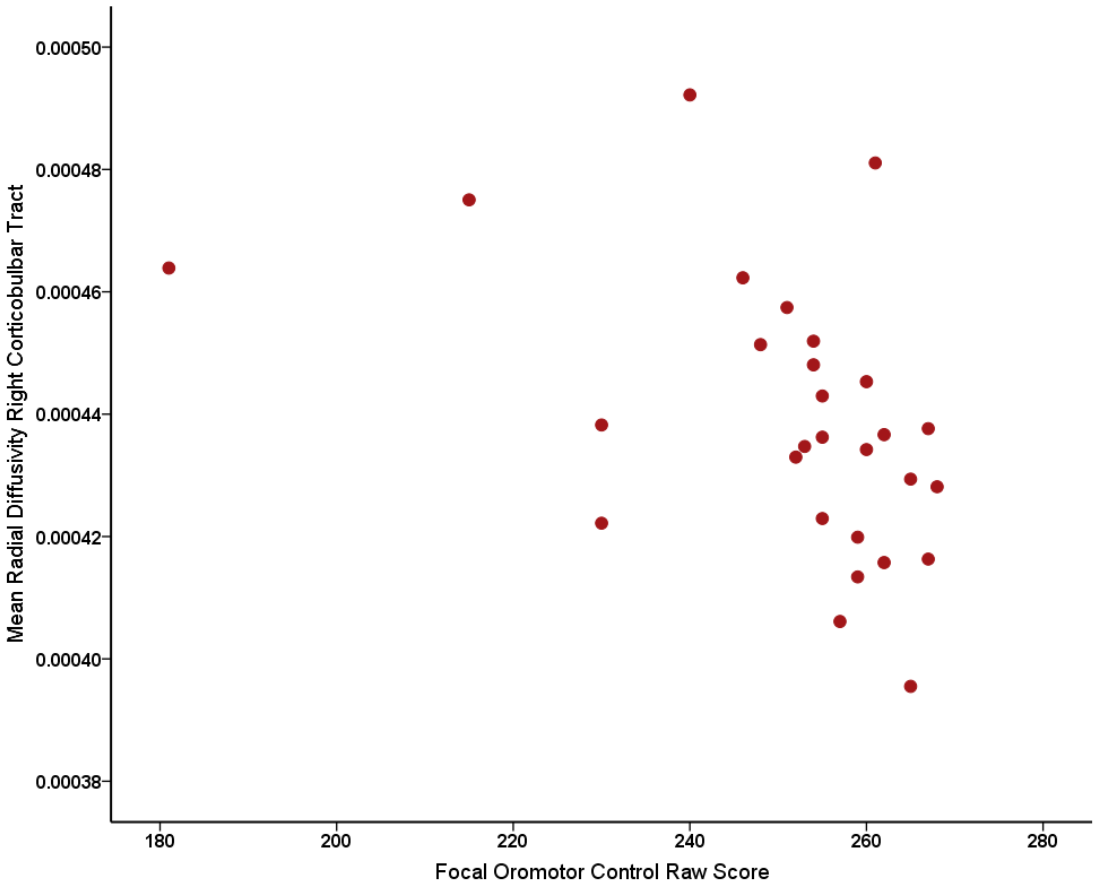

Figure 7.12 Correlation between focal oromotor control and radial diffusivity in the right CBT in children with DCD

Table 7.18 Predicting speech motor control impairments with MCP FA once FSIQ and handedness are taken into account

Focal oromotor control impairment in children with DCD				
	B (SE)	**Exp(B)**	**Significance**	**Chi-Square**
MCP FA	-36.8(29.3)	0	0.209	6.256 p=0.1
Handedness	1.1(1.39)	2.979	0.434	
FSIQ	-0.035(0.025)	0.965	0.151	
Sequencing impairment in children with DCD				
	B (SE)	**Exp(B)**	**Significance**	**Chi-Square**
MCP FA	-73 (50.8)	0	0.151	13.9 p=0.003
Handedness	-0.515 (1.78)	0.597	0.772	
FSIQ	-0.105 (0.053)	0.900	0.046	

Fixel-based Fibre Morphology

Focal Oromotor control z-score was significantly correlated with bilateral CBT FC in children with DCD (Table 7.19; Figure 7.13). As before, the correlations remained significant when the child with severe focal oromotor impairment (score of 181) was removed (left Rho= 0.480 p=0.010; right Rho=0.479 p-0.010). Speech sequencing and focal oromotor control also correlated with MCP FDC however this was no longer significant once FSIQ was taken into account (Table 7.20). There were no significant results in the fixel-by-fixel analyses.

Table 7.19 Correlations between fibre morphology and speech motor control scores in children with DCD

	Oromotor control	**Sequencing speech**
Left CBT FD	Rho=0.043 p=0.825	-
Left CBT FC	**Rho=0.420 p=0.023**	-
Left CBT FDC	Rho=0.350 p=0.063	-
Right CBT FD	Rho=-0.138 p=0.475	-
Right CBT FC	**Rho=0.437 p=0.018**	-
Right CBT FDC	Rho=0.307 p=0.103	-
MCP FD	Rho=0.147 p=0.445	Rho=0.147 p=0.445
MCP FC	**Rho=0.512 p=0.005**	**Rho=0.541 p=0.002**

MCP FDC	**Rho=0.482 p=0.008**	**Rho=0.510 p=0.005**

Results in bold survive correction for multiple comparisons (p<0.0017)

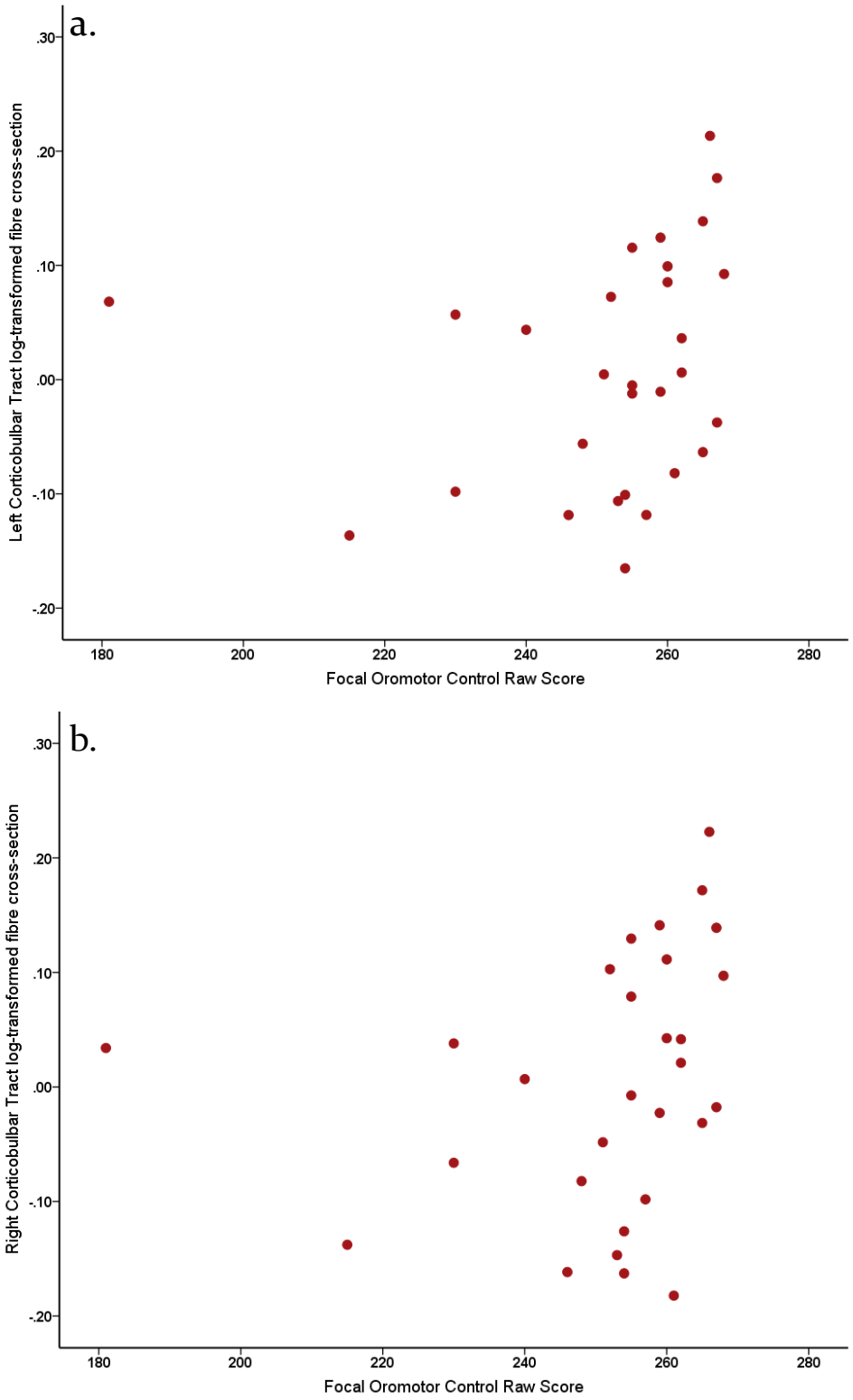

Figure 7.13 Correlation between a. left and b. right Corticobulbar tract fibre cross-section and focal oromotor control raw score in children with DCD

Table 7.20 Relationship between MCP FDC and speech motor control impairment in children with DCD with FSIQ and handedness taken into account

Focal oromotor control Impairment				
predictors	B (SE)	Exp(B)	Significance	Chi-Square
MCP FDC	-16.294 (13.224)	0	0.218	4.602 (p=0.203)
Handedness	1.616(1.395)	5.034	0.247	
FSIQ	-0.023 (0.023)	0.978	0.314	
Sequencing impairment				
predictors	B (SE)	Exp(B)	Significance	Chi-Square
MCP FDC	-16.647 (19.802)	0	0.401	12.625 (p=0.006)
Handedness	-1.774 (1.728)	0.170	0.305	
FSIQ	-0.107 (0.05)	0.898	0.032	

Predictors of speech impairment

Right CBT RD and bilateral CBT FC were entered into a logistic regression to determine significant predictors of presence of focal oromotor control impairment in children with DCD. Right CBT RD was the only significant predictor of group membership (Table 7.21; sensitivity=61.5%; specificity= 83.3%) .

Table 7.21 Predictors of Focal Oromotor control impairment in children with DCD

	B (SE)	Exp(B)	Significance	Chi-Square
Step 1 (final model)				
Right CBT RD	42298 (200385)	.	0.038	5.452 p=0.020

7.4 Discussion

In this chapter I analysed microstructural and morphological features from five white matter tracts which have been implicated in DCD. As hypothesised, measures of track microstructure and morphology in the pyramidal tracts, corpus callosum and cerebellum were significantly correlated with aiming and catching ability, sustained attention and focal oromotor control.

White Matter Correlates of motor abilities

Aiming and catching abilities across the whole sample were best predicted by FDC in the left CST and FA in the fibres of the corpus callosum connecting the postcentral gyri.

The left CST is the descending motor execution pathway associated with control of the right side of the body. Two previous studies with small samples have reported changes in the CST associated with DCD. One reported a positive correlation between FA in the right CST and a global motor index across adults both with and without DCD (Kashuck et al. 2017) and the other reported reduced MD in the CST and a positive correlation between AD and MABC-2 percentile score across the sample (Zwicker et al. 2012). We did not replicate results from either study. Inclusion of participants that do not meet full criteria for DCD may account for these differences.

Alterations in FDC in the left CST found here were not accompanied by changes in FA, AD or RD suggesting this novel measure may identify subtle correlates that are not reflected in traditional measures of tract microstructure, this is may reflect a reduction in size of the fibre bundle and reduced intra-axonal volume associated with reduced capacity to relay information (Raffelt et al. 2017). The correlations between FA in the fibres connecting postcentral gyri and aiming and catching score could reflect poor integration of somatosensory information across hemispheres. In Langevin and colleagues' (Langevin et al. 2014) study children with DCD had lower FA in the body of the corpus callosum which includes the fibres connecting the postcentral gyri. We have provided further anatomical specificity to this result by identifying a relationship between aiming and catching scores and microstructure of the corpus callosal fibres that connect the postcentral gyri. Our results suggest that alterations in structures associated with sensorimotor integration, and execution of motor commands are a feature of DCD. As this is not a prospective study it is not possible to determine whether this is the cause or an effect of poor aiming and catching abilities. Longitudinal MRI and behavioural research in infants and young children at risk for DCD would help clarify whether this is a causal relationship. The relationship between left corticospinal tract morphology, FA in the postcentral corpus callosum and aiming and Catching score compliments the relationships between motor scores and cortical morphology in left sensorimotor cortices identified in chapter six.

Pearsall-Jones and colleagues (Pearsall-Jones et al. 2010) suggested DCD may fall on a continuum of motor difficulties with cerebral palsy. Our results may lend support to this notion as microstructural changes in the CST are common in cerebral palsy, as are visible

lesions, and are associated with motor abilities in the condition (Scheck et al. 2012). Some children with DCD display similar risk factors for cerebral palsy in their medical history such as perinatal oxygen perfusion difficulties, or preterm birth (Pearsall-Jones et al. 2009; Jongmans et al. 1998). It is therefore possible that for some children with DCD may fall on Pearsall-Jones and colleagues' proposed continuum. Indeed, in our sample some parents of children with DCD reported various gestational and postnatal complications such as polyhydramnios, pre-eclampsia, preterm birth, and postnatal infection.

White Matter correlates of attention abilities

Within the sample of children with DCD, sustained attention was predicted by FA in the right SCP. The cerebellum has been implicated in attention and other cognitive abilities as well as motor skills (Stoodley & Schmahmann 2009; Keren-Happuch et al. 2014; Riedel et al. 2015; Salman & Tsai 2016). Recent functional connectome work has included the cerebellum in the sustained attention network (Rosenberg et al. 2016). Our results suggest connectivity between the cerebellum and cortical regions in the sustained attention network may be reduced in children with DCD and sustain attention difficulties. Further research utilising structural and functional network analysis would reveal whether this reduction in FA impacts this particular network.

There as a trend for the same effect in the left superior cerebellar peduncles (0.081 before correction for multiple comparisons) suggesting that this effect is larger in the right rather than truly right lateralised. Cerebellar fibres cross the midline and connect with the contralateral hemisphere of the cortex therefore the right superior cerebellar peduncle connects to the left cerebral hemisphere. As with the results from chapter six, there is likely a stronger effect of structure in the left cerebral hemisphere.

Nicolson and Fawcett (Nicolson & Fawcett 2007) propose that changes in the cortico-cerebellar networks underlie ADHD in children. Nevertheless our results are contrary to the limited research published regarding cerebellar white matter and ADHD which has implicated the middle cerebellar peduncles (Stoodley 2014; Stoodley 2016; Kasparek et al. 2015). Our results in this chapter and in chapter five suggest that sustained attention impairments in children with DCD are not solely caused by co-occurring ADHD.

With the methods utilised here it is not possible to know if specific connections between cerebellar lobules and regions of cortex are altered. Further research into the connectivity between the cerebellum and the cortex using graph theoretical analysis and fMRI paradigms examining sustained attention in children with DCD would yield further information regarding this relationship.

White matter correlates of Speech Motor Control

Children with DCD had significantly lower FA and AD but higher RD in the right speech motor tract (CBT) compared to typically developing children. RD in the right CBT and fibre cross-section in the bilateral CBT correlated with focal oromotor control z-score, despite no diagnoses of dysarthria or any visible lesions in the internal capsule in the sample. RD in the right CBT was the best predictor of focal oromotor control impairment in children with DCD. In contrast to children born prematurely and with traumatic brain injury (Northam et al. 2012; F Liegeois et al. 2013), the relationship between CBT and focal oromotor control in our sample was right, not left, lateralised. In addition, results from all other brain-behaviour analyses in this thesis were left lateralised. This may be unexpected however in a child with a FOXP2 mutation, FA in the right but not left corticobulbar track was reduced relative to controls (Liegeois, Hildebrand, et al. 2016). In chapter six we reported reduced bilateral thalamus volume was associated with focal oromotor control impairments which were also reported in the child with FOXP2. As this was a case study the authors were unable to explore brain-behaviour relationships however it is possible that focal oromotor impairments that are not the result of brain injury involve the thalamus and right CBT. Of note, movements necessary for speech recruit bilateral primary motor cortices and therefore require both corticobulbar tracts (Liegeois, Butler, et al. 2016).

Future directions

There were no correlations between white matter track features and manual dexterity, balance, speech sequencing abilities or set-switching scores. The neuroanatomical correlates of these abilities may lie in alternate white matter tracts such as the superior longitudinal fasciculus, cingulum bundle, cortico-striatal white matter or posterior thalamic radiations. Alternatively these abilities may not be related to white matter microstructure or morphology but either to grey matter structures identified in chapter six or functional and network organisation metrics not explored in this study. Further research using graph theoretical analysis of diffusion MRI data and functional MRI analysis methods would further delineate the neural correlates of these skills in children with DCD.

7.5 Conclusions

Diffusion-weighted MRI analysis in this chapter identified relationships between aiming and catching skills and features in tracts associated with sensorimotor functions but not the cerebellum. Children with poor aiming and catching abilities may display more

changes in white matter whereas difficulties with manual dexterity and balance may be cortical in nature. Taken together with the grey matter alterations identified in sensorimotor cortex identified in chapter six our results suggest children with DCD show alterations in circuits involved in sensorimotor integration. In addition, poor oromotor control was linked to primary motor pathways involved in movements of orofacial muscles. Taken together with the correlation with bilateral thalamus volume in chapter six this may suggest children with DCD and speech motor difficulties have disrupted sensorimotor circuitry across effectors. Cortico-cerebellar circuits may underlie sustained attention impairments in children with DCD. To our knowledge this is the first study to report white matter correlates of specific motor skills, speech motor control and sustained attention in children with DCD.

Chapter Eight: General discussion

Developmental Coordination Disorder is a common developmental disorder characterised by poor motor skills. DCD frequently co-occurs with ADHD, speech difficulties and language disorders. This thesis has characterised the nature of impairments outside of the motor domain in children with DCD and the relationship between additional impairments and motor skills. Despite occurring in 5% of school age children, little consensus exists regarding the neuroanatomical correlates of DCD. Utilising advanced T1-weighted and diffusion-weighted MRI analysis methods I have presented a body of work describing the neural correlates of poor motor skills in children aged 8-10. In addition, I have described neuroanatomical correlates of co-occurring oromotor control and sustained attention impairments in children with DCD.

8.1 Cognitive, speech and motor abilities in children with DCD

Chapter five provided an in-depth characterisation of the motor, IQ, attention, speech and language profiles of children with DCD aged 8-10 recruited in this PhD project. Children with DCD were impaired across all three domains of the M-ABC2, yet motor skills were not correlated with one another reflecting the heterogeneity of motor profiles in this condition. Once maternal education was accounted for, mean IQ within the sample was not significantly different to that of typically developing children.

Little evidence for impairments specific to the language domain

Eight children in our sample displayed language impairments but these were accompanied by non-verbal IQ impairments suggesting children with DCD do not display 'specific' language impairments. Additionally, language abilities were highly correlated with balance skills in children with DCD even once IQ was taken into account. Future research should include language and motor assessments in a large sample of children with DCD and those with DLD to test this hypothesis. Additionally, the balance subscale of the M-ABC2 is a composite of both static and dynamic balance tasks, further analysis of subtests would clarify whether these are equally impaired in our subgroup.

Sustained attention and attentional control impairments are prevalent

Performance on sustained attention, attentional control and processing speed tasks were significantly impaired in children with DCD independent of IQ or maternal education.

Together these tasks probe different domains of executive functions. An increasing body of literature had already shown children with DCD are impaired on experimental tasks of executive functions and Wechsler processing speed indices (Wilson et al. 2017; Biotteau, Albaret, et al. 2017; Sumner, Pratt, et al. 2016). We confirmed these findings utilising sustained attention, attentional control and processing speed tasks which do not require motor skills, indicating these cognitive impairments are unlikely to be the result of the core motor impairment. Previous work, particularly by Alloway and colleagues, has also shown widespread working memory impairments, another component of executive functions, in children with DCD. In our study, these cognitive scores were highly correlated and using regression followed by factor analysis I have shown that these skills aggregate into one factor likely representing impaired executive functions.

Speech and oromotor control difficulties are prevalent in children with DCD

We provided the first evidence from standardised assessments that children with DCD show widespread speech and oromotor deficits, indicating many show motor impairments across both limb and articulatory effector systems. Contrary to our hypothesis impairments in precise execution of simple orofacial commands were more widespread than deficits in sequencing of orofacial and speech movements. Little research has been done regarding early speech and oromotor difficulties, such as speech delay or feeding difficulties, in children with suspected DCD however our results may reflect a persistence of early speech and oromotor deficits.

Poorer motor skills are not associated with more co-occurring impairments

Finally, motor skills were not correlated with attention, processing speed or speech scores in children with DCD. Thus we found no evidence that children with more severe motor deficits were more likely to display additional impairments. We also did not find any evidence that a certain profile of motor impairments detectable using the M-ABC2 is associated with speech or attention impairments.

8.2 The neural correlates of DCD and associated impairments

Sensorimotor grey and white matter structure is associated with poor motor skills

In chapter six I explored the cortical and subcortical grey matter correlates of motor skills in DCD. In chapter seven I explore white matter correlates of these abilities in the superior and middle cerebellar peduncles, corpus callosum and corticospinal tract. As children with DCD fall on the severe end of a spectrum of motor skills, I used not only group differences but also brain-behaviour relationships across the whole sample and within the clinical group.

As hypothesised correlates of motor impairment were identified in cortical sensorimotor regions, however contrary to our hypotheses no subcortical structures were associated with poor motor skills. Children with DCD showed reduced cortical thickness in the left central sulcus compared to controls. Additionally, cortical thickness in this region was positively correlated with manual dexterity scores independent of IQ, handedness or total intracranial volume. Surface area across a larger region of left sensorimotor cortex inversely correlated with manual dexterity schools. Poorer aiming and catching scores were also inversely correlated with surface area in a more medial region of left sensorimotor cortex. In chapter seven, I explored morphological and microstructural properties of white matter tracts and their relationship to motor skills. Aiming and catching scores across the whole sample were predicted by FA in fibres of the corpus callosum connecting primary sensory cortices and by fibre morphology in the left corticospinal tract. These results suggest that impairments in fine motor and aiming and catching skills are characterised by alterations in the cortical regions responsible for final preparation and execution of motor commands and those receiving sensory information. The alterations that extend from primary motor into primary sensory cortex may support the hypothesis that children with DCD have poor sensorimotor representations of movement and poorly integrate sensory information with motor commands to control movement (See (Gomez & Sirigu 2015) for a review).Contrary to predictions derived from the automatization deficit and internal modelling deficit hypotheses, we did not find any relationship between poor motor skills and the cerebellum, basal ganglia or parietal cortex.

Structure in regions of domain general networks is associated with poor motor skills

In chapter six I provided evidence from exploratory analyses that some motor deficits in children with DCD also correlated with cortical thickness in regions of the brain implicated in domain-general cognitive networks. Aiming and catching score correlated with cortical thickness in the posterior cingulate cortex which forms part of the default mode network. Additionally, cortical thickness in the anterior insula, which forms part of the salience network, correlated with balance scores in children with DCD. The default mode network is active when a person is not engaged with a stimulus and the central executive network is active when the participant engages with a task (Raichle 2015). The salience network is responsible for switching between these two states (Goulden et al. 2014). Alterations in the default mode network have been implicated in a number of psychiatric and developmental disorders including ADHD and ASD (Padmanabhan et al. 2017; Faraone et al. 2015).

The relationship between balance and anterior insula thickness, which was not hypothesised, suggests that children with particular difficulties with balance may have alterations in the salience network. Little research has been done examining salience network functions in children with developmental disorders however there is some evidence of dysfunction in children with ASD (Green et al. 2016; Uddin et al. 2013; Uddin 2015). As we did not include a measure of social communication or ASD symptomatology it was not possible to identify whether children with particularly poor balance also had features of ASD. More work is needed studying the structure and function of the anterior insula in children with DCD. As only eight children displayed language impairments in this group we lacked the power to detect neural correlates of language abilities in DCD. Targeted recruitment of children with language impairments and examining the neural correlates would further this line of inquiry.

Although there is evidence from previous fMRI research into DCD of functional changes in the posterior cingulate (see chapter three for details), to date no resting state functional MRI literature examining default mode or salience network activity has been published. Based on my structural MRI findings I hypothesise that domain-general impairments in default mode and salience networks alongside alterations in sensorimotor networks underlie DCD. Domain general impairments may also leave a child vulnerable to additional developmental disorders. Alternatively, disruption of domain-general networks may distinguish children with DCD from children whose poor motor skills do not interfere with their daily lives. Further research is needed to test these hypotheses utilising functional MRI methods as well as replication of structural findings in independent datasets.

Cortical and subcortical structures are associated with co-occurring impairments in children with DCD

In chapters six and seven I explored the neuroanatomical correlates of attention, processing speed and speech abilities in children with DCD. Poor processing speed was associated with lower total surface area of the cortex. Poor sustained attention was associated with low FA in the right superior cerebellar peduncle. Finally, impaired focal oromotor control was associated with bilateral thalamus volume and radial diffusivity in the right corticobulbar tract. This is the first evidence of neural correlates of processing speed, sustained attention or focal oromotor control impairments in children with DCD. While the neural correlates of motor skills were primarily cortical in nature, co-occurring deficits may be associated with structure in subcortical circuits.

We found no evidence for a neural substrate of attentional control. This may be due to a stringent correction for multiple comparisons. Alternatively, the neural correlates of this impairment in children with DCD may be localised in tracts not examined in this thesis such as the cingulum bundle or superior longitudinal fasciculus (Bettcher et al. 2016; Murray et al. 2015). Attentional control may also be better explained by graph theoretical measures of structural network organisation, or by functional activation patterns (Bathelt et al. 2018; Daamen et al. 2015; Sripada et al. 2014). We also did not identify a neural basis for features of Childhood Apraxia of Speech or impaired sequencing of articulatory movements in children with DCD. It is important to note the neural correlates of CAS and speech sequencing impairments in children without brain injuries are still poorly understood (Liegeois et al. 2014; Morgan et al. 2016).

8.3 Theoretical Implications of this work

We did not find any evidence of cerebellar or basal ganglia correlates of motor skills in children with DCD. Correlates were confined to sensorimotor networks and domain-general networks responsible for efficient cognitive functioning. Our theoretical understanding of the neurobiology of DCD may therefore need to be revised to account for the role of domain-general networks in the impairment.

Our work also provides both behavioural evidence that motor deficits in children with DCD are heterogeneous, and neuroimaging evidence that these impairments have different neural correlates. Thus, it is unlikely that there is one region or pattern of regions that form an MRI marker for DCD. Instead DCD is likely a multivariate disorder characterised by structural changes in sensorimotor and domain-general regions where different patterns of structural changes are associated with different motor deficits but the same clinical diagnosis. This view provides a novel neuroanatomical explanation for the heterogeneous motor profiles of children with DCD.

From the behavioural characterisation reported in this thesis, it is clear that a high proportion of children with DCD display impairments in executive functions and speech/oromotor functions. Only four children out of thirty-six in our sample did not fall into the impaired range on any of these tests, and we cannot rule out that these children show impairments on selective attention, social communication, reading or symptoms of ADHD not assessed here. The range of abilities in children with DCD and lack of a relationship between impairments identified in this work suggests independent axes of impairment rather than distinct subtypes or a singular spectrum of severity.

I have addressed many of the methodological issues with previous imaging research in children with DCD (see section 3.9).I characterised the largest sample of children with DCD who meet DSM diagnostic criteria with adequate power to detect MRI correlates of behavioural variables in children with DCD. Shaw and colleagues (Shaw et al 2016) included a larger sample of children with DCD (22 DCD alone, 41 DCD +ADHD) however they did not necessarily meet DSM criteria and were from a large age range (4-16.9). I tested a small age range which limited the effect of age-related brain changes on the results. I also recruited children with DCD regardless of co-occurring disorders to ensure the results were more representative of the larger population of children with DCD than previous literature. In MRI analyses I corrected for IQ in order to remove the effect of general cognitive abilities when examining group differences and brain-behaviour relationships and utilised stringent statistical corrections to reduce the chance of false-positive statistical errors.

As this study did not include fMRI measures we were not able address the methodological limitations of this literature.

8.4 Clinical Implications of this work

Assessment of children with DCD

As discussed above, we have identified extensive impairments outside of the motor domain in children with DCD. In current NHS clinical practice, children with suspected DCD are assessed by an occupational therapist or physiotherapist before a paediatrician makes a formal diagnosis based on standardised and clinical assessments, school and parental reports, and medical history. Our data suggest assessment by a multidisciplinary team including a clinical or educational psychologist and speech and language therapist is necessary to fully characterize the impairments in a child with DCD. Indeed we show evidence that children with DCD who are about to move to secondary school are at high risk of speech and attention impairments likely to impact their school functioning (Amso & Scerif 2015; Skebo et al. 2013).

Intervention and support

Based on the results of our research, further research is needed regarding the impact of cognitive impairments on motor intervention strategies. Of particular interest is the Cognitive Orientation to Daily Occupational Performance (CO-OP) approach. CO-OP is designed to enable skill acquisition through use of cognitive strategies (Missiuna et al. 2001; Milller et al. 2001; Smits-Engelsman et al. 2013; Jokic et al. 2013). In this intervention typically a child follows a 'think-plan-do-check' model to achieve a skill of their choice.

Additional impairments in executive functions such as processing speed, sustained attention and attentional control may impact on the efficacy of this intervention, requiring adaptation. These findings should be brought to the attention of both teachers and parents so that educational support for executive functions and speech difficulties are available to children as well as support with motor skills. Refining our knowledge of the brain networks implicated in DCD may help with the future development of targeted behavioural or pharmacological interventions.

8.5 Limitations of this work

Recruitment and sample selection

Most children with DCD who participated in this study were recruited through charities and private clinicians rather than through NHS sites. It is possible that families engaged with these recruitment sites have children with an increased rate of additional impairments, more difficulties at school, and for whom NHS and school-based assessments have proved inadequate. An alternative approach to a study into children with DCD would be to foster relationships with schools rather than medical clinics. This would allow i) the recruitment of children with DCD who are not involved with charities ii) the recruitment of typically developing children matched for socioeconomic status and educational environment.

Additionally, not all children in our sample had a confirmed diagnosis of DCD from a paediatrician. As there was no paediatrician on the research team we cannot rule out that some children in our sample had alternate motor disorders such as mild cerebral palsy or genetic syndromes which a paediatrician would detect. We also included children who have had differing levels of intervention for motor and speech disorders as well as those taking/have recently taken medication for ADHD. The child's brain is a dynamic system which is constantly maturing, with major changes occurring in the first decade of life as a result of interactions between environment, gene influences and brain development (Johnson 2011). Therefore it is not possible to rule out the effects of medication or intervention on our behavioural or neuroimaging analyses. Recruiting a sample of medication and intervention naïve children would eliminate these effects.

Sample Size

Although we met our targeted sample size for children with DCD, recently published neuroimaging literature examining the neural correlates of developmental disorders or neuropsychological impairments include samples of over 100 children (Bathelt et al 2018; Bathelt et al 2017; Stephens et al 2017). Although we included a small age range, subtle

neurobiological effects that nevertheless are likely to contribute to the multivariate nature of DCD were likely missed. It is possible our negative results in the basal ganglia and cerebellum reflect a lack of statistical power. Indeed, Hoogman and colleagues detected a difference in basal ganglia volumes in a multi-centre sample of 1713 children and adults with ADHD compared to 1529 controls (Hoogman et al 2017). A larger sample would also allow us to determine the effects of individual impairments while controlling for additional deficits such as ADHD symptoms and attention. Further recruitment including collaborations with other research groups to build a large sample of children with DCD who have had both MRI and behavioural testing will allow researchers to elucidate these effects.

We also recruited fewer typically developing children than expected which may have resulted in under-powered group difference comparisons. It is likely that recruitment of more typically developing children would result in more significant group differences.

Motor Assessment

Although we utilised a standardised clinical assessment of motor skills, the M-ABC2 does not provide insight into the underlying deficit in DCD. Thus we were not able to determine whether children in this sample had difficulties with motor learning, planning, online motor control or sensory feedback. It may be that no single deficit underlies DCD, but rather different underlying impairments manifest as coordination difficulties. It is also possible that different underlying deficits are associated with i) different additional impairments and ii) different neural correlates.

Statistical Interactions

Statistically while we examined brain-behaviour relationships throughout our sample we did not test for interactions, brain-behaviour relationships that distinguish between children with DCD and typically developing children. These statistical models were not utilised because our control group consisted of only 17 children, limiting the ability to detect robust parametric correlations. Utilising interaction models would further elucidate brain-behaviour relationships that are significantly different from typical children compared to those that form a spectrum across children of all abilities.

Attention and ADHD

As discussed in chapters two and five, ADHD is not diagnosed using results from standardised tests of attention and the TEA-Ch is not utilised clinically to identify children with DCD. Indeed, previous literature has indicated that performance on various subtests of the TEA-Ch can be preserved in children with ADHD (see Paton et al. 2014 for an

overview). In our sample removing those children with a diagnosis of ADHD did not alter the differences in sustained attention or attentional control. This could be because the TEA-Ch is not measuring the same impairment as that found in ADHD, or because many children in our sample who did not have a diagnosis of ADHD may meet the diagnostic criteria. Most children with DCD who participated in our study did not have a diagnosis of ADHD nor had they ever been assessed for the disorder to our knowledge. As we did not have access to clinical tools for diagnosing ADHD nor was a clinician included in the research team, it was not possible to accurately examine ADHD symptomatology. Future collaboration with researchers who works with children with ADHD would allow us to characterise motor impairments in ADHD, ADHD symptomatology in DCD, and the behavioural and neuroanatomical nature of co-occurrence. Nevertheless, our study provides evidence of everyday attention impairments in children with DCD, which have not been thoroughly examined in the previous literature.

8.6 Future directions

Replication of findings

We have reported novel findings regarding deficits outside of the motor domain in children with DCD and the MRI correlates of impairments. Although we have used statistical correction it is possible these results may include false positives. Replication in an independent sample would confirm our findings. Collaborations with other research groups would also allow us to test these effects in larger samples and different age groups.

A Dimensional Approach

Another approach to determining the relationship between impairments in childhood would be to recruit a large sample of children with difficulties at school regardless of diagnosis and testing for relationships between impairments. For example, Bathelt and colleagues applied data-driven clustering methods to understand the relationship between conner-3 rating scale scores in 442 children with difficulties at school (Bathelt et al 2018). The authors also identified white matter correlates of subtypes. As discussed above, recruitment of a larger sample would allow researchers to use these methods.

The nature of co-occurring deficits

In this study we have extensively characterised motor, attention and speech difficulties in a sample of children with DCD. We did not characterise all additional co-occurring difficulties such as working memory, social communication or reading (see chapter two for a summary of the existing literature). Future work to understand the nature of these deficits in children with DCD will increase our understanding of the disorder.

Additionally, this thesis focussed on co-occurring impairments in children with DCD. The occurrence of DCD in children with other neurodevelopmental disorders was not examined. Future work examining the neural correlates of motor abilities in children with DLD, ADHD, everyday attention difficulties and speech disorders will enrich our understanding of the neural correlates of these frequently co-occurring impairments.

Functional imaging analysis

It is necessary to determine whether structural MRI correlates are accompanied by fMRI activation or connectivity changes, particularly in the functionally derived default mode and salience networks. The limited fMRI literature available (see chapter three) provides evidence of activation differences across frontal, parietal and cerebellar cortices however there has been limited replication due to differences in fMRI task. Task-based and resting state fMRI methods may be more sensitive to the neural correlates of additional impairments in children with DCD. Further research using resting state fMRI to characterise sensorimotor, default mode and salience networks will allow us to explore whether structural brain correlates identified in this thesis are accompanied by functional changes in the brain, independent of fMRI task.

Early behavioural markers of DCD and additional impairments

DCD is emerges in early childhood and is typically diagnosed from the age of five. Future research should examine whether the additional impairments identified in this study are present in young children when a motor impairment is emerging. Assessing motor, attention, language and speech/oromotor functions in children below age six would determine whether these impairments co-occur early or whether additional impairments emerge in later childhood. Additionally, diagnostic tools to assess poor motor skills in infants and toddlers should be developed. Early assessment tools would allow researchers to develop early interventions which could prevent motor deficits from emerging rather than attempting to intervene when the deficit is already present at school age.

Additional impairments in DCD in adulthood

As discussed in chapter one, DCD is increasingly recognised as a lifelong condition that persists into adulthood. Future research to examine whether the pattern of co-occurring impairments identified here is present in adults would determine whether these co-occurring deficits persist. Additionally, the presence of additional impairments may give insight into why some adults with DCD have significant difficulties with activities of daily living, while others do not. A Long-term prospective longitudinal study would allow us to

determine whether behavioural and imaging correlates identified in this study predict long term outcome in children with DCD.

Does DCD reflect a delay or deviance from normal development?

The brain is a dynamic system which undergoes myelination, network organisation and cortical maturation throughout childhood (Berardi et al. 2015; Blakemore 2012; Raznahan et al. 2011; Houston et al. 2014; Weiss-Croft & Baldeweg 2015; Wierenga et al. 2018). Longitudinal studies are needed to understand whether behaviour and neuroanatomical features identified in this thesis are persistent in DCD throughout childhood, or whether they are transient and only occur at a particular age. In addition, we need to understand whether these behavioural impairments and neural features represent a delay or deviance from normal developmental trajectories.

The Aetiology of DCD

The aetiology of DCD is currently unknown and it is unclear whether different patterns of impairments are present in different aetiological groups. Motor, attention, speech and language abilities should be investigated in children with DCD and i) benign epilepsy with centrotemporal spikes (Kirby et al. 2017) ii) premature birth iii) histories of adversities during gestation or postnatally iv) family histories suggesting a genetic aetiology. Understanding the behavioural and neuroanatomical nature of DCD in these clinical groups would determine whether separable subtypes of DCD can be identified based on aetiology. Additionally, if we can determine different profiles are associated with different aetiology, clinical practice may be tailored and effective interventions adapted. A prospective longitudinal study of infants and toddlers at risk of DCD including MRI and behavioural assessments in infancy and childhood would also allow researchers to determine causal mechanisms and associations that remain constant throughout childhood.

8.7 Conclusions

In conclusion, the data presented in this thesis provides evidence that children with DCD are likely to have impairments in executive functions and speech/oromotor control alongside motor difficulties. We have provided novel evidence that suggests, while cerebellar and basal ganglia structures are intact, structure of sensorimotor circuits and cortical regions that form part of the default mode and salience networks may be related to DCD (Figure 8.1). This may result in poor sensorimotor integration during motor

control. Additional oromotor and sustained attention difficulties in children with DCD were associated with structural alterations in the subcortical networks. Our work suggests that the neural correlates of DCD are multivariate, possible reflecting different aetiological pathways to motor impairments. Clinically children with DCD should routinely be assessed for attention and speech/oromotor impairments and that the impact of additional impairments on intervention studies should be elucidated.

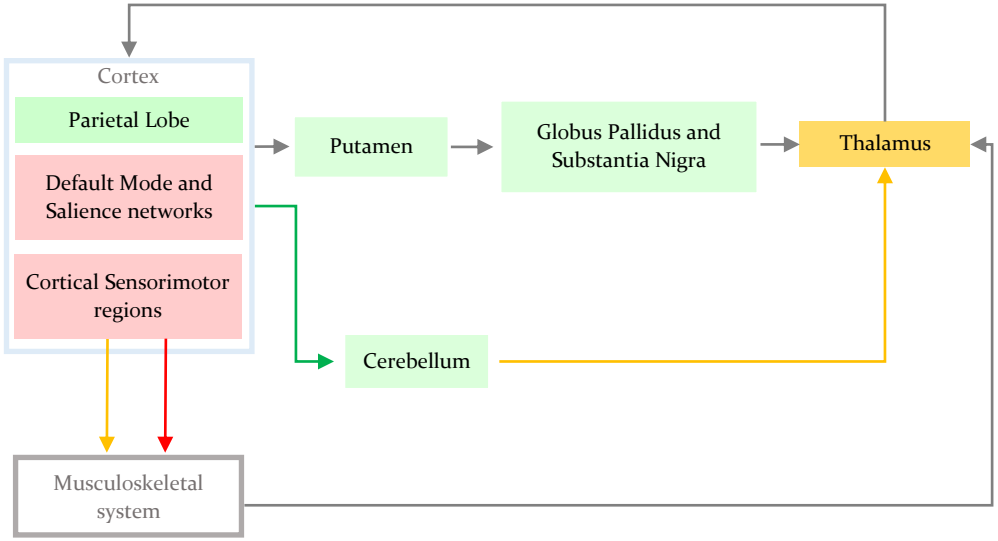

Figure 8.1 Proposed neurobiological model of DCD. Boxes represent grey matter structures and arrows represent white matter. Red= motor correlates; Orange= co-occurring impairment correlates; green=preserved; Grey=not examined in this thesis

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Appendix A: Missing data

Table A.1 Number of missing datasets for each assessment and questionnaire for children with DCD and typically developing children

	Number of children with DCD	Number of typically developing children
Motor Assessment		
M-ABC2 Manual Dexterity	0	0
M-ABC2 Aiming and Catching	0	1
M-ABC2 Balance	1	0
DCD-Q	3	0
M-ABC2 checklist	1	0
IQ Assessment		
WASI-II	0	0
Attention and ADHD Assessment		
TEA-Ch Sky Search	0	0
TEA-Ch Score!	0	0
TEA-Ch Creature Counting	0	0
TEA-Ch Sky Search DT	2	0
TEA-Ch Same/opposite worlds	1	2
Conners-3 Parental Questionnaire	2	0
Speech and Language Assessment		
CELF-IV	0	1
VMPAC Focal Oromotor control categorisation	3	2
VMPAC Focal Oromotor control z-score	6	2
VMPAC sequencing categorisation	2	2
VMPAC sequencing z-score	5	2
Park play	3	2

Note: Some children started but did not complete the VMPAC assessment. For some of these children it was still possible to categorise them into either impaired or unimpaired on the focal oromotor or sequencing subscales. The procedure was as follows:

i) Score and sum the completed stimuli as expected

ii) Determine the child's lowest possible score by summing the completed stimuli score and the lowest possible scores on stimuli not completed

iii) Determine the child's highest possible score by summing the completed stimuli score and the highest possible scores on stimuli not completed

iv) If the highest possible score on a subscale is below the cut-off for categorisation as impaired then the child is placed in the impaired group

v) If the lowest possible score on the subscale is above the cut-off for categorisation as impaired then the child is placed in the unimpaired group

vi) If neither iv nor v were possible then the data was missing