Coordination and sensorimotor difficulties in children with 22q11.2 deletion syndrome: relationships with cognition and psychopathology

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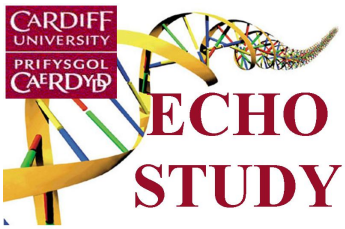

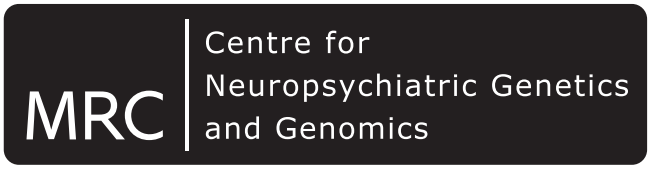

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I would firstly like to thank my primary supervisor, Prof. Marianne van den Bree for her invaluable advice, guidance, feedback and patience. I would also like to thank my secondary supervisors, Prof. David Linden and Prof. Michael Owen, for their insightful feedback and support. I have been extremely lucky to have such a helpful and supportive supervisory team over the last four years.

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I must thank all past and present members of the ECHO study team for providing the resources to allow me to carry out this project, along with all the participants and families who have taken part.

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Last but certainly not least, special thanks must also go to my partner and closest friend Zoe Evans for looking out for me, listening to me and motivating me when needed, through the roller coaster of experiences that make up a PhD. I, therefore, dedicate this thesis to her.

Contributions

I carried out all literature reviews and summarised all background information for the projects contained in this thesis.

With regards to analyses based on the developmental coordination disorder questionnaire (DCDQ), I calculated all scores and assigned diagnoses. I carried out all analyses using the DCDQ data and interpreted the results

Neurocognitive and sensorimotor data was primarily collected by members of the ECHO field team, as part of data collection visits to families' homes. Data from a small number of individuals were collected by myself. I derived and summarised all neurocognitive variables for analysis. I derived all cognitive and sensorimotor variables. I also cleaned and formatted the sensorimotor data for analysis and storage. I trained members of the ECHO field team on how to conduct the sensorimotor battery. I carried out all analyses using the sensorimotor data and interpreted the results.

Psychiatric interview data was mostly collected by members of the ECHO field team; again I conducted psychiatric interviews for approximately 10 individuals whose home visits I attended. I derived all symptom counts, and helped with the assignment of research diagnosis, through scoring and checking completed interviews.

For the projects based on the Occupational Therapy data, I conducted all Pre-and Post-intervention psychiatric interviews and pre and post questionnaire data collection. I conducted neurocognitive and sensorimotor testing for two of the Pre-and Post-occupational therapy intervention sessions. Members of the ECHO team collected the Neurocognitive data for the

remaining two sessions. The COPM interviews were carried out by the Occupational Therapists Sue Delport and Wendy Cumines. Movement ABC and Beery VMI assessments were also carried out by the Occupational Therapists. During these interviews and assessments, they were supported by occupational therapy students who were employed as research assistants. I helped design the pilot intervention study with Prof. Monica Busse, Sue Delport and Wendy Cumines, particularly in selecting psychiatric outcome measures. I recruited all participants who took part in the occupational therapy assessments and pilot intervention. I carried out all statistical analysis of the data from occupational therapy assessments and pilot intervention and interpreted the results.

With regards to neuroimaging data, Dr Joanne Doherty and I organised all MRI data collection visits. I processed and analysed all imaging data presented in this thesis and interpreted the results.

All work was carried out according to the guidance of my supervisors, Prof. Marianne van den Bree, Prof. Michael Owen and Prof. David Linden.

Manuscripts resulting from the work in Chapter 3 were commented on by my supervisors along with Prof. Jeremy Hall, Prof. Monica Busse, Sue Delport and Wendy Cumines. These comments were incorporated into the thesis.

Manuscripts resulting from the work contained in Chapter 4 were commented on by my supervisors, along with Dr Liam Hill and Prof. Mark Mon-Williams. These comments were incorporated into the thesis.

Publications based on this thesis

Adam C Cunningham, Sue Delport, Wendy Cumines, Monica Busse, David E J Linden, Jeremy Hall, Michael J Owen, and Marianne B M van den Bree. **Developmental coordination disorder, psychopathology and IQ in 22q11.2 deletion syndrome.** (Under review)

Adam Cunningham, Liam Hill, Mark Mon-Williams, David E. J. Linden, Jeremy Hall, Michael J. Owen and Marianne B.M. van den Bree. **Sensorimotor processing in 22q11.2 deletion syndrome and links with psychiatric disorder and cognition.** (In preparation)

Publications to which I have contributed

Daqiang Sun, Christopher Ching, Amy Lin, Jennifer Forsyth, Leila Kushan, Ariana Vajdi, Maria Jalbrzikowski, Laura Hansen, Julio Villalon-Reina, Xiaoping Qu, Rachel K. Jonas, Boris A. Gutman, Therese van Amelsvoort, Geor Bakker, Wendy R. Kates, Kevin M. Antshel, Wanda Fremont, Linda E. Campbell, Kathryn L. McCabe, Eileen Daly, Maria Gudbrandsen, Clodagh M. Murphy Declan G. Murphy Michael Craig, Jacob Vorstman, Ania Fiksinski, Liz Gras, Kosha Ruparel, David Roalf, Raquel E. Gur, J. Eric Schmitt, Tony. J Simon, Naomi J. Goodrich-Hunsaker, Courtney A. Durdle, Anne S. Bassett, Eva W. C. Chow, Nancy Butcher, Fidel Vila-Rodriguez, Joanne Doherty, Adam Cunningham, Marianne van den Bree, David Linden, Michael Owen, Beverly Emanue, Theo Van Erp, Jessica Turner, Paul M. Thompson, Carrie E. Bearden. **Large-Scale Mapping of Cortical Alterations in 22q11.2 Deletion Syndrome: Convergence with Idiopathic Psychosis and Effects of Deletion Size.** (Under review)

Katy Hamana, Sue Delport, Wendy Cumines, Adam Cunningham, Monica Busse, Lynsey Thain, Jessica Hufflett, Marianne Van den Bree. **Experiences of everyday living with 22q11.DS; child and parent perceptions.** (In preparation)

Summary

In this thesis, I explored the relationships between motor ability, psychopathology and cognition in children with 22q11.2 deletion syndrome (22q11.2DS). Firstly, I established the prevalence of coordination difficulties in a sample of children with 22q11.2DS and investigated if coordination difficulties were related to psychopathology or cognitive ability. I found that rates of coordination difficulties were very high (~80%) in children with 22q11.2DS and that poorer coordination was related to psychopathology, IQ and attention performance. Second, I investigated sensorimotor performance in children with 22q11.2DS and its relationships with psychopathology and cognition. I found that children with 22q11.2DS had deficits in sensorimotor performance and that sensorimotor performance was related to attention, spatial planning and spatial working memory ability, but not psychopathology. Third, I investigated coordination using occupational therapy assessments in 10 children who previously screened positive for coordination difficulties, to assess how well a questionnaire measure captured coordination difficulties in this population. Eight of ten of the children assessed were assigned a diagnosis of developmental coordination disorder. In addition, I describe a pilot intervention study in two individuals with 22q11.2DS, which attempted to help improve their coordination skills. Finally, I investigated the brain structure of children with 22q11.2DS and how coordination is related to brain structure. The results showed that children with 22q11.2DS have changes in cortical surface area and volume of the parietal lobe and a larger caudate than unaffected sibling controls, but no relationship was found with coordination. Using diffusion imaging, I investigated the integrity of the cerebellar input and output tracts and found differences in the structure of the inferior cerebellar peduncle. These changes were not related to coordination scores. These results have potentially important implications for our understanding of the relationships between coordination difficulties and other commonly seen psychiatric disorders in 22q11.2DS.

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1 Introduction

1.1 Copy number variation

Genetic variation in individuals can take a number of forms. Single Nucleotide Polymorphisms (SNP's) are single base pairs of DNA that differ between individuals. These SNPs can have beneficial, deleterious or no effect on the genes they occur in, and therefore on the proteins that are encoded from the affected section of DNA. Many SNPs have been shown to be associated with diseases when particular genes are disrupted, and are related to risk for many psychiatric disorders.

However, many diseases and disorders, both psychiatric and physical, are not simply caused by changes in a single gene. Complex disorders such as Diabetes, Schizophrenia, and Alzheimer's disease are still being researched actively in order to find genetic changes that are associated with risk of developing the disorders. Investigations into genetic variation found that in addition to these small single nucleotide changes throughout the genome, larger scale changes can occur which disrupt the physical arrangement of genes on chromosomes. These can range from the deletion or duplication of entire chromosomes, and all the genes contained on the chromosome, to deletions, duplications or translocations of either single genes or a section of the chromosome containing multiple genes. Changes of this type are called copy number variants (CNV's).

A number of CNVs have been associated with increased risk of developing disease. Schizophrenia has been associated with 22q11.2 deletions, 1q21 deletions/duplications, 3q29 deletions and many others (Rees *et al.*, 2014). Autism spectrum disorder has been associated with deletions and duplications at 16p11.2, 22q11.2 deletions, along with 1q21.1 deletions and

duplications (Doherty and Owen, 2014). In addition, many CNVs that confer risk for psychiatric problems, do so for multiple disorders. For example, 16p11.2 deletion/duplication is associated with intellectual disability, schizophrenia, autism spectrum disorder, attention deficit disorder, mood disorders and anxiety disorders (Guilmatre *et al.*, 2009; Shinawi *et al.*, 2010; Zufferey *et al.*, 2012; Doherty and Owen, 2014; Hanson *et al.*, 2014; Rees *et al.*, 2014). Patients with copy number variants can have complex combinations of physical and mental health difficulties, which highlights the multi-system effects of pathogenic CNVs.

1.2 22q11.2 Deletion Syndrome

22q11.2DS is a CNV disorder that is caused by a hemizygous deletion on the long (q) arm of chromosome 22 (Driscoll, Budarf and Emanuel, 1992) and is estimated to occur in approximately 1 in 2000 to 4000 live births. Deletions and duplications occur at a high rate in this region due to the presence of low copy repeats (LCRs) which increase the chance of non-allelic homologous recombination (Emanuel, 2008). There are four areas of LCRs in the 22q11.2 that deletions can occur between. The typical 3Mb deletion region is flanked by breakpoints LCR22A and LCR22D and it is deletions between these regions are found in the majority (≈90%) of patients (Carlson *et al.*, 1997; Edelmann, Pandita and Morrow, 1999). Smaller nested deletions can occur between LCR22A and LCR22B or LCR22C, resulting in deletions of 1.5Mb or approximately 2Mb respectively. Patients with these nested deletions have similar phenotypic presentations as those with the typical deletion, but these nested deletions make up only approximately 5-10% of patients with the syndrome (McDonald-McGinn *et al.*, 2015). It is currently not well understood why the phenotypic presentation of the larger and smaller deletions are so similar despite the difference in loss of genetic material.

A large number of symptoms are associated with the loss of the 22q11.2 region including cleft palate, conotruncal heart defects, immune dysfunction and minor facial abnormalities, which led to different groupings of symptoms to be termed different syndromes. A number of syndromes were thus identified, all associated with deletion of the same region on chromosome 22q, including DiGeorge syndrome (Di George, 1965); 'conotruncal anomaly face syndrome' or Takao syndrome (Kinouchi *et al.*, 1976), Sedlácková syndrome (Sedlácková, 1967), Cayler syndrome (Cayler, 1969), Shprintzen syndrome, and velocardiofacial syndrome (VCFS) (Shprintzen *et al.*, 1981). Identification of the presence of the 22q11.2 deletion in most of these patients ultimately led to the unification of the syndromes under the label 22q11.2DS.

Phenotypic presentation of the deletion can be variable. While a common reason for genetic testing is the combination of a cleft palate and conotruncal heart defects, immune dysfunction and hypocalemia are also common (Bassett *et al.*, 2011). There can be facial dysmorphism, including a bulbous nasal tip, small low set ears, increased distance between the eyes and hooded eyelids, amongst other signs. Some patients may have many dysmorphic features while others may show little or none, and similarly, some patients with 22q11.2DS may require treatment for many medical problems while others may show few or no symptoms at all.

Approximately 90% of deletion cases are de novo (Mcdonald-Mcginn *et al.*, 2001), meaning that the deletion is not inherited from the parents. The remaining 10% of cases are inherited, but it is not uncommon for the parent to be unaware that they carried the deletion. There is some evidence that inherited deletions have a more severe phenotype (Swillen *et al.*, 1999).

In addition to physical symptoms, 22q11.2DS is associated with a mild to moderate learning disability, with children with the deletion having an IQ around 30 points lower than controls

as found by the 22q11.2 International Brain and Behaviour Consortium (IBBC) (Schneider *et al.*, 2014) and other studies (De Smedt *et al.*, 2007; Niarchou *et al.*, 2014). 22q11.2DS also confers high risk for the development of various psychiatric disorders. The most striking of which is a strong association with the development of schizophrenia. Around 25% of people with 22q11.2DS will go on to develop schizophrenia (Murphy, Jones and Owen, 1999; Monks *et al.*, 2014; Schneider *et al.*, 2014). The deletion is also associated with increased rates of Attention Deficit Hyperactivity disorder (ADHD), primarily of the inattentive subtype, anxiety disorders and ASD (Angkustsiri *et al.*, 2014; Niarchou *et al.*, 2014; Schneider *et al.*, 2014; Richards *et al.*, 2015). Similar to the pattern of physical symptoms seen in 22q11.2DS, the psychiatric phenotype is variable, and children can display symptoms from a range of DSM diagnoses, while not meeting full diagnostic criteria for any one disorder.

Very few post-mortem studies have been carried out on individuals with 22q11.2DS. The only post mortem study carried out in adults with 22q11.2 deletion syndrome reported neuropathologic findings from three individuals with 22q11.2DS and a diagnosis of schizophrenia. They found bilateral periventricular nodular heterotopia in the frontal lobes and ectopic neurons distributed in the frontal white matter in one individual, along with evidence of cerebrovascular pathology in the remaining two (Kiehl *et al.*, 2009). A single study using perinatal tissue from a single individual, found a failure to differentiate upper layer projection neurons in the cortex (Sarnat and Flores-Sarnat, 2013). Finally, a study on a single three month old infant found changes in cortical lamination, involving an excess of interstitial white matter neurons as compared to an age matched control sample. In addition, an increase in the number of medium spiny neurons in the caudate was observed (Wu *et al.*, 2014). Overall, these post-mortem studies suggest abnormalities in neuronal migration are associated with the 22q11.2 deletion.

Animal models of 22q11.2 deletion syndrome also exist. Studies using these models have found alterations in cortical development suggestive of neuronal migration deficits, particularly of interneurons and of cortical neurogenesis. For example, parvalbumin labelled interneurons have been found to be distributed anomalously through the cortex of *LgDel* mouse (Meechan *et al.*, 2009). *LgDel* mice have also been found to have deficits in proliferative activity of cortical precursor cells, which suggests that the disrupted gene dosage due to the loss of genetic material contributes to a disruption of cortical projection neurogenesis (Meechan *et al.*, 2009). Recently, expression of TBX1 in the mesoderm has been demonstrated to be required for proper cortical development in mice through regulation of differentiation of cortical progenitors (Flore *et al.*, 2016). TBX1 is one of the genes included in the deleted region and is therefore haploinsufficient in individuals with 22q11.2DS.

A specific model (*Df(16)A*$^{+/-}$) has been found to show very similar changes in brain volume to those seen in individuals with 22q11.2 deletion syndrome using neuroimaging. This model was found to have an enlarged caudate, with a trend towards increased volume of the left caudate compared to the right. Similar findings of an enlarged caudate (Sugama *et al.*, 2000; Kates *et al.*, 2004) and disruption of the basal ganglia, such as calcification (Sieberer *et al.*, 2005), have been reported in humans with the 22q11.2 deletion. In addition, the cerebellar cortex was found to be 5% smaller than wild type littermates, along with a bilateral reduction in size of the cerebellar flocculus and para-flocculus of the cerebellum (Ellegood *et al.*, 2014). A smaller flocculus has also been found in children with the deletion (Bish *et al.*, 2006), and reductions in cerebellar volumes are widely reported in individuals with the deletion.

As shown here, evidence from post-mortem and animal work converges on the idea that a neuronal migration deficit is a key contributor to the changes in the brain seen in 22q11.2 deletion syndrome. This is also a likely cause of some of the changes seen in neuroimaging studies of individuals with the deletion, such as an enlarged caudate (Sugama *et al.*, 2000; Kates *et al.*, 2004) and reductions in grey and white matter (Campbell *et al.*, 2006; Tan *et al.*, 2009; Jalbrzikowski *et al.*, 2013), along with rarer observations such as polymicrogyria (Worthington *et al.*, 2000; Robin, 2006) and other cortical malformations.

Despite the many different approaches used, research into 22q11.2DS has so far failed to identify the reasons behind the variable phenotype shown by patients with 22q11.2DS, including why the deletion is only partially penetrant for psychosis. Researchers are following children with 22q11.2DS over their development to attempt to discover indicators or risk factors that predispose to the development of schizophrenia. Topics of interest include IQ or cognitive decline, environmental factors such as family environment or traumatic experiences in early life, along with others.

1.3 Schizophrenia

Schizophrenia has a high burden for the affected individual, their families as well as wider society, with the economic cost estimated to be £11.8 billion a year in the UK alone (Schizophrenia Commission, 2012). Around a third of this is direct spending on care both in hospitals and the community. It is one of the top 25 causes of death worldwide (Vos *et al.*, 2015), as in addition to its hallmark psychiatric symptoms, it is accompanied with increased mortality and a reduction in average life expectancy of approximately 10 – 20 years (Laursen, 2011). While outcomes are not always negative, it is associated with extremely high levels of unemployment (Marwaha and Johnson, 2004), and around 50% of sufferers will have

intermittent psychiatric problems, while 20% are chronically affected and disabled by the disorder (Barbato, 1998). Despite much research, the causes of schizophrenia remain poorly understood, although twin studies have indicated a high genetic loading (heritability of ~80%) (Sullivan, Kendler and Neale, 2003).

Schizophrenia was first described by Emil Kraepelin in 1896, through the combination of hebephrenia (now known as disorganised schizophrenia), catatonia, and dementia paranoides, which were all characterized by a deterioration in mental health and cognitive ability. He argued that the definitions of these disorders were not well defined and that patients could be seen to transition between the disorders. He also observed that they tended to have an onset early in life, without much effect on mood. He, therefore, combined the disorders under the label of dementia praecox.

Dementia praecox was later renamed schizophrenia by Bleuler in 1911, who also held the idea that because the presentation of the disorder was so variable, it may be more appropriate to call the disorder the group of schizophrenias similar to our current understanding of a spectrum of schizophrenia associated disorders. Kraepelin and Bleuler envisioned a four-way classification of schizophrenia disorders which included the three disorders that were combined under the label of dementia praecox and simple schizophrenia, first described by Diem in 1903. (Diem, 1903). Subclassificiations of Schizophrenia have changed many times since its original description. Kraepelin and Bleuler later further subdivided the disorders into nine clinical forms, and later authors similarly have had different ideas of what symptoms were key for diagnosis. Some individual countries formed their own classification systems such as France (Kellam, 1989) and Russia (Piatnitski, Dech and Mundt, 1998), some of which are still used there today. Modern classification systems such as the Diagnostic and Statistical Manual of

Mental Disorders (DSM-5) (American Psychiatric Association, 2013) and International Statistical Classification of Diseases and related health problems (ICD-10) (World Health Organisation, 2016) still regard schizophrenia as a syndromic concept, but the sub-classifications contained in these systems may have little relationship with the underlying causes. Like most other psychiatric disorders there are no diagnostic tests or biological markers for schizophrenia that can be used to definitively assign the diagnosis, rather this still relies on the constellation of symptoms observed. Many psychiatric disorders share similar symptoms, meaning that the boundaries between psychiatric disorders are often blurred. It is also increasingly realized that healthy members of the population may show varying degrees of subthreshold psychiatric symptoms. Psychotic symptoms, such as paranoid thinking and auditory hallucinations, for example, may occur in around 8% of the healthy population (van Os *et al.*, 2009).

Schizophrenia is characterized by a set of core symptoms which are often termed positive and negative, along with cognitive impairments. Positive symptoms consist of hallucinations and delusions, where the perception and contact with reality is distorted. Negative symptoms consist of reduced motivation, reduction in speech and social withdrawal. These symptoms tend to have different time courses with the positive symptoms tending to relapse and remit, while the negative symptoms are more chronic and insidious. As mentioned earlier, the first episode of schizophrenia tends to be in late adolescence and early adulthood, with men presenting earlier than women. There is often a prodromal stage where non-clinical symptoms, difficulties in functioning, and attenuated positive symptoms appear. (An Der Heiden and Häfner, 2000). Sometimes pre-morbid impairments in functioning can manifest many years before the first episode (Lewandowski, Cohen and Ongur, 2011).

There is substantial evidence that schizophrenia risk is heavily influenced by genetics. It is well known that first degree relatives of schizophrenia patients are at increased risk of developing schizophrenia, and that risk tapers the less related an individual is to a family member with schizophrenia.

A number of environmental factors are also thought to contribute to schizophrenia risk, and it has been hypothesized that a combination of genetic and environmental risk pushes individuals past a threshold where they will develop schizophrenia (McGue, Gottesman and Rao, 1983). Amongst these environmental factors are exposures to infection in the womb (Mednick *et al.*, 1988), time of year of birth (Torrey *et al.*, 1997), migration (Cantor-Graae and Selten, 2005), and cannabis use in adolescence (Moore *et al.*, 2007).

1.4 22q11.2 Deletion Syndrome and Schizophrenia risk

22q11.2 Deletion has been identified as a strong genetic risk factor for the development of schizophrenia through two lines of evidence. Firstly, there is a significantly elevated rate of 22q11.2DS in patients with schizophrenia, compared to controls, with 0.3% - 1% of cases having a 22q11.2 Deletion compared to none in controls (with an associated p-value of $22x10^{-6}$) (Rees *et al.*, 2014) Secondly, there is a high rate of schizophrenia in children and adults with 22q11.2DS. The deletion was the first copy number variant to be associated with schizophrenia, over 20 years ago (Shprintzen *et al.*, 1992; Karayiorgou *et al.*, 1995; Bassett *et al.*, 2010). Since then, this finding has been replicated several times, and current estimates suggest that approximately 25-40% of individuals with 22q11.2DS will go on to develop schizophrenia (Baker and Skuse, 2005; Schneider *et al.*, 2014). This is in contrast to other psychotic disorders, for example, bipolar disorder is found at similar rates to those in the general population (Murphy, Jones and Owen, 1999). There is no evidence that indicates that

the length of the 22q11.2 Deletion can predict schizophrenia development in 22q11.2DS (Weksberg *et al.*, 2007).

The manifestation of schizophrenia in 22q11.2DS patients does not differ markedly from schizophrenia seen in the general population. It shares similar prodromal features, a similar age of onset, core symptoms, responses to treatment and cognitive profile, other than the often lower initial IQ. However, there may be differences in other features often seen in combination with schizophrenia such as lower rates of substance use disorders in patients with 22q11.2DS and schizophrenia (Bassett *et al.*, 2003).

Currently, there are no identified genetic or environmental factors that allow for prediction of development of schizophrenia in individuals with 22q11.2DS, though models of accumulating risk might be informative, e.g. as in Lee et al. 2012. Similarly, it is unclear what genetic or environmental factors lead to the variable expressivity of the overall 22q11.2 deletion phenotype. It is likely that genes outside the deleted region are affected by the hemizygosity of the 22q11.2 region resulting in the deleterious effects of the syndrome.

1.5 Cognitive deficits in 22q11.2 Deletion Syndrome

22q11.2DS is the second most common genetic cause of intellectual disability after Down's syndrome and has been found in 2.4% of patients with idiopathic developmental delay (Rauch *et al.*, 2006). Mild to moderate intellectual disability is common, but severe intellectual disability is uncommon in carriers of the deletion. The mean IQ in individuals with 22q11.2DS is approximately 30 points lower than in unaffected sibling controls (Niarchou *et al.*, 2014), but IQ score follows a normal distribution similar to the general population. It has been noted that there is often a discrepancy between verbal comprehension and perceptual reasoning

abilities, with higher ability in the verbal domain compared to the performance domain (De Smedt *et al.*, 2007). While IQ is generally thought to be a stable trait over time in typically developing children, there is some evidence that IQ may decrease as children with 22q11.2DS get older. This has been demonstrated by cross-sectional studies where negative correlations between IQ and Age were found (Green *et al.*, 2009; Niklasson and Gillberg, 2010; Niarchou *et al.*, 2014), and by longitudinal studies where a decline in IQ has been found (Duijff *et al.*, 2012; Vorstman *et al.*, 2015). One study demonstrated an average decline of 7 full scale IQ points in individuals with 22q11.2DS between 8 and 24 years old (Vorstman *et al.*, 2015). In contrast, work from our group found no evidence for such a decline, in the only study to include unaffected siblings as a control group (Chawner *et al.*, 2017). Problems with mathematics are often seen in children with 22q11.2DS and involve difficulties with counting, comparisons of numbers of objects, and comparisons of object and numerical magnitude. Problems with visuospatial memory and judgements of quantity are accompanied by difficulties in time perception, memory for the order of things and in focusing and orienting attention across space. Some mechanisms have been suggested to underlie the cognitive profile of children with 22q11.2DS, including deficits in retrieval of information about context that accompanies memories (Debbané, Glaser and Eliez, 2008), impairments in the resolution of spatial, temporal and numerical information (Simon, 2008), and executive control of directing visual attention (Sobin *et al.*, 2004).

Early in life, gross and fine motor difficulties (Swillen *et al.*, 2005), along with delays in the development of expressive language and speech are often observed. Delays in language onset are common, with early work indicating that approximately 70% of children with the deletion did not speak, or only used a few words or signs at 24 months of age (Solot *et al.*, 2000). It has been suggested that this delay in language development may also be attributable to difficulties

caused by palatal problems often seen in 22q11.2DS. However, speech deficits due to palatal abnormalities improve after corrective surgery, while difficulties due to an inherent language disorder do not.

Deficits in neurocognitive functioning are a key feature of schizophrenia not caused by the 22q11.2 deletion, with deficits in global cognition and in specific domains such as memory, executive and social functioning are well demonstrated (Fioravanti *et al.*, 2005; Green and Leitman, 2008; Horan *et al.*, 2008) Similarly, impairments in these domains are also found in individuals at high risk for the development of schizophrenia, such as relatives of patients with the disorder (Gur *et al.*, 2007). The pattern of neurocognitive deficits seen in non-genotyped individuals with schizophrenia is similar to the pattern seen in 22q11.2DS.

Children with 22q11.2DS show deficits in a variety of neurocognitive domains including attention, executive functioning, planning, spatial working memory and processing speed (Gerdes *et al.*, 1999; Cannon *et al.*, 2000; Niarchou *et al.*, 2014). Previous work has shown that deficits on at least some cognitive tests are independent of IQ (Niarchou *et al.*, 2014) and that performance in one cognitive domain, therefore, does not predict performance in other domains. Social cognition seems to be particularly impaired in children with 22q11.2DS (Gur *et al.*, 2014), though this may be due to a combination of low level perceptual or attentional difficulties (McCabe *et al.*, 2016) and deficits in cognitive processes such as theory of mind or overall intelligence (Campbell *et al.*, 2015).

1.6 Other psychiatric disorders in 22q11.2 deletion syndrome

22q11.2DS is associated with a range of psychiatric disorders of childhood, including neurodevelopmental disorders, and mood disorders. The presentation of the most commonly seen disorders is described below.

1.6.1 Anxiety disorders

Excessive worry is often seen in children with 22q11.2DS. Many different anxiety disorders are seen in 22q11.2DS with obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD), specific phobia, social phobias and separation anxiety being common (Baker and Skuse, 2005; Niarchou *et al.*, 2014; Schneider *et al.*, 2014). It is not clear what predisposes children with 22q11.2DS to anxiety disorders. While the loss of genetic material may have a direct effect, it could also be that children with 22q11.2DS are at increased risk for anxiety due to negative experiences early in life. Patients with 22q11.2DS often have multiple medical conditions that can require several surgeries or hospitalizations. These experiences could predispose children to anxiety through excessive stress caused by the repeated medical procedures or a poor sense of control over their own body (Beaton and Simon, 2011). Traumatic early life experiences affect the physiological stress response during development and can predict levels of atypical hypothalamic-pituitary-adrenal axis activation and problems in regulating the neuroendocrine systems (Plotsky and Meaney, 1993; Heim and Nemeroff, 2001). The excessive stresses put on children with 22q11.2DS early in life may, therefore, lead to problems in their physiological stress responses. These problems could cause physiological changes which can have a deleterious effect on both brain and behaviour over time. In turn, this could predispose children to anxiety. In addition, anxiety can interact with cognitive deficits. If a child is finding schoolwork difficult, it may cause them stress and anxiety which

would encourage them to avoid school or academic pursuits, despite possibly having talents that have not been discovered. Similarly, difficulties in social situations which cause anxiety could cause children to avoid social situations, thus limiting opportunities for proper integration and construction of friendships and therefore the development of social skills. Social development can also be influenced by bullying due to lower intellectual ability, social skills or because of the dysmorphology that is seen with the syndrome

In a recent large cross sectional study (Schneider *et al.*, 2014), the prevalence of anxiety disorders was highest in children with 22q11.2DS, with 36% of children displaying any anxiety disorder. Prevalence fell to around 25% in adults, but across all ages, anxiety was more common in females. Rates of OCD and GAD were similar across different age groups while rates of specific phobia, social phobia and separation anxiety decreased with age. Panic disorder was the only anxiety disorder to increase with age while post-traumatic stress disorder was very rarely diagnosed. Rates of specific phobia were comparable to those for an ID population, but social phobia was overrepresented in 22q11.2DS. As in the general population, anxiety disorders were often seen in combination with mood disorders (Schneider *et al.*, 2014).

1.6.2 Mood disorders

Depression is seen in children with 22q11.2DS, while bipolar disorder rarely occurs. Rates of mood disorders increase as children with 22q11.2DS get older, similar to in the general population (Schneider *et al.*, 2014). This could be due to poor social skills and lack of social integration causing children with 22q11.2DS to become lonely and withdrawn, which can worsen as they grow older and gain insight into how they may differ from other children. The transition from being closely looked after in a school environment to independence is an experience that can cause significant stress in young people with developmental disability of

any type. Indeed, levels of employment and financial independence are low for individuals with 22q11.2DS (Butcher *et al.*, 2012). This lack of independence can cause friction with carers and compound poor self-esteem in individuals with the deletion, potentially triggering depression. In addition, late childhood and adolescence is a period of significant brain maturation. Improper development and maturation of brain areas responsible for mood regulation may also play a role.

Importantly, anxiety and depression profiles in children with 22q11.2DS, as reported by parents, have been found to be associated with psychotic symptoms (Debbané *et al.*, 2006), and the only prospective study on this topic conducted to date found that psychotic symptoms were predicted by baseline anxiety and depression symptoms along with lower baseline verbal IQ (Gothelf *et al.*, 2007). Research comparing children with non-syndromic orofacial clefts with children with 22q11.2DS and clefts found that the high rates of emotional problems in children with 22q11.2DS could not be attributed by their speech or intellectual disabilities alone (Klaassen *et al.*, 2013).

1.6.3 ADHD

ADHD is characterized by persistent symptoms of inattention, hyperactivity and impulsivity that impairs functioning in a variety of settings. It is usually diagnosed in childhood and can have severe effects on academic and daily life. In the general population, it is thought to affect around 3-5% of children depending on sampling strategy and diagnostic criteria used (American Psychiatric Association, 2013). It is much more common in boys than girls. Despite most often being diagnosed in childhood, it is considered to be a lifelong neurodevelopmental condition, with symptoms commonly persisting into adulthood. ADHD can be split into three subtypes, inattentive, hyperactive and combined. Inattentive ADHD is characterized by

symptoms of attentional impairment and distractibility, while hyperactive ADHD is distinguished by inappropriate levels of activity and impulsiveness. Combined ADHD is diagnosed when an individual meets criteria for both hyperactive and inattentive subtypes.

ADHD is one of the most common psychiatric diagnoses seen in children with 22q11.2DS. The 22q IBBC found that 37.10% of children with 22q11.2DS had a diagnosis of ADHD (Schneider *et al.*, 2014). While less frequent in adults with the deletion, the rate of 15.59% was higher than for adults in the general population. This along with present findings suggests that ADHD persists over childhood and into adulthood in individuals with 22q11.2DS (Antshel *et al.*, 2013). The presentation of ADHD in 22q11.2DS differs from that seen in idiopathic, non-genotyped populations. Firstly, diagnoses of inattentive ADHD make up the majority of cases seen in 22q11.2DS (Schneider *et al.*, 2014; Niarchou *et al.*, 2015). This is in contrast to the general population where combined ADHD is more common. Secondly, ADHD in 22q11.2DS presents more commonly with generalized anxiety disorders than idiopathic ADHD, but less together with oppositional defiant disorder (ODD) and conduct disorder (CD) symptoms (Niarchou *et al.*, 2015). Finally, ADHD is present at similar rates in males than females with 22q11.2DS (Niarchou *et al.*, 2015), in contrast to the pattern seen in the general population.

There is a lack of specific research into the safety and efficacy of stimulants such as methylphenidate in 22q11.2DS. Only two studies have specifically investigated the use of methylphenidate in children with 22q11.2DS, but both found the drug to be safe and effective. However, it was recommended that individuals with 22q11.2DS who are receiving methylphenidate are monitored closely for cardiovascular side effects, including increased blood pressure and heart rate (Gothelf *et al.*, 2003; Green *et al.*, 2011; Kates *et al.*, 2015).

1.6.4 Oppositional defiant disorder and conduct disorder

ODD is characterized by pervasive patterns of disobedience, defiance and hostile behaviour. This includes not accepting responsibility for own behaviour, deliberately annoying others, difficulty accepting rules, and easily losing their temper when things do not go one's way. It is diagnosed when these symptoms are impacting on social or occupational functioning (American Psychiatric Association, 2013).

ODD is more common in boys than girls, though gender differences in the ways aggression is expressed may mean the disorder is more likely to be missed in girls (Steiner and Remsing, 2007). Girls may tend to use verbal rather than physical aggression, and spread rumours or exclude other children. There is no single agreed cause or risk factor for the development of ODD. It may be that children with ODD have specific deficits in emotional or cognitive skills that leave them less able to comply with an adult's request. An example would be a tendency towards emotional overreaction caused by a lack of ability in affective modulation. Alternatively, a cognitive deficit in attention, or memory, for example, may undermine a child's ability to carry out instructions, leading to frustration and outbursts.

Conduct Disorder (CD) is defined by more serious actions such as stealing, assault, and cruelty to people and animals. Children with ODD may progress to CD, but a substantial sub group do not. Conduct Disorder has high diagnostic overlap with ODD, and ODD symptoms represent one of the strongest predictors of CD development (Loeber *et al.*, 1995) and course (Burke *et al.*, 2005). However, if criteria for conduct disorder are met then a diagnosis of ODD cannot be assigned, as the diagnoses of CD will supersede it. Like ADHD both ODD and CD are often diagnosed in childhood, and ODD is often seen to be comorbid with ADHD in the general

population. ODD is also associated with anxiety, depression, and externalizing disorders (Burke *et al.*, 2005; Nock *et al.*, 2007).

ODD is seen in children with 22q11.2DS with the largest study of psychiatric disorders in 22q11.2DS with a prevalence of approximately 14% in children and adolescents. This is similar to rates found in populations with intellectual disabilities. Our own group has found a rate of approximately 15% (Niarchou *et al.*, 2014). Like in the general population, ODD was found to be more common in boys than girls (Schneider *et al.*, 2014). Only 2 of 138 adults in this study (1.45%) between the ages of 18-25 were diagnosed with conduct disorder. Overall, my experience, along with the experiences of other researchers that work alongside me, suggests that oppositional behaviour in the children with 22q11.2DS we see is generally restricted to the family setting. Outside of the family, these children are often seen as shy or introverted by others. The extremely low rate of CD compared to the general population suggest that individuals with ODD and 22q11.2DS are unlikely to develop conduct disorder.

1.6.5 ASD

Autism spectrum disorder (ASD) represents a group of disorders which are diagnosed in approximately 1% of children born in the US, and are characterized by a pattern of social difficulties, communication difficulties, along with repetitive or stereotyped behaviours and interests. ASD is made up of three types depending on diagnostic criteria used or symptoms present: ASD, Asperger's syndrome and pervasive developmental disorder. Following a change in diagnostic criteria in the DSM-5, the symptoms of ASD are now defined using two categories of behaviour, deficits in social communication and stereotyped behaviours (American Psychiatric Association, 2013). However, there can be a great deal of heterogeneity in symptoms, severity, and intellectual functioning between individuals. Hyper or hypo-

sensitivity to sensory inputs can be seen in some individuals, along with hyperactivity, tantrums and delays in motor skills. Boys are more often affected by ASD, with four times as many boys as girls diagnosed with the disorder. Many CNV's have been associated with ASD risk, including 22q11.2 deletion (Devlin and Scherer, 2012), and 22q11.2 duplication (Wenger *et al.*, 2016), 16p11.2 deletion and duplication as well as other chromosomal syndromes such as Fragile X, Tuberous sclerosis, Rett syndrome and rare mutations in single genes (reviewed in Devlin & Scherer 2012).

While 22q11.2DS has been associated with ASD, there is some debate as to whether children with 22q11.2DS show all the symptoms required to reach a diagnosis. In studies to date, rates of repetitive or stereotyped behaviours have been low in children with 22q11.2DS (Kates *et al.*, 2015). Few studies in 22q11.2DS have used gold standard assessments and may have overestimated rates of ASD. Results from the IBBC, found rates of approximately 13% in children aged 6-12, 27% in adolescents aged 13-17 and 16% in individuals 18 or older using cohorts diagnosed with both the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) (Schneider *et al.*, 2014). There is little doubt that children with 22q11.2 often show deficits in social communication (Angkustsiri *et al.*, 2014), but these alone are not enough to warrant a diagnosis of ASD. These deficits include problems with social competence, especially in interactions with children of their own age in settings such as school or social occasions. In addition, similar to findings in ASD, young people with 22q11.2DS have been found to spend less time fixating on the eyes of faces, and more on the mouth during emotion processing tasks (Glaser *et al.*, 2010). It has been suggested that these impairments are context specific, rather than pervasive across environments, as is usually the case in idiopathic ASD.

Despite this, children with 22q11.2DS and ASD have lower levels of joint attention with others, lower levels of make believe play and higher levels of repetitive behaviours than carriers without ASD. Children with ASD and 22q11.2DS also have higher levels of psychiatric comorbidity than children with ASD but not 22q11.2DS (Angkustsiri *et al.*, 2014). Interestingly it has been reported that children with 22q11.2DS and ASD have higher levels of socioemotional reciprocity than children with idiopathic ASD (Kates *et al.*, 2007).

1.7 Motor difficulties in Schizophrenia

Motor disturbances have been known to be a feature of schizophrenia since the late 1800's, with catatonia first documented by Karl Kahlbaum (Kahlbaum, 1874), and later as mentioned as one of Emil Kraepelin's nine clinical forms of dementia praecox (Kraepelin, 1921). Later research focused more on cognitive and positive symptoms of schizophrenia such as hallucinations, delusions and disorders of self-perception, while the motor and emotional deficits took a back seat to these other symptoms. Once antipsychotics were introduced, extrapyramidal side effects and the intrinsic motor difficulties of schizophrenia became hard to differentiate. Motor symptoms in schizophrenia were thought to be solely due to side effects of medication (Crane and Naranjo, 1971). In the 1980's neurological signs were once again attributed to the neurobiology of schizophrenia and have been a topic of active research since, utilizing rare populations of patients that had never received neuroleptic drugs (Fenton *et al.*, 1997), or first episode patients (Compton *et al.*, 2015). Motor dysfunctions observed in schizophrenia include involuntary movements, neurological signs, catatonic symptoms, Parkinsonism, and psychomotor slowing. It is now relatively well accepted that motor symptoms are a part of the manifestation of schizophrenia, and difficulties with motor performance have been shown in both relatives of patients with schizophrenia (Chan *et al.*, 2010) and in children who later go on to develop schizophrenia. Large birth cohort studies have

shown delayed gross motor milestones, and impaired motor skills before age 11 in youngsters who developed schizophrenia later in life (Jones *et al.*, 1994; Rosso *et al.*, 2000; Keskinen *et al.*, 2015). In a slightly less conventional study, analysis of home videos showed that subjects who later developed schizophrenia had poorer motor skills and increased neuromotor abnormalities compared to their healthy siblings (Schiffman *et al.*, 2004).

Neuroimaging studies in schizophrenia also provide some convergent evidence for motor dysfunction, with abnormalities of the cerebellum (Levitt *et al.*, 1999; Nopoulos *et al.*, 1999) and basal ganglia (Brandt and Bonelli, 2008) being repeatedly found, but it remains unclear if these are related to the biology of the disorder, or treatment effects.

Taken together these separate lines of evidence suggest that motor symptoms might be a useful phenotype for identifying those who are at risk of developing schizophrenia.

1.8 Motor difficulties in 22q11.2 Deletion Syndrome

Motor difficulties are increasingly recognized as a feature of 22q11.2DS, in particular: problems with balance, bimanual coordination and visuomotor skills (Sobin *et al.*, 2006; Van Aken *et al.*, 2007, 2010) and there is some evidence that these difficulties are not accounted for by intellectual disability (Roizen *et al.*, 2011). This is in addition to common reports of hypotonia in childhood that can persist into adolescence, delays in the attainment of developmental milestones (Swillen *et al.*, 1999), asymmetric crying facies (Pasick *et al.*, 2013), along with seizures and tremor or tetany due to hypocalcaemia (Weinzimer, 2001). Juvenile myoclonic seizures have also been associated with 22q11.2DS (Strehlow *et al.*, 2016). However, overall research on motor difficulties in children and adults with 22q11.2DS is sparse at best, despite having been identified early on as a symptom often seen in these children.

With regards to coordination difficulties, children with 22q11.2DS have been observed to perform worse on the manual dexterity (Van Aken *et al.*, 2009; Roizen *et al.*, 2011) and balance (Roizen *et al.*, 2011) subsections of the Movement Assessment Battery for Children (MABC) along with worse scoring on the visual and motor subsections of the beery visual motor integration task compared to IQ matched controls. This would suggest that there are problems with visual perception and visual integration, beyond those that are present in age and IQ matched controls. Thus, lower IQ in the 22q11.2DS population may not entirely explain deficits in perception, visual motor integration, or fine motor skills. This agrees with earlier research looking at neuromotor performance in children with 22q11.2DS, which found poorer fine motor dexterity and precision, along with graphomotor control, to be the most uniformly impaired domain in affected children (Sobin *et al.*, 2006). They observed that in young children, hand movements were imprecise, jerky and there was low pincer grip strength. For older children, they observed that grasp strength was poorly controlled, either being too tight or too loose, leading to poor control.

There is very little research on movement problems in adults with 22q11.2DS. These could be due to a range of factors, including congenital malformations, drug side effects, and neurodegenerative processes. At this stage, while movement disorders are seen in adults with 22q11.2DS, it is unclear how the deletion relates to specific movement symptoms, due to the complex constellations of symptoms seen in these individuals. Boot et al. described a series of patients with 22q11.2DS with movement disorders and highlighted the range of potential causes in this population. Firstly, one patient had movement difficulties due to a congenital vertebral and skull base abnormality that caused spinal cord compression. This can cause muscle weakness, hyperreflexia, stiffness and coordination problems. The individual presented

with a progressively worsening gait disorder which resulted in the use of a wheeled walker at the relatively young age of 31 years (Boot *et al.*, 2015). Surgical correction allowed the individual to walk unaided.

Secondly, seizures are common in 22q11.2DS, and these can either be idiopathic or related to hypocalcaemia, hyperprolinemia, fever, ischemia/hypoxia or medication. Boot et al. describe two patients who suffered seizures while receiving antipsychotic medication, along with Clozapine induced myoclonus which they suggested was subcortical in origin. However, in one patient facial myoclonus was related to EEG spike and waves on EEG, so a cortical cause could not be completely disregarded. It may be that individuals with 22q11.2DS are at higher risk of experiencing seizures while receiving antipsychotics (Krahn, Maraganore and Michels, 1998; Butcher *et al.*, 2015).

Antipsychotics may also aggravate or cause movement disorders such as Parkinsonism, akathisia, dystonia and dyskinesia. Boot et al., described two patients who displayed Parkinsonism while receiving clozapine, which is an extremely rare side effect of clozapine treatment. They also described one patient who developed an oculogyric crisis while receiving olanzapine or quetiapine which is another very rare side effect of these medications. As well as the cases described by Boot et al., a case of acute dystonia in a young adult who received haloperidol has also been described by Kontoangelos et al. Both papers suggest that individuals with 22q112DS may be more prone to developing antipsychotic induced movement disorders.

Endocrine abnormalities may also play a role in movement problems, by increasing risk of seizures, and through hypocalcaemia induced tetany, muscle cramps and tremors (Weinzimer, 2001). Dysfunction of the thyroid and treatment for thyroid problems can also cause tremor.

Therefore, patients should be investigated for endocrine problems if movement symptoms are present.

Additionally, for reasons currently unknown, adults with 22q11.2DS seem to be at particularly high risk for the development of early onset Parkinson's disease (Zaleski *et al.*, 2009; Butcher *et al.*, 2013; Mok *et al.*, 2016), further highlighting possible abnormalities of motor circuitry. It has been reported that the presentation of Parkinson's disease in individuals with 22q11.2DS is similar to the typical presentation, other having an early onset: Onset of symptoms has been seen from the age of 30 onwards (Rehman *et al.*, 2015). Symptoms include asymmetrical onset of motor symptoms and tremor, bradykinesia and rigidity (Mok *et al.*, 2016). It has been reported that patients with 22q11.2DS tend to have a good initial response to levodopa or dopamine agonist treatment (Mok *et al.*, 2016). Reported differences from typical presentation included early drug related dyskinesia and motor fluctuations, along with additional cognitive and psychotic features associated with the 22q11.2DS.

There are a few descriptions of catatonia in individuals with 22q11.2DS (Graf *et al.*, 2001; Faedda *et al.*, 2015), but it is not currently known how common this presentation is.

The parallel findings of changes in the caudate and cerebellum of animal models and humans with the deletion (as outlined in Section 1.2) may suggest that disruption to the structure and function of these areas is a plausible explanation for the motor deficits in the syndrome, along with some of the cognitive deficits.

1.9 Developmental Coordination Disorder

Many children exhibit difficulties with gross or fine motor coordination. While most children will have areas of coordination they are comparatively strong or weak in, some children have severe difficulties that will impact on their daily and academic ability. When these difficulties are hindering the child's ability to function appropriately, they may be given a diagnosis of Developmental Coordination Disorder (DCD), often also known as dyspraxia.

DCD is classified as a neurodevelopmental disorder characterized by motor function that is markedly deficient given the person's chronological age and measured intelligence and is not explained by any overt motor or sensory deficit (Zwicker *et al.*, 2012). The DSM-5 criteria for diagnosis are as follows:

A. Motor performance that is substantially below expected levels, given the person's chronological age and previous opportunities for skill acquisition. The poor motor performance may manifest as coordination problems, poor balance, clumsiness, dropping or bumping into things; marked delays in achieving developmental motor milestones (e.g., walking, crawling, sitting) or in the acquisition of basic motor skills (e.g., catching, throwing, kicking, running, jumping, hopping, cutting, colouring, printing, writing).
B. The disturbance in Criterion A, without accommodations, significantly and persistently interferes with activities of daily living or academic achievement.
C. Onset of symptoms is in the early developmental period.
D. The motor skill deficits are not better explained by intellectual disability (intellectual development disorder) or visual impairment and are not attributable to a neurological

> condition affecting movement (e.g., cerebral palsy, muscular dystrophy, degenerative disorder). (American Psychiatric Association, 2013, page 74).

DCD can involve difficulties with fine motor skills, gross motor skills, or both. The performance will generally be slower, less accurate and more variable than peers. As demonstrated by the DSM-5 criteria, the motor performance is not simply the low end of a spectrum of ability; the difficulties must have a significant impact on daily and academic life.

According to the DSM, 5% of school aged children may meet the diagnostic criteria for developmental coordination disorder, though estimates vary from 1.8% in a UK based study to 19% in a Greek study (Tsiotra *et al.*, 2006; Lingam *et al.*, 2009). Estimates of the gender ratios also vary, though large population based studies vary between a 1.9:1 male to female ratio (Lingam *et al.*, 2009) to almost equal distribution (Missiuna *et al.*, 2008). While DCD is generally considered to be a disorder of childhood, it can, and does, persist into adulthood. It has been estimated that nearly three-quarters of children with DCD will continue to have difficulties as adults (Kirby *et al.*, 2008). While progression and presentation of the disorder is variable, it has documented negative effects, including increased risk for anxiety and depression (Kirby, Sugden and Purcell, 2014), and worse educational and employment outcomes (Kirby *et al.*, 2013).

The causes of DCD are as yet unknown. Symptoms may be related to a central nervous system pathology, either due to an (unknown) insult to the brain early in development or atypical brain development. Stress due to preterm birth has been suggested as a cause of DCD as up to 50% of children born preterm have motor impairments that are similar to DCD (Missiuna *et al.*, 2008; Goyen and Lui, 2009; Roberts *et al.*, 2011), and may be more likely to develop the

disorder (Edwards *et al.*, 2011). The idea that DCD is caused by abnormal brain development is supported by the fact that the condition is often found to be comorbid with other neurodevelopmental disorders, particularly ADHD, but also anxiety disorders and ASD (Miyahara and Piek, 2006; Piek *et al.*, 2008). Up to 50% of children with DCD have a diagnosis of ADHD, primarily of the inattentive, rather than the hyperactive subtype (Kadesjö and Gillberg, 1999; Loh, Piek and Barrett, 2011). DCD is often also accompanied by specific learning difficulties such as dyslexia (Biotteau, Chaix and Albaret, 2015) or difficulties with mathematical skills (Gomez *et al.*, 2015).

Three possible mechanisms underlying the motor difficulties shown by children with DCD have been hypothesized. Firstly, the automatization deficit hypothesis suggests that children with DCD have difficulties performing motor skills automatically. This hypothesis was developed based on observations that children with dyslexia have difficulties with balance when asked to perform a secondary task such as counting backwards (Fawcett and Nicolson, 1992). Therefore, it was suggested that children with dyslexia might have difficulty automating cognitive and motor skills at the same time. The same mechanism has been suggested to be involved in the motor deficits seen in DCD, such that children with DCD have difficulties in automating motor processes (Tsai *et al.*, 2009).

The second hypothesis states that children with DCD have a deficit in internal modelling of motor actions (Wilson, 2005). Internal modelling allows a model of the spatiotemporal profile of prospective actions to be constructed, with the same force and timing characteristics as real movements. This internal model can then be used as a template with which to compare the accuracy of a motor action, while it is taking place. If there is an impairment in the modelling process, accuracy of performed motor actions will decrease. In addition, if the model is

insufficient, any motor action that is performed would have to be evaluated on the basis of reafferent motor signals from the body such as proprioceptive information, which adds time and error to movements performed, especially if conditions are changing. A meta-analysis of performance deficits shown in DCD found that many of the impairments seen in children with DCD involve motor prediction and internal modelling. These deficits were generalized to a variety of tasks and paradigms, for example, difficulty with adjusting reaching movements to rapid visual perturbation (Hyde and Wilson, 2011), and coordinating grip and load force when lifting objects (Plumb *et al.*, 2008). The ability to use an internal model or forward estimation of limb position is required to integrate the efferent and afferent information in short time frames, allowing rapid and accurate corrections of movement in response to changes in the environment (Desmurget and Grafton, 2003). This forward estimation and correction of movements is thought to be performed by a functional loop between the parietal cortex and cerebellum (Blakemore and Sirigu, 2003; Shadmehr, R. Krakauer, 2008). Overall there is much evidence that children with DCD are less able to construct and train internal models for actions, meaning that they require more practice to build adequate models for particular movement patterns. These difficulties can be further exacerbated temporarily, by changing biomechanics of the body during maturation, such as changes in muscle strength, or limb and body size due to periods of rapid growth.

A third hypothesis for some of the motor learning deficits seen in children with DCD is a problem involving the mirror neuron system (Rizzolatti and Craighero, 2004). The mirror neuron system (MNS) is thought to be related to imitation of others. This system was discovered in macaque monkeys in experiments using single cell recording of surgically implanted electrodes. It was found to fire when monkeys perform an action but also when they observe another individual (monkey or human) perform a similar action. The mirror neuron,

therefore, has a representation of both an individual's own motor action and the sensory observation of the action as performed by others. Based on the animal work, the human analogy of the mirror neurons is thought to be located in the pars opercularis of the inferior frontal gyrus. Indirect evidence for a mirror neuron network in frontal and parietal brain regions has been found using neuroimaging techniques and is reviewed by Rizzolatti and Craighero (Rizzolatti and Craighero, 2004). Single neuron recordings have allowed the discovery of some specific properties of mirror neurons in macaques that have implications for their role in coordination. Firstly, actions must be goal directed, for example reaching for an object, in order to stimulate activity in mirror neurons (Gallese *et al.*, 1996). This means that, at least in macaques, the mirror neurons are storing a representation of the conceptual goal of an action but not a single body part or specific object. Second, a large proportion of the mirror neurons will respond to more than one action as long as they are visually similar or conceptually related to previously performed or observed actions (Gallese *et al.*, 1996). About one-third of mirror neurons will only respond to a particular action, where the observed or performed action must match exactly. An example would be how to hold a specific object using a particular way of grasping (Gallese *et al.*, 1996). Third, partial movement sequences will activate mirror neurons in monkeys who have seen the full action sequence (Umiltà *et al.*, 2001), suggesting that the animal is able to infer the missing parts of the sequence. This also means that mirror neurons are involved in the understanding of actions by storing representations of them, which can be used even when complete visual information is not available. While in humans the MNS is also thought to facilitate imitation of actions, there is conflicting evidence for the role of the MNS in imitation in monkeys. This may mean that imitation as a function of the MNS (and other neural areas) is an evolved function.

While there is little work directly investigating the mirror neuron system as a cause of DCD, there is some converging evidence that suggests that the MNS may be involved. Children with DCD often show impairments in imitation of gestures and actions (Werner, 2012; Reynolds *et al.*, 2015), along with the deficits in motor imagery that have been discussed earlier. Functional neuroimaging evidence has also found different patterns of activity in children with DCD, in frontal, parietal and temporal regions that are thought to be involved in the MNS (Werner, 2012).

The motor imagery and automatization hypotheses both suggest that the cerebellum has a key role in the pathology of DCD, as this brain structure is thought to be at least partially responsible for both functions.

1.10 DCD and cognition

In addition to the deficits in motor coordination, children with DCD have been found to also present with neurocognitive impairments, particularly in the domain of executive functioning. Deficits have been found in working memory, both visuospatial and verbal, inhibitory control and control of attention (Wilson *et al.*, 2013), and it has been suggested that generalized impairment of executive functioning is common in children with DCD. The frequent comorbid presentation of cognitive and motor deficits has led to the suggestion that DCD is the product of atypical brain development (Gilger and Kaplan, 2001). This framework argues that deficits across a broad range of modalities are the result of a generalized aberration in cortical maturation. With regards to the deficits seen in children with DCD, there are two potential pathways that could explain why cognitive and sensorimotor deficits could be related. Either intrinsic genetic or environmental factors that affect cortical maturation result in generalized disruptions to the neural architecture that support these processes; or due to the reduced

competency in motor activities, the developing brain is not exposed to sufficient learning experiences and stimulation required to create and optimize the architecture that supports the cognitive processes required for working memory and executive control of attention.

There is increasing realization that sensorimotor development has profound impacts on the development of other cognitive skills and processes functioning (Wilson *et al.*, 2013). By extension deficits in sensorimotor function early in life could increase the likelihood of the development of mental health disorders (Green, Baird and Sugden, 2006; Loh, Piek and Barrett, 2011; Zwicker *et al.*, 2012). Human development consists of the gradual acquisition and improvement of sensorimotor abilities. There is evidence that these abilities are required for the proper development of cognitive skills. For example, in infants, hand-eye coordination skill is related to the ability to engage in joint attention activities with parents (Yu and Smith, 2013, 2017), and prospective control of reaching is related to early forms of executive function (Gottwald *et al.*, 2016).

However, an alternative explanation for the deficits seen in DCD and 22q11.2DS is that abnormal development of specific brain areas or systems is responsible for the cognitive and motor deficits seen in the syndrome.

1.11 Cerebellar dysfunction as a common theme in schizophrenia and DCD

As was stated earlier, abnormalities of the cerebellum are well reported in the schizophrenia literature (Section 1.7), along with disturbances of motor performance. While the nature of the motor disturbances in schizophrenia and DCD does not match exactly, it is plausible to think that both disorders may involve some deficit of the cerebellum. While mainly thought to be responsible for motor performance, the cerebellum is also recognized to be involved in

cognitive and emotional processes. Damage to the cerebellum can cause a range of changes in personality and cognitive ability in addition to changes in motor ability (Schmahmann, 2004). Neuroimaging and post mortem studies have demonstrated that there are many connections linking the cerebellar cortex to the cerebral cortex, other than those that link the motor cortex areas to the cerebellum (Popa, Hewitt and Ebner, 2014).

1.12 Cerebellar dysfunction in other psychiatric disorders

The cerebellum has also been found to be abnormal in other disorders such as psychiatric disorders ASD, ADHD and post-traumatic stress disorder.

In autism, abnormalities of the cerebellum have been demonstrated by both neuroimaging and postmortem assessment (Bauman and Kemper, 1985; Becker and Stoodley, 2013; Stoodley, 2014). Across different studies, grey matter reductions are consistently reported in the right Crus I, left lobule VIII, and medial IX areas. In addition, abnormalities of the connections between the cerebellum and cortex have been demonstrated using diffusion imaging (Catani *et al.*, 2008) in individuals with Asperger's syndrome. Volume changes in the cerebellum have also been found to correlate with core autism symptoms (D'Mello *et al.*, 2015).

In ADHD, smaller cerebellar volumes were some of the first reported differences from neuroimaging studies (Valera *et al.*, 2007). Medication for ADHD may also have effects on the cerebellum, leading to changes in cerebellar activation patterns in children with ADHD (Rubia *et al.*, 2009), and may prevent or rescue reductions in cerebellar volume in children with ADHD (Ivanov *et al.*, 2014), though these results are debated.

Damage to the cerebellum has resulted in individuals being diagnosed with ASD, dyslexia and attention problems (Stoodley, 2014), providing further evidence that the cerebellum is not only concerned with motor performance. Importantly, damage to the cerebellum during childhood can have more severe outcomes than damage to the cortex (Wang, Kloth and Badura, 2014), suggesting that the cerebellar networks are less able to repair or adapt to overcome damage.

Due to the overlap of evidence from schizophrenia, developmental coordination disorder, and other psychiatric disorders, along with the common finding of structural abnormalities of the cerebellum in individuals with 22q11.2 deletion syndrome and animal models, further investigation of the neuroanatomic features of the cerebellum could be valuable. While many of the motor and cognitive symptoms shown by children with 22q11.2DS could also be explained by basal ganglia abnormalities, abnormalities of the basal ganglia have been described previously in the literature. To my knowledge, no studies have focused on detailed investigation of the white matter of the cerebellum in children with 22q11.2DS.

1.13 Purpose of the thesis

The main purpose of this thesis is to explore the prevalence and severity of motor difficulties in children with the 22q11.2 deletion syndrome, and the relationships between motor difficulties and cognition and psychopathology in this group. Therefore, this thesis focuses on delineating the motor difficulties that are present in the syndrome, at both the level of overall coordination and functional impairment, and at the level of sensorimotor impairment. In order to probe relationships with cognition and psychopathology, it was also necessary to assess cognition and psychopathology. However, assessing these domains was not a primary aim of the study, as these aspects of the syndrome have already been described in detail in the literature.

In order to fulfil this purpose, the following key hypotheses were tested: 1) that children with 22q11.2 deletion syndrome will have higher rates of indicated coordination difficulties than their unaffected sibling controls. 2) That sensorimotor performance will be lower in children with 22q11.2 deletion syndrome compared to unaffected sibling controls. 3) That coordination/sensorimotor difficulties will not be related to full scale IQ or cognitive ability in children with the syndrome. 4) That coordination/sensorimotor difficulties will be related to ADHD, ASD and Anxiety severity in children with the syndrome. 5) That individuals with 22q11.2DS will have differences in brain morphometry of cortical and subcortical areas that are related to motor systems. 6) That children with 22q11.2DS will show changes in diffusion metrics of motor relevant white matter tracts including the corticospinal tract and cerebellar peduncles.

1.14 Summary

In this introduction, I have outlined some of the major characteristics of 22q11.2DS, and the cognitive and psychiatric disorders associated with it. Motor dysfunction is apparent in 22q11.2DS but remains poorly understood. It is not known if there is a generalised motor deficit in the syndrome, or if specific domains of motor functioning are predominantly affected. Similarly, it is unclear if the deficits in motor function are only evident as a deficit in daily functioning or participation in society, or if there are fundamental sensorimotor processing and control deficits. In addition, relationships between coordination and cognition, and psychopathology have not been explored in this population.

This thesis, therefore, aims to address these gaps in the existing literature. The prevalence of developmental coordination disorder and motor functioning at the level of activities and participation was investigated using the DCDQ questionnaire, and the relationship between these coordination deficits and psychopathology were explored. Second, fundamental sensorimotor processes were probed using a battery of tasks designed to capture deficits in the fundamental processes of tracking, aiming and steering. The interrelationships between sensorimotor and cognitive function and psychopathology were also explored. To ensure that coordination deficits were accurately captured, gold standard occupational therapy assessments were also carried out in a small subsample of children with 22q11.2DS whom we had found to screen positive for coordination difficulties. In addition, a small pilot investigation exploring how best to help children with coordination difficulties was conducted. Finally, the relationship between brain structure and motor difficulties in 22q11.2DS was explored using magnetic resonance imaging to investigate the grey and white matter, in combination with the coordination and sensorimotor data collected.

1.15 References

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2 General Methodology

Assessments and methods that are relevant to all experimental chapters are presented in the following sections. In addition, the diffusion imaging processing pipeline along including isolation of the corticospinal tract and cerebellar tracts is described (section 2.5).

2.1 Participants and procedure

All participants who took part in experiments were members of the ongoing ExperienCes of people witH cOpy number variants (ECHO) study http://medicine.cardiff.ac.uk/psychological-medicine-neuroscience/areas-research/copy-number-variant-research/research-projects/.

Participants with 22q11.2DS and their unaffected siblings closest in age, were recruited through genetics clinics across the UK, charities for chromosomal conditions as well as 22q11.2DS specifically (Unique, 22Crew and Max Appeal) and word of mouth. Control siblings were excluded if they had a diagnosis of any copy number variant (CNV). Patients and controls were excluded if younger than six years old. Presence of the deletion was confirmed for all children with 22q11.2DS by medical genetics laboratories and in the laboratory of the Department of Psychological Medicine and Clinical Neurosciences at Cardiff University. Recruitment of participants was not restricted based on deletion size as there is little evidence for phenotypic differences between individuals with the typical 3Mb deletion and the nested smaller deletions (see section 1.2). Three individuals recruited carried a smaller (1.5Mb) nested deletion.

Informed and written consent was obtained prior to recruitment from the carers of the children and recruitment was carried out in agreement with protocols approved by the appropriate research National Health Service ethics and research and development committees.

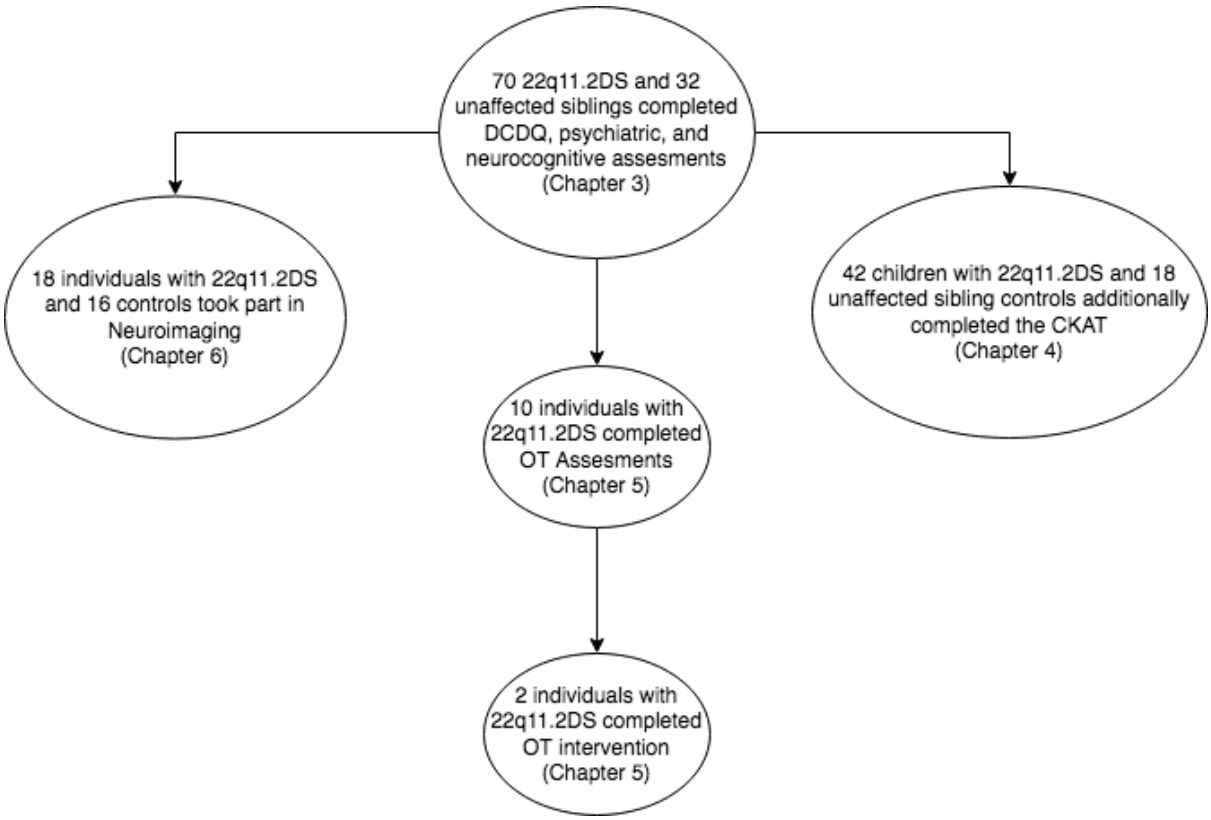

Figure 2-1. Flow chart detailing samples used in each chapter. 70 children with 22q11.2DS and 32 siblings comprise the overall sample used in chapter 3. Other chapters consist of individuals from this initial sample.

2.2 Cognitive assessments

Full scale, verbal and performance IQ were obtained by administering the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Participants also completed the CANTAB battery of neuropsychological tests (Cambridge Cognition Limited, 2006) which included: Reaction Time, Spatial Working Memory, Stockings of Cambridge, Rapid Visual Processing and Match to Sample tasks. Executive functioning was further probed using the Wisconsin Card Sorting Test (Heaton et al., 1993). All tasks were administered and scored by experienced psychologists. Cognitive assessments were carried out in either the participant's homes or during visits to Cardiff University. The tasks and respective outcome measures used are described below. The CANTAB provides standardised outcome measures based on a normative sample of healthy individuals aged 4-90 years old.

Cognitive assessments were carried out as part of the ongoing ECHO study, and as such were not collected for this study alone. The WASI and CANTAB data can therefore be considered as ECHO study data that was used alongside coordination and sensorimotor data in order to investigate relationships between motor ability and cognition. It would be expected that children with 22q11.2DS would perform more poorly on the cognitive tasks, and this has been demonstrated previously in the ECHO sample (Niarchou et al., 2014). Most cognitive testing sessions were carried out by members of the ECHO study field team, with myself carrying out only a small number.

2.2.1 Wechsler Abbreviated Scale of Intelligence

Participants completed four subtests, Vocabulary, Block Design, Similarities and Matrix Reasoning. The WASI is shorter than many other IQ tests making it well suited for populations where attention and engagement may be an issue, like in individuals with 22q11.2DS. The WASI differs from other Wechsler scales due to the fact that subtest total raw scores are converted to *T*-scores instead of using the subtest scaled scores (Wechsler, 1999). This is used as the *T*-score scale has a wider range of score points, and can better differentiate between levels of ability shown by subtest total raw scores. An individual's IQ scores are calculated by:

- Calculating the subtest raw scores by adding together the item scores contained in each subtest.
- Converting the subtest raw scores to *T*-scores using the raw score to *T*-score conversion tables contained in the WASI manual.
- Add the *T*-scores for the vocabulary and similarities subtests to obtain the sum of *T*-scores for the verbal scale. Also add together the *T*-scores for the Block Design and Matrix Reasoning Subtests to obtain the sum of *T*-scores for the Performance Scale.

- Add the *T*-scores for all four subtests to obtain the sum of *T*-scores for the Full Scale.
- The sums of *T*-scores are converted to WASI IQ equivalents by using the appropriate sum of *T*-score to IQ equivalent conversion table for each of the verbal, performance and full scales.

Abnormal subtest scatter, where an individual has a large difference between their highest subtest raw score and their lowest, could influence the full scale IQ's that are calculated from the WASI. In our sample of 22q11.2DS children it was found that the average difference between highest and lowest subtest T-scores was 14.64 points. The largest difference was 62 points and the lowest was 1 point. In the siblings, the average difference was 15.97 points, the maximum being 33 points and the minimum 6 points. The average difference did not differ between deletion carriers and siblings (p=0.439).

2.2.2 CANTAB Tasks

2.2.2.1 Spatial working memory

The spatial working memory task is a test of the participant's ability to retain spatial information and manipulate this information in working memory. It is self-ordered and can assess heuristic strategy. It is sensitive to frontal lobe dysfunction and deficits in executive function. The subject is presented with an array of boxes on a screen, which they must touch to find a "token". Once a token has been found, they must search again for a new token, but the token can only be hidden in a box that has not already contained a token. Searches are repeated until a token has been found in every box on the screen. An error is defined as touching any box in which a token has already been found. The participant can search the boxes in any order. The "clinical" mode was used, where there is a practice phase of four three box sets, and then twelve assessed trials, where there are four each of four, six and eight boxes. The outcome measures obtained are "Between Errors" and "Strategy Score". Between errors is defined as

the number of times the subject revisits a box in which a token has previously been found. This is calculated for all trials of four or more tokens, with lower numbers of errors indicating better performance. Strategy score is an estimate of the use of heuristic strategy when searching for tokens. (Owen et al., 1990) suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with a specific box and once a blue token has been found, to return to that box to start each new search sequence.

2.2.2.2 Reaction time

This task is designed to assess a subject's response speed to a visual target where the stimulus is both predictable, or unpredictable. Using one hand, the participant must hold down a button on the press pad and release it to touch the stimulus that appears on the screen. This is termed release and touch. In the initial stages, the stimulus is predictable as it can only appear in one place. Later the participant is given a choice of five possible positions, meaning the stimulus in unpredictable. The "Child Mode" was used, which consists of the following stages:

- Simple release and touch, which is not assessed. This is repeated five times.
- Simple release and touch which is assessed.
- Five-choice release and touch which is not assessed, and repeated five times.
- Five choice release and touch, which is repeated 15 times and assessed.

Outcome measures are reaction time and movement time. Reaction time is the time between the stimulus appearing on screen and the press pad button being released. As such, it is the speed with which the participant responds to the on-screen stimulus. A mean reaction time is calculated for each participant across trials of each type. Movement time is the time taken to touch the target after the press pad button has been released. Again, a mean movement time is calculated for each participant across trials of each type.

2.2.2.3 Stockings of Cambridge

The stockings of Cambridge is a spatial planning and spatial working memory task which is sensitive to frontal lobe function. The participant is presented with two displays with three coloured balls. The balls are presented as if they are stacked on top of each other, or held in stockings suspended from above. The subject must copy a pattern presented to them. The target pattern is always visible. The balls can only be moved one at a time, and are moved by touching the required ball, then touching the position the ball should be moved to. The time taken to complete the pattern and the number of moves required can be used as a measure of the participants planning ability. In the beginning, it is only necessary to move a single ball, with the number of balls needing to be moved increasing in steps to four moves. Then, a procedure for controlling for motor performance is included. In this phase, the target display moves one ball at a time, and the participant must follow the moves themselves. After this, a second block of planning problems is completed, along with another block of motor control trials. The outcome measures used were: the number of problems solved in minimum moves, mean initial thinking time and subsequent thinking time. Problems solved in minimum moves relates to overall planning accuracy (Robbins et al., 1998). Mean initial thinking time, which is the difference in the time taken to select the first ball for the same problem under the copy and follow conditions, gives a measure of the time taken to plan a solution to the problem. Subsequent thinking time measures the speed of movement after an initial movement has been made.

2.2.2.4 Rapid visual processing

This task is a measure of sustained visual attention. The participant is shown a white box in the centre of the screen which the digits 2 to 9, appear in a pseudorandom order. The digits appeared at a rate of 100 digits per minute. The task is split into two parts, first a warm up

practice phase which lasts for two minutes and is not scored and an assessment phase which lasts four minutes, where the last three and a half minutes are assessed. The participant must detect a target sequence of the digits 3-5-7, and register a response on a press pad. The target sequences appeared at a rate of 16 every two minutes. For the purposes of scoring, the number of responses within 1800 milliseconds of the final digit of the target sequence being presented are recorded. The number of false alarms and misses are also recorded. The outcome measure used here is RVP A' (A prime). This is a measure of sensitivity to the target, regardless or response tendency. In other words, this is a measure of how good the participant is at detecting target sequences using the probability of a correct response and the probability of a false alarm.

2.2.2.5 Match to sample visual search

Match to sample is a matching task with a speed or accuracy trade-off. The participant is presented with an abstract pattern, made up of four coloured elements, in the middle of the screen. After a delay, several similar patterns are presented around the edge of the screen. Only one of the patterns on the edge of the screen matches the middle pattern. The subject must choose which one they think matches. The incorrect patterns are made up of juggled elements of the target pattern or distractor elements. The participant must make their choice by touching the pattern, after releasing a button on the press pad. The task has four practice trials before the test begins and then twelve trials with differing number of patterns to make choices from, presented in a randomised order. The outcome measure for this task is the percentage of correct responses.

2.2.3 Wisconsin card sorting test

The Wisconsin card sorting test (WCST) (Heaton et al., 1993) is a widely used test of set shifting ability, or the ability to change cognitive strategies due to changes in the environment,

and aspects of executive functioning ability. The WCST 64 was used in this study, meaning that participants had to sort 64 cards with symbols that vary in colour, shape, and number. The sorting rule changes during the task without the participant's knowledge, and therefore the ability of the participant to switch among the sorting categories without randomly responding or persisting with unsuccessful strategies. Outputs from the test that are used in the following chapters include perseverative errors and non-perseverative errors. Perseverative errors are the number of errors where the participant has used the same rule as their previous response. Perseverative errors are a measure of set shifting ability. Non-perseverative errors are all remaining errors that do not fit the criteria for a perseverative error.

2.3 Psychiatric assessments

2.3.1 CAPA

The semi-structured interview Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al., 2009) was conducted with the primary caregiver and children themselves where possible and appropriate. Interviews were audiotaped, and DSM-IV-TR diagnosis obtained during consensus meetings lead by a child and adolescent psychiatrist. We did not consider diagnoses to be mutually exclusive. The CAPA was used to obtain ADHD and anxiety symptom counts. A symptom was counted as present if the individual had scored a two or three on the relevant CAPA question. Anxiety symptoms included any symptom of generalised anxiety disorder, social phobia, specific phobia, separation anxiety, panic disorder with and without agoraphobia, agoraphobia and obsessive-compulsive disorder. An individual with a research diagnosis of one of these anxiety disorders was classified as having “any anxiety disorder”.

2.3.1.1 Social communication questionnaire

The Social Communication Questionnaire (SCQ), screens for ASD symptoms. Total scores can range from 0 to 39. A score of 15 or greater is suggestive of putative autism spectrum disorder (ASD). The SCQ yields a total score and three subscale scores (behaviour, social, and communication). The behaviour subscale measures repetitive and stereotyped behaviours, the social scale probes aspects of reciprocal social interaction such as eye gaze and social smiling, and the communication subscale asks about communication ability including social chat and gestures.

2.4 Coordination assessments

2.4.1 DCDQ

The Developmental Coordination Disorder Questionnaire (DCDQ) (Wilson et al., 2009), is designed to screen for coordination difficulties in children 5-15 years old and is well validated (Wilson et al., 2009, 2000). The DCDQ can be used to indicate whether a child is likely to have DCD, although additional assessments are necessary to establish the diagnosis (Kirby et al., 2014). DCDQ scores range from 15 to 75, with discrimination thresholds that are dependent on age. In general, lower scores indicate greater coordination problems. The DCDQ generally assesses either coordination while moving or when using the hands and yields a total score as well as three subscores: control during movement, fine motor/handwriting and general coordination scores.

2.4.2 Kinematic assessment: The Clinical Kinematic Assessment Tool

The Clinical Kinematic Assessment Tool (CKAT) is a portable, tablet computer based kinematic skill assessment that allows detailed study of the profile and quality of movement. It involves the participant interacting with stimuli presented on a screen with a stylus. All

movements made while the stylus is in contact with the screen are recorded. There are three types of task in the battery: a tracking task, where the participant must follow a target dot on the screen as closely as they can; an aiming task where participants must draw a line from a starting position to targets that appear around the screen, while stopping within the target; and a tracing task, where participants must trace a maze attempting to keep within the lines. During testing, the participant was seated at a desk or table with the computer as if it was a page to be written on. The battery was implemented on two Motion Computing J3500 computers, each with a 12.1 inch, 1280x800 resolution, 32mb colour, 60 Hz display. The CKAT battery consists of three main tasks, tracking, aiming and steering. Detailed descriptions of the tasks can be found in (Flatters et al., 2014).

2.4.2.1 Tracking

The tracking task involves following a target dot (10mm in diameter) that moves in a figure eight pattern around the screen. The trial lasts 84 seconds, through a total of nine revolutions around the figure eight pattern. The target moves at a slow pace for the first three revolutions, a medium pace for the 4^{th}-6^{th} revolutions, and a fast pace for the final three revolutions. The tracking task is completed under two conditions. First, the target dot is displayed alone, in the second condition the dot is overlaid on a spatial guide that describes the figure eight pattern. The conditions are called with guide and no guide respectively.

2.4.2.2 Aiming

The aiming subtask required 75 successive movements towards target dots on the tablet screen. Participants begin by placing the stylus in a start position labelled on the screen, triggering the first 5mm diameter target to appear. Participants were instructed to respond as quickly and accurately as possible to the target by drawing a line to the target dot. Arrival within the target

causes the target to disappear and a new target to appear. The participant then draws a line to the new target and the process repeats. There were five possible target locations, that were presented in order, before starting again at position one. The distance between targets was constant, and the position of the targets described an approximate star shape. The last 25 targets had six jump events programmed within them. On these events, the target-dot instantaneously disappeared within 40mm of the intended target, while a new target appeared simultaneously at the next to be cued location. Therefore, the participant must make an online correction of their initial aimed movement. Participants were not told about the possibility of jump events, or of the repeating pattern of movements.

2.4.2.3 Steering

The steering subtask was made up of six trials. In each trial, the participant began in a labelled start zone, and after one second, a 4mm wide tracing path appears between the start zone and a finish position. To complete the trial, the participant had to move the stylus along the tracing path, staying within the lines as much as possible. The path the stylus had taken was indicated by an on-screen ink trail, resembling a real pen or pencil, providing visual feedback to the participants. Each trial was one of two paths which had identical geometry but were mirrored vertically. The paths were presented in alternate trials, meaning each path was shown three times. To attempt to standardise for completion speed, a black transparent box was displayed on the screen next to the start zone. This box covered about $1/7^{th}$ of the length of the path, and at five-second intervals the box shifted along the path until after seven shifts and 35 seconds; it had arrived at the finish zone. Participants were asked to attempt to remain within this box, either increasing speed of completion to keep up with the box or waiting at the edge of the box so as to not move ahead.

2.5 Neuroimaging methodology

Participants with 22q11.2DS and their unaffected siblings were recruited from the existing **E**xperien**c**es of People wit**h** C**o**py Number Variants (ECHO) study. Neuroimaging took place at the Cardiff University Brain Research and Imaging Centre (CUBRIC). MRI data were acquired on a 3T General Electric HDx MRI system (GE Medical Systems, Milwaukee, WI).

Structural T1 images were acquired with a 3D fast spoiled gradient echo sequence (TR = 7.8 ms, TE = 3.0 ms, voxel size = 1 mm^3 isomorphic).

A cardiac-gated, diffusion weighted, spin echo, echo planar imaging sequence was used to acquire high angular resolution diffusion weighted images. Thirty gradient orientations and 3 unweighted (b=0 s/mm^2) images were acquired with the following parameters: TE= 87ms (effective), FoV: 230 mm x 230mm, Acquisition matrix: 96×96, Slice Thickness: 2.4mm, 60 slices, 30 directions, bvalue=1200s/mm^2, 3B0. Resulting data had a 2.4 x 2.4 x2.4mm isotropic resolution. Zero filling was used to create a 128 x 128 in plane matrix for the fast Fourier transform. The final image resolution was 1.8 x1.8 x 2.4 mm.

2.5.1 Diffusion imaging processing

An overview of diffusion imaging processing steps is given in Figure 2-2. First, raw diffusion and T1 data were downloaded and extracted from the CUBRIC servers. A T1 4D .nifti file was created using dcm2nii (https://www.nitrc.org/projects/dcm2nii/) and skull stripped using bet (Smith, 2002), which is part of the FSL package (Jenkinson et al., 2012). The resulting skull stripped T1 images were then downsampled to 1.5mm^3 resolution using the afni 3dresample command (https://afni.nimh.nih.gov/about_afni). The outputs from this command were then visually checked to ensure that the resampling was to the correct resolution and the skull was

removed properly. In parallel, a MATLAB .mat file containing the diffusion imaging data was created using ExploreDTI 4.8.3 (Leemans et al., 2009). Diffusion imaging preprocessing, including eddy current, subject movement and EPI distortion correction was carried out in the ExploreDTI program (Leemans et al., 2009). Motion artefacts and eddy current distortions were corrected using B-matrix rotation, as in (Leemans and Jones, 2009). Field inhomogeneities were corrected by nonlinearly warping each Diffusion Weighted Image (DWI) to the T1- weighted image using the Fractional Anisotropy (FA) map from the DWI's as a reference, as in (Wu et al., 2008). Elastix (Klein et al., 2010; Shamonin et al., 2013) was used to calculate the warps, by using a normalized mutual information cost function and constraining deformations to the phase-encoding direction, resulting in corrected DWI's that are in the same space as the T1 images. After correction, the resulting FA and T1 images were visually inspected in ExploreDTI to ensure correct registration. Whole brain tractography was performed using the damped Richardson-Lucy algorithm (Dell'acqua et al., 2010). This is a spherical deconvolution method which has been modified to be less sensitive to spurious peaks in the fibre orientation distribution than standard spherical deconvolution methods. Seedpoint resolution was 2 × 2 × 2 mm, the step size was 0.5 mm, $L_{max.}$ was 8 and tracking was terminated when the angle threshold of the pathway changed through >45°. The resulting tractography files were taken forward for targeted tractography of the motor tracts of interest, the corticospinal tract and cerebellar peduncles.

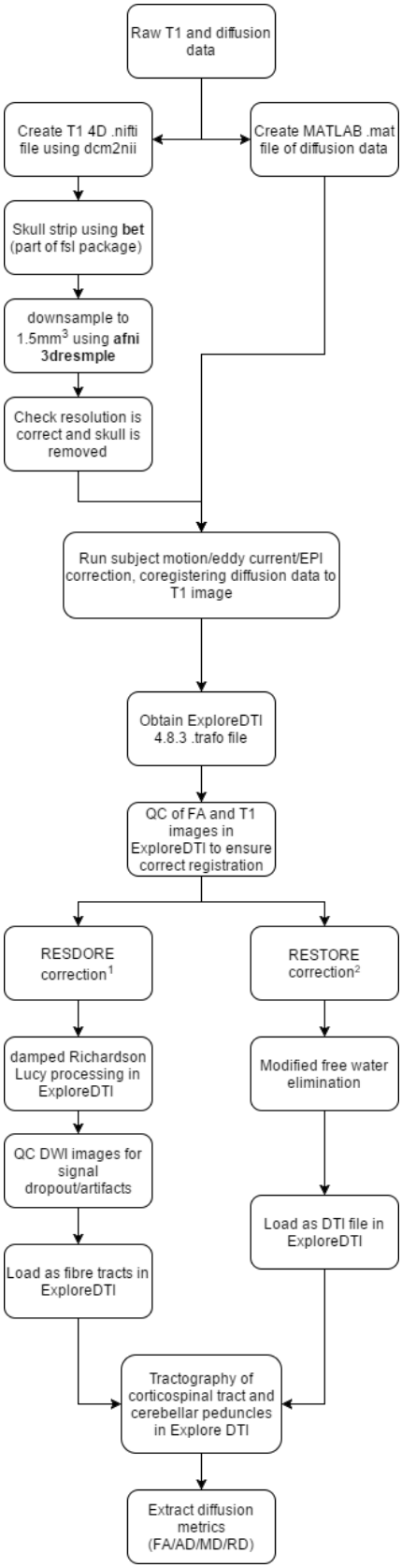

Figure 2-2. Flow diagram showing diffusion imaging processing procedure. [1]RESDORE and [2]RESTORE correction carried out using scripts created by Dr Greg Parker. Figure based on CUBRIC standard operating procedures for single shell DTI processing, created by Dr Sonya Bozorgzad.

2.5.2 Tractography procedure

Tract delineation was carried out in ExploreDTI (version 4.8.6), and diffusion metrics were exported for whole tracts after reconstruction. All tracts were delineated in each hemisphere separately, apart from the middle cerebellar peduncle, which crosses the midline and is therefore considered one continuous tract.

2.5.2.1 Corticospinal tract

Tract delineation was also carried out in ExploreDTI. The Region of Interest (ROI) placement for corticospinal tract reconstruction consisted of a SEED gate placed around the precentral gyrus (Figure 2-3) and an AND gate around the crus cerebri at the level of the decussation of the superior cerebellar peduncle (Figure 2-4). Tracking was initiated using these two gates. This resulted in a vertically orientated tract that does not cross the midline, as shown in Figure 2-5. Any spurious streamlines or streamlines projecting towards the cerebellum were removed with NOT gates as required.

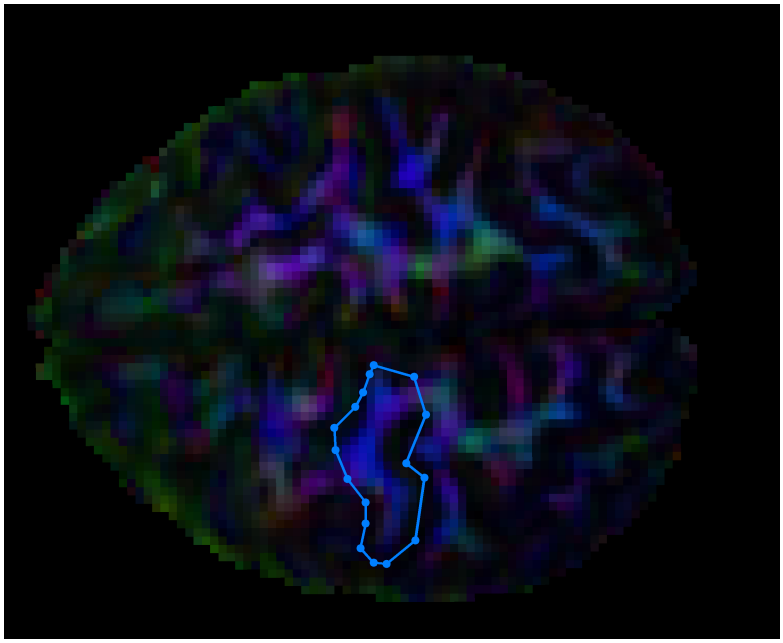

Figure 2-3. SEED region placement around the precentral gyrus for delineating the corticospinal tract.

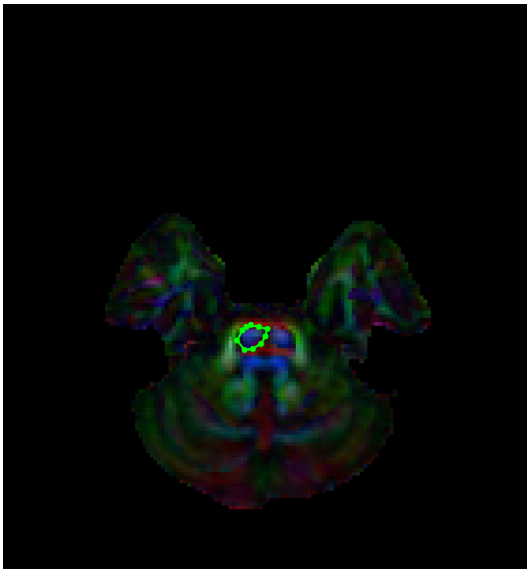

Figure 2-4. AND gate placement around crus cerebri for isolating the corticospinal tract.

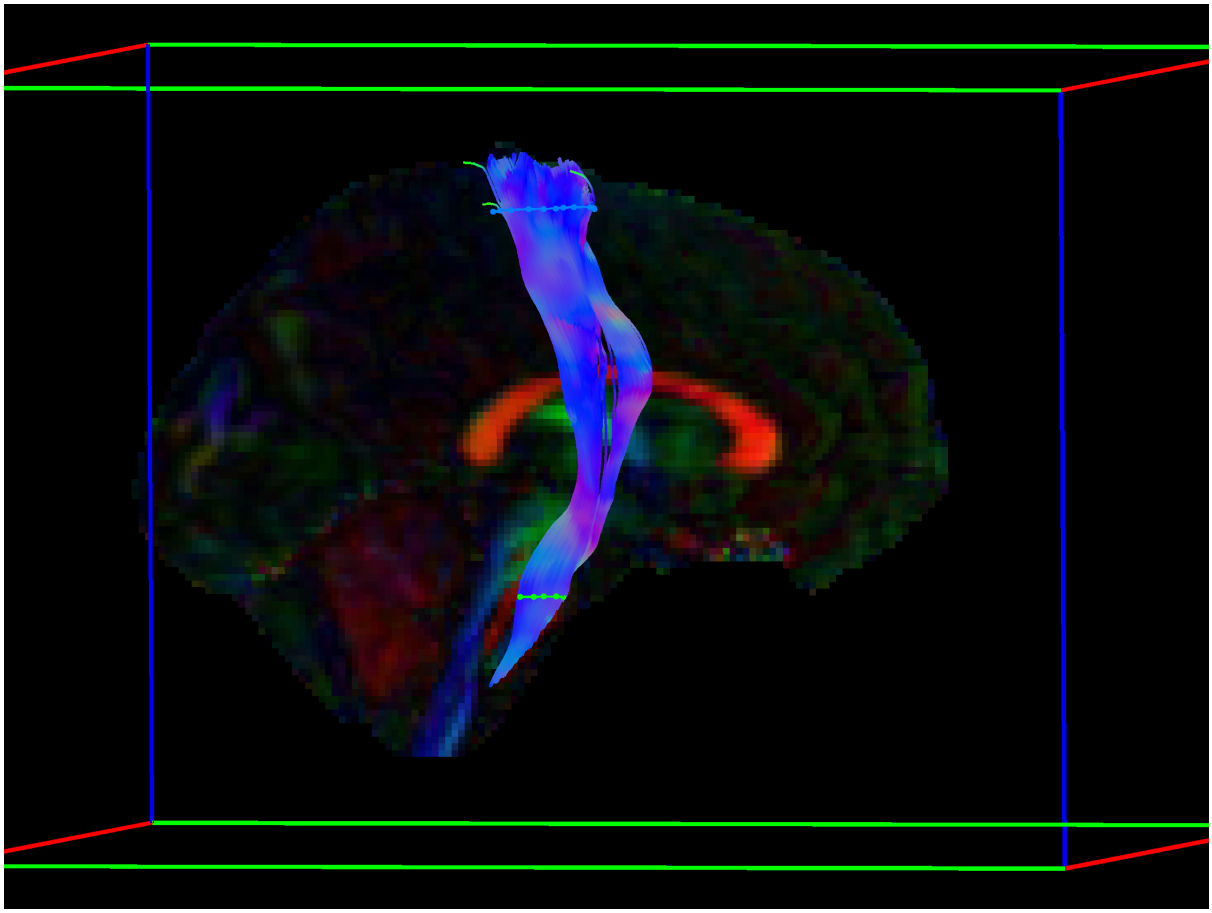

Figure 2-5. Complete corticospinal tract as results from initiating tracking between SEED region shown in Figure 2-3 and the AND gate shown in Figure 2-4. The corticospinal tract should project vertically, as a single bundle. Extraneous streamlines were removed with NOT gates if required.

2.5.2.2 Superior cerebellar peduncle

A NOT gate was placed anterior to the thalamus, along with another just superior to the fornix, to exclude streamlines passing anteriorly and superiorly past the thalamus (Figure 2-6). A single AND gate was placed in the coronal view around the superior cerebellar peduncle in the brainstem (light blue oval) as shown in Figure 2-7. A NOT gate was placed around the corticospinal tract and inferior cerebellar peduncle to exclude any streamlines projecting vertically into the cerebellum. Any streamlines that projected across the midline were excluded with NOT gates. This results in the isolation of the superior cerebellar peduncle projecting from the cerebellum, diagonally towards the thalamus, without crossing the midline Figure 2-8.

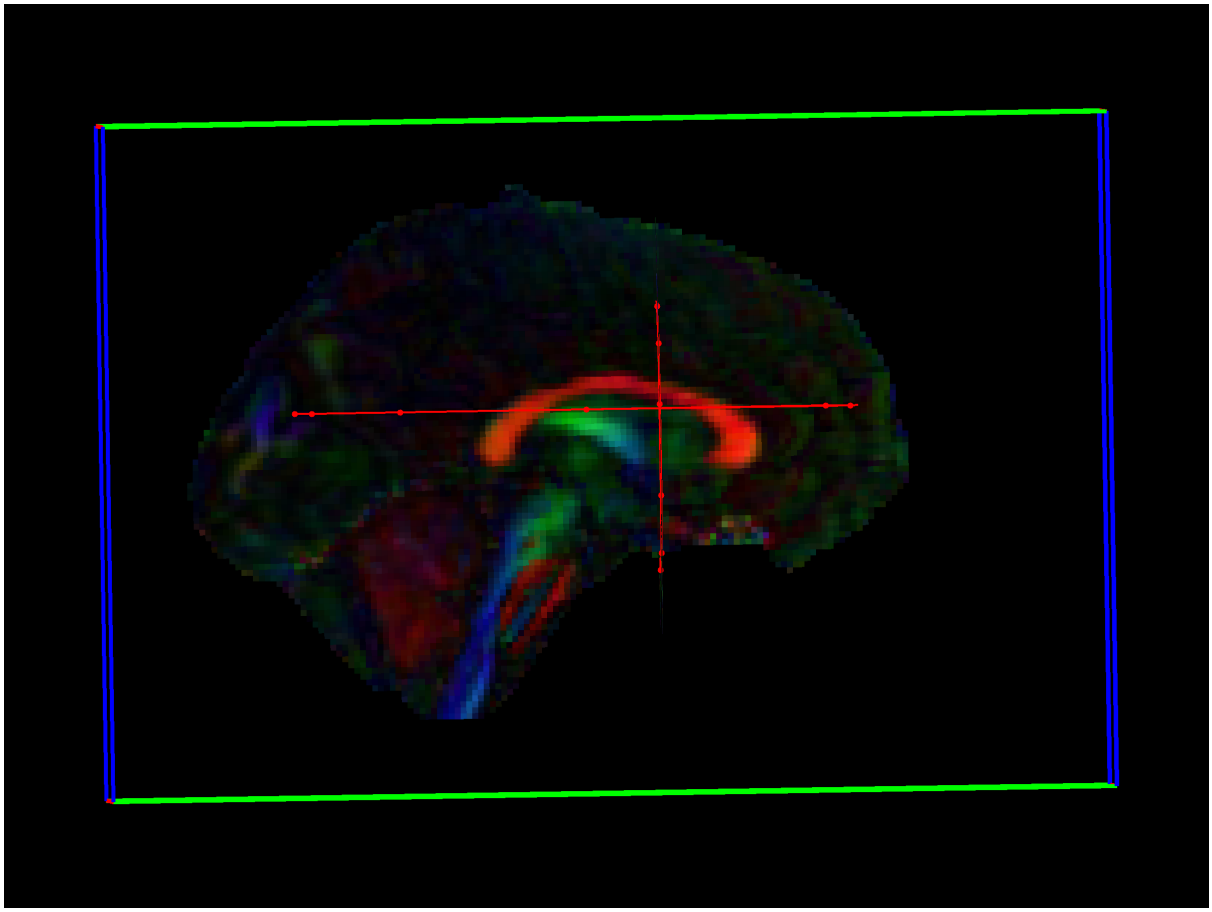

Figure 2-6. NOT gate placement for isolating the superior cerebellar peduncle. One NOT gate is placed just superior to the fornix in the Z-plane, to exclude any streamlines projecting towards the dorsal aspect of the brain, past the fornix. A second NOT gate is placed anterior to the thalamus in the x-plane to exclude any streamlines projecting anteriorly into the frontal lobe.

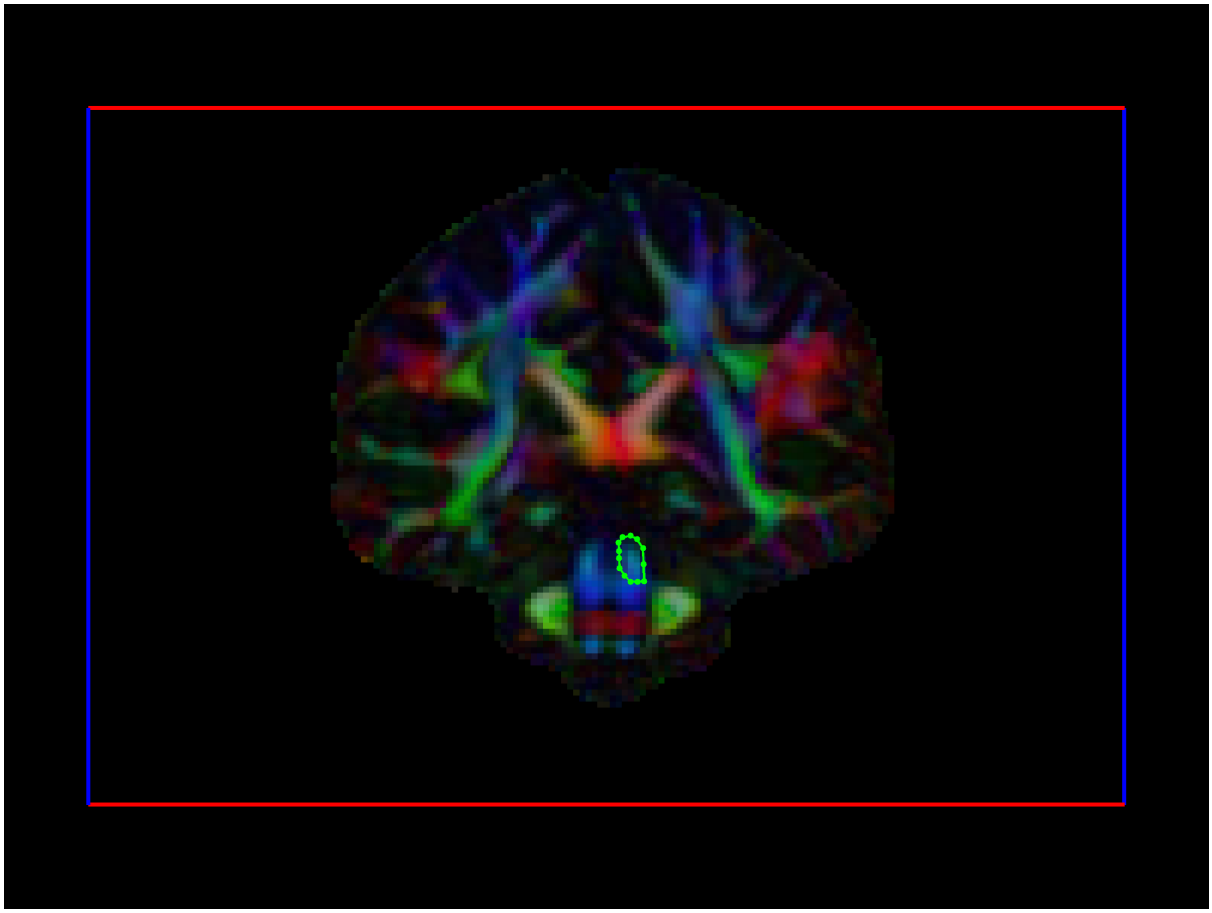

Figure 2-7. AND gate placement for isolating the superior cerebellar peduncle. The superior cerebellar peduncle can be seen on the false colour fractional anisotropy map as a light blue region in the brainstem in the coronal plane.

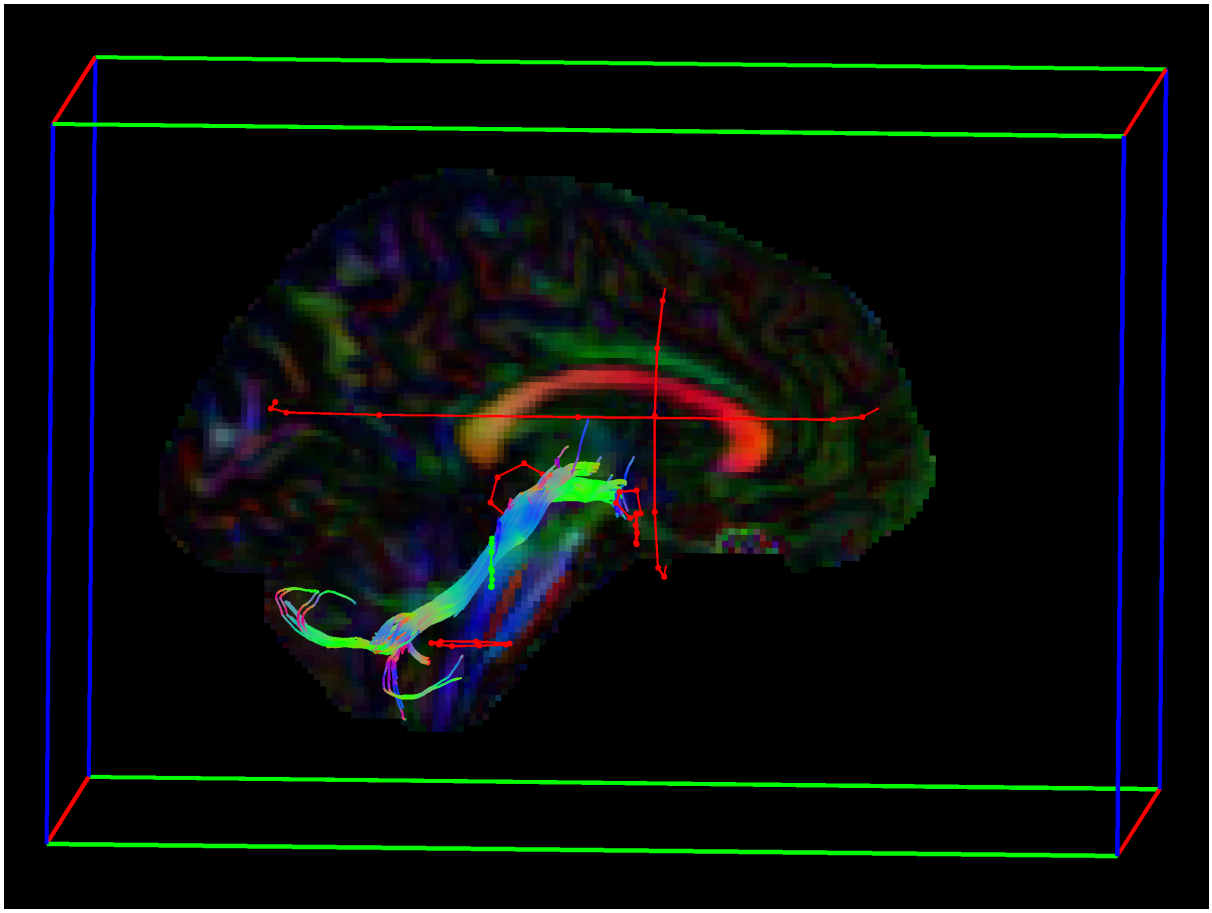

Figure 2-8. Complete superior cerebellar peduncle, isolated by analysing tracking from AND gate shown in Figure 2-7. Spurious streamlines are removed with NOT gates as required. The superior cerebellar peduncle should resemble a Z shape, streamlines that cross the midline, or project ventrally towards the spine should be removed.

2.5.2.3 Middle cerebellar peduncle

To isolate the middle cerebellar peduncle, two AND gates were placed around the middle cerebellar peduncle, one in each hemisphere, in the coronal view (Figure 2-9). These can be identified as bundles of fibres projecting in the anterior-posterior direction either side of the brainstem and are as such coloured bright green on the false colour FA map. Streamlines that crossed the midline in the white matter of the cerebellum were excluded using a NOT gate drawn in between the two cerebellar hemispheres as shown in Figure 2-10.

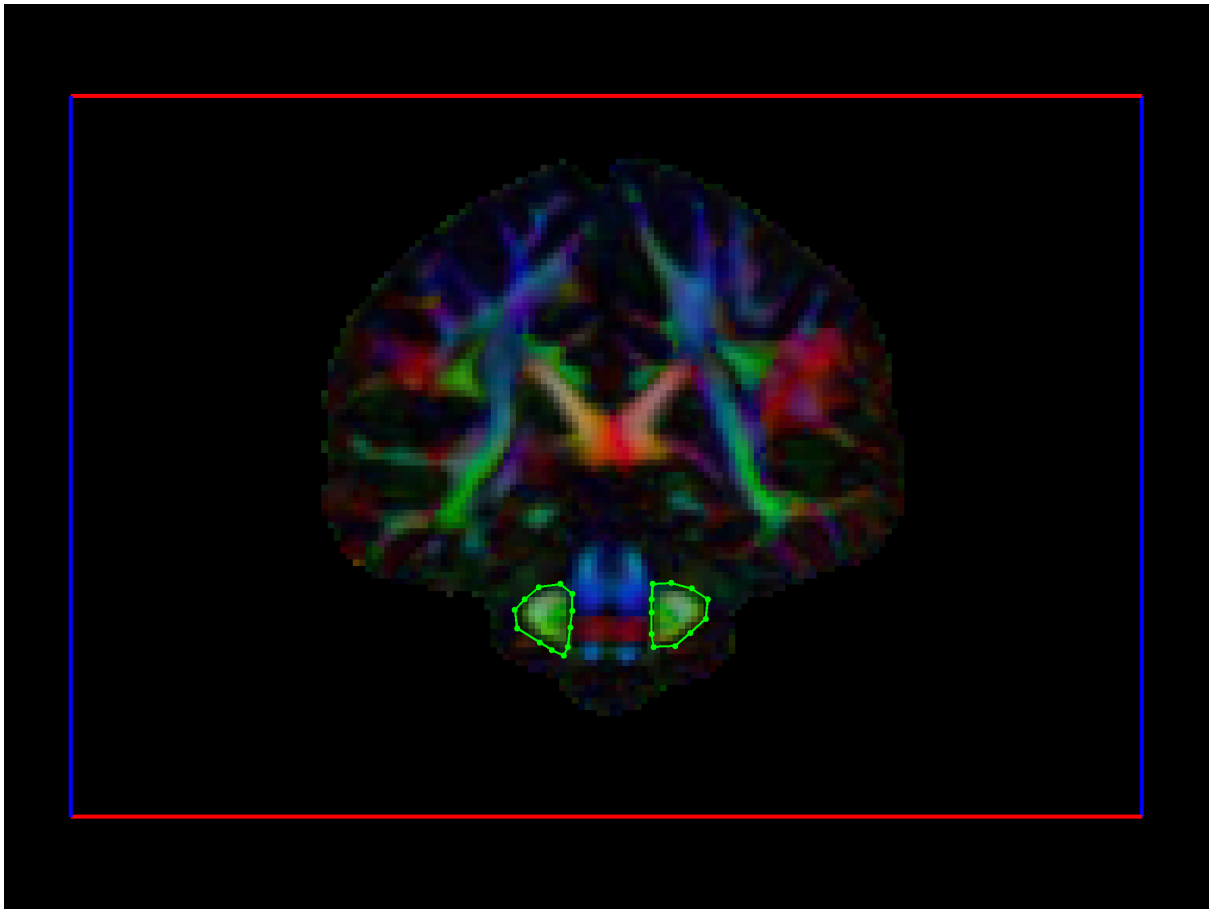

Figure 2-9. AND gate placement for isolating the middle cerebellar peduncle. Two AND gates are placed bilaterally around the middle cerebellar peduncle which can be identified in green on either side of the brainstem, at the level of the superior cerebellar peduncle on the coronal view.

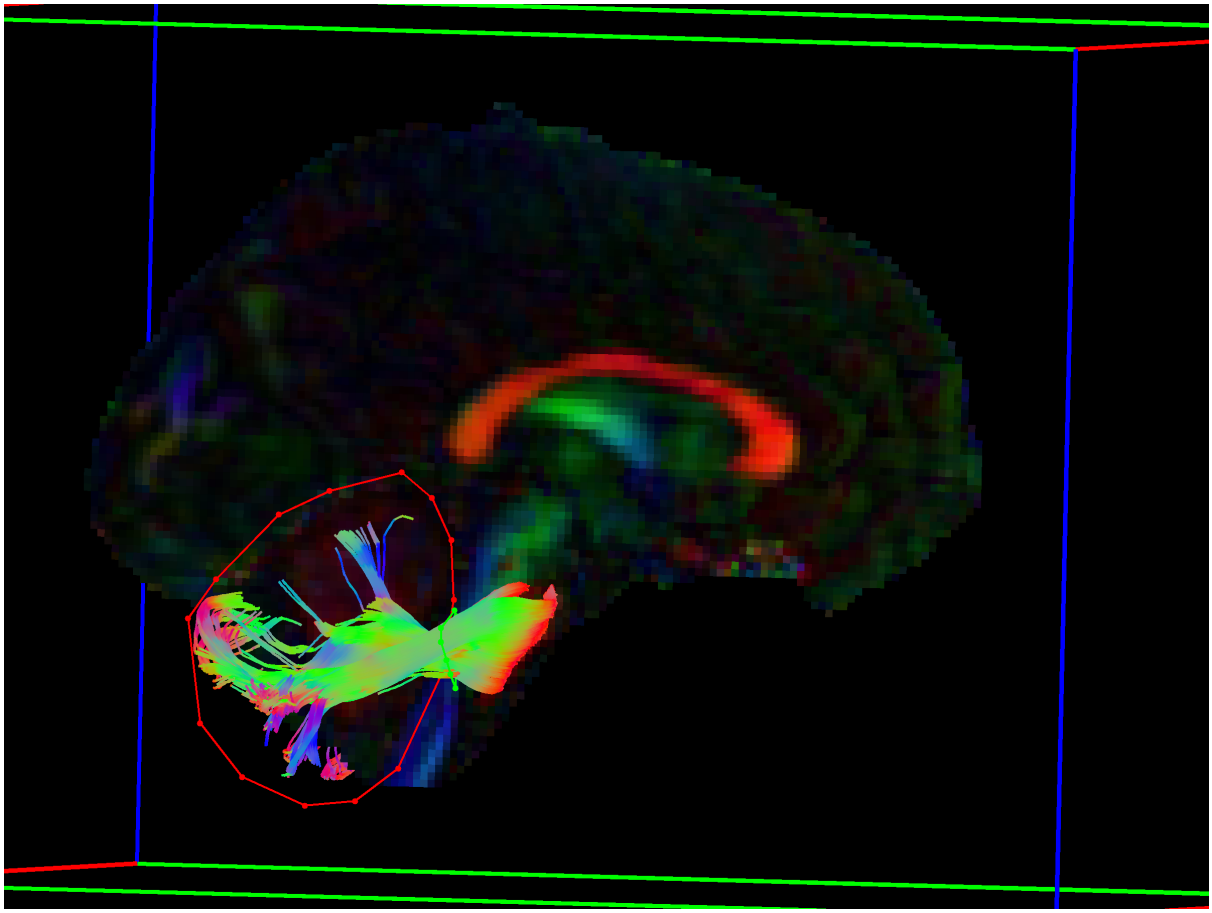

Figure 2-10. Complete middle cerebellar peduncle. Analysing streamlines between the two AND gates shown in Figure 2-9 should result in a single fibre bundle that crosses the midline and projects bilaterally into the cerebellum. Streamlines that cross the midline in the main body of the cerebellum should be excluded with NOT gates. Streamlines that curl back and project rostrally should also be excluded.

2.5.2.4 Inferior cerebellar peduncle

A single AND gate was drawn around the inferior cerebellar peduncle at the level of the base of the Pons. It can be identified as the most lateral (blue) vertically projecting bundle of fibres (Figure 2-11). The more medial and slightly larger bundle is the medial lemniscus. A second AND gate is placed 3-5 slices superiorly in the cerebellum to encompass the curve of the inferior cerebellar peduncle. NOT gates are used to exclude streamlines that cross the midline or project upward into the rest of the brain. This should result in a single fibre tract that runs upward from the brainstem before curving posteriorly and inferiorly into the contralateral cerebellum to resemble an “r” shape.

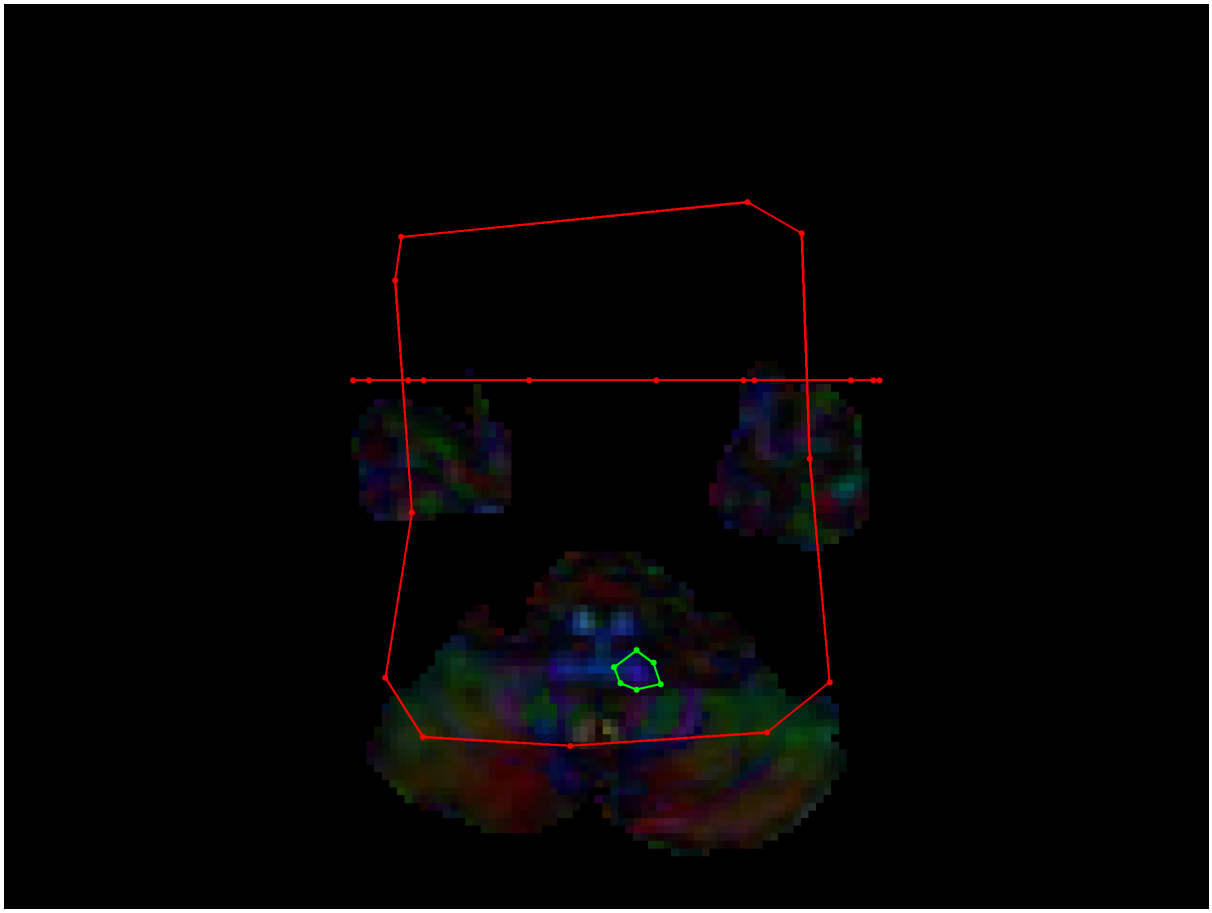

Figure 2-11. AND gate placement for isolating the inferior cerebellar peduncle. First, a single AND gate is drawn around the inferior cerebellar peduncle at the level of the base of the pons.

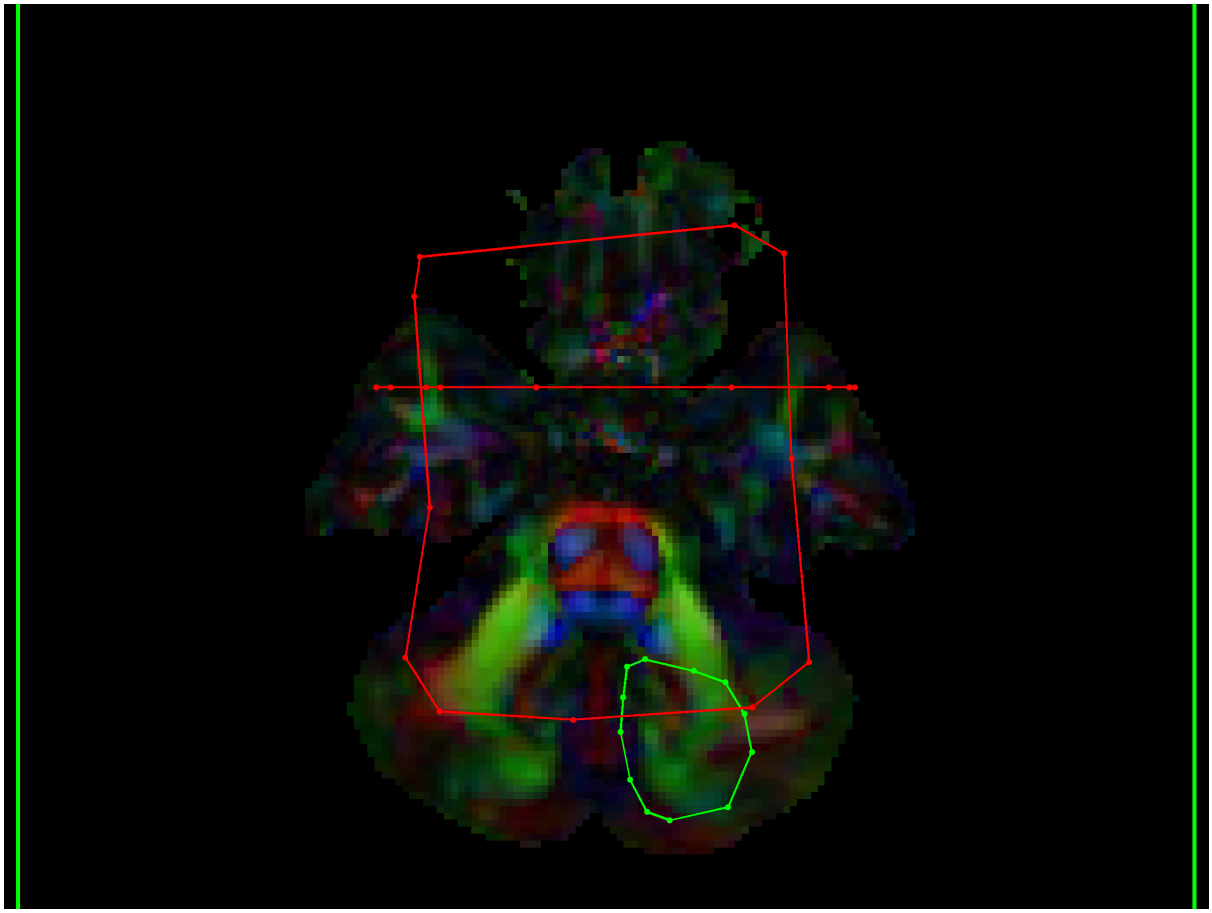

Figure 2-12. Second AND gate placement for isolation of the inferior cerebellar peduncle, A second AND gate is placed 3-5 slices superior to the first to encompass where the inferior cerebellar peduncle curls and projects into the cerebellum.

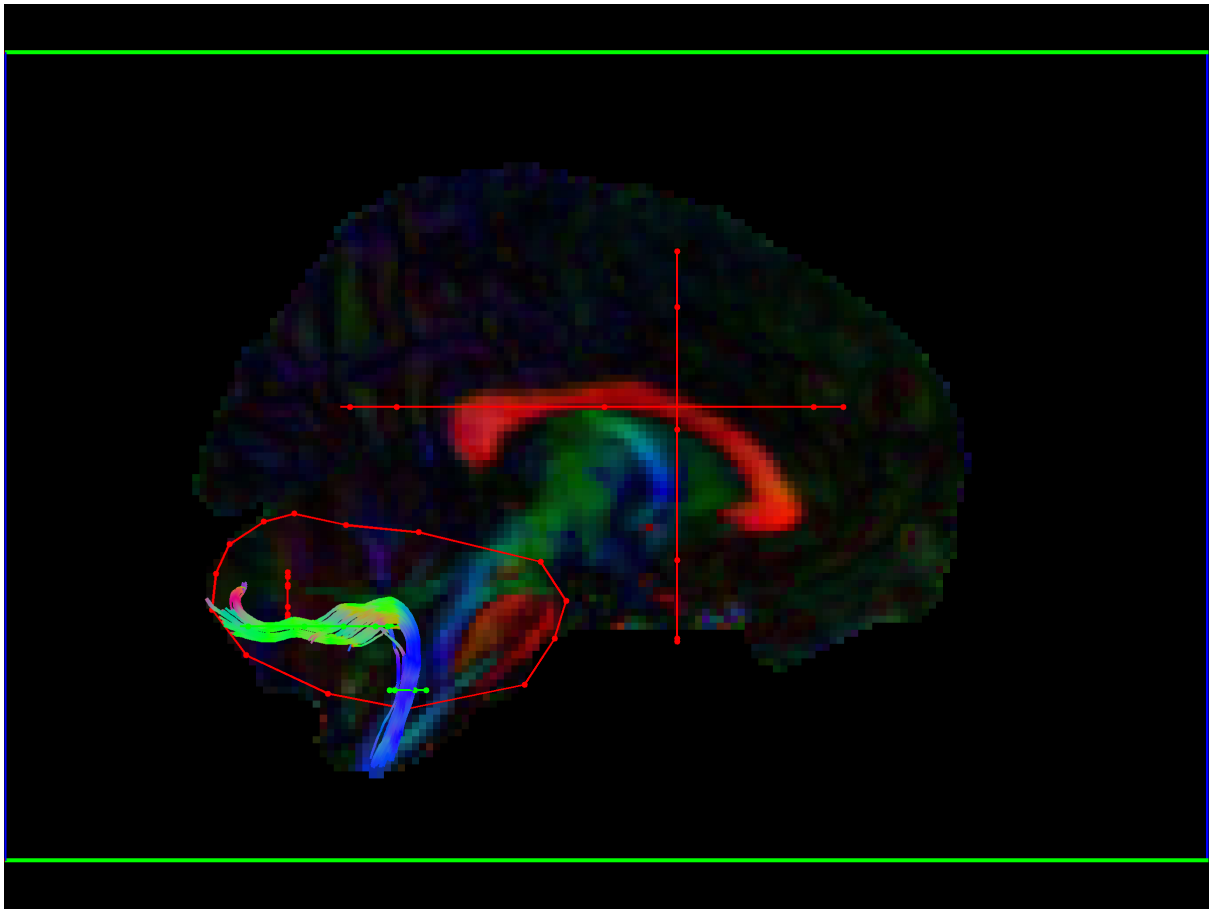

Figure 2-13. Complete inferior cerebellar peduncle. Analysing tracking between the AND gates for the inferior cerebellar peduncle should result in an r-shaped tract climbing from the spine and brainstem before curling into the cerebellum. Any streamlines that cross the midline, or curl back to project rostrally, should be removed using NOT gates.

2.5.3 FreeSurfer segmentation

FreeSurfer segmentation was carried out on 36 individuals. (18 22q11.2 Deletion syndrome carriers and 18 unaffected siblings). In brief, the recon-all command was used to segment the cortex and subcortical regions, and volumes for regions were extracted after quality control. FreeSurfer version 5.3.0 was used for segmentation. Segmentation and quality control was carried out on a Linux workstation. A detailed description of segmentation and analysis of cortical and subcortical regions follows in the next sections.

2.5.3.1 Cortical segmentation

The recon-all command was used to segment the cortex into different regions. Processing for each subject took around 20 hours. Once segmentation was complete, values for cortical surface area, thickness and volume were extracted for each subject. The output of recon all was then subjected to quality control, as recommended by the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols). The ENIGMA QC protocol recommends three steps, outlier detection, checking of the internal surface, and checking the external surface. Outlier detection is completed using an R script (in R version 3.2.2) which identifies outliers, with respect to your sample, for the cortical surface area, thickness and volume. Segmentations of subjects identified as outliers were then inspected manually for accurate segmentation. Failed reconstructions were manually edited using control points and re-run to ensure correct segmentation. The internal surface approach uses a MATLAB (The MathWorks Inc, 2015) function to plot cortical surface segmentation onto a given subjects structural scan and then collates snapshots of internal slices of the brain into a webpage to facilitate easy review of segmentations for multiple subjects. Similarly, the external surface approach creates a web page with external views of segmentations from different viewpoints. Subjects with incorrect segmentations were excluded after reviewing outputs of all three QC steps if re-running recon-all was not successful.

FreeSurfer's QDEC software (https://surfer.nmr.mgh.harvard.edu/fswiki/Qdec) was used to analyse the cortical brain surface data generated by the FreeSurfer pipeline. It allows for the identification of regions of the brain that differences occur between groups across the whole brain. QDEC is a GUI frontend to a statistics engine (mri_glmfit included in FreeSurfer) and allows selection of the subjects to be included in each analysis, the creation of a design matrix containing the explanatory variables of interest, a parameter estimate matrix and a contrast

vector, and visualisation of analysis results. QDEC and FreeSurfer use a general linear model, with notation $y = X(\beta)$ where y is the vector observed data (thickness, surface area, or volume for each subject at a vertex), X is the known design matrix (explanatory variables, such as gender, age etc.) and β is the vector of unknown parameter estimates. Interpretation of parameter estimates will change depending on how X is constructed, for example it could be interpreted as a slope corresponding to the change in observed data (e.g. thickness) as the explanatory (age, for example) variable changes. The estimation is the process of computing β given the input data y and the design matrix X. A null hypothesis is constructed using the contrast matrix and inferences can be drawn by testing against this null hypothesis.

As a very high number of statistical comparisons are being run, it is necessary to correct for multiple comparisons. This was carried out using Monte Carlo simulation to perform a cluster wise correction for multiple comparisons. This allows us to obtain a measure of the maximum cluster size under the null hypothesis. This is achieved by repeating the following steps (iterating) many times (usually >5,000). 1) Synthesize a z map, 2) use residual full width at half maximum (FWHM) to smooth z map, 3) threshold z map for absolute level and sign, 4) find clusters in the thresholded map, 5) record area of the maximum cluster, 6) iterate required number of times. Once the distribution of maximum cluster size has been obtained, we can use it to correct the original results for multiple comparisons by thresholding the results using the same level and sign, finding clusters in the thresholded map and calculating a p value for each cluster, corresponding to the probability of seeing a maximum cluster that size or larger during the simulation.

For analyses reported here, a cluster forming threshold of $p<0.01$ was used for simulations and a cluster-wise significance threshold of $p<0.01$ was used for visualisation. Results are overlaid on the "fsaverage" subject which was created in MNI-305 space.

2.5.3.2 Subcortical segmentation

Subcortical reconstructions were quality controlled using the methods set out by the ENIGMA consortium (http://enigma.ini.usc.edu/). This involved extracting subcortical volumes obtained from FreeSurfer and generating histogram plots and summary statistics for inspection, using R (version 3.2.2). These histograms of the volumes of each subcortical region were created for proband and sibling groups separately and inspected for approximate normality. The summary statistics were then taken into a semi-automated outlier detection script. This script calculates the interquartile interval, defined as (Quartile 1 - 1.5 times the interquartile range to Quartile 3 + 1.5 times the interquartile range. For a normal distribution, this is the same as the mean +/- 2.698 standard deviations. This semi-automated script assumed a normal distribution for outlier detection, as such the histograms created previously should at least resemble a normal distribution. Individuals with structures identified as being outliers based on a volume that is larger or smaller than expected were then inspected using the program FSLView, overlaying the subcortical segmentation mask created by FreeSurfer. I then decided if the structure had been segmented correctly in that individual. (One 22q11.2 deletion carrier's right hippocampus was excluded due to poor segmentation, and one sibling's left hippocampus and left amygdala were excluded due to poor segmentation). MATLAB was then used to create a web page displaying summary images of each individual's subcortical segmentation. Poor segmentations were excluded on the basis of outlier detection, histogram plots, and visual quality check. Volume values for each parcellated subcortical structure were then exported into R for statistical analysis.

2.6 Multiple comparison corrections

Throughout this thesis, a correction for multiple comparisons, such as a false discovery rate analysis (other than the clusterwise correction used by FreeSurfer), has not been applied. Due to the rarity of the sample and the exploratory nature of this research it was felt by myself and my supervisors that it would be appropriate to present all results before correction. However, this means that statistical results presented should be viewed with caution, particularly in Chapters 3 and 4 where a large number of comparisons are being conducted. Any significant results should be taken forward for further studies in order for replication and to confirm their validity. If correction for all comparisons in this thesis was made, it is unlikely that many of the results of comparisons presented would reach statistical significance.

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3 Developmental coordination disorder, psychopathology and cognition in 22q11.2 deletion syndrome.

3.1 Chapter overview

Motor deficits in 22q11.2 deletion syndrome were identified early on in research into the syndrome, but interest waned in the face of the many other more immediately serious symptoms that are characteristic of the syndrome. More recently, research has again begun to investigate the sorts of motor deficits that are present in 22q11.2 deletion syndrome and how they are related to other aspects of the syndrome. The prevalence of developmental coordination disorder (DCD) in this population has never been formally assessed, and links between motor functioning and psychiatric and neurocognitive outcomes have not been investigated thoroughly. It remains unclear whether the motor deficits seen in children with 22q11.2DS are in excess of what would be expected given the common occurrence of intellectual disability in this population. This chapter examines the prevalence of indicative DCD in the 22q11.2DS population and explores links between motor functioning, cognition, and psychiatric disorders. First, the prevalence of coordination difficulties in 22q11.2DS is explored. Then, relationships between coordination and the commonly comorbid neurodevelopmental disorders seen in 22q11.2DS, ADHD, ASD and anxiety disorder are investigated. Finally, the relationships between cognition and indicative DCD are examined. The results show that there is a very high prevalence of indicative DCD in 22q11.2DS, that coordination ability is related to IQ; and visual and sustained attention performance, along with ADHD, anxiety and autism symptoms. In addition, children who screened positive for DCD often also met criteria for other psychiatric disorders. This provides evidence that coordination difficulties are a key feature of 22q11.2DS and that they often co-occur alongside psychopathology in 22q11.2DS.

3.2 Introduction

Motor coordination problems can have serious impacts on a child's daily life, including in activities of daily living such as eating, dressing and grooming, self-esteem, pastime activities, social relationships and academic attainment (Cantell, Smyth and Ahonen, 1994; Losse *et al.*, 2008; Sumner, Leonard and Hill, 2016). There is also evidence that motor dysfunction can increase the risk of developing psychopathology (Pratt and Hill, 2011), which can persist into adulthood (Kirby *et al.*, 2013). Despite this, coordination and motor difficulties are under researched in populations with chromosomal disorders, such as 22q11.2 deletion syndrome (22q11.2DS).

As previously outlined in the introduction to this thesis (Chapter 1), 22q11.2DS is a rare copy number variant disorder that is associated with mild to moderate learning disability along with increased risk of psychopathology in both childhood and adulthood (Niarchou *et al.*, 2014). Approximately 40% of adults with the disorder will develop a schizophrenia spectrum disorder (Schneider *et al.*, 2014). In childhood, the deletion is associated with high rates of ADHD, ASD, anxiety disorders, and oppositional defiant disorder (Baker and Skuse, 2005; Angkustsiri *et al.*, 2014; Niarchou *et al.*, 2014; Schneider *et al.*, 2014; Richards *et al.*, 2015).

Difficulties in motor coordination are emerging as a key aspect of 22q11.2DS, particularly problems with balance, bimanual coordination and visuomotor skills (Van Aken *et al.*, 2010a, 2010b) with some evidence that these problems are not explained by intellectual disability (Roizen *et al.*, 2011). There is also converging evidence of problems with motor pathways in patients with 22q11.2DS. Adults with the deletion are at an increased risk of developing early onset Parkinson's Disease (Butcher *et al.*, 2013; Mok *et al.*, 2016), and MRI studies have shown abnormalities of the cerebellum, including consistent reductions in volume.

Abnormalities of other motor circuit areas have also been observed, including increased volume of the striatum (Sugama *et al.*, 2000; Kates *et al.*, 2011), and calcification of the basal ganglia (Sieberer *et al.*, 2005).

Motor difficulties may also be related to risk of developing schizophrenia. Motor symptoms are observed in schizophrenia and feature in even some of the earliest descriptions of the disorder. Video evidence has shown that children who are clumsy may be at greater risk of development of schizophrenia (Schiffman *et al.*, 2004). This, combined with the association of coordination difficulties with other neurodevelopmental disorders that are common in 22q11.2DS, points to the importance of undertaking more research in this area.

If coordination difficulties have a significant impact on daily life and seem to be neurodevelopmental in origin, rather than due to an acquired injury or overt neurological disorder, a child can be diagnosed with Developmental Coordination Disorder (DCD). As described in the introduction to this thesis (Section **1.9**), DCD is a neurodevelopmental disorder characterised by motor functioning that is slower, less accurate and more variable than that of peers. It can only be diagnosed in the absence of any other cause that would better explain the deficits in motor coordination, such as a neurological deficit. In children, DCD is often seen to be comorbid with other neurodevelopmental disorders such as ASD (Dziuk *et al.*, 2007) and ADHD (Kaiser *et al.*, 2015). It is thought that around 50% of children with ADHD also meet criteria for DCD, with inattentive rather than hyperactivity symptoms being more commonly seen in combination with coordination difficulties (Kaiser *et al.*, 2015). DCD is often also accompanied by specific learning difficulties such as dyslexia (Biotteau, Chaix and Albaret, 2015) or difficulties with mathematical skills (Gomez *et al.*, 2015). It is very commonly

accompanied by other difficulties or psychiatric symptoms, and a "pure" presentation of DCD is extremely rare (Zwicker *et al.*, 2012b).

Generally, studies that have investigated the incidence of DCD in both the general population and clinical populations (such as those with a diagnosis of ADHD) have excluded subjects with a learning disability as defined by IQ less than 70 (Zwicker *et al.*, 2012a; Peters, Maathuis and Hadders-Algra, 2013). This has simplified analysis as it removes the confound of whether any motor deficit is in excess of what would be expected due to intellectual disability. However, it may not give a full picture of the incidence and presentation of DCD. The current study investigated the prevalence of DCD in children with 22q11.2DS as well as their unaffected siblings but did not exclude subjects on the basis of IQ. This allowed us to make some inferences as to whether deficits found are indeed in excess of what would be expected due to the individual's intellectual disability. A dearth of previous studies means that it is not clear if coordination difficulties in 22q11.2DS are related to any comorbid intellectual disability, or are a separate, specific deficit. It is also not clear how any coordination deficit present in 22q11.2DS is related to other phenotypes such as attention, social skills, or anxiety.

Previous research into coordination difficulties in children has primarily been conducted in participants selected because of their phenotype of coordination difficulties. This means that it is likely that samples recruited for these studies are made up of children who are genetically heterogeneous. As such, any coordination deficits could be caused by a wide range of genetic factors, which may often be unknown. Sometimes, this may involve the presence of a (possibly large) number of common genetic variants and sometimes a single variant, such as the 22q11.2 deletion. Investigating coordination in a genetically homogenous population with a known contributory factor for coordination deficits, such as children with 22q11.2DS, may allow

clearer insights into the pathways between a genetic lesion and the coordination deficit phenotype.

The 22q11.2 deletion has a large number of associated outcomes and therefore has a pleiotropic effect on many traits including IQ, psychopathology and potentially coordination. We know that 22q11.2 deletion lowers IQ and increases the risk for psychopathology. However, it is not yet clear if coordination difficulties are a direct outcome, or an indirect effect of the deletion, mediated by the other deficits in IQ or cognition, or psychopathology. As such there are several models that could explain the relationships between the three outcomes explored here.

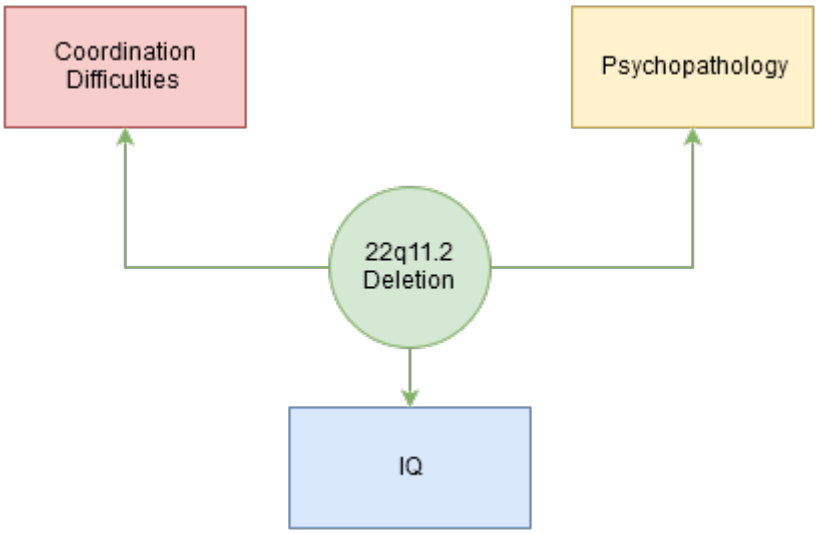

Figure 3-1. Model 1, 22q11.2 Deletion has effects on IQ, Coordination, and Psychopathology; but affects each separately. Each outcome is unrelated to the other.

Firstly, the 22q11.2 deletion could cause lowered IQ, increase the risk of psychopathology, and coordination difficulties, but do so through separate mechanisms that have little or no overlap (Figure 3-1). If this is the case, we would expect that coordination difficulties would not be associated with IQ or psychopathology. This has been found to be the case in previous work by our group, where the deletion was found to have separate effects on IQ and childhood psychopathology separately (Niarchou *et al.*, 2014).

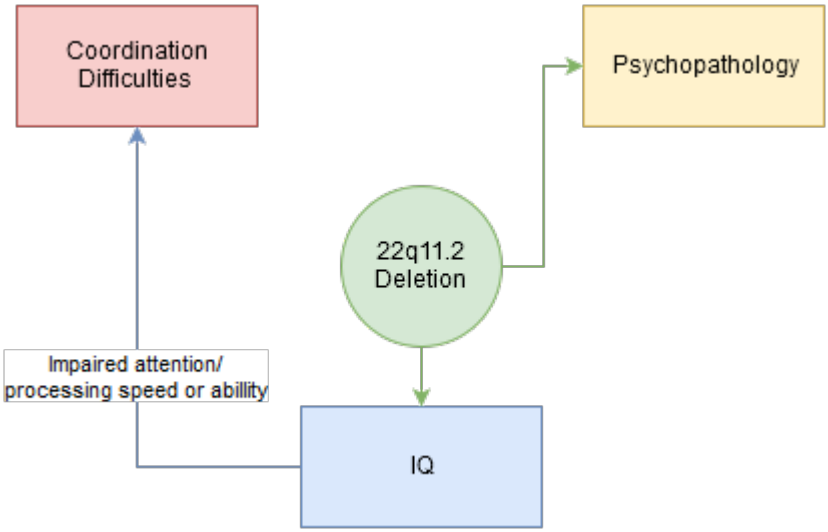

Figure 3-2. Model 2, 22q11.2 Deletion directly affects IQ and Psychopathology but does not directly affect coordination. Coordination difficulties are a result of lowered IQ such that impaired cognition results in impairments in coordination.

Secondly, the loss of the 22q11.2 region could cause coordination difficulties as a secondary effect of lower IQ and other cognitive deficits (Figure 3-2). It would be plausible to think that the impairments in cognition such as impaired attentional ability and reduced processing speed would result in deficits in coordination. In this case, we would expect an association between IQ/cognition and coordination difficulties, but not between coordination and psychopathology.

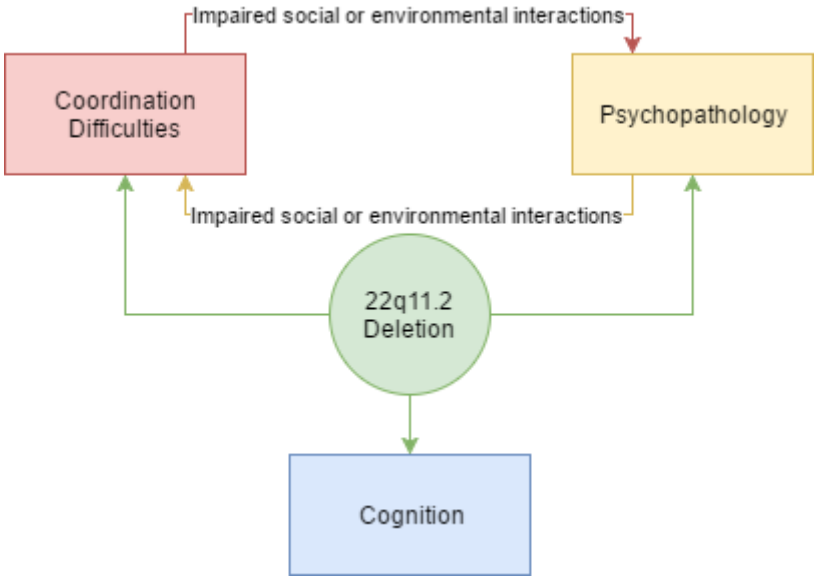

Figure 3-3. Model 3, 22q11.2 Deletion has direct effects on IQ, psychopathology and coordination, but effects on coordination and psychopathology are separate to the effect on IQ. Coordination is related to psychopathology, such that both influence and reinforce each other.

Thirdly, the 22q11.2 deletion could cause deficits in cognition, coordination difficulties and psychopathology, but only coordination and psychopathology are related to each other. This could be through a common neural deficit or insult caused by the deletion that impacts on both outcomes, or separate biological mechanisms, but the outcomes influence each other. For example, social exclusion due to being unable to perform well in sports or in school could increase risk for developing psychopathology such as anxiety. This model is supported by evidence from studies of coordination difficulties and DCD in other non-genotyped populations where high rates of coordination difficulties have been found in children with ADHD and ASD, which may point towards a shared neural deficit, as mentioned previously in this chapter. If this model is supported, we would expect coordination difficulties to be associated with psychopathology but not IQ.

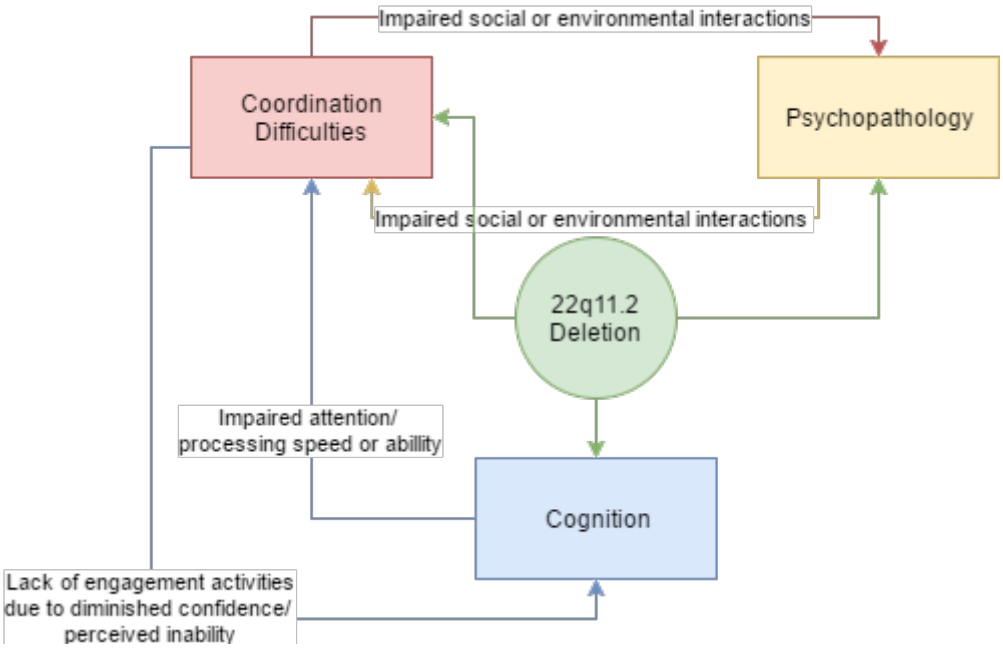

Figure 3-4. Model 4, 22q11.2DS affects coordination, psychopathology and IQ, and coordination difficulties have reciprocal interactions with IQ and psychopathology.

The fourth model states that both IQ and psychopathology are intimately linked with coordination difficulties, but IQ is not related to psychopathology, as in (Niarchou et al. 2014). In this model, the 22q11.2 deletion would cause deficits in all outcomes through common mechanisms. The macroscopic neurological abnormalities seen in 22q11.2DS, such as general reductions in the volume of grey and white matter, and midline brain abnormalities (Chow *et al.*, 1999; Van Amelsvoort *et al.*, 2001a; Bearden *et al.*, 2004; J E Schmitt *et al.*, 2014) may be markers of a generalised atypical brain development that could have diffuse effects over many brain systems. As such the cognitive, motor and psychological changes seen in 22q11.2DS are a product of overall abnormal brain development and are therefore all related. Evidence for this comes from the aforementioned findings of midline brain abnormalities in 22q11.2DS populations and reductions in brain volume, particularly in more posterior brain areas such as the parietal lobe, occipital lobe and cerebellum (Eliez *et al.*, 2002; Bearden *et al.*, 2004;

Squarcione *et al.*, 2013; J Eric Schmitt *et al.*, 2014). In addition, it is known that the migration of parvalbumin containing interneurons is disrupted in a mouse model of 22q11.2DS, while the overall number of PV+ interneurons remains the same (Meechan *et al.*, 2009). If this model is true, we would expect associations between IQ and coordination and between coordination and psychopathology.

The models presented are various methods of explaining the pleiotropic effects of the 22q11.2 deletion on IQ, psychopathology and its potential effect on coordination. There may be truly pleiotropic effects on IQ, psychopathology and coordination (as in Model 1) or mediated pleiotropy (as in Model 2), where the deletions effects on coordination are a secondary effect of lowered cognitive ability. However, these pleiotropic effects may also be correlated with overall syndrome severity, where the separate effects on coordination, IQ and psychopathology are modified by the overall severity of symptoms an individual expresses (including symptoms that are not be measured in this study). Finally, there may not be pleiotropic effects, but rather differences in each individual's specific deletion affect overall syndrome severity, and this causes associations between IQ, psychopathology and coordination.

The diagnostic criteria for DCD stipulate that the coordination difficulties must not be due to any known neurological or physical problem, and in excess of what would be expected given any intellectual disability. Therefore, it is debatable whether individuals with 22q11.2 deletion syndrome would fit criteria for DCD as there are known effects of the deletion on the nervous system and body. Previous research has demonstrated that the coordination difficulties seen in children with 22q11.2DS may be in excess of what would be expected given the average IQ of individuals with the syndrome, but it remains that the individuals have an organic syndrome that could be considered to cause the coordination difficulties. Therefore, is it appropriate to

diagnoses individuals with 22q11.2DS with DCD? Using an entirely literal definition of DCD, the answer would likely be no. However, it is entirely likely that many individuals with a diagnosis of DCD may carry genetic changes that may contribute to poor coordination, and be unaware of them. If a child with a diagnosis of DCD is subsequently given a diagnosis of a genetic lesion such as 22q11.2DS, should the genetic diagnosis override the diagnosis of DCD? Many individuals with genetic syndromes are given diagnoses of physical and mental health problems in addition to the genetic diagnosis. If individuals with 22q11.2DS do show coordination problems that are in excess of what would be expected given intellectual level, and the motor deficits are having a severe impact on daily functioning, then a diagnosis of DCD may help in facilitating the correct support for these children.

Coordination difficulties can be measured in a variety of ways. Fine or gross motor skills can be investigated separately and at different levels. In keeping with the ICF framework of disability ('WHO | International Classification of Functioning, Disability and Health (ICF)') , coordination difficulties can be attributed to four separate levels, being caused by: a problem at the level of body functions, of the body's structure, difficulties through a lack of participation, or through environmental factors. DCD in general manifests as difficulties in participation or activities of daily life. As such it can be screened for using a questionnaire such as the DCDQ (Wilson *et al.*, 2009). The DCDQ is a well-validated measure to screen for coordination difficulties and is regularly used in clinical practice in the process of diagnosis. The DCDQ provides an output of whether an individual has indicated DCD or not, further motor assessments should be used to assign a final diagnosis. Using a questionnaire measure allows for large populations to be screened efficiently, with the potential for more information to be gathered on subpopulations of interest.

While neurodevelopmental disorders have been investigated in 22q11.2DS samples, motor and coordination difficulties are an area that has received much less interest, in fact I am not aware of previous studies investigating the prevalence and impact of developmental coordination disorder in a 22q11.2DS sample and very few in a sample of patients with a chromosomal disorder (Hanson *et al.*, 2014). There are no previous studies investigating the links between risk of psychopathology and coordination difficulties in individuals with 22q11.2DS, and similarly, we currently have a poor understanding of how cognition is related to coordination in children with 22q11.2DS. As such, this experiment set out to address these gaps in the literature surrounding coordination difficulties in 22q11.2DS. Our first aim was to investigate the prevalence of indicative DCD in children with 22q11.2DS in comparison with siblings without the deletion using the DCDQ. Second, we investigated the relationships between indicative DCD and psychiatric problems that are common in children with 22q11.2DS, (ADHD, ASD and anxiety disorder). Our third aim was to explore the relationship between indicative DCD and IQ in this population. The final aim was to investigate if neurocognitive performance is related to DCD, using the CANTAB neurocognitive battery. We hypothesized that there would be a high incidence of indicative DCD in children with 22q11.2DS and that most of the children who screened positive would meet diagnostic criteria for DCD, that indicative DCD would be associated with risk of ADHD, ASD and Anxiety disorder, that coordination difficulties would not be related to IQ, or neurocognitive performance, as reported by previous studies of motor function in 22q11.2 deletion syndrome referenced above.

3.3 Materials and methods

3.3.1 Participants and procedure

The current study was based on 70 children with 22q11.2DS (58.6% male, mean age 11.2 years, s.d. 2.2) and 32 unaffected siblings (43.8% male, mean age 11.5, s.d. 2.1). Children with

22q11.2DS did not differ in age (p=0.50) or gender distribution (p=0.16) from the control siblings. Presence of the deletion was confirmed by Medical Genetics laboratories, using standard methods (FISH/Microarray), and subsequently in the laboratory of the MRC Centre for Neuropsychiatric Genetics and Genomics at Cardiff University, using microarray. Informed and written consent was obtained prior to recruitment from the carers of the children and recruitment was carried out in agreement with protocols approved by the appropriate research and National Health Service Ethics and Research and Development committees. The primary carers of the children provided information on the children's physical health. Ten children (13.2%) with 22q11.2DS were born earlier than 37 weeks, as compared to three (9.4%) unaffected siblings. A history of epileptic fits was reported for twelve (17.1%) children with 22q11.2DS, whilst thirty-four (48.6%) had experienced a heart problem and two (2.9%) had reported previous low calcium levels. None of the children were receiving medication for ADHD. One child with 22q11.2DS was taking sodium valproate for epilepsy, along with fluoxetine and risperidone for a psychotic disorder.

3.3.2 Coordination assessment (DCDQ)

The Developmental Coordination Disorder Questionnaire (DCDQ) was completed by the primary carer. It is designed to screen for motor coordination impairments in children 5-15 years old and is well validated (Wilson *et al.*, 2000, 2009). DCDQ scores range from 15 to 75, with discrimination thresholds that are dependent on age. In general, lower scores indicate greater coordination problems. The DCDQ assesses either coordination while moving or when using hands. It yields a total score as well as separate scores for three subscales: control during movement, fine motor/handwriting and general coordination scores. Subjects were categorized into those with and without indicative DCD based on DCDQ total score compared to the appropriate age threshold. The DCDQ can be used to indicate whether a child is likely to have

DCD, although additional assessments are necessary to establish the diagnosis (Kirby, Sugden and Purcell, 2014).

3.3.3 Developmental milestones

Parents also completed questions on three developmental milestones: age at which the child learnt to ride a bike, do up their shoelaces and fasten buttons. These milestones give a general measure of gross and fine motor skill development, complementing other information. Sample sizes for milestone comparisons differ as only a proportion of participants had attained the milestones at the time of data collection.

3.3.4 Full scale IQ, neurocognitive and psychopathology assessment

A full outline of assessment of full scale IQ and psychopathology is given in the General Methodology (Chapter 2). In brief, we obtained IQ data using the WASI (Wechsler, 1999) and neurocognitive data with the CANTAB (Cambridge Cognition Limited, 2006) and Wisconsin Card Sorting Test (WCST) (Heaton *et al.*, 1993). Psychiatric symptoms of ADHD and Anxiety were obtained through the CAPA, while SCQ score was used as a measure of ASD symptoms. IQ, neurocognitive and psychiatric assessments were carried out as part of the on-going ECHO study, either in participants' homes or during visits to our laboratory at Cardiff University. Sample sizes for analyses using the IQ data and symptom data differ, as complete datasets were not available for some participants, mainly because they had difficulties in completing measures.

3.3.5 Statistical analysis

Statistical analysis was carried out in R version 3.3.3 (https://www.R-project.org/) on Mac OS X 10.11.1. CANTAB and WCST outcome measures were standardised to have a mean and

standard deviation of one. Differences in group statistics scores between the 22q11.2DS and sibling groups were established using t-tests or Wilcoxon tests where appropriate with respect to normality. Indicative DCD and mental disorder prevalence in children with 22q11.2DS compared to control siblings was examined using a Chi-Squared test. Comparisons within individuals screening positive for DCD was examined using a Fisher's exact test due to low counts in one or more cells. Spearman correlations were used to assess associations between the DCDQ total score and age of attaining milestones. Associations between psychiatric symptoms (ADHD, SCQ score, any anxiety disorder), or IQ, or CANTAB outcome variables and DCDQ score were established using linear regression. Predictors were entered hierarchically, age first, then gender and finally the psychopathology, neurocognitive or IQ variable. Sensitivity analyses were carried out to investigate whether comorbid factors (preterm birth, medication use, a history of epileptic fits, or reported heart problems) contributed to our findings. For these sensitivity analyses, rates of indicative DCD were calculated when children with these medical factors were excluded and covariates for preterm birth, epileptic fits and heart problems were included in the regressions. As only one child was receiving medication for ADHD or antipsychotics, this was not entered as a covariate.

3.4 Results

Descriptive statistics about the families are presented in Table 3-1.

Table 3-1. Descriptive statistics of sample.

Mother's Ethnic Background			
European	69 (92.0%)		
Mixed	5 (6.7%)		
Unknown	1 (1.3%)		
Origin of Deletion			
De Novo	58 (82.9%)		
Inherited	6 (8.6%)		
Unknown	6 (8.6%)		
Highest Maternal Qualification			
High (University Degree and/or other higher postgraduate qualification	18 (24.0%)		
Middle (A-Levels/Highers/Vocational Training	34 (45.3%)		
Low (O-Levels/GCSEs)	15 (20.0%)		
No School Leaving Exams	8 (10.7%)		
Family Income			
≤ £19,999	19 (25.3%)		
£20,000 - £39,999	22 (29.3%)		
£40,000 - £59,999	16 (21.3%)		
≥£60,000	15 (20.0%)		
Unknown	3 (4.0%)		
Age			
22q11.2DS	**Mean Age**	**SD**	**Range**
Male	11.10	2.20	6.20-14.87
Female	11.58	2.31	7.11-14.75
Siblings			
Male	11.75	1.58	9.24-14.89
Female	11.39	2.40	6.18-14.88
Gender			
22q11.2DS		**X^2**	**P**
Male	41 (58.6%)		
Female	29 (41.4%)		
Siblings		1.940	0.163
Males	14 (43.8%)		
Female	18 (56.2%)		
22q11.2DS, 22q11.2 Deletion Syndrome			

3.4.1 Prevalence of indicative DCD in 22q11.2DS

Children with 22q11.2DS had lower scores on the DCDQ (22q11.2DS median=39.5, controls median=73.5, $p<0.001$) and all subscales (control during movement $p<0.001$, fine motor $p<0.001$, general coordination $p<0.001$), reflecting poorer coordination. Fifty-seven children with 22q11.2DS met criteria for indicative DCD (81.4%) compared to two control siblings (6.3%) ($\chi^2=50.9$, $p<0.001$, OR=36.7). Similar numbers of males and females (36, 87.8% of males, 21, 72.4% of females) with 22q11.2DS met criteria for indicative DCD ($\chi^2=2.66$, $p=0.103$, OR= 2.05). Males had a median score of 36 on the DCDQ versus 45 in females ($p=0.013$).

Children with 22q11.2DS had a higher mean age of learning to ride a bike and do up buttons compared to control siblings (difference of 14.26 months for learning to ride a bike; 22.21 months for doing up buttons, Table 2). Developmental coordination problems correlated with age of attainment of doing up buttons ($r=-0.51$, $p<0.001$); but not tying shoelaces ($r=-0.43$, $p=0.060$), or riding a bike ($r=-0.27$, $p=0.086$); whilst no associations were found for the siblings.

Table 3-2. Results of group comparisons of measures between children with 22q11.2DS and controls.

	22q11.2 DS			Control Siblings					
Measure	**Total**	**DCD +**	**DCD -**	**Total**	**DCD +**	**DCD -**	**χ^2**	**OR**	**P Value**
Individuals positive for indicative DCD	70	57	13	32	2	30	50.9	36.7	<0.001
Age Motor Milestones Achieved (Months)	**n (able)**	**Mean**	**S.D.**	**n (able)**	**Mean**	**S.D.**	**t**	**95% CI**	**P Value**
Learnt to ride a bike	40	75.88	20.45	27	61.62	18.66	2.95	4.58, 23.91	0.005
Learnt to do up buttons	48	72.21	24.74	25	50.00	14.83	4.78	12.95, 31.47	<0.001
Learnt to tie shoelaces	20	95.45	29.97	24	82.17	22.7	1.63	-3.26, 29.83	0.112
	n	**Median**	**IQR**	**n**	**Median**	**IQR**	**Z**	**95% CI**	**P Value**
ADHD Symptom Count	70	5	7.75	30	0	0.00	5.87	3, 7	<0.001
Putative ASD Score	67	11	11.00	32	1	2.00	6.94	7, 12	<0.001
Anxiety Symptoms	66	3	9.75	29	0	1.00	3.79	1, 3	<0.001
	n	**Mean**	**S.D.**	**n**	**Mean**	**S.D.**	**t**	**95% CI**	**P Value**
FSIQ	70	70.75	11.94	31	104.58	15.71	-10.65	-40.22, -27.44	<0.001
PIQ	67	74.55	12.87	31	102.68	17.46	-8.02	-35.19, -21.06	<0.001
VIQ	68	70.97	12.73	31	105.581	15.68	-10.78	-41.07, -28.15	<0.001

DCD: Developmental coordination disorder, FSIQ: Full Scale IQ, PIQ: Performance IQ, VIQ: Verbal IQ

3.4.2 Associations between indicative DCD and psychopathology

32.9% (23/70) of children with 22q11.2DS met criteria for ADHD, compared to 3.3% (1/30) of siblings. 29.0% (20/69) of children with 22q11.2DS met criteria for any anxiety disorder, compared to 6.7% (2/30) of siblings. Twenty-three children with 22q11.2DS (34.3%, 23/67) screened positive for putative ASD while no siblings did (0/32). Similarly, the rates of ADHD, putative ASD and anxiety symptoms were higher in children with 22q11.2DS than siblings Table 3-2.

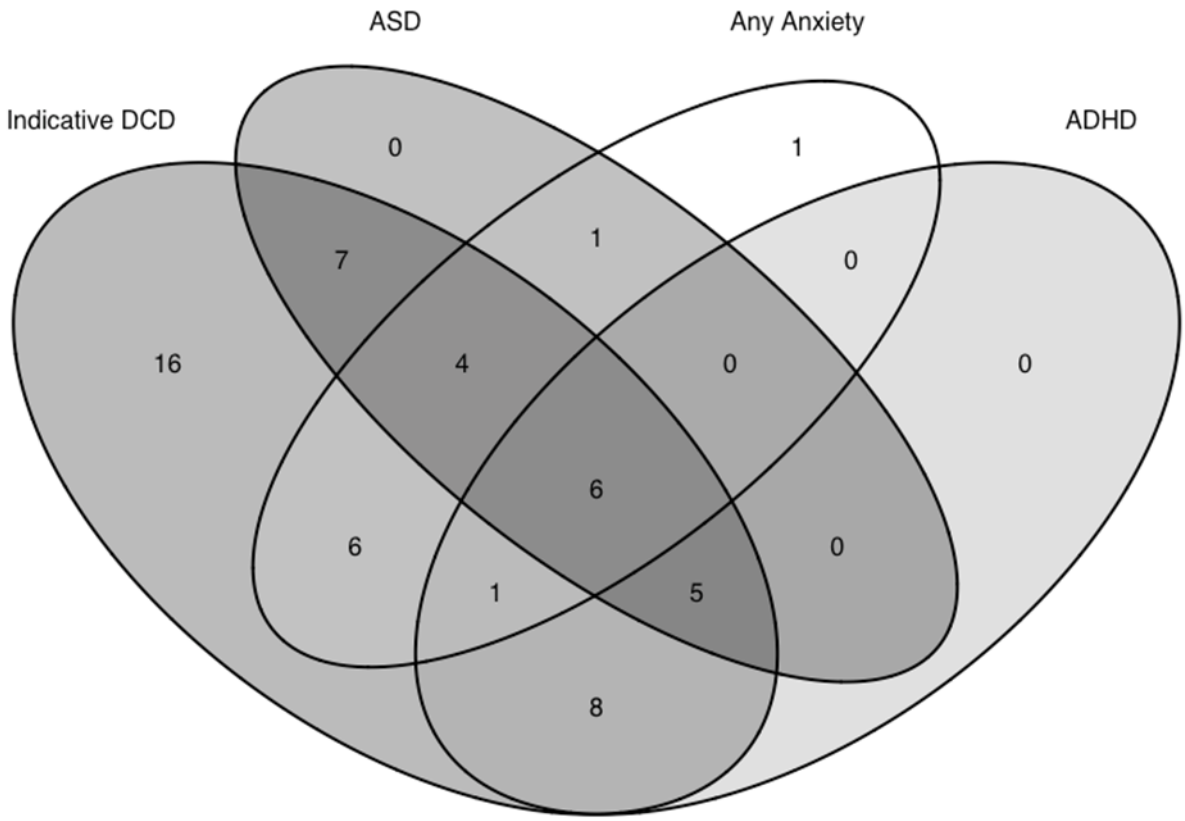

Figure 3-5. Comorbidity in the sample of 22q11.2 Deletion Syndrome. ASD, Autism Spectrum Disorder, ADHD, Attention Deficit Hyperactivity Disorder, DCD, Developmental Coordination Disorder.

Of the 53 children with indicative DCD and complete diagnosis data for ASD, ADHD and anxiety, 69.8% (37/53) had at least one psychiatric disorder compared to 15.4% (2/13) of individuals without indicative DCD ($p<0.001$, OR=5.84). Figure 1 shows the high rate of co-occurrence between motor dysfunction and psychopathology. 30.2% (16/53) of individuals with indicative DCD met criteria for at least two, and 11.3% (6/53) for all three disorders. Thirty eight percent (20/53) of children with 22q11.2DS and indicative DCD met the criteria for ADHD, compared to 0% (0/13) of children without indicative DCD ($p=0.008$, OR=3.47) Percentages for putative ASD were 41.5% (22/53) vs 7.7% (1/13) ($p=0.022$, OR=2.46), and for anxiety disorder were 32.1% (17/53) versus 15.4% (2/13) ($p=0.234$, OR=1.7) in children with and without indicative DCD, respectively. 100% (20/20) of children with ADHD had indicative DCD, as did 89.5% (17/19) of children with any anxiety disorder and 95.7% (22/23) of children with putative ASD.

The DCDQ total score was associated with ADHD symptom count ($p<0.001$), but not age ($p=0.768$) or gender, and this association was driven by inattentive symptoms ($p<0.001$) but not hyperactivity symptoms ($p=0.051$). Scores on all three subscales of the DCDQ were associated with ADHD symptoms (fine motor skill $p<0.001$; control during movement: $p<0.001$, general coordination: $p<0.001$).

DCDQ total score was associated with putative ASD score ($p<0.001$), but not age ($p=0.304$) or gender ($p=0.188$). The control during movement ($p<0.001$), general coordination ($p=0.003$), as well as fine motor ($p<0.001$) subscales were all associated with putative ASD score. Further analysis showed that all three subtests of the putative ASD score (behaviour $p<0.001$, communication $p<0.001$, social $p=0.026$) predicted DCDQ total score.

DCDQ total score was also associated with anxiety symptoms ($p<0.001$), along with gender ($p=0.041$), with boys having lower DCDQ scores, but not age ($p=0.341$). Scores on the fine motor skill subscale were associated with anxiety symptoms ($p=0.004$) and gender ($p=0.005$). The scores on the general coordination subscale were also associated with anxiety symptoms ($p=0.001$) and gender ($p=0.033$). Anxiety symptoms ($p=0.004$) but not gender predicted the control during movement score.

3.4.3 Association between indicative DCD and IQ

Mean FSIQ of the siblings was higher than in children with 22q11.2DS (Table 2). Of the children with 22q11.2DS, four (5.97%) had moderate intellectual disability (IQ<55), 29 (43.3%) had mild intellectual disability (IQ 55-70), 24 (35.8%) had an IQ in the borderline range (71-85), and 10 (14.9%) had average IQ (86-115). This is in comparison to one (3.1%) sibling with mild intellectual disability. DCDQ score was associated with FSIQ ($p=0.038$).

3.4.4 Coordination and neurocognitive performance

Children with 22q11.2DS performed more poorly than siblings on the sustained attention, visual attention, processing speed, spatial planning and spatial working memory tasks. Children with 22q11.2DS had lower scores for non-perseverative errors indicating they made a higher number of errors of this type (Table 3-3).

Table 3-3. Performance on CANTAB neurocognitive tasks in children with 22q11.2DS and controls.

	22q11.2 DS	Controls						
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	**t**	**p**
Set Shifting: Perseverative Errors	66	0.06	0.82	30	-0.14	1.32	0.76	0.450
Set Shifting: Non-Perseverative Errors	66	-0.32	0.99	30	0.70	0.60	-6.25	<0.001
Sustained attention	55	-0.26	1.10	30	0.47	0.56	-4.04	<0.001
Visual Attention	60	-0.23	1.08	31	0.45	0.61	-3.81	<0.001
Processing Speed: Reaction time	61	-0.18	1.16	31	0.36	0.38	-3.30	0.001
Processing Speed: Movement time	62	0.05	1.22	31	-0.10	0.13	1.00	0.321
Spatial Planning: Initial thinking time	54	0.09	1.23	28	-0.17	0.06	1.55	0.128
Spatial Planning: Subsequent thinking time	53	0.06	1.22	26	-0.12	0.10	1.10	0.277
Spatial planning: Problems solved in minimum moves	57	-0.27	0.99	29	0.52	0.81	-3.96	<0.001
Spatial working memory: errors	67	-0.34	0.92	31	0.72	0.77	-5.96	<0.001
Spatial working memory: Strategy Score	68	-0.24	0.80	31	0.53	1.19	-3.31	0.002
Measures correspond to the following tasks: Set Shifting: Wisconsin Card Sorting Task, Sustained attention: Rapid Visual Processing, Visual Attention: Match to sample, Processing speed: Reaction time task, Spatial Planning: Stockings of Cambridge.								

Using hierarchical linear regression analysis entering first age, then gender, then the neurocognitive outcome measure of interest, I found that DCDQ score was associated with sustained attention and visual attention. No other CANTAB or WCST outcome measures were associated with DCDQ score. Regression results are shown in Table 3-4.

Table 3-4. Regression results for developmental coordination disorder questionnaire score predicted by CANTAB outcome variables.

Variable	R^2	B	B SE	β	Prob
	0.08				
Age		1.04	0.93	0.14	0.266
Gender	n=66	-6.42	3.96	-0.20	0.110
Set Shifting: Perseverative errors		-1.86	2.41	-0.09	0.444
	0.08				
Age		0.97	0.93	0.13	0.304
Gender	n=66	-7.05	3.93	-0.22	0.078
Set Shifting: Non-perseverative errors		-1.52	2.00	-0.09	0.449
	0.22				
Age		1.02	0.90	0.14	0.260
Gender	n=55	-4.68	4.20	-0.15	0.270
Sustained attention		5.40	1.89	0.37	0.006
	0.18				
Age		1.57	0.88	0.22	0.078
Gender	n=60	-4.96	4.14	-0.15	0.235
Visual attention		3.98	1.87	0.26	0.038
	0.12				
Age		2.06	0.91	0.29	0.027
Gender	n=61	-4.78	3.95	-0.15	0.231
Processing Speed: Reaction time		0.36	1.63	0.03	0.827
	0.11				
Age		1.82	0.90	0.25	0.048
Gender	n=61	-5.02	3.88	-0.16	0.201
Processing Speed: Movement time		1.34	1.66	0.10	0.424
	0.14				
Age		2.00	0.96	0.28	0.042
Gender	n=54	-6.72	4.31	-0.21	0.125
Spatial Planning: Initial thinking time		0.23	1.76	0.02	0.897
	0.14				
Age		2.25	0.99	0.32	0.027
Gender	n=53	-4.83	4.48	-0.15	0.287
Spatial Planning: Subsequent thinking time		0.47	1.80	0.04	0.793
	0.12				
Age		1.60	0.93	0.23	0.090
Gender	n=57	-6.85	4.15	-0.22	0.105
Spatial Planning: Problems solved in minimum moves		-0.63	2.09	-0.04	0.765
	0.11				
Age		1.55	0.88	0.21	0.085
Gender	n=71	-7.53	4.00	-0.23	0.065
Spatial Working Memory: Errors		0.75	2.17	0.04	0.733
	0.11				
Age		1.44	0.88	0.20	0.105
Gender	n=68	-8.92	3.98	-0.27	0.028
Spatial Working Memory: Strategy Score		-1.70	2.53	-0.08	0.504

Measures correspond to the following tasks: Set Shifting: Wisconsin Card Sorting Task, Sustained attention: Rapid Visual Processing, Visual Attention: Match to sample, Processing speed: Reaction time task, Spatial Planning: Stockings of Cambridge.

3.5 Discussion

3.5.1 DCD prevalence

The findings presented here indicate that serious motor coordination problems are common in 22q11.2DS, with over 80% of our sample of deletion carriers meeting criteria for indicative DCD. Furthermore, indicative DCD indexed risk of ADHD, ASD and anxiety disorder. We found a link between motor dysfunction and IQ as well as visual and sustained attention. The prevalence of indicative DCD in our sample differed between males and females with 22q11.2DS, conforming to the pattern of male preponderance of DCD in the general population (Tsiotra *et al.*, 2006). This contrasts with some psychiatric disorders such as ADHD, where the prevalence seems to be equal between the sexes in 22q11.2DS (Schneider *et al.*, 2014), compared to the general population where it is more common in males. DCDQ total score was correlated with age of attainment of developmental milestones providing further support for the validity of the DCDQ in this population. The present study shows that developmental coordination is affected by deletion of 22q11.2 and adds to previous studies showing deficits in tracking tasks (Van Aken *et al.*, 2010b), and axial stability (Roizen *et al.*, 2011).

3.5.2 Psychopathology and coordination

The majority of children with indicative DCD (70%) were found to have at least one psychiatric disorder, including high rates of ADHD, anxiety disorder and ASD symptoms. Indicative DCD was found to be related to ADHD, with children with more inattentive symptoms having greater difficulties with motor coordination. Studies in children with ADHD not selected for the presence of a copy number variants have also indicated they are more likely to have impairments in motor skills, particularly if the child has ADHD of the inattentive subtype. Previously published work from our research group comparing children with ADHD with and without 22q11.2DS has found that the deletion is associated with a considerably higher rate of

the inattentive subtype as well as a lower rate of hyperactive-impulsive symptoms (Niarchou *et al.*, 2015). We also found that children with 22q11.2DS and higher numbers of ASD symptoms had poorer coordination, a finding that is similar to studies of children with DCD not selected for a chromosomal disorder (Green *et al.*, 2002; Kopp, Beckung and Gillberg, 2010). Our finding that children with indicative DCD had higher levels of anxiety symptoms is in line with other research showing links between anxiety and DCD (Piek *et al.*, 2008; Pratt and Hill, 2011). Excessive worry is a well-documented phenomenon in 22q11.2DS (Niarchou *et al.*, 2014; Schneider *et al.*, 2014). However, it is not clear whether anxiety and DCD share biological pathways, or whether DCD contributes to anxiety due to worries about performance or social exclusion (Pratt and Hill, 2011). Future longitudinal studies investigating the developmental links between motor function and psychopathology can contribute to better understanding of these issues.

3.5.3 Coordination and IQ

Indicative DCD was related to IQ in children with 22q11.2DS. This suggests that the observed coordination difficulties seen in this population can at least in part be explained by a general deficit in IQ. This is in agreement with studies of children with DCD not selected for having a chromosomal disorder (Wilson *et al.*, 2013) and suggests that within an intellectually disabled population, level of intellectual impairment is associated with motor dysfunction. This is a different pattern of results to those seen between psychopathology and cognition in children with 22q11.2DS, where no relationship between cognition and psychopathology has been found (Niarchou *et al.*, 2014). The results presented here also conflict with previous research in 22q11.2DS where motor difficulties were found to not be explained by IQ (Van Aken *et al.*, 2009; Roizen *et al.*, 2011). Research in coordination difficulties in other populations has often excluded individuals with low IQ, under the assumption that it is a confounding and potentially

causative factor behind much of an individual's coordination difficulties. However, in populations such as 22q11.2DS, the relationship between IQ and motor difficulties is not clear. Therefore, more research should be carried out to better delineate the relationship between intellectual ability and coordination in 22q11.2DS and other chromosomal disorders.

3.5.4 Coordination and neurocognition

While the individuals with 22q11.2DS performed worse on most CANTAB tasks compared to controls, only measures of visual and sustained attention were associated with lower DCDQ scores. Together with the here reported association between motor coordination difficulties and the inattentive subtype of ADHD, this suggests common processes underlying coordination and attention. However, it is unclear if coordination is impaired due to an inability to direct attention appropriately, or if the same brain processes are required for good coordination and attention. The sensitivity analysis showed that the associations between coordination and IQ and visual attention were sensitive to other physical health conditions. Therefore more research may be necessary to disentangle the relationships between these variables. Executive functioning deficits have been demonstrated in non-genotyped populations with DCD (Wilson *et al.*, 2013). As such we might have expected to see associations with some of the CANTAB neurocognitive outcome variables such as the stockings of Cambridge measures, which tap into spatial planning ability and with perseverative errors on the WCST which is a measure of set shifting ability. Relationships between cognitive skills and coordination are complex and currently not well understood. While there is some evidence that coordination is linked to the development of skills such as attention (Yu and Smith, 2017) and language (Rowe, Özçalışkan and Goldin-Meadow, 2008), early in the development of healthy children, there is little evidence of links later in childhood.

3.5.5 Theoretical implications

The high rate of indicative DCD in 22q11.2DS is a novel finding. The presence of coordination deficits raises the question of the changes in neural substrates that result from 22q11.2 deletion. The coordination deficits may be due to disruption of the cerebellum, which has been implicated in both motor and cognitive syndromes (Schmahmann, 2004), and shows consistent abnormalities in 22q11.2DS (Van Amelsvoort *et al.*, 2001b; Bish *et al.*, 2006). Cerebellar dysfunction has also been repeatedly observed in neurodevelopmental disorders, including ASD and ADHD. Other biological mechanisms that could be involved include striatal dysfunction as increased volume of the striatum (Sugama *et al.*, 2000; Eliez *et al.*, 2002; Kates *et al.*, 2004), and calcification of the basal ganglia (Eliez *et al.*, 2002; Sieberer *et al.*, 2005) have been observed in 22q11.2DS. In addition, the 22q11.2 deletion is associated with early-onset Parkinson disease (Zaleski *et al.*, 2009; Butcher *et al.*, 2013; Ogaki and Ross, 2014; Mok *et al.*, 2016). The high comorbidity between anxiety disorder, ADHD and ASD may also point towards common neural disruptions. The precise origin of the coordination impairments is not yet known, and it is unclear whether motor coordination problems are a common feature of other copy number variant disorders (for example, duplication of 22q11.2, or deletion/ duplication of 1q21.1 or 16p11.2). More generally DCD may index a general neurodevelopmental impairment in fronto-striatal and related circuitry that may reflect risk for other psychopathologies. Future studies should utilise detailed assessment of fundamental motor control processes, using kinematic assessment for example. This would allow investigation of deficits of these fundamental processes and may help identify a cause of coordination difficulties.

In terms of the models of relationships between coordination, cognition and psychopathology presented in the introduction, the results of this study would support the fourth model, shown

in Figure 3-4. This model suggested that the 22q11.2DS affects coordination, psychopathology and IQ, and coordination difficulties have reciprocal interactions with IQ and psychopathology. This is supported by the associations between IQ and attention performance and DCDQ score; and the associations between ADHD, ASD and anxiety symptoms and coordination.

3.5.6 Strengths and limitations

To our knowledge, this is the first study to examine the prevalence of DCD and its relationship with IQ and other neurodevelopmental symptoms in 22q11.2DS. The relatively large sample and availability of sibling controls for comparisons are additional strengths. Also, sensitivity analysis showed that the high rates of indicated DCD could not be explained by premature birth, a history of epileptic fits, heart problems or antipsychotic medication use. However, most of our information is obtained through parental report, as both the DCDQ and CAPA were completed by the parent or primary carer. Parental report can introduce variability in measurements, as parents may over, or underestimate symptoms in their children. Finally, the DCDQ is a measure of overall coordination and does not allow insights into underlying sensorimotor and visual information processing deficits. As the data collection was based on a questionnaire measure, it was not possible to carry out neurological or medical assessments to ensure that coordination difficulties were not caused by another medical problem, such as hypo, or hypertonia, or skeletal problems which can cause difficulties with motor skills. As such we cannot exclude the possibility that some of the coordination difficulties identified in this study are better attributed to another primary medical cause, rather than an effect of the deletion on coordination per se. The age range included in the study also spans a period of considerable development, which could affect the results presented here.

3.6 Conclusions

The evidence presented in this chapter suggests that coordination difficulties are extremely common in children with 22q11.2DS, and the high rates of positive screening would suggest that these coordination difficulties have severe impacts on daily functioning, in all areas of life. These coordination difficulties are also associated with higher numbers of neurodevelopmental symptoms, which may mean coordination is a useful marker of vulnerability in other areas. There should be an increased vigilance for motor impairments in children with 22q11.2DS so that appropriate support measures can be introduced as early as possible (especially as there is a documented positive effect of such intervention (Taylor *et al.*, 2015)). In addition, DCD is not usually diagnosed or considered in those with intellectual disability, as the motor deficit must be demonstrated to be in excess of what would be expected for a given IQ, but our findings indicate that the majority of children in this study are affected by potentially serious motor problems. A formal diagnosis of DCD may facilitate access to appropriate support and interventions. Linked to this, future research in DCD should investigate in more detail the links between low IQ and coordination ability, particularly in populations with other comorbid disorders. Further work should also make use of more detailed assessments of movement, such as using kinematic techniques to investigate exactly which types of fundamental movement skills children with 22q11.2DS find difficult. This may shed light on the neurobiological mechanisms that underpin overall coordination difficulties. In addition, gold standard movement assessments should be carried out to ensure that the DCDQ is correctly capturing the coordination difficulties reported in these results.

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4 Kinematic assessment of sensorimotor function in children with 22q11.2 Deletion Syndrome

4.1 Chapter overview

The accurate control of movement is a key skill that is gradually obtained over childhood. Accurate movement requires integration of sensory information from multiple sources and the subsequent use of this information to modify movement commands as required. In the previous chapter, I demonstrated that children with 22q11.2 deletion syndrome have difficulties in their overall motor coordination skills, but I was unable to make inferences about any fundamental deficits in sensorimotor control that may be present. In the current chapter, I outline investigations into the fundamental sensorimotor skills of tracking, aiming and steering using a computerised kinematic battery in children with 22q11.2DS. I explored if performance on these tasks was related to IQ, performance on neurocognitive tasks, or ADHD, ASD and anxiety symptomatology. I found that children with 22q11.2DS perform worse on all three sensorimotor tasks compared to unaffected sibling controls. With regard to associations with other neurodevelopmental deficits seen in 22q11.2DS, I found that tracking performance was related to attention and FSIQ, and aiming peak speed to spatial planning and spatial working memory. However, sensorimotor performance was not associated with the presence of ADHD, ASD or anxiety symptoms. The results presented in this chapter show that there are fundamental sensorimotor control deficits in 22q11.2 deletion syndrome and that there are closer associations between sensorimotor skill and cognition than between sensorimotor skill and psychopathology. I conclude the chapter with speculations about the possible reasons for these results.

4.2 Introduction

Good coordination of complex functional movements is underpinned by the ability to perform basic sensorimotor skills. Deficits in motor control have been reported to have impacts on other areas of development, including social and cognitive functioning (Wilson *et al.*, 2013), along with severe consequences for many aspects of daily functioning. Children with impaired motor skills are at higher risk of developing problems in other domains such as anxiety (Pratt and Hill, 2011), obesity (Joshi *et al.*, 2015), and academic performance (Hill *et al.*, 2016). Also, strong associations between ADHD, autism spectrum disorder (ASD) and impaired motor skills are widely reported (Green, Baird and Sugden, 2006; Loh, Piek and Barrett, 2011; Zwicker *et al.*, 2012). The impacts of poor motor skills have been demonstrated to persist into adulthood and to be associated with increased levels of anxiety and lower wellbeing (Kirby *et al.*, 2013).

In the previous chapter (Chapter 3), I demonstrated that children with 22q11.2DS display high rates of coordination deficits. These coordination problems were associated with ADHD, ASD and anxiety symptoms, highlighting how problems with coordination can compound the already high risk for psychopathology in this population. The methods used in the previous chapter did not allow any inference to be made about underlying mechanisms, such as deficits in sensorimotor skills, however. This is because the analysis was based on the DCDQ which does not probe fundamental sensorimotor skills, it is only sensitive to functional deficits in skills. Therefore, it was desirable to attempt to collect more information about the quality of movements and fundamental sensorimotor ability in children with 22q11.2DS, under the assumption that deficits in sensorimotor skill would be associated with the poorer coordination in this population. To do this, a so called “kinematic” assessment was used.

4.2.1 Kinematic assessment

Kinematic assessments allow for the investigation of the quality of movements, under controlled conditions. For example, a task might involve reaching out to touch a stimulus that has appeared on a screen, where the movement of the arm and hand can be measured and recorded. The visual stimuli represent a controlled input to the motor control system, and the movement performed (which is the output of the motor control system) is measured. The processes involved in integrating the input and producing the outputs represent the sensorimotor control system. Tasks of these types are widely used to investigate the motor control systems in both healthy and patient populations. However, studying motor control requires very precise control of the input provided to the system and accurate measurement of the resulting movement. This requires bespoke equipment and software to accommodate the requirements of the investigation. Whatever method used, there is a trade-off between the detail of information captured, and the time, expense and equipment required. For the current study, I was interested in the movement of the hand, which is required for many tasks of daily life that require fine motor skill, such as handwriting. Specific items on the DCDQ had provided evidence that children with 22q11.2DS struggle in this domain. Furthermore, these difficulties can be expected to have a major impact on daily living, including school performance. Many systems are available to measure the movement of the hand and upper limbs, but these will vary in their cost, set-up time and equipment required. Systems that use magnetic or opto-electronic methods for motion capture can provide detailed information about movement, but often have a significant setup time, requiring attachment of sensors to the participant as well as calibration. Mechanical methods in contrast, for example using a stylus and computer tablet, can only collect information about the endpoint of movement (i.e. the movement of the hand holding the stylus) but are much easier to use. As the ECHO study collects most data in the participant's homes, we required an assessment that was portable and could be operated by

researchers with relatively little training. We, therefore, decided to use a computerised tablet based assessment, called the Clinical Kinematic Assessment Tool (CKAT) (Flatters *et al.*, 2014). The CKAT allows for detailed recording of the movement of a stylus while it is in contact with the computer screen and requires minimal set-up and assessment time. The CKAT was developed by the Perception Action and Cognition Lab at Leeds University (http://www.leeds.ac.uk/paclab/), with whom we collaborate. Using this tool, detailed information about three key sensorimotor skills, tracking, aiming and steering, was collected.

4.2.2 Sensorimotor skill and cognition and psychopathology

There is growing interest in the associations between fundamental sensorimotor processes and higher order cognitive skills and behavioural disorders. Human development is marked by the gradual acquisition of sensorimotor skills, with higher order cognitive skills, such as the abstract representation of information, dependent on the development of sensorimotor processes. Research in typically developing infants has shown that hand eye coordination skill helps facilitate toddler's ability to engage in joint-attention activities with parents (Yu and Smith, 2013, 2017), that frequency of gesture usage can predict later vocabulary size (Rowe, Özçalışkan and Goldin-Meadow, 2008) and that prospective motor control during reaching tasks is associated with early forms of executive function (Gottwald, Achermann, Marciszko, Lindskog, & Gredeback, 2016). However, relationships between these domains in older children are less clear, and there is no research investigating the relationships between sensorimotor ability and higher cognition in children with chromosomal disorders.

In ADHD, motor deficits are well documented, with reports that approximately 50% of children with ADHD also have comorbid DCD as outlined in the previous chapter. Motor deficits reported in ADHD span all areas from fine to gross motor skill deficits (Pitcher, Piek and Hay,

2003; Watemberg *et al.*, 2007). Poor handwriting has been demonstrated in children (Mayes and Calhoun, 2007) and similar graphomotor deficits in adults with ADHD (Duda, Casey and McNevin, 2014), along with gait abnormalities (Leitner *et al.*, 2007; Naruse *et al.*, 2017), primarily consisting of longer stride length, which is more pronounced under dual task conditions. In a small sample, Papadopoulos et al. have demonstrated deficits in a task requiring aiming movements between two targets that vary in either size or distance compared to typically developing controls (Papadopoulos *et al.*, 2015).

Similarly, motor skill deficits are commonly reported in autism spectrum disorders but tend to attract less research than social-communication and cognitive impairments. Sensorimotor deficits span a range of areas and include: reductions in postural stability (Minshew *et al.*, 2004; Fournier *et al.*, 2010; Travers *et al.*, 2013), atypical gait in children and adults (Hallett *et al.*, 1993; Vernazza-Martin *et al.*, 2005; Lim *et al.*, 2016), reduced ability to coordinate movements of the upper limbs (Cook, Blakemore and Press, 2013; Stoit *et al.*, 2013; Yang, Lee and Lee, 2014), impairments in handwriting (Fuentes, Mostofsky and Bastian, 2009) including abnormally large handwriting (or macrographia) (Beversdorf *et al.*, 2001), atypical grasping behaviour and force control deficits (Mosconi *et al.*, 2015; Wang *et al.*, 2015). Kinematic assessment has found that individuals with ASD tend to make less smooth movements, in both gross motor (Stoit *et al.*, 2013; Yang, Lee and Lee, 2014) and fine motor tasks (Johnson *et al.*, 2013).

Despite some evidence that anxiety is associated with coordination deficits (Piek *et al.*, 2008; Pratt and Hill, 2011), there is little to no research on links with kinematic or sensorimotor performance. The only clinical study conducted to date found that 46% of children with an anxiety disorder scored below the 5th percentile on the movement assessment battery for

children, which is a widely used and standardised coordination assessment (Skirbekk *et al.*, 2012). Performance on a fine motor skill sensorimotor battery has however been associated with increased difficulties on the strengths and difficulties questionnaire, which is a dimensional measure of psychopathology (Hill *et al.*, 2016).

4.2.3 Sensorimotor skill in 22q11.2DS

Studying a genetically homogeneous high-risk population, such as individuals with 22q11.2DS, can yield insights into the aetiology of the complex links between sensorimotor function and neurodevelopmental deficits that may provide the basis for subsequent hypothesis testing in other groups. Previous studies comparing children with 22q11.2DS with an IQ-matched sample have reported evidence of higher rates of specific motor problems in the deletion group, including difficulties with balance and lower performance on a rhythmic visuo-manual tracking task (Van Aken *et al.*, 2009; Roizen *et al.*, 2011). More detailed sensorimotor assessment has not been performed before in individuals with 22q11.2DS, and no previous studies have investigated the links between sensorimotor performance and cognitive ability or psychopathology in this population. As such the sensorimotor profile of children with 22q11.2DS remains ill defined, and its relationships with other cognitive and psychiatric outcomes in the syndrome are unknown.

4.2.4 Chapter aims

It is not clear if the genetic lesion that causes the myriad of symptoms seen in individuals with 22q11.2DS also causes sensorimotor deficits, or if sensorimotor deficits are related to deficits in cognition or worse psychiatric outcomes. Therefore, in the current chapter, I set out to investigate the fundamental sensorimotor ability of children with 22q11.2DS using a kinematic assessment battery. This was achieved by assessing the children's performance on three

sensorimotor tasks that underpin more complex movements: tracking objects, aiming movements and steering, in comparison to unaffected sibling controls. Secondly, I investigated the relationships between sensorimotor skill and cognitive ability in children with 22q11.2DS, guided by theory and evidence that suggests that sensorimotor skill may influence the development of higher order cognitive skills such as executive function. Thirdly, I examined the relationship between sensorimotor ability and psychopathology, based on evidence of links reported in non-syndromic individuals. I focussed specifically ADHD, ASD and anxiety symptoms, as these were shown to be related to coordination in children with 22q11.2DS in the previous chapter. The finding of specific links would allow me to begin to make inferences about the basic processes that may underlie motor control and links with neurodevelopmental disorder. I hypothesised that 1) children with 22q11.2DS would have deficits in sensorimotor skill compared to unaffected sibling controls; 2) poorer sensorimotor skill in 22q11.2DS would be associated with poorer cognitive ability; 3) poorer sensorimotor skill in 22q11.2DS would be associated with higher levels of psychopathology.

4.3 Methods

Details of recruitment of participants and exclusion criteria are outlined in the General Methodology (Section 2.1). In brief, participants were all part of the ongoing ExperienCes of people witH COpy number variants (ECHO) study (http://www.cardiff.ac.uk/mrc-centre-neuropsychiatric-genetics-genomics/research/themes/developmental-disorders/echo-study-cnv-research). Participants were children with genetically confirmed 22q11.2DS (aged 6 or older) and unaffected siblings who were closest in age. Kinematic information was successfully collected on 42 children with 22q11.2DS (73.8% male, mean 12.67 years, s.d. 3.72) and 18 unaffected sibling controls (66.7% male, mean age 13.33 years, s.d. 3.34). Children with 22q11.2DS did not differ in age ($p<.250$) or gender distribution ($p<.250$) from the control

siblings. One child with 22q11.2 deletion was receiving Aripiprazole for psychosis, but no other relevant medication use was noted.

4.3.1 Sensorimotor assessment

The Clinical Kinematic Assessment Tool (CKAT) was used to assess sensorimotor skill in these children. The CKAT is a portable, tablet computer-based kinematic skill assessment that allows detailed study of the kinematic profile of movement. It involves the participant interacting with stimuli presented on a screen using a stylus. All movements made while the stylus is in contact with the screen are recorded. All tasks are explained in detail by Flatters *et al.*, 2014, and outlined in the general methodology section (Section 2.4.2).

The outcome measures of interest from the CKAT were as follows:

Tracking: Was measured by Root Mean Square Error (RMSE) which indicates the spatial and temporal accuracy of the individuals' tracking performance. RMSE is calculated as the straight-line distance in millimetres from the centre of a moving target and the tip of the stylus for each sampled point in the time series. For statistical analysis of this measure, a reciprocal transformation was applied to resolve outliers and normalise the distribution. The tracking subtest is comprised of two trials, "No guide", where the target dot is presented alone, and "With guide", where a black line spatial guide is presented in addition to the target. This guide indicates the path the target will take.

Aiming: Peak speed (PS), time to peak speed (TPS) and normalised jerk (NJ) were extracted for each of the 50 movements made by participants. A median score for each outcome metric was then calculated for each participant. Peak speed reflects the highest velocity of movement

achieved by the participant, TPS reflects the time taken to reach this peak speed, and NJ is a measure of the "smoothness" of movements. This is implemented in the CKAT as the normalised jerk index as described in Culmer et al. (Culmer *et al.*, 2009). Time to peak speed and normalised jerk were transformed using a reciprocal transformation to resolve outliers and normalise the distributions. As peak speed was already normally distributed, it was not transformed.

Steering: Penalised Path Accuracy (PPA) was calculated as the mean in millimetres from an idealised reference path or path accuracy (PA), within each trial, inflated by the percentage deviation from an ideal completion time of 36 seconds. This gives a unit-less measure of the spatial and temporal accuracy on the task. For statistical analysis of this outcome, a reciprocal transformation was applied to resolve outliers and normalise the distribution.

4.3.2 Cognitive assessment

Cognitive ability was assessed as outlined in the general methodology (Chapter 2). In brief, the Wechsler Abbreviated Scale of Intelligence was used to obtain FSIQ, and cognitive function was assessed using tasks that are relevant for risk of psychopathology. Processing speed/reaction time (five choice reaction time task (RTI)), sustained attention (rapid visual processing task (RVPA)), spatial working memory (SWM), spatial planning (stockings of Cambridge) and visual attention (match to sample task (MTS)) were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Limited, 2006). Furthermore, the Wisconsin Card Sorting Test 64 (WCST) (Heaton *et al.*, 1993) was also administered, where the number of perseverative errors measures set shifting ability. The number of non-perseverative errors was also recorded. All neurocognitive

measures were standardised to have a mean of zero and a standard deviation of one, with the exception of IQ, which was already normally distributed.

4.3.3 Psychiatric assessment

Psychopathology was assessed using the Child and Adolescent Psychiatric Assessment (CAPA) and social communication questionnaire (SCQ). Description of how symptom counts were obtained is presented in the general methodology (Section 2.3). The CAPA was used to obtain symptom counts for ADHD and Anxiety while SCQ score was used to measure ASD symptomatology.

Both cognitive and psychiatric assessments were carried out as part of the on-going ECHO study, either in participants' homes or during visits to our laboratory at Cardiff University. ADHD and anxiety data was not available for two unaffected siblings, and SCQ data was excluded due to missingness for two children with 22q11.2DS and one unaffected sibling.

4.3.4 Statistical analysis

Statistical analysis was carried out in R version 3.3.3.

4.3.4.1 Tracking

Multilevel linear modelling (MLM) was used to analyse the effect of group (e.g. deletion carrier or control), age, gender and trial type (e.g. With guide or No guide) on performance of the tracking task. The effect of these variables on reciprocal RMSE was modelled using the maximum likelihood method, with age as a between subject independent variable. Within the model, two repeated measures, each nested within participants were included to examine the effect of the presence or absence of a spatial guide line (Trial type), and speed of the target

(Speed). The MLM analysis was carried out as follows: a baseline model containing only the intercept was predicted. Then a sequence of nested models was constructed that added each of the main effects (Group, Age, Sex, Trial type, Speed) and associated interaction terms until a full factorial model was created. The effect of the model containing each added term for the first time was compared to the immediately preceding model in the sequence, using a likelihood-ratio test. This allowed each likelihood-ratio test to determine if the addition of a new term significantly increased the explained variance of the model being constructed. We would expect that tracking performance would be lower in children with 22q11.2 deletion compared to controls, which would be evidenced by lower reciprocal RMSE, across all trial speeds and trial types. Performance is likely to also decrease as the speed of the target increases, and this effect should be evident in both the children with 22q11.2DS and controls. Performance is also likely to improve with age.

4.3.4.2 Aiming and steering

Between group differences in the aiming and steering outcome measures were analysed using an ANCOVA with age and gender as covariates. Plots of each aiming and steering outcome measure were visually inspected to look for evidence interactions between covariates. Where there was evidence of an interaction, an appropriate interaction term was added to the original models. We would expect poorer aiming and steering performance in the deletion carrier group compared to controls. This would be shown by decreased peak speed, decreased reciprocal time to peak speed and decreased reciprocal normalised jerk for aiming movements, and decreased reciprocal penalised path accuracy on the steering task.

4.3.4.3 Relationship between sensorimotor measures and DCDQ score

Pearson correlations were used, to investigate the relationship between the sensorimotor measures and Developmental Coordination Disorder Questionnaire score in individuals who had carried out both assessments. Correlations between sensorimotor variables and total score on the DCDQ were calculated first in the overall sample (children with 22q11.2DS and their siblings combined), and then in the children with the deletion alone. In addition, Spearman correlations between individual questions on the DCDQ and sensorimotor performance variables were calculated to assess relationships between specific types of actions asked about on the DCDQ and sensorimotor performance in children with 22q11.2DS.

4.3.4.4 Relationships between cognition and sensorimotor skill

Differences in group statistics scores between the 22q11.2DS and sibling groups on IQ and neurocognitive measures were compared using t-tests.

Before using hierarchical regression, the associations between the cognitive and sensorimotor variables were checked using pairwise Pearson correlations.

The relationships between the sensorimotor variables and full-scale IQ or other neurocognitive variables were investigated using hierarchical regressions. Each neurocognitive variable was predicted first by age, then the sensorimotor variable of interest. This process was repeated using each other sensorimotor outcome variable as the variable of interest. Change in model fit at each step was testing using ANOVA's between models. Sensorimotor measures were not included in models together due to multicollinearity.

4.3.4.5 Relationships between psychopathology and sensorimotor skill

Associations between psychiatric symptoms (ADHD, SCQ score, any anxiety disorder) and sensorimotor variables were analysed using hierarchical regressions using the same method as described for IQ and neurocognitive measures.

4.4 Results

4.4.1 **Performance on sensorimotor tasks**

4.4.1.1 Tracking, with and without spatial guide

Multilevel linear modelling of the reciprocal RMSE measure found significant main effects for Group (deletion status) (χ^2=13.02, p<0.001), age (χ^2=24.97, p<0.001) such that older children performed better, and speed of target (χ^2=459.57, p<0.001) such that performance was worse as the target moved faster. At the fastest speed, both carriers of the deletion and controls are very close in performance. This would suggest that both groups are finding the task difficult at the fastest speed. Significant two-way interactions between, Group x Speed (χ^2=497.61, p<0.001), Group x Sex (χ^2=4.95, p=0.03), Age x Trial type (χ^2=16.78, p<0.001), and Age x Speed (χ^2=24.66, p<0.001), were also identified. In addition, the model identified the following three-way interactions, Group x Age x Trial Type (χ^2=19.39, p<0.001), Group x Age x Speed (χ^2=6.15, p=0.046), Group x Speed x Sex (χ^2=8.97 p=0.011) and Speed x Sex x Age (χ^2=17.16, p<0.001). The Group x Age x Trial Type interaction can be interpreted as the presence of a difference in performance between individuals with 22q11.2DS and controls on the with guide and no guide states, but also that each group improves in tracking performance as they get older, but at different rates depending on the trial type. The Group x Age x Speed interaction suggests that performance differs between children with 22q11.2DS and controls, but as the children get older, rates of performance increase differ between groups. The effects of the Group x Age x Trial type and Group x Age x Speed interactions can be seen in Figure 4-1. The

Group x Speed x Sex interaction suggests that the difference in performance between 22q11.2DS and control groups is also affected by the speed of the target and gender. There is a bigger reduction in tracking performance between male children with 22q11.2DS and male controls that between females with 22q11.2DS and female controls, with the difference increasing with increasing speed of target, as shown in Figure 4-2. Finally, the Speed x Sex x Age interaction suggests that males and females, regardless of deletion status, improve performance as they age by different amounts. This can be seen in Figure 4-3 where performance increases with age and decreasing speed, but the rate of change by age is different for males and females.

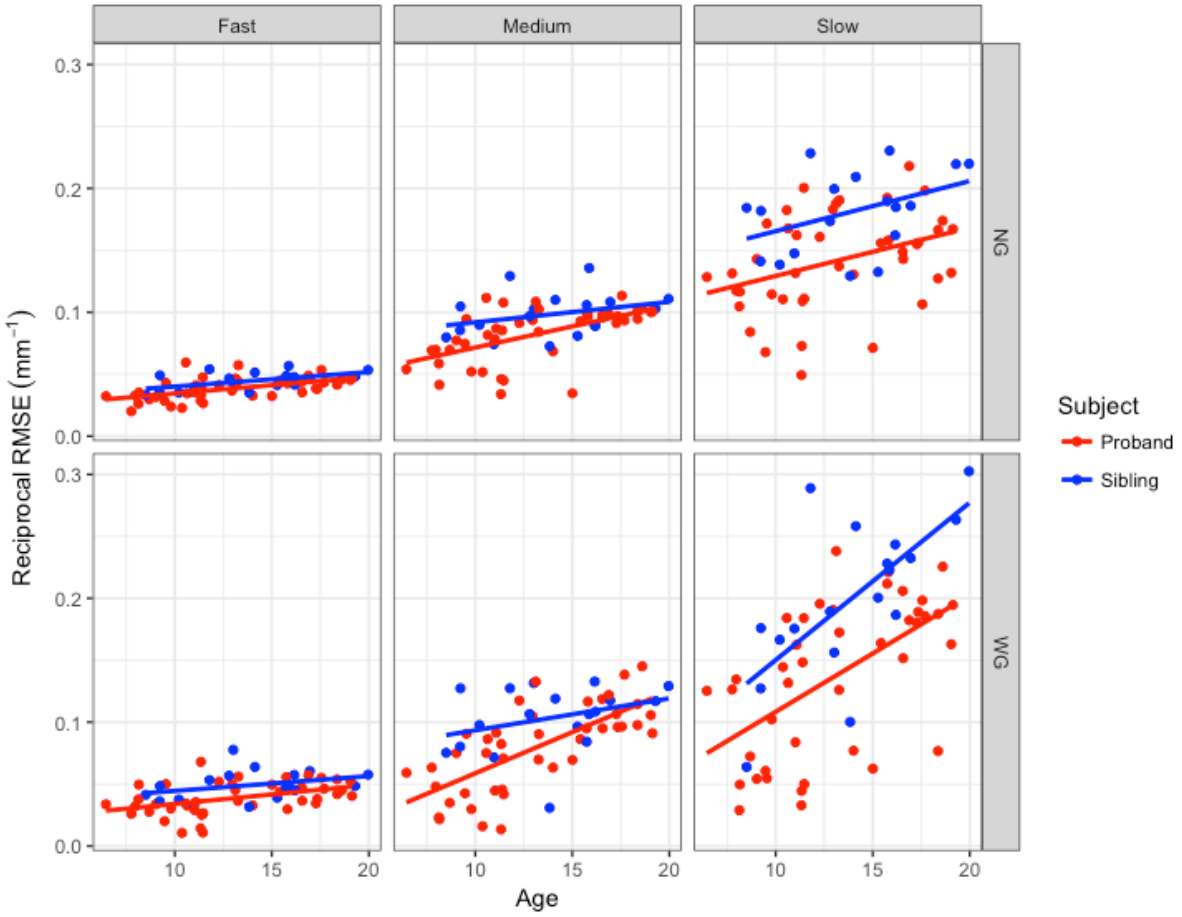

Figure 4-1. Scatterplots of tracking performance (reciprocal root mean square error (RMSE)) for each speed, against age in years, split by guide state (No Guide (NG) upper panels), With Guide (WG) lower panels) for deletion carriers (in red) and control siblings (in blue).

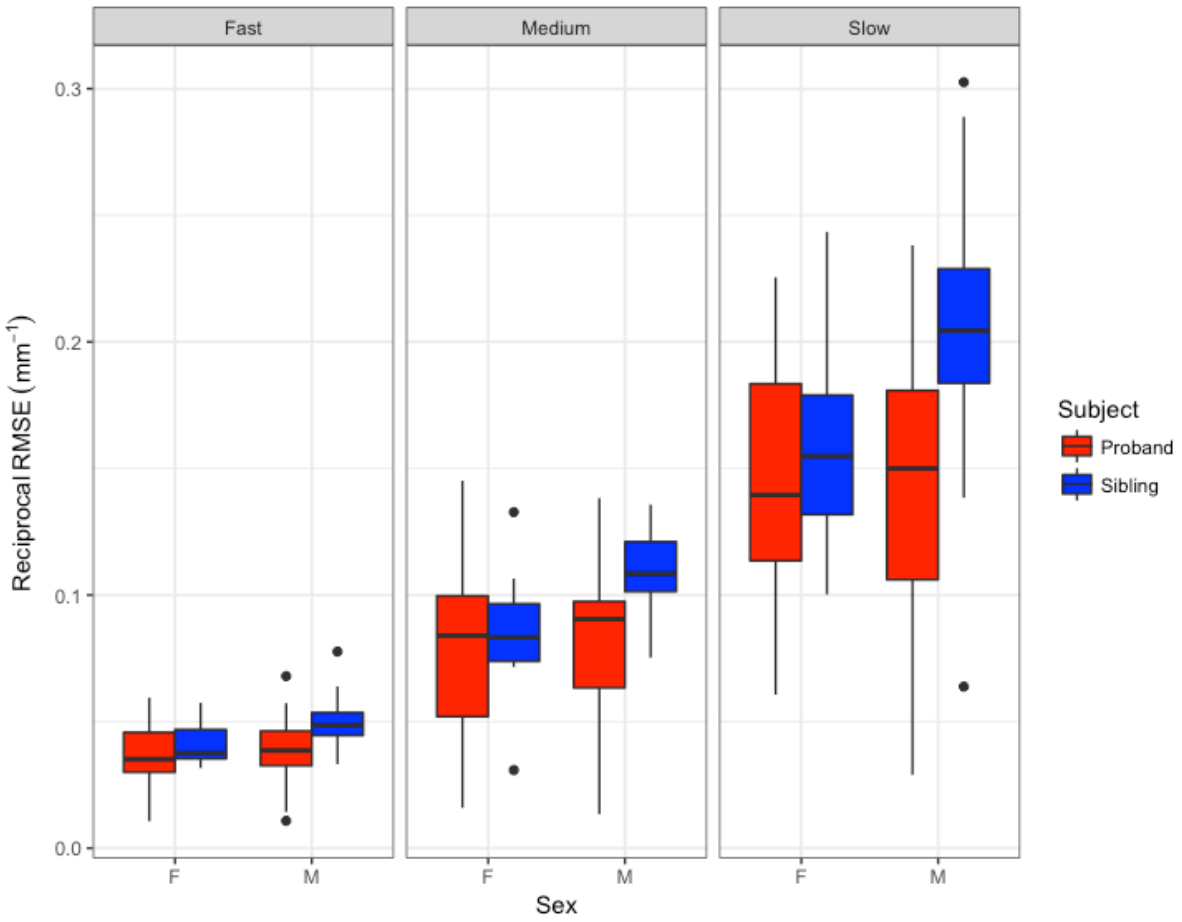

Figure 4-2. Boxplots of tracking performance (reciprocal root mean squared error (RMSE)) by age and speed of task for children with 22q11.2DS (in red) and control siblings (in blue).

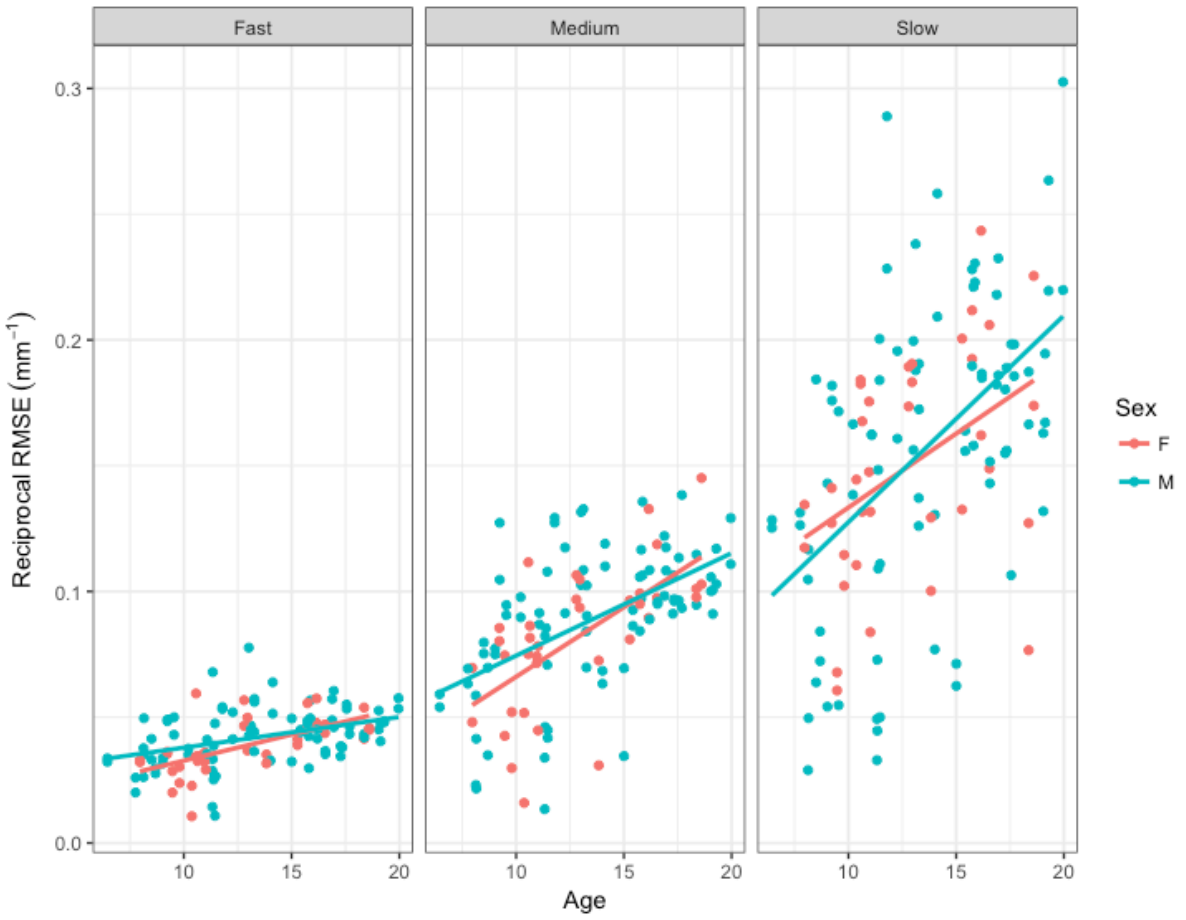

Figure 4-3. Tracking performance (reciprocal root mean squared error (RMSE)) of the complete sample of males (blue) and females (pink) plotted against age in years, across the three target speeds.

4.4.1.2 Aiming

ANCOVA's, with age and gender as covariates, found a significant effect of group status on peak speed, ($F=4.66$, $p=0.035$), time to peak speed ($F=6.81$, $p=0.012$) and normalised jerk ($F=21.05$, $p<0.001$). Age had a significant effect on time to peak speed ($F=29.73$, $p<0.001$) and normalized jerk ($F=34.95$, $p<0.001$). Gender had a significant effect on time to peak speed only ($F=8.44$, $p=0.005$). There was no evidence of interactions between covariates for any aiming task. These results suggest that individuals with 22q11.2DS had lower peak speed, took longer to reach their peak speed and had more jerky movements than controls, as was expected.

4.4.1.3 Steering

ANCOVA of reciprocal PPA found a significant effect of group status ($F=20.59$, $p<0.001$) and age ($F=20.63$, $p<0.001$) on steering performance, but no effect of gender. Individuals with 22q11.2DS performed more poorly on the steering task as expected. Due to evidence for an interaction between group and age, an Age*Group interaction term was added to the original model, but this interaction term did not reach significance. Splitting the PPA metric into its component parts of path accuracy and the time taken to complete the pattern revealed that there was no effect of group on time taken to complete the trials. However, age did affect time taken, such that older children took less time ($F=4.37$, $p=0.041$) to complete each path. There was an effect of Group status on path accuracy ($F=19.43$, $p<0.001$), along with Age ($F=28.97$, $p<0.001$), such that children with 22q11.2DS were further from an idealised path, and older children performed better.

4.4.1.4 ***Correlation between neurocognitive and sensorimotor variables.***

Table 4-1 shows the correlations between the sensorimotor and neurocognitive variables in the children with 22q11.2DS. The matrix shows that all tracking variables were strongly correlated with each other. The aiming outcome measures time to peak speed (TPS) and normalised jerk (NJ) are correlated with each other, but peak speed is not correlated with normalised jerk. Steering performance (PPA) was moderately correlated with tracking performance and normalised jerk. With regard to relationships between CKAT and CANTAB measures, tracking performance was related to reaction time (RTIreact), sustained attention (RVPA), and visual attention (MTSPer). Time to peak speed was related to reaction time performance (RTIreact and RTImov), along with visual attention (MTSPer). Peak speed was not related to any CANTAB measure. Normalised Jerk was related to reaction time, sustained attention and

visual attention. Steering performance was related to reaction time, visual attention and spatial working memory. Full Scale IQ was not correlated with any sensorimotor measure.

As the tracking variables were strongly correlated with each other and the slow no guide state showed the largest difference between children with 22q11.2DS and controls, only this tracking variable (Slow NG) was taken forward for analyses along with the three aiming measures (peak speed, time to peak speed and normalised jerk) and steering performance.

		Tracking						Aiming				Processing Speed		Sustained Attention	Visual Attention	Spatial Planning			Spatial Working Memory		Set Shifting	
		Slow NG	Med NG	Fast NG	Slow WG	Med WG	Fast WG	TPS	PS	NJ	PPA	RTImov	RTIreact	RVPA	MTSPer	SOCInit	SOCProb	SOCsub	SWMStrat	SWMer	Persev	NPersev
Tracking	Slow NG																					
	Med NG	0.74***																				
	Fast NG	0.65***	0.80***																			
	Slow WG	0.71***	0.76***	0.64***																		
	Med WG	0.69***	0.74***	0.65***	0.73***																	
	Fast WG	0.28	0.29	0.49**	0.19	0.58***																
Aiming	TPS	0.31	0.45**	0.60***	0.46**	0.61***	0.55***															
	PS	0.11	0.09	0.21	0.04	-0.01	0.08	0.48**														
	NJ	0.36*	0.62***	0.66***	0.53***	0.67***	0.48**	0.64***	-0.07													
Steering	PPA	0.51***	0.48**	0.35*	0.57***	0.57***	0.33*	0.30	-0.12	0.50**												
Processing Speed	RTImov	0.13	0.35*	0.31*	0.18	0.37*	0.22	0.40*	-0.06	0.57***	0.22											
	RTIreact	0.40**	0.24	0.35*	0.42**	0.40**	0.43**	0.44**	0.21	0.29	0.46**	0.11										
Sustained Attention	RVPA	0.39*	0.44**	0.40*	0.51**	0.51**	0.17	0.33	0.02	0.43*	0.23	-0.01	0.21									
Visual Attention	MTSPer	0.29	0.36*	0.39*	0.43**	0.45**	0.35*	0.37*	0.10	0.45**	0.37*	0.12	0.63***	0.42**								
Spatial Planning	SOCInit	0.30	0.09	0.01	0.31	0.17	-0.05	0.10	0.27	-0.21	-0.11	-0.14	-0.29	0.06	0.06							
	SOCProb	0.10	0.15	0.19	0.24	0.19	0.16	0.01	-0.19	0.18	0.02	0.11	0.18	0.26	0.17	-0.03						
	SOCsub	-0.11	-0.12	-0.04	-0.22	-0.16	0.16	-0.06	0.04	-0.10	0.06	-0.10	-0.23	-0.18	-0.03	0.15	0.09					
Spatial Working Memory	SWMStrat	0.00	0.13	0.15	0.18	0.04	0.05	0.07	-0.07	0.26	0.22	0.07	0.08	0.22	0.06	-0.33*	0.19	-0.15				
	SWMer	0.26	0.30	0.13	0.34*	0.24	0.12	0.02	-0.22	0.28	0.37*	0.09	0.27	0.32	0.38*	-0.10	0.54***	-0.06	0.51***			
Set Shifting	Persev	-0.06	0.12	0.09	-0.06	-0.12	-0.01	0.09	0.12	-0.10	-0.19	-0.07	-0.07	0.04	0.18	0.00	-0.03	0.26	-0.15	-0.01		
	NPersev	-0.03	-0.14	-0.17	-0.14	-0.21	-0.17	-0.09	0.30	-0.12	-0.02	-0.25	0.03	-0.15	0.01	0.11	-0.13	0.13	0.04	-0.04	-0.16	
	FSIQ	0.15	0.18	0.24	0.23	0.08	0.12	0.22	0.23	0.11	0.19	0.09	0.28	0.29	0.35*	0.14	0.53***	0.21	-0.01	0.34*	0.20	-0.08

NG: No Guide, WG: With Guide, TPS: Time to Peak Speed, PS: Peak Speed, NJ: Normalised Jerk, PPA: Penalised Path Accuracy, RTImov: Reaction time task-movement time, RTIreact: Reaction time task-reaction time, RVPA: Rapid Visual Processing, MTSPer: Match to Sample Percent correct, SOCInit: Stockings of Cambridge- Initial thinking time, SOCProb: Stockings of Cambridge-Problems Solved in Minimum Moves, SOCSub: Stockings of Cambridge- Subsequent thinking time, SWMStrat: Spatial working memory- strategy score, SWMer: Spatial Working Memory errors, Persev: Perseverative errors, NPersev: Non-Perseverative errors, FSIQ:Full Scale IQ

*Table 4-1. Correlation matrix of Sensorimotor and Neurocognitive measures in the children with 22q11.2DS. *p<0.05, **p<0.01, ***p<0.001*

4.4.1.5 Relationship of sensorimotor measures with the DCDQ

Under the assumption that good coordination performance requires good fundamental sensorimotor skills, we would expect that coordination scores as measured by the DCDQ would be associated with sensorimotor performance. By comparing CKAT with DCDQ scores for individuals who have completed both assessments, I set out to assess if fundamental sensorimotor skills are associated with coordination performance.

Testing the correlation between the sensorimotor variables and DCDQ score in the overall sample of children who carry the 22q11.2 deletion and their sibling controls revealed that tracking (r=0.35, p=0.02), aiming normalised jerk (r=0.49, p<0.001) and steering (r=-0.53, p<0.001) were correlated with DCDQ score, whilst peak speed or time to peak speed on the aiming task were not. Figure 4-4 shows plots of sensorimotor task performance against developmental coordination disorder score.

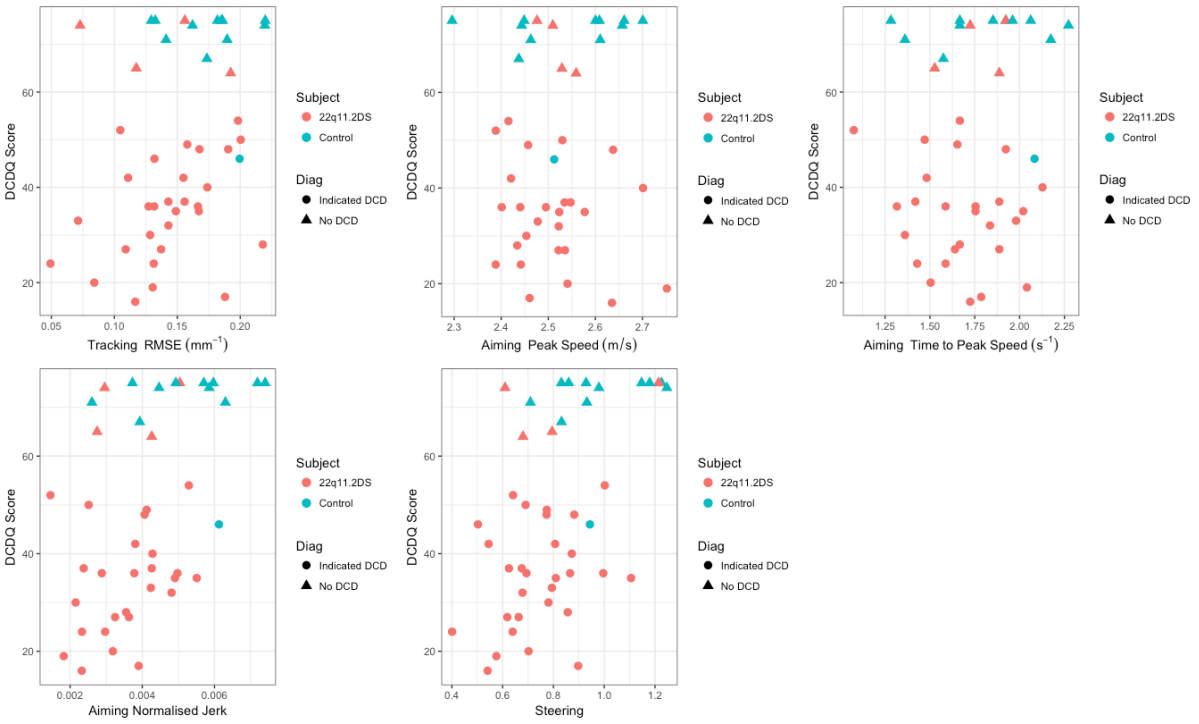

Figure 4-4. Scatterplots of sensorimotor task performance against developmental coordination disorder questionnaire score in children with 22q11.2DS and their sibling controls.

However, performance on the sensorimotor tasks was not associated with total DCDQ score in the children with 22q11.2 deletion syndrome alone (Table 4-2).

Table 4-2. Correlations between CKAT measures and DCDQ total score in children with 22q11.2DS.

	r	P
Tracking (1/RMSE)	-0.15	0.409
Aiming: Peak Speed (mm/s)	-0.12	0.520
Aiming: Time to Peak Speed (1/s)	-0.01	0.950
Aiming: Normalised Jerk	0.21	0.266
Steering: PPA	0.29	0.103
RMSE: reciprocal root mean square error, PPA: penalised path accuracy		

When individual items on the DCDQ were correlated with sensorimotor performance, I found that better tracking performance was associated with better scores on the "hits ball accurately" item (r=0.40, p=0.020) and higher reciprocal normalised jerk was associated with better scores on the "your child would never be described as a bull in a china shop" (r=0.37, p=0.04). This suggests that less jerky movements (shown by higher reciprocal normalised jerk) are associated with lower overall clumsiness. No other sensorimotor measures were associated with scores on individual DCDQ items.

	Tracking (1/RMSE)	Aiming: Peak Speed (mm/s)	Aiming: Time to Peak Speed (1/s)	Aiming: Normalised Jerk	Steering: PPA
Throws ball	0.32	0.02	0.04	0.03	0.24
Catches ball	0.36	0.07	0.04	0.21	0.22
Hits ball	0.40*	0.14	0.07	0.28	0.28
Jumps over	0.17	-0.12	-0.03	0.06	0.22
Runs	0.02	-0.21	0.01	0.06	0.15
Plans Activity	-0.09	-0.14	0.02	0.3	0.12
Writing fast	0.28	0.03	0.06	0.13	0.19
Writing legibly	0.22	-0.16	-0.1	0.23	0.29
Effort and pressure (Writing)	0.19	-0.08	-0.08	0.17	0.23
Cuts shapes	0.22	0.02	0.01	0.36	0.13
Likes Sport	0.2	0.1	0.1	0.17	0.13
Learning new skills	0.12	-0.25	-0.16	0.1	0.15
Quick and competent	-0.06	-0.15	-0.14	0.2	0.07
"Bull in china shop"	-0.01	-0.11	0.08	0.37*	0.19
Does not fatigue easily	0.01	-0.11	0.08	0.05	0.13
RMSE: reciprocal root mean square error, PPA: penalised path accuracy					

*Figure 4-5. Correlations between sensorimotor measures and DCDQ questions. *p<0.05, **<p<0.01, ***p<0.001.*

Of the 33 individuals with 22q11.2DS who had completed both the DCDQ and the CKAT, 29 screened positive for indicated DCD. There was no difference in sensorimotor performance in those children with 22q11.2DS who screened positive on the DCDQ for indicative DCD compared to those who did not (Table 4-3).

Table 4-3. Sensorimotor performance in children with 22q11.2DS with and without Indicative DCD.

	Indicated DCD (n=29)		No DCD (n=4)			
	Mean	**sd**	**Mean**	**sd**	**t**	**P**
Tracking (1/RMSE)	0.14	0.04	0.13	0.05	0.30	0.781
Aiming: Peak Speed (mm/s)	2.51	0.09	2.52	0.03	-0.37	0.715
Aiming: Time to Peak Speed (1/s)	1.68	0.25	1.77	0.18	-0.87	0.426
Aiming: Normalised Jerk	0.0036	0.0011	0.0038	0.0011	-0.34	0.751
Steering: PPA	0.74	0.34	0.82	0.35	-0.62	0.573
RMSE: reciprocal root mean square error, PPA: penalised path accuracy						

4.4.2 Performance on neurocognitive tasks

Mean FSIQ of the siblings was higher than in children with 22q11.2DS (Table 4-4, see also Section 3.4.3 of previous chapter). Children with 22q11.2DS performed worse than their siblings on sustained attention (Rapid Visual Processing), and vigilance/ visual attention (Match to Sample visual search), processing speed (Reaction time) planning (Stockings of Cambridge), spatial working memory and set shifting on the WCST (Table 4-4).

Table 4-4. Summary statistics for IQ and neurocognitive measures.

	22q11.2 DS			Control Siblings			
IQ							
FSIQ	42	73.62	11.98	18	111.50	19.81	-7.54	p<.001
Performance IQ	42	77.02	13.06	18	108.22	21.1119	-5.81	p<.001
Verbal IQ	42	74.71	13.67	18	112.78	17.30	-8.29	p<.001
Neurocognitive Tasks							
Sustained Attention	37	-0.298	1.009	17	0.649	0.608	-4.27	p<.001
Visual Attention	40	-0.225	1.119	18	0.500	0.312	-3.78	p<.001
Processing Speed, Reaction time	42	-0.131	1.153	18	0.306	0.354	-2.22	0.030
Processing Speed, Movement time	42	-0.061	1.065	18	0.142	0.840	-0.79	0.436
Spatial Planning, initial thinking time	37	0.137	0.911	17	-0.298	1.144	1.38	p<.001
Spatial Planning, problems solved in minimum moves	37	-0.192	1.045	17	0.418	0.763	-2.41	p<.001
Spatial Planning, subsequent thinking time	37	-0.025	1.107	17	0.054	0.743	-0.31	p<.001
Spatial working memory, between errors	42	-0.269	0.828	18	0.628	1.104	-3.10	p<.001
Spatial working memory, Strategy Score	42	-0.299	0.767	18	0.698	1.147	-3.38	0.003
Set Shifting, Perseverative Errors	38	-0.131	0.870	17	0.292	1.221	-1.29	0.211
Set Shifting, Non-Perseverative Errors	38	-0.232	1.040	18	0.489	0.713	-3.03	0.004
FSIQ, full scale IQ. For all measures, apart from initial thinking time, lower scores indicate poorer performance. Initial thinking time is a measure of the time taken before the first move is made. Here longer times indicate poorer performance								

4.4.3 Sensorimotor performance and IQ in children with 22q11.2DS

Hierarchical regressions were conducted where full scale IQ was first predicted by age, then the sensorimotor variable of interest. Sensorimotor measures were not included together in models due to multicollinearity. This was repeated, using each sensorimotor measure as the variable of interest. This showed that tracking performance was a significant predictor of full scale IQ after controlling for age. This relationship disappeared, however, with the addition of other sensorimotor measures as covariates. No other sensorimotor measures were found to be predictive of full scale IQ. Regression results and test for significant changes in model fit are shown in Table 4-5.

Table 4-5. Regression results for full scale IQ predicted by sensorimotor measures in children with 22q11.2DS.

Tracking	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**		
Step 1	0.03						
Age		-0.56	0.51	-0.18	0.283	**F**	**P**
Step 2	0.15					4.73	0.037
Age		-1.07	0.54	-0.35	0.056		
Tracking		103.63	47.63	0.38	0.037		
Aiming: Peak Speed	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**		
Step 1	0.03						
Age		-0.56	0.51	-0.18	0.283	**F**	**P**
Step 2	0.09					1.99	0.168
Age		-0.64	0.51	-0.21	0.219		
Aiming: Peak Speed		27.68	19.64	0.23	0.168		
Aiming: Time to Peak Speed	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**		
Step 1	0.03						
Age		-0.56	0.51	-0.18	0.283	**F**	**P**
Step 2	0.12					3.46	0.072
Age		-1.29	0.63	-0.42	0.049		
Aiming: Time to Peak Speed		17.57	9.45	0.38	0.072		
Aiming: Normalised Jerk	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**		
Step 1	0.03						
Age		-0.56	0.51	-0.18	0.283	**F**	**P**
Step 2	0.06					1.06	0.311
Age		-1.10	0.73	-0.36	0.143		
Aiming: Normalised Jerk		2399.07	2332.78	0.24	0.311		
Steering	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**		
Step 1	0.03						
Age		-0.56	0.51	-0.18	0.283	**F**	**P**
Step 2	0.11					3.13	0.086
Age		-1.08	0.58	-0.35	0.071		
Steering		21.30	12.04	0.33	0.086		

4.4.4 Sensorimotor performance and cognition

A set of hierarchical regressions using each CANTAB variable as the dependent variable were constructed. For each regression, age was the first predictor, then the sensorimotor variable of interest. This was repeated using each sensorimotor variable as the variable of interest. This analysis revealed that addition of tracking performance significantly improved model fit, after controlling for age and full-scale IQ when predicting sustained and visual attention performance. Tracking performance was also a significant predictor of initial thinking time on the spatial planning task after controlling for age but not FSIQ. Aiming Peak Speed was associated with the number of problems solved in minimum moves on the spatial planning task and with errors made on the spatial working memory task, after controlling for age and FSIQ. Aiming peak speed was also associated with non-perseverative errors in set shifting, when controlling for age alone, though approached significance after controlling for FSIQ. Aiming time to peak speed was also associated with reaction time after controlling for age, but not FSIQ. Aiming normalized jerk was related to movement time on the reaction time task after controlling for age and FSIQ. Steering performance was associated with reaction time and errors made on the spatial working memory subtask when controlling for age. However, both became insignificant predictors after controlling for FSIQ. Regression results are shown in Table 4-6.

Table 4-6. Regression and F-test results for CANTAB variables predicted by sensorimotor performance in children with 22q11.2DS.

			Tracking				
Sustained Attention	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=33
Step 1	0.14						
Age		0.10	0.05	0.38	0.031	**F**	**P**
Step 2	0.25					4.48	0.043
Age		0.06	0.05	0.23	0.19		
Tracking		9.90	4.68	0.37	0.04	**F**	**P**
Step 3	0.34					3.80	0.061
Age		0.10	0.05	0.35	0.056		
Tracking		6.82	4.74	0.25	0.161		
FSIQ		0.03	0.01	0.32	0.061		
Visual Attention	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=36
Step 1	0.15						
Age		0.12	0.05	0.39	0.019	**F**	**P**
Step 2	0.18					1.05	0.313
Age		0.10	0.05	0.31	0.081		
Tracking		4.91	4.80	0.18	0.313	**F**	**P**
Step 3	0.32					6.59	0.015
Age		0.14	0.05	0.45	0.012		
Tracking		0.67	4.73	0.02	0.888		
FSIQ		0.04	0.02	0.41	0.015		
Processing Speed: Movement Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.16						
Age		0.11	0.04	0.40	0.014	**F**	**P**
Step 2	0.16					0.05	0.816
Age		0.11	0.05	0.38	0.035		
Tracking		1.03	4.41	0.04	0.816	**F**	**P**
Step 3	0.17					0.45	0.507
Age		0.12	0.05	0.42	0.030		
Tracking		-0.08	4.74	0.00	0.987		
FSIQ		0.01	0.02	0.12	0.507		
Processing Speed: Reaction Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.11						
Age		0.11	0.05	0.33	0.049	**F**	**P**
Step 2	0.19					3.54	0.068
Age		0.06	0.06	0.19	0.281		
Tracking		9.55	5.07	0.32	0.068	**F**	**P**
Step 3	0.26					3.31	0.078
Age		0.10	0.06	0.29	0.107		
Tracking		6.22	5.24	0.21	0.244		
FSIQ		0.03	0.02	0.29	0.078		
Spatial Planning: Initial thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.00						
Age		-0.02	0.05	-0.06	0.736	**F**	**P**
Step 2	0.14					4.69	0.039
Age		-0.05	0.05	-0.20	0.276		
Tracking		10.04	4.64	0.40	0.039	**F**	**P**
Step 3	0.17					0.93	0.343
Age		-0.03	0.05	-0.14	0.487		
Tracking		8.48	4.92	0.34	0.096		
FSIQ		0.01	0.01	0.18	0.343		

Spatial Planning: Subsequent thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.08						
Age		0.09	0.05	0.28	0.122	**F**	**P**
Step 2	0.08					0.00	0.979
Age		-0.09	0.06	-0.28	0.157		
Tracking		-0.16	6.00	-0.01	0.979	**F**	**P**
Step 3	0.10					0.54	0.471
Age		-0.07	0.06	-0.23	0.281		
Tracking		-1.70	6.41	-0.05	0.792		
FSIQ		0.01	0.02	0.14	0.471		
Spatial Planning: Problems solved in minimum moves	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.03						
Age		-0.05	0.05	-0.18	-0.311	**F**	**P**
Step 2	0.09					1.80	0.190
Age		-0.08	0.05	-0.28	0.156		
Tracking		7.16	5.34	0.25	0.190	**F**	**P**
Step 3	0.24					5.67	0.024
Age		-0.03	0.05	-0.12	0.525		
Tracking		3.04	5.25	0.11	0.567		
FSIQ		0.04	0.02	0.43	0.024		
Spatial Working Memory: Errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.01						
Age		0.03	0.04	0.12	0.485	**F**	**P**
Step 2	0.03					2.22	0.145
Age		0.00	0.04	0.00	0.997		
Tracking		5.75	3.86	0.27	0.145	**F**	**P**
Step 3	0.19					3.06	0.090
Age		0.03	0.04	0.11	0.576		
Tracking		3.30	4.00	0.16	0.415		
FSIQ		0.02	0.01	0.30	0.090		
Spatial Working Memory: Strategy	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.06						
Age		0.05	0.04	0.24	0.157	**F**	**P**
Step 2	0.07					0.41	0.528
Age		0.06	0.04	0.29	0.126		
Tracking		-2.29	3.59	-0.12	0.528	**F**	**P**
Step 3	0.08					0.61	0.442
Age		0.07	0.04	0.34	0.094		
Tracking		-3.34	3.85	-0.17	0.393		
FSIQ		0.01	0.01	0.14	0.442		
Set Shifting: Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.07						
Age		0.06	0.04	0.27	0.121	**F**	**P**
Step 2	0.08					0.21	0.649
Age		-0.07	0.04	-0.31	0.117		
Tracking		1.95	4.23	0.09	0.649	**F**	**P**
Step 3	0.08					0.09	0.767
Age		-0.08	0.05	-0.33	0.121		
Tracking		2.54	4.74	0.12	0.595		
FSIQ		0.00	0.01	-0.06	0.767		

Set Shifting: Non-Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.00						
Age		-0.01	0.05	-0.04	0.838	**F**	**P**
Step 2	0.01					0.23	0.634
Age		0.00	0.06	0.01	0.976		
Tracking		-2.62	5.44	-0.10	0.634	**F**	**P**
Step 3	0.03					0.73	0.401
Age		0.02	0.06	0.07	0.750		
Tracking		-4.77	6.02	-0.17	0.434		
FSIQ		0.02	0.02	0.17	0.401		
		Aiming: Peak Speed					
Sustained Attention	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=33
Step 1	0.14						
Age		0.10	0.05	0.38	0.031	**F**	**P**
Step 2	0.14					0.03	0.873
Age		0.10	0.05	0.38	0.034		
Peak Speed		-0.29	1.80	-0.03	0.873	**F**	**P**
Step 3	0.30					6.78	0.014
Age		0.13	0.04	0.48	0.005		
Peak Speed		-1.21	1.68	-0.11	0.480		
FSIQ		0.04	0.01	0.42	0.014		
Visual Attention	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=36
Step 1	0.15						
Age		0.12	0.05	0.39	0.019	**F**	**P**
Step 2	0.15					0.06	0.806
Age		0.12	0.05	0.38	0.023		
Peak Speed		0.48	1.93	0.04	0.806	**F**	**P**
Step 3	0.32					7.92	0.008
Age		0.15	0.05	0.47	0.003		
Peak Speed		-0.72	1.80	-0.06	0.694		
FSIQ		0.04	0.02	0.43	0.008		
Processing Speed: Movement Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.16						
Age		0.11	0.04	0.40	0.014	**F**	**P**
Step 2	0.17					0.56	0.458
Age		0.12	0.04	0.41	0.013		
Peak Speed		-1.31	1.74	-0.12	0.458	**F**	**P**
Step 3	0.19					0.85	0.364
Age		0.13	0.05	0.44	0.009		
Peak Speed		-1.69	1.79	-0.15	0.352		
FSIQ		0.01	0.02	0.15	0.364		
Processing Speed: Reaction Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.11						
Age		0.11	0.05	0.33	0.049	**F**	**P**
Step 2	0.14					1.25	0.272
Age		0.10	0.05	0.31	0.064		
Peak Speed		2.33	2.08	0.18	0.271	**F**	**P**
Step 3	0.24					4.56	0.040
Age		0.13	0.05	0.38	0.021		
Peak Speed		1.30	2.04	0.10	0.526		
FSIQ		0.04	0.02	0.34	0.040		

Spatial Planning: Initial thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.00						
Age		-0.02	0.05	-0.06	0.736	**F**	**P**
Step 2	0.09					2.67	0.113
Age		-0.02	0.04	-0.09	0.632		
Peak Speed		2.75	1.68	0.29	0.113	**F**	**P**
Step 3	0.14					1.60	0.217
Age		-0.01	0.05	-0.03	0.889		
Peak Speed		2.28	1.71	0.24	0.192		
FSIQ		0.02	0.01	0.23	0.217		
Spatial Planning: Subsequent thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.08						
Age		-0.09	0.05	-0.28	0.122	**F**	**P**
Step 2	0.08					0.08	0.773
Age		-0.09	0.06	-0.28	0.123		
Peak Speed		0.61	2.11	0.05	0.773	**F**	**P**
Step 3	0.09					0.40	0.531
Age		-0.08	0.06	-0.25	0.188		
Peak Speed		0.31	2.18	0.03	0.887		
FSIQ		0.01	0.02	0.12	0.531		
Spatial Planning: Problems solved in minimum moves	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.03						
Age		-0.05	0.05	-0.18	0.311	**F**	**P**
Step 2	0.08					1.55	0.224
Age		-0.05	0.05	-0.17	0.359		
Peak Speed		-2.35	1.89	-0.22	0.223	**F**	**P**
Step 3	0.34					10.96	0.003
Age		-0.01	0.04	-0.03	0.863		
Peak Speed		-3.54	1.67	-0.34	0.043		
FSIQ		0.05	0.01	0.54	0.003		
Spatial Working Memory: Errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.01						
Age		0.03	0.04	0.12	0.485	**F**	**P**
Step 2	0.07					2.23	0.145
Age		0.03	0.04	0.15	0.387		
Peak Speed		-2.29	1.53	-0.25	0.145	**F**	**P**
Step 3	0.25					7.68	0.009
Age		0.06	0.04	0.24	0.138		
Peak Speed		-3.23	1.44	-0.35	0.032		
FSIQ		0.03	0.01	0.44	0.009		
Spatial Working Memory: Strategy	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.06						
Age		0.05	0.04	0.24	0.157	**F**	**P**
Step 2	0.06					0.30	0.587
Age		0.05	0.04	0.25	0.148		
Peak Speed		-0.78	1.43	-0.09	0.587	**F**	**P**
Step 3	0.08					0.43	0.519
Age		0.06	0.04	0.27	0.125		
Peak Speed		-1.01	1.48	-0.12	0.500		
FSIQ		0.01	0.01	0.11	0.519		

Set Shifting: Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.07						
Age		-0.06	0.04	-0.27	0.121	**F**	**P**
Step 2	0.09					0.48	0.492
Age		-0.06	0.04	-0.28	0.114		
Peak Speed		1.04	1.49	0.12	0.492	**F**	**P**
Step 3	0.09					0.07	0.799
Age		-0.07	0.04	-0.29	0.115		
Peak Speed		1.14	1.56	0.13	0.473		
FSIQ		0.00	0.01	-0.05	0.799		
Set Shifting: Non-Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.00						
Age		-0.01	0.05	-0.04	0.838	**F**	**P**
Step 2	0.13					4.41	0.044
Age		-0.02	0.05	-0.06	0.707		
Peak Speed		3.80	1.81	0.35	0.044	**F**	**P**
Step 3	0.13					0.01	0.922
Age		-0.02	0.05	-0.06	0.730		
Peak Speed		3.75	1.90	0.35	0.057		
FSIQ		0.00	0.02	0.02	0.922		
		Aiming: Time to Peak Speed					
Rapid Visual Processing	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=33
Step 1	0.14						
Age		0.10	0.05	0.38	0.031	**F**	**P**
Step 2	0.15					0.23	0.637
Age		0.08	0.06	0.31	0.159		
Time to Peak Speed		0.47	0.99	0.10	0.637	**F**	**P**
Step 3	0.29					5.98	0.021
Age		0.14	0.06	0.50	0.027		
Time to Peak Speed		-0.20	0.95	-0.04	0.839		
FSIQ		0.04	0.01	0.41	0.021		
Visual Attention	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=36
Step 1	0.15						
Age		0.12	0.05	0.39	0.019	**F**	**P**
Step 2	0.17					0.60	0.442
Age		0.09	0.06	0.29	0.167		
Time to Peak Speed		0.79	1.01	0.16	0.442	**F**	**P**
Step 3	0.32					7.08	0.012
Age		0.15	0.06	0.47	0.025		
Time to Peak Speed		-0.05	0.98	-0.01	0.959		
FSIQ		0.04	0.02	0.42	0.012		
Processing Speed: Movement Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.16						
Age		0.11	0.04	0.40	0.014	**F**	**P**
Step 2	0.19					1.14	0.294
Age		0.08	0.06	0.27	0.184		
Time to Peak Speed		0.90	0.85	0.21	0.294	**F**	**P**
Step 3	0.19					0.17	0.679
Age		0.09	0.06	0.30	0.170		
Time to Peak Speed		0.79	0.90	0.18	0.387		
FSIQ		0.01	0.02	0.07	0.679		

Processing Speed: Reaction Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.11						
Age		0.11	0.05	0.33	0.049	**F**	**P**
Step 2	0.21					4.24	0.047
Age		0.03	0.07	0.08	0.701		
Time to Peak Speed		2.02	0.98	0.40	0.047	**F**	**P**
Step 3	0.28					3.43	0.073
Age		0.07	0.07	0.20	0.330		
Time to Peak Speed		1.46	0.99	0.29	0.151		
FSIQ		0.03	0.02	0.29	0.073		
Spatial Planning: Initial thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.00						
Age		-0.02	0.05	-0.06	0.736	**F**	**P**
Step 2	0.05					1.37	0.251
Age		-0.05	0.06	-0.22	0.340		
Time to Peak Speed		1.00	0.86	0.26	0.251	**F**	**P**
Step 3	0.10					1.64	0.211
Age		-0.03	0.06	-0.11	0.647		
Time to Peak Speed		0.69	0.88	0.18	0.441		
FSIQ		0.02	0.02	0.25	0.211		
Spatial Planning: Subsequent thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.08						
Age		-0.09	0.05	-0.28	0.122	**F**	**P**
Step 2	0.09					0.23	0.633
Age		-0.11	0.07	-0.34	0.131		
Time to Peak Speed		0.51	1.05	0.11	0.633	**F**	**P**
Step 3	0.10					0.33	0.572
Age		-0.09	0.07	-0.29	0.229		
Time to Peak Speed		0.33	1.11	0.07	0.767		
FSIQ		0.01	0.02	0.11	0.572		
Spatial Planning: Problems solved in minimum moves	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.03						
Age		-0.05	0.05	-0.18	0.311	**F**	**P**
Step 2	0.04					0.05	0.830
Age		-0.06	0.06	-0.21	0.353		
Time to Peak Speed		0.21	0.97	0.05	0.830	**F**	**P**
Step 3	0.24					7.64	0.010
Age		0.00	0.06	0.00	0.998		
Time to Peak Speed		-0.49	0.91	-0.11	0.595		
FSIQ		0.04	0.02	0.49	0.010		
Spatial Working Memory: Errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.01						
Age		0.03	0.04	0.12	0.485	**F**	**P**
Step 2	0.03					0.41	0.528
Age		0.05	0.05	0.20	0.351		
Time to Peak Speed		-0.49	0.77	-0.14	0.528	**F**	**P**
Step 3	0.19					6.49	0.016
Age		0.09	0.05	0.38	0.080		
Time to Peak Speed		-1.08	0.75	-0.30	0.162		
FSIQ		0.03	0.01	0.43	0.016		

Spatial Working Memory: Strategy	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.06						
Age		0.05	0.04	0.24	0.157	**F**	**P**
Step 2	0.06					0.17	0.679
Age		0.06	0.05	0.29	0.177		
Time to Peak Speed		-0.29	0.70	-0.09	0.679	**F**	**P**
Step 3	0.07					0.44	0.513
Age		0.08	0.05	0.34	0.141		
Time to Peak Speed		-0.44	0.74	-0.13	0.556		
FSIQ		0.01	0.01	0.12	0.513		
Set Shifting: Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.07						
Age		0.06	0.04	0.27	0.121	**F**	**P**
Step 2	0.12					1.80	0.189
Age		0.10	0.05	0.44	0.044		
Time to Peak Speed		0.96	0.72	0.28	0.189	**F**	**P**
Step 3	0.13					0.27	0.606
Age		0.11	0.05	0.48	0.042		
Time to Peak Speed		1.09	0.76	0.32	0.165		
FSIQ		0.01	0.01	0.09	0.606		
Set Shifting: Non-Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.00						
Age		-0.01	0.05	-0.04	0.838		
Step 2	0.00					**F**	**P**
Age		-0.02	0.06	-0.05	0.814	0.02	0.901
Time to Peak Speed		0.12	0.95	0.03	0.901		
Step 3	0.01					**F**	**P**
Age		0.00	0.07	-0.01	0.963	0.31	0.583
Time to Peak Speed		-0.05	1.01	-0.01	0.957		
FSIQ		0.01	0.02	0.11	0.583		
			Aiming: Normalised Jerk				
Rapid Visual Processing	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=33
Step 1	0.14						
Age		0.10	0.05	0.38	0.031	**F**	**P**
Step 2	0.18					1.27	0.268
Age		0.05	0.07	0.17	0.499		
Normalised Jerk		265.82	235.61	0.28	0.268	**F**	**P**
Step 3	0.31					5.38	0.028
Age		0.09	0.07	0.34	0.173		
Normalised Jerk		163.43	224.49	0.17	0.472		
FSIQ		0.03	0.01	0.38	0.028		
Visual Attention	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=36
Step 1	0.15						
Age		0.12	0.05	0.39	0.019	**F**	**P**
Step 2	0.19					1.75	0.195
Age		0.05	0.07	0.16	0.510		
Normalised Jerk		341.15	257.73	0.31	0.195	**F**	**P**
Step 3	0.33					6.76	0.014
Age		0.10	0.07	0.31	0.178		
Normalised Jerk		220.32	242.30	0.20	0.370		
FSIQ		0.04	0.02	0.39	0.014		

Processing Speed: Movement Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.16						
Age		0.11	0.04	0.40	0.014	**F**	**P**
Step 2	0.31					7.17	0.011
Age		0.00	0.06	0.01	0.972		
Normalised Jerk		500.08	186.75	0.55	0.011	**F**	**P**
Step 3	0.31					0.10	0.750
Age		0.01	0.06	0.02	0.910		
Normalised Jerk		489.34	192.18	0.54	0.016		
FSIQ		0.00	0.01	0.05	0.750		
Processing Speed: Reaction Time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.11						
Age		0.11	0.05	0.33	0.049	**F**	**P**
Step 2	0.11					0.27	0.607
Age		0.08	0.08	0.24	0.306		
Normalised Jerk		128.54	247.41	0.12	0.607	**F**	**P**
Step 3	0.23					5.18	0.029
Age		0.12	0.08	0.37	0.112		
Normalised Jerk		34.82	237.08	0.03	0.884		
FSIQ		0.04	0.02	0.36	0.029		
Spatial Planning: Initial thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.00						
Age		-0.02	0.05	-0.06	0.736	**F**	**P**
Step 2	0.05					1.37	0.251
Age		0.04	0.06	0.15	0.558		
Normalised Jerk		-230.37	196.79	-0.30	0.251	**F**	**P**
Step 3	0.16					3.59	0.069
Age		0.08	0.06	0.30	0.251		
Normalised Jerk		-303.59	192.48	-0.40	0.126		
FSIQ		0.03	0.01	0.35	0.069		
Spatial Planning: Subsequent thinking time	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.08						
Age		-0.09	0.05	-0.28	0.122	**F**	**P**
Step 2	0.08					0.18	0.674
Age		-0.11	0.08	-0.36	0.170		
Normalised Jerk		102.42	241.09	0.11	0.674	**F**	**P**
Step 3	0.10					0.37	0.547
Age		-0.09	0.08	-0.31	0.266		
Normalised Jerk		71.93	248.81	0.08	0.775		
FSIQ		0.01	0.02	0.12	0.547		
Spatial Planning: Problems solved in minimum moves	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=32
Step 1	0.03						
Age		-0.05	0.05	-0.18	0.311	**F**	**P**
Step 2	0.14					3.66	0.066
Age		-0.14	0.07	-0.52	0.043		
Normalised Jerk		399.53	208.87	0.47	0.066	**F**	**P**
Step 3	0.29					6.02	0.021
Age		-0.09	0.07	-0.34	0.165		
Normalised Jerk		302.50	196.84	0.35	0.136		
FSIQ		0.04	0.01	0.41	0.021		

Spatial Working Memory: Errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.01						
Age		0.03	0.04	0.12	0.485	**F**	**P**
Step 2	0.08					2.48	0.124
Age		-0.04	0.06	-0.15	0.537		
Normalised Jerk		282.22	179.15	0.37	0.124	**F**	**P**
Step 3	0.18					3.80	0.060
Age		-0.01	0.06	-0.03	0.887		
Normalised Jerk		222.98	174.85	0.29	0.211		
FSIQ		0.02	0.01	0.32	0.060		
Spatial Working Memory: Strategy	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=37
Step 1	0.06						
Age		0.05	0.04	0.24	0.157	**F**	**P**
Step 2	0.09					1.18	0.285
Age		0.01	0.05	0.06	0.816		
Normalised Jerk		179.69	165.43	0.25	0.285	**F**	**P**
Step 3	0.09					0.11	0.744
Age		0.02	0.05	0.08	0.761		
Normalised Jerk		169.97	170.23	0.24	0.325		
FSIQ		0.00	0.01	0.06	0.744		
Set Shifting: Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.07						
Age		-0.06	0.04	-0.27	0.121	**F**	**P**
Step 2	0.07					0.00	0.998
Age		-0.06	0.06	-0.27	0.269		
Normalised Jerk		0.54	173.35	0.00	0.998	**F**	**P**
Step 3	0.07					0.01	0.935
Age		-0.06	0.06	-0.28	0.282		
Normalised Jerk		3.16	179.02	0.00	0.986		
FSIQ		0.00	0.01	-0.01	0.935		
Set Shifting: Non-Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**		n=34
Step 1	0.00						
Age		-0.01	0.05	-0.04	0.838	**F**	**P**
Step 2	0.00					0.01	0.928
Age		-0.01	0.07	-0.02	0.935		
Normalised Jerk		-20.25	222.63	-0.02	0.928	**F**	**P**
Step 3	0.01					0.35	0.559
Age		0.00	0.07	0.02	0.951		
Normalised Jerk		-44.18	228.61	-0.05	0.848		
FSIQ		0.01	0.02	0.11	0.559		
			Steering				
Rapid Visual Processing	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**	n=33	
Step 1	0.14						
Age		0.10	0.05	0.38	0.031		
Step 2	0.16					**F**	**P**
Age		0.08	0.05	0.30	0.132	0.54	0.468
Steering		0.90	1.22	0.14	0.468		
Step 3	0.29					**F**	**P**
Age		0.12	0.05	0.46	0.025	5.59	0.025
Steering		0.14	1.18	0.02	0.905		
FSIQ		0.04	0.01	0.39	0.025		

Visual Attention	R^2	Estimate	Std. Error	Beta	Pr(>|t|)	n=36	
Step 1	0.15						
Age		0.12	0.05	0.39	0.019		
Step 2	0.20					**F**	**P**
Age		0.08	0.06	0.25	0.176	2.04	0.162
Steering		1.69	1.19	0.26	0.162		
Step 3	0.33					**F**	**P**
Age		0.12	0.06	0.39	0.036	6.10	0.019
Steering		0.84	1.16	0.13	0.472		
FSIQ		0.04	0.02	0.38	0.019		

Processing Speed: Movement Time	R^2	Estimate	Std. Error	Beta	Pr(>|t|)	n=37	
Step 1	0.16						
Age		0.11	0.04	0.40	0.014		
Step 2	0.16					**F**	**P**
Age		0.11	0.05	0.38	0.046	0.06	0.812
Steering		0.26	1.09	0.04	0.812		
Step 3	0.17					**F**	**P**
Age		0.12	0.06	0.42	0.038	0.45	0.508
Steering		0.04	1.15	0.01	0.974		
FSIQ		0.01	0.02	0.11	0.508		

Processing Speed: Reaction Time	R^2	Estimate	Std. Error	Beta	Pr(>|t|)	n=37	
Step 1	0.11						
Age		0.11	0.05	0.33	0.049		
Step 2	0.24					**F**	**P**
Age		0.04	0.06	0.11	0.520	5.90	0.021
Steering		2.96	1.22	0.42	0.021		
Step 3	0.31					**F**	**P**
Age		0.07	0.06	0.21	0.242	3.27	0.080
Steering		2.31	1.23	0.33	0.070		
FSIQ		0.03	0.02	0.28	0.080		

Spatial Planning: Initial thinking time	R^2	Estimate	Std. Error	Beta	Pr(>|t|)	n=32	
Step 1	0.00						
Age		-0.02	0.05	-0.06	0.736		
Step 2	0.00					**F**	**P**
Age		-0.01	0.05	-0.05	0.806	0.01	0.926
Steering		-0.11	1.18	-0.02	0.926		
Step 3	0.09					**F**	**P**
Age		0.02	0.05	0.07	0.760	2.67	0.114
Steering		-0.62	1.19	-0.11	0.606		
FSIQ		0.02	0.02	0.31	0.114		

Spatial Planning: Subsequent thinking time	R^2	Estimate	Std. Error	Beta	Pr(>|t|)	n=32	
Step 1	0.08						
Age		-0.09	0.05	-0.28	0.122		
Step 2	0.16					**F**	**P**
Age		-0.14	0.06	-0.44	0.032	2.83	0.103
Steering		2.28	1.36	0.33	0.103		
Step 3	0.16					**F**	**P**
Age		-0.13	0.07	-0.42	0.057	0.08	0.778
Steering		2.18	1.43	0.31	0.139		
FSIQ		0.01	0.02	0.05	0.778		

Spatial Planning: Problems solved in minimum moves	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**	n=32	
Step 1	0.03						
Age		-0.05	0.05	-0.18	0.311		
Step 2	0.07					**F**	**P**
Age		-0.08	0.06	-0.29	0.170	1.08	0.307
Steering		1.33	1.28	0.21	0.307		
Step 3	0.24					**F**	**P**
Age		-0.03	0.06	-0.12	0.555	6.29	0.018
Steering		0.53	1.22	0.08	0.668		
FSIQ		0.04	0.02	0.44	0.018		
Spatial Working Memory: Errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**	n=37	
Step 1	0.01						
Age		0.03	0.04	0.12	0.485		
Step 2	0.16					**F**	**P**
Age		-0.03	0.04	-0.11	0.556	6.05	0.019
Steering		2.23	0.91	0.45	0.019		
Step 3	0.22					**F**	**P**
Age		0.00	0.04	-0.02	0.930	2.60	0.117
Steering		1.80	0.93	0.36	0.061		
FSIQ		0.02	0.01	0.26	0.117		
Spatial Working Memory: Strategy	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**	n=37	
Step 1	0.06						
Age		0.05	0.04	0.24	0.157		
Step 2	0.07					**F**	**P**
Age		0.04	0.04	0.17	0.387	0.51	0.480
Steering		0.63	0.89	0.14	0.479		
Step 3	0.07					**F**	**P**
Age		0.04	0.05	0.19	0.365	0.10	0.756
Steering		0.55	0.94	0.12	0.563		
FSIQ		0.00	0.01	0.06	0.756		
Set Shifting: Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**	n=34	
Step 1	0.07						
Age		-0.06	0.04	-0.27	0.121		
Step 2	0.11					**F**	**P**
Age		-0.03	0.05	-0.15	0.467	1.24	0.273
Steering		-1.11	1.00	-0.23	0.273		
Step 3	0.11					**F**	**P**
Age		-0.03	0.05	-0.13	0.557	0.09	0.768
Steering		-1.22	1.07	-0.25	0.265		
FSIQ		0.00	0.01	0.05	0.768		
Set Shifting: Non-Perseverative errors	**R^2**	**Estimate**	**Std. Error**	**Beta**	**Pr(>|t|)**	n=34	
Step 1	0.00						
Age		-0.01	0.05	-0.04	0.838		
Step 2	0.00					**F**	**P**
Age		-0.02	0.06	-0.06	0.768	0.05	0.817
Steering		0.31	1.31	0.05	0.817		
Step 3	0.01					**F**	**P**
Age		-0.01	0.07	-0.03	0.910	0.27	0.608
Steering		0.06	1.40	0.01	0.963		
FSIQ		0.01	0.02	0.10	0.608		

4.4.5 Sensorimotor performance and psychopathology.

Hierarchical regressions predicting number of psychopathology symptoms were carried out using the same method as for the relationship between sensorimotor variables and cognitive tasks. Number of symptoms was first predicted by age, then the sensorimotor variable of interest, then FSIQ. This analysis showed that sensorimotor performance was not predictive of psychopathology symptoms. Addition of sensorimotor performance variables did not improve model fit for any psychopathology symptoms (Table 4-7).

Table 4-7. Regression results for psychopathology symptom counts predicted by Age, sensorimotor performance and FSIQ in children with 22q11.2DS.

ADHD							
Tracking							
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.08						
Age		-0.39	0.22	-0.28	0.091		
Step 2	0.12					**F**	**P**
Age		-0.25	0.24	-0.18	0.318	1.75	0.195
Tracking		-28.48	21.54	-0.24	0.195		
Step 3	0.20					**F**	**P**
Age		-0.10	0.25	-0.08	0.683	3.26	0.080
Tracking		-42.53	22.27	-0.35	0.065		
FSIQ		0.14	0.08	0.30	0.080		
Aiming: Peak Speed							
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.08						
Age		-0.39	0.22	-0.28	0.091	**F**	**P**
Step 2	0.13					2.05	0.161
Age		-0.42	0.22	-0.31	0.065		
Aiming: Peak Speed		12.22	8.52	0.23	0.161	**F**	**P**
Step 3	0.15					0.75	0.393
Age		-0.38	0.23	-0.28	0.103		
Aiming: Peak Speed		10.43	8.80	0.20	0.245		
FSIQ		0.06	0.07	0.15	0.393		
Aiming: Time to Peak Speed							
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.08						
Age		-0.39	0.22	-0.28	0.091	**F**	**P**
Step 2	0.14					2.55	0.119
Age		-0.66	0.28	-0.48	0.023		
Aiming: Time to Peak Speed		6.64	4.16	0.32	0.119	**F**	**P**
Step 3	0.16					0.54	0.469
Age		-0.59	0.30	-0.43	0.054		
Aiming: Time to Peak Speed		5.66	4.39	0.28	0.206		
FSIQ		0.06	0.08	0.13	0.469		
Aiming: Normalised Jerk							
ADHD	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.08						
Age		-0.39	0.22	-0.28	0.091	**F**	**P**
Step 2	0.11					1.35	0.253
Age		-0.12	0.32	-0.09	0.700		
Aiming: Normalised Jerk		-1173.55	1009.39	-0.27	0.253	**F**	**P**
Step 3	0.17					2.00	0.167
Age		-0.01	0.32	-0.01	0.976		
Aiming: Normalised Jerk		-1421.42	1010.29	-0.33	0.169		
FSIQ		0.10	0.07	0.23	0.167		

Steering							
	R^2	Estimate	Std. Error	Beta	P	n=37	
Step 1	0.08						
Age		-0.39	0.22	-0.28	0.091	**F**	**P**
Step 2	0.10					0.96	0.334
Age		-0.26	0.26	-0.19	0.323		
Steering		-5.28	5.39	-0.18	0.334	**F**	**P**
Step 3	0.17					2.38	0.133
Age		-0.13	0.27	-0.10	0.618		
Steering		-7.76	5.52	-0.27	0.170		
FSIQ		0.12	0.08	0.26	0.132		

ASD							
Tracking							
	R^2	Estimate	Std. Error	Beta	P	n=37	
Step 1	0.00						
Age		0.03	0.41	0.01	0.935	**F**	**P**
Step 2	0.03					1.049	0.313
Age		0.25	0.46	0.11	0.590		
Tracking		-42.29	41.28	-0.20	0.313	**F**	**P**
Step 3	0.06					0.87	0.3578
Age		0.12	0.49	0.05	0.804		
Tracking		-29.64	43.53	-0.14	0.501		
FSIQ		-0.14	0.15	-0.17	0.358		
Aiming: Peak Speed							
ASD	R^2	Estimate	Std. Error	Beta	P	n=37	
Step 1	0.00						
Age		0.03	0.41	0.01	0.935	**F**	**P**
Step 2	0.01					0.22	0.639
Age		0.01	0.42	0.01	0.975		
Aiming: Peak Speed		7.62	16.12	0.08	0.639	**F**	**P**
Step 3	0.06					1.88	0.180
Age		-0.10	0.42	-0.04	0.821		
Aiming: Peak Speed		13.22	16.42	0.14	0.427		
FSIQ		-0.20	0.14	-0.25	0.180		
Aiming: Time to Peak Speed							
ASD	R^2	Estimate	Std. Error	Beta	P	n=37	
Step 1	0.00						
Age		0.03	0.41	0.01	0.935	**F**	**P**
Step 2	0.01					0.23	0.637
Age		0.20	0.54	0.08	0.715		
Aiming: Time to Peak Speed		-3.86	8.10	-0.11	0.637	**F**	**P**
Step 3	0.04					1.23	0.276
Age		0.02	0.57	0.01	0.979		
Aiming: Time to Peak Speed		-1.37	8.37	-0.04	0.871		
FSIQ		-0.16	0.15	-0.20	0.276		
Aiming: Normalised Jerk							
	R^2	Estimate	Std. Error	Beta	P	n=37	
Step 1	0.00						
Age		0.03	0.41	0.01	0.935	**F**	**P**
Step 2	0.00					0.04	0.840
Age		0.14	0.65	0.06	0.836		
Aiming: Normalised Jerk		-432.12	2125.20	-0.06	0.840	**F**	**P**
Step 3	0.04					1.40	0.245
Age		0.01	0.66	0.00	0.991		
Aiming: Normalised Jerk		-228.72	2119.36	-0.03	0.915		
FSIQ		-0.17	0.14	-0.21	0.245		

			Steering				
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.00						
Age		0.03	0.41	0.01	0.935	**F**	**P**
Step 2	0.09					3.09	0.088
Age		0.45	0.47	0.19	0.336		
Steering		-17.02	9.68	-0.34	0.088	**F**	**P**
Step 3	0.10					0.61	0.439
Age		0.35	0.49	0.14	0.482		
Steering		-14.83	10.13	-0.30	0.153		
FSIQ		-0.11	0.14	-0.14	0.439		
			Anxiety				
			Tracking				
Anxiety	**R^2**	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.11						
Age		-0.68	0.33	-0.33	0.048	**F**	**P**
Step 2	0.12					0.29	0.595
Age		-0.59	0.37	-0.29	0.119		
Tracking		-17.57	32.76	-0.10	0.595	**F**	**P**
Step 3	0.12					0.20	0.658
Age		-0.65	0.40	-0.31	0.110		
Tracking		-12.04	35.38	-0.07	0.736		
FSIQ		-0.05	0.12	-0.08	0.658		
			Aiming: Peak Speed				
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.11						
Age		-0.68	0.33	-0.33	0.048	**F**	**P**
Step 2	0.11					0.24	0.626
Age		-0.70	0.34	-0.34	0.046		
Aiming: Peak Speed		6.42	13.03	0.08	0.626	**F**	**P**
Step 3	0.13					0.55	0.463
Age		-0.75	0.35	-0.36	0.037		
Aiming: Peak Speed		8.77	13.49	0.11	0.520		
FSIQ		-0.09	0.11	-0.13	0.463		
			Aiming: Time to Peak Speed				
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.11						
Age		-0.68	0.33	-0.33	0.048	**F**	**P**
Step 2	0.11					0.03	0.874
Age		-0.72	0.43	-0.35	0.102		
Aiming: Time to Peak Speed		1.02	6.41	0.03	0.874	**F**	**P**
Step 3	0.12					0.47	0.499
Age		-0.83	0.46	-0.40	0.081		
Aiming: Time to Peak Speed		2.43	6.79	0.08	0.722		
FSIQ		-0.08	0.12	-0.12	0.499		

Aiming: Normalised Jerk							
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.11						
Age		-0.68	0.33	-0.33	0.048	**F**	**P**
Step 2	0.13					0.94	0.338
Age		-0.35	0.48	-0.17	0.466		
Aiming: Normalised Jerk		-1469.18	1511.90	-0.22	0.338	**F**	**P**
Step 3	0.14					0.20	0.656
Age		-0.41	0.50	-0.20	0.420		
Aiming: Normalised Jerk		-1347.84	1553.57	-0.20	0.392		
FSIQ		-0.05	0.11	-0.08	0.656		
Steering							
	R^2	**Estimate**	**Std. Error**	**Beta**	**P**	n=37	
Step 1	0.11						
Age		-0.68	0.33	-0.33	0.048	**F**	**P**
Step 2	0.11					0.06	0.801
Age		-0.73	0.39	-0.35	0.069		
Steering		2.06	8.14	0.05	0.801	**F**	**P**
Step 3	0.12					0.50	0.484
Age		-0.82	0.41	-0.39	0.055		
Steering		3.82	8.56	0.09	0.658		
FSIQ		-0.08	0.12	-0.12	0.484		

4.5 Discussion

In the current chapter, I have described the investigation of sensorimotor ability in children with 22q11.2 deletion syndrome. Using a computerised fine motor skill assessment, I have demonstrated that children with 22q11.2DS have significant deficits in fundamental sensorimotor skills, including tracking, aiming and steering. I also demonstrated that sensorimotor performance is not correlated with coordination score, as measured by the DCDQ. Additionally, I present evidence that suggests that tracking ability is related to full scale IQ, visual attention, sustained attention, and spatial planning performance after controlling for age and FSIQ, that peak speed of aiming movements was associated with spatial planning and spatial working memory performance after controlling for age and FSIQ, that normalised jerk was associated with movement time on the reaction time task after controlling for age and FSIQ, and that steering performance was related to reaction time and spatial working memory performance when controlling for age alone. In contrast, sensorimotor ability was not related to ADHD, ASD or anxiety symptoms. This is the first study to attempt to define how sensorimotor ability in 22q11.2DS, is related to other deficits in cognition and psychopathology in these individuals.

4.5.1 Sensorimotor ability

I assessed performance on the three fundamental sensorimotor processes of tracking, aiming and steering. These processes reflect core visuomotor processes that underpin numerous motor skills. Deficits in these processes can, therefore, be expected to impact negatively on a child's ability to acquire core motor skills. The individuals with 22q11.2DS performed more poorly across these three domains compared to unaffected sibling controls. The data presented here adds to previous studies showing motor deficits in tracking tasks (Van Aken *et al.,* 2010), with additional insight from our work that aiming and steering tasks are also affected, providing

information about performance of ballistic movements and steering. It should be noted that sensorimotor performance did improve with age in children with 22q11.2DS, which aligns with findings in the general population that as children grow older, they improve their sensorimotor processing abilities (Flatters *et al.*, 2014).

The analyses found significant effects for four, three-way interactions, Group x Age x Trial Type, Group x Age x Speed, Group x Age x Speed, Group x Speed x Sex, and Speed x Sex x Age. Overall, the evidence presented here suggests that children with 22q11.2DS perform more poorly than control siblings on the tracking task, particularly at slower speeds and differences in performance are more pronounced for males with the 22q11.2 deletion compared to male controls. In addition, while both groups improve in performance as they grow older, they improve at differing rates depending on deletion status, the speed of the target and gender. Differences in tracking performance between groups were most evident at the slowest target speed, at the fastest speed, there was little difference between carriers of the deletion and controls. This would suggest that both carriers of the deletion and controls find the task difficult at the fastest speed. The only other studies conducted using a tracking task in 22q11.2DS, by van Aken et al., found that children with 22q11.2DS had larger time and distance errors compared to IQ and age matched controls, meaning that the children with 22q11.2DS were less spatially accurate in their movements (Van Aken *et al.*, 2010a). They suggested that the increased error compared to IQ matched controls indicated that this deficit is caused by an additional (syndrome specific) processing deficit that is not attributable to the lower intellectual abilities of the 22q11.2DS group (Van Aken *et al.,* 2010). The results presented in this chapter replicate these deficits in tracking performance in children with 22q11.2DS but demonstrate evidence that tracking ability may be related to the IQ of the individual. Good tracking

performance is required for tasks such as ball skills and interception of moving objects, where the target's speed and path must be predicted accurately.

Aiming performance was poorer in children with 22q11.2 deletion than controls, with lower peak speed reached during movements, increased time to reach peak speed and increased jerkiness of movements. This would suggest that in 22q11.2 deletion syndrome, ballistic movements are less smooth, indicating a reduced ability to plan and control fast movements, which is an aspect of prospective motor control. Typically, ballistic movements are made up of three phases, an acceleration phase to a peak velocity, a period at this peak velocity, and a deceleration phase to reach the target. Good prospective motor control would be shown by a high peak speed, low time to peak speed and low normalised jerk, signifying smooth motion. Compared to tracking performance, I found no association between aiming performance and FSIQ, suggesting that deficits in aiming performance may not be explained fully by deficits in IQ. Aimed movements of the type assessed in the CKAT are typically used in reaching actions, for example, to reach out and press a button, or reach to a target object in order to grasp it.

Steering performance was poorer in individuals with 22q11.2 deletion compared to unaffected control siblings. Decomposing overall PPA into its component elements of path accuracy and time revealed that while children with 22q11.2DS did not differ from siblings in the time taken to complete each steering trial, they did differ on path accuracy, meaning they were further from the idealised path. This is consistent with an increased error on the steering task, likely as a result of deficits in the ability to control the amount of force exerted on the stylus. Good force control is required to steer the stylus accurately and remain within the path boundaries. Performance on the steering task did improve with age for overall PPA, along with both time taken and accuracy, suggesting that in both groups ability to control force improves with age.

Similar to the findings for aiming performance, there was no association between FSIQ and steering performance, again suggesting that deficits in steering performance cannot be fully explained by lower IQ. Examples daily life skill that are directly comparable to the steering task, and that requires good force control are drawing and writing. However, accurate force control is also required in order to grasp objects with the appropriate strength.

Sensorimotor performance was associated with DCDQ score (as described in the previous chapter) when sensorimotor performance and DCDQ scores were correlated in the entire sample of children with 22q11.2DS and controls. However, correlating sensorimotor performance with DCDQ total score in the children with 22q11.2DS alone, resulted in no association between the two measures. Correlating individual questions on the DCDQ with sensorimotor measures in children with 22q11.2DS revealed that better tracking performance was associated with higher parental opinion of their child's ability to hit a ball accurately and that more jerky movements were associated with higher overall clumsiness. Tracking ability is required to hit a moving object such as a ball, and jerky movements are by implication less well controlled than smooth movements and could be considered a marker of clumsiness. However, tracking performance was not associated with other similar skills asked about on the DCDQ such as catching a ball, making it difficult to draw strong conclusions about the generalisability of the sensorimotor measures to other skills. I expected that poor coordination scores on the DCDQ would be associated with poorer sensorimotor performance, under the assumption that the sensorimotor skills assessed by the CKAT are required for good coordination ability. This idea is supported by the association between sensorimotor measures and the DCDQ in the overall sample, but these correlations are likely influenced by the controls scoring very highly on the DCDQ. It is also supported by the associations between the ability to hit a ball accurately and tracking performance, and clumsiness and normalised jerk in

children with 22q11.2DS. However, the lack of correlation between DCDQ total score and sensorimotor performance in children with 22q11.2DS would suggest that sensorimotor performance is not directly related to overall coordination ability at the level measured by the DCDQ. Coordination is a complex construct that can be measured at many levels. The DCDQ is sensitive to deficits in coordination that have an impact on daily life and functioning. However, the total score on the DCDQ is created through the combination of scores on questions on the DCDQ that ask about complex actions such as dressing or planning a task, which require many skills in addition to simple sensorimotor ability. As such, it is likely that the DCDQ and CKAT are capturing different aspects of motor ability, with the DCDQ assessing at a higher level (more complex actions) than the CKAT's detailed assessment of object tracking, aiming and force control (single actions). Therefore, the lack of association between DCDQ total score and sensorimotor ability in children with 22q11.2DS may be due to the DCDQ and CKAT measuring different aspects of coordination, both of which are important, but at different levels. In addition, the relationship between sensorimotor ability and coordination is unlikely to be simple and will be influenced by other aspects such as developmental stage, as evidenced by the increase in sensorimotor performance with age, along with any compensatory strategies a child may develop and personal activity or exercise levels. Further work should be undertaken to map the pathways of how sensorimotor difficulties impact daily life, as this would help understanding of coordination difficulties, as well as the development of optimal intervention strategies.

4.5.2 Sensorimotor ability and Cognition

I found evidence that tracking performance was the only sensorimotor variable associated with full scale IQ after controlling for age. This contrasts with previous literature that suggested that deficits in tracking ability are in excess of what would be expected given the lower average IQ

of children with 22q11.2DS (Van Aken, et. al, 2010). It also agrees with the results of the previous chapter (Chapter 3) where a link between FSIQ and overall coordination was found.

Additionally, when performance on the neurocognitive tasks was compared between children with 22q11.2DS and siblings, I found that children with 22q11.2DS performed worse on most neurocognitive tasks compared to unaffected sibling controls. This is in line with previous work in the syndrome, where deficits in cognitive ability have been widely reported (Outlined in Section 1.5) Some associations were seen between sensorimotor and cognitive performance. Tracking performance was associated with both sustained attention and visual attention, after controlling for IQ and age, and with spatial planning, when controlling for age alone. This suggests that either attentional processes are required for good tracking performance, or that there are common processes that underlie both tracking and attentional performance. In addition, peak speed on the aiming task was associated with spatial planning and spatial working memory. This may suggest that awareness of spatial coordinates is related to planning and prospective control ability. If an individual has a poor ability to represent objects in space around them, then it would make coordinating a smooth aimed movement difficult. Finally, normalised jerk on the aiming task was associated with movement time on the reaction time task after controlling for age and FSIQ. This likely due to the nature of the movement time measure of the processing speed/reaction time task. The movement time comprises the time taken to reach out and touch the CANTAB screen after responding to the target by taking a finger off of the press pad. Less jerky movements are therefore likely to be associated with lower movement times on the reaction time task and therefore better performance.

It should be noted that all of the CANTAB tasks require some sort of motor activity in order to respond to stimuli. Therefore, relationships between CKAT and CANTAB tasks could be more

simply explained by overlap in the types of movement required to perform the CANTAB tasks. However, if this was the case, we may expect the strongest links between aiming task performance and CANTAB measures such as visual attention, where the participant must reach out and touch a target accurately.

The finding of relationships between sensorimotor and neurocognitive performance agrees with the literature from non-genotyped populations with coordination difficulties, where similar deficits in cognitive domains such as executive functioning have been found (Wilson *et al.*, 2013). However, these samples are usually selected on the basis of the presence of severe coordination problems. Therefore, there is likely to be considerable heterogeneity in the genetic aetiology of the difficulties. The sample presented here was selected on the basis of the presence of a single genetic lesion, and therefore we may be able to assume a clearer genotype-phenotype association. One of the diagnostic points for developmental coordination disorder in the DSM-5 is that motor difficulties are in excess of what would be expected given the individuals IQ. The current chapter provides some evidence that motor difficulties in 22q11.2DS, at least in the aiming and steering domains, are not related to the individual's IQ. This complements the results of the previous chapter where a relationship between FSIQ and DCDQ score was found.

A borderline association between aiming peak speed and non-perseverative errors in set shifting was found after controlling for age and FSIQ. This may be related to the requirement of the individual to reach out and indicate which card they have chosen. A borderline association was also found between steering performance and errors made on the spatial working memory task. This may suggest that spatial working memory is required for the steering task, in order to remain within the tracing path adequately. While these associations

did not reach significance, power issues may have played a role, and these findings may be targets for further investigation in larger samples.

4.5.3 Sensorimotor ability and psychopathology

In the previous chapter, I found evidence that coordination was related to psychopathology in children with 22q11.2DS, such as ASD, ADHD and anxiety. However, I found no associations between sensorimotor ability and psychopathology in the current sample of children with 22q11.2DS. This contrasts with previous research in children with anxiety disorder or with ASD who were not selected for the study based on a having a CNV. In these groups associations between these disorders and motor difficulties, including in studies using kinematic assessments, have been found (Dziuk *et al.*, 2007; Watemberg *et al.*, 2007; Cook, Blakemore and Press, 2013; Kirby, Sugden and Purcell, 2014; Lim *et al.*, 2016). This suggests that there is not a direct relationship between poor sensorimotor performance and psychopathology in children with 22q11.2DS. Psychopathology data in our study was collected through either parental interview or questionnaire, while sensorimotor performance was a direct measure of the participants' performance. This may have obscured the relationship between sensorimotor performance and psychopathology. It is possible that more direct measures of individual psychopathological domains such as inattention or restlessness may provide clearer insights into relationships between these areas. For example, restlessness, as measured using actigraphy, may be more likely to be associated with sensorimotor performance, similar to the relationships seen between direct measures of attentional performance and sensorimotor performance presented in this chapter. The lack of association is also in contrast to the findings of an association between psychopathology and coordination as measured by the DCDQ. The DCDQ may also be more sensitive to behaviour associated with psychopathology, compared to the sensorimotor tasks. The DCDQ is also collected from the parent who also provides the

psychopathology information. This may lead to reporter bias and result in a closer relation than with the direct sensorimotor measure of participant performance and parental report of child psychopathology. Finally, as the sample of individuals who completed the sensorimotor tasks is smaller than the sample who completed the DCDQ, we have less power to detect relationships. Despite the lack of associations between sensorimotor performance and severity of psychopathology, there may be other interesting effects on sensorimotor performance that could be explored. For example, you might expect that children with ADHD may have faster, more impulsive movements than a child with ASD. This could be an avenue for further research, in order to investigate if there are disorder specific patterns of sensorimotor performance.

4.5.4 Possible biological pathways

The tasks assessed by the CKAT involve motor skills that are thought to rely on a range of brain areas. Tracking and aiming performance are thought to be related to prospective motor control, or the ability to plan movements and execute them effectively while adjusting for task demands and goals. Smooth movement on the aiming task is a marker of good prospective motor control. Various brain structures have been shown to be abnormal in individuals with 22q11.2DS, and this could help explain the observed deficits in sensorimotor performance. Firstly, the cerebellum has often been found to be abnormal in individuals with 22q11.2DS (Van Amelsvoort *et al.*, 2001; Bish *et al.*, 2006). The cerebellum has been implicated in both motor and cognitive syndromes, and is thought to subserve tracking and aiming performance via internal modelling and predictive control of movements (Miall, Reckess and Imamizu, 2001), along with being a key area involved in force control more generally (Charles, Okamura and Bastian, 2013). In addition, striatal dysfunction could be involved, as increased volume of the striatum (Sugama *et al.*, 2000; Eliez *et al.*, 2002; Kates *et al.*, 2004) and calcification of the

basal ganglia (Eliez *et al.*, 2002; Sieberer *et al.*, 2005) have been observed in 22q11.2DS. These are both structures that are important for initiation and control of movements. Finally, 22q11.2DS is associated with early onset Parkinson's disease in adults. It is not known if there are early motor signs that can be observed in those individuals with 22q11.2DS who will go on to develop Parkinson's disease.

4.5.5 Strengths and limitations

This is one of the first studies to investigate fundamental sensorimotor ability, beyond tracking ability in 22q11.2DS. It is also the first study to investigate relationships between sensorimotor ability and cognition and psychopathology in this syndrome. The sensorimotor measures used compliment the other measures of coordination collected and reported in the previous chapter (Chapter 3) by providing evidence of a fundamental sensorimotor deficit in this syndrome. The sensorimotor assessment itself is easily administered and takes a short amount of time. Engagement with the task was good, with participants across ages and abilities able to complete the task reliably.

The sensorimotor measures are restricted in that they only involve fine motor skills, as they only require interaction with stimuli on a tablet computer with a stylus. This means that the most directly comparable skills involve using similar tools, such as pen or pencil on paper for drawing or writing. Although there was some evidence that, tracking performance is associated with ability to hit a ball, and that jerkiness of movements is related to overall clumsiness in children with 22q11.2DS it is still unclear how generalizable the sensorimotor deficits shown here are to other gross motor skills. Although characteristics of joint level movement such as the elbow and shoulder were not directly recorded, they will influence the movement of the hand. Further work should include more detailed kinematic assessment of different skills, such

as reaching and grasping, gait and postural control to help build a picture of other key motor skills that are required for daily functioning in individuals with this deletion.

I did not find any evidence for an association between sensorimotor difficulties and psychopathology. This contrasts with the links seen in Chapter 3 where poorer coordination was associated with higher numbers of psychopathology symptoms. Reasons for the difference in findings may include the smaller sample size of children who completed the sensorimotor measures. This smaller sample size may have restricted our power to be able to detect associations between psychopathology or cognition and sensorimotor performance. As the ECHO study is currently ongoing, data collection is continuing.

The age range covered by the study was wide (range 6-19 years) and included a period of significant physical and psychological development. Although I did correct for age in the analysis, I cannot completely rule out that changes in development are affecting the results presented here. Performance on the CKAT tasks is related to age, with performance improving as individuals age. Further work to profile the development of performance on these tasks should be undertaken, along with longitudinal assessment of individuals to make it clearer whether and how deficits in sensorimotor skills improve over time and at the same rate as in children without the syndrome. While there are some descriptions of motor abnormalities in adults with 22q11.2DS, I am not aware of any kinematic studies of the quality of movement in adults with the syndrome. It is not clear if these deficits persist into adulthood.

Little is known about the control of eye movements in 22q11.2DS. It is possible that the children have difficulty with motor coordination and with the sensorimotor tasks specifically due to deficits in ability to follow moving targets with the eyes. Problems with visual

perception have been demonstrated in individuals with 22q11.2DS, which may also influence their ability to perform the sensorimotor tasks. To what extent eye movement problems contribute to their motor difficulties is an important topic for future research.

Similarly, medical conditions such as hypo-or hypertonia can influence the ability of children to grasp objects such as the pen like stylus used to complete the sensorimotor tasks. Confounding conditions like these would be detected through neurological examination. Unfortunately, I was unable to carry out neurological examinations on these children to exclude the presence of any other neurological deficit that could impact their ability to perform the tasks.

Finally, the number of comparisons carried out in the current study is very large due to the number of cognitive and sensorimotor variables included. Therefore, some of the weaker associations found, such as between FSIQ and tracking ability ($p=0.037$), would not survive multiple testing correction. Multiple testing correction was not carried out as this was an exploratory study and the associations found should be viewed as potential targets for further research in order to verify if they are true.

4.6 Conclusions

In this chapter, I have presented objective kinematic evidence for fundamental sensorimotor deficits in tracking, aiming and steering ability in children with 22q11.2DS compared to unaffected sibling controls. These deficits cannot be completely explained by the IQ of the child, but are related to performance in neurocognitive domains such as attention, planning and spatial working memory. I found no evidence that sensorimotor performance is related to ADHD, ASD or anxiety symptoms in the syndrome. It is unclear how these fundamental

sensorimotor deficits are related to the functional deficits in coordination as established with the DCDQ individuals with 22q11.2 deletion syndrome (Chapter 3). Further work should be undertaken to better outline the profile of fundamental sensorimotor deficits in the syndrome, across all ages and in other skills, such as postural control and gait. This could help understanding of the development of these sensorimotor skills in the syndrome and if they do influence development of other aspects of the syndrome such as cognitive skills or psychopathology. In addition, it would be useful to investigate if sensorimotor difficulties are a feature of other copy number variant disorders that convey risk for neurodevelopmental and psychiatric disorders.

4.8 References

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5 Occupational therapy assessment of coordination and a pilot intervention for coordination difficulties in 22q11.2 deletion syndrome.

5.1 Chapter overview

In previous chapters, I have demonstrated that children with 22q11.2DS have coordination difficulties that can be measured using a parental response questionnaire and that there are concurrent deficits in fundamental sensorimotor skills. Questionnaires and screening tools such as the DCDQ are well suited for assessing the functional impact of motor difficulties but are less able to give specific information about individual domains, or skills that an individual finds difficult. In addition, it is unclear if the DCDQ was correctly assigning children with 22q11.2DS with coordination difficulties. To address this, a more detailed and direct movement assessment was required. In this chapter, I describe a more detailed motor assessment of ten children with 22q11.2DS who screened positive on the DCDQ for coordination difficulties. I worked together with the Cardiff University Occupational Therapy Clinic in order to be able to administer several "gold-standard" (i.e. measures currently regarded as part of best practice in OT settings) and well-validated measures. These included the Movement Assessment Battery for Children to establish overall motor coordination, as well as the Beery Visual Motor Integration battery to investigate problems with visual perception, and communication between visual and motor systems. I found that eight of the ten children with 22q11.2DS who screened positive on the DCDQ had severe difficulties with coordination, and that mean visual perception and visual motor integration scores indicated problems with visual perception and communication between visual and motor systems. I also describe a pilot intervention study where two of the 8 children with severe coordination difficulties attended ten one hour sessions of therapy with the occupational therapists, in order to improve performance on functional

goals identified by the children and their parents. Descriptive and qualitative improvements were observed in both children. The findings provide further evidence that many children with 22q11.2DS experience serious motor problems and highlight the need for more research in designing motor interventions for this population.

5.2 Chapter acknowledgements

As this chapter involved collaboration with occupational therapists and input from Prof. Monica Busse, it is appropriate to gratefully acknowledge their contributions. The occupational therapists Sue Delport and Wendy Cumines performed all Movement ABC, Beery VMI, and Canadian Occupational Performance Measure (COPM) interviews. They also carried out the weekly treatment sessions with the participants. They were supported by Occupational Therapy students employed as research assistants. Prof. Monica Busse helped design the pilot trial structure and helped in the selection of assessments and outcome measures. I carried out all recruitment, ADHD and anxiety symptom data collection, neurocognitive data collection, questionnaire data collection, assisted in assessment sessions where necessary and completed all data analysis.

5.3 Introduction

Proper coordination of movement is required for most tasks of daily life. Seemingly simple tasks that we carry out every day such as dressing, washing and working, are much more problematic for individuals with coordination difficulties. Traditionally, if coordination difficulties are suspected in a child, they can be assessed through clinical services, such as an occupational therapy clinic. These services use well-validated movement assessments to collect information about an individual's performance in different domains of coordination such as balance, fine motor skills, or catching that are required for many functional tasks. In

combination with information about the individual's ability to function in daily life and any impact that coordination difficulties might have on functioning, the child may be diagnosed with a movement disorder such as developmental coordination disorder. This diagnosis helps to enable the individual to access support through health services, hopefully resulting either in the improvement of their coordination ability, or the implementation of strategies to ameliorate the difficulties.

As has been discussed throughout this thesis, children with 22q11.2DS are at risk of difficulties with coordination that span fine motor and gross motor skills. In the previous chapters, I have demonstrated that a very high percentage of children with 22q11.2DS screen positive for coordination difficulties using a parental response questionnaire (Chapter 3) and that they are also likely to have fundamental deficits in sensorimotor skills, assessed with a computer-based task (Chapter 4). In addition, I demonstrated that the sensorimotor skills did not correlate well with the DCDQ total scores (see Section 4.4.1.5). There are many potential reasons for this, the simplest being that the DCDQ and sensorimotor measures are measuring different aspects of motor ability. The DCDQ is a parental response questionnaire that asks about the outward appearance of coordination deficits, while the sensorimotor tasks are much more direct measures of sensorimotor skill, which may be more likely to reflect underlying brain pathways. Due to this lack of association between the sensorimotor tasks and the DCDQ score, more information about the accuracy of assignment of diagnosis using the DCDQ was desired. In addition, if coordination difficulties are a clinically significant feature of 22q11.2DS, finding ways to help children with coordination may be a useful way to improve their daily living experience. There is mounting research that indicates coordination processes are linked to mental wellbeing in children and adults (Kopp, Beckung and Gillberg, 2010; Pratt and Hill, 2011; Kirby *et al.*, 2013; Hill *et al.*, 2016), and I have demonstrated in previous chapters that

psychopathology is associated with poorer coordination. The results of Chapter 3 show that increasing numbers of ADHD, ASD and anxiety symptoms are related to greater difficulties with coordination and that there are extremely high levels of comorbidity in children with 22q11.2DS who meet criteria for DCD. However, links between coordination and psychopathology, including directions of causality, are not well understood. Coordination difficulties can be helped through interventions designed and delivered by occupational therapists. These usually take the form of strategies to mitigate any functional coordination difficulties experienced by an individual, so that a specific skill can be learned. There is no research investigating whether individuals with 22q11.2DS display a homogenous set of coordination deficits. It is also not known what the best methods of helping individuals with 22q11.2 deletion overcome coordination deficits are. Therefore, we wanted to try and design and pilot an intervention to help children with 22q11.2DS with identified coordination difficulties to improve their coordination. We assessed cognition and behaviour before and after a short intervention to investigate whether there were effects on domains outside of the motor skills being targeted by the intervention. This chapter is therefore split into two parts: part one describes the initial assessment of ten children with 22q11.2DS who screened positive on the DCDQ for coordination difficulties in order to validate how well the DCDQ was capturing clinically significant problems in this population, and part two describes a pilot intervention delivered to two children with 22q11.2DS and results of the intervention.

5.4 Part 1: Occupational therapy assessment of coordination in children with 22q11.2DS

Coordination difficulties can be assessed in a variety of ways, which reflects the complexity of relationships between the skills required for coordinated movement, and the impacts of deficits. At the lowest level, individual aspects of movements can be measured, such as velocity, spatial

error, or timing, to provide insight into how fine control over movements can impact functioning. At the highest level, overall disability can be measured, using tools such as the DCDQ, or interview. In between these levels, an individual's coordination can be assessed, usually split into fine or gross coordination, by the performance of tasks that are related to those skills that are normally carried out in daily life. These styles of assessments might ask participants to throw and catch balls, perform balancing tasks, manipulate and construct puzzles, or perform writing. Although these tasks are nominally determined to be "motor" tasks, they are likely to also involve cognitive processes. Previously in this thesis, I have shown that there was little association between the total coordination scores individuals with 22q11.2DS obtained on the DCDQ and performance on a sensorimotor battery (see Chapter 4). The sensorimotor battery was intended to allow investigation of fundamental skills that are thought to underlie coordinated movements such as ballistic aimed movements. This meant it was unclear if the DCDQ was appropriately capturing coordination difficulties in children with 22q11.2DS, and a whether a more detailed coordination assessment was required.

Occupational therapists use well validated, age appropriate and standardised movement assessments to investigate coordination, and rate performance compared to the general population. One of these measures is the Movement Assessment Battery for Children -2 (MABC) (Henderson and Sugden, 1992). This is a widely used measure of coordination that covers three major domains of coordination: aiming and catching manual dexterity, and balance. An overall performance score on the MABC below the 5th percentile would signify that an individual has severe coordination difficulties that would require intervention. A score below the 15th percentile would indicate some problems that might require attention. To help verify that the DCDQ is indeed sensitive to coordination difficulties in our sample of children with 22q11.2DS, we assessed a small subset of children who had screened positive on the

DCDQ using the MABC. This also allowed us to gain more information about the specific difficulties in the domains of manual dexterity, balance and aiming/catching that individuals might be facing.

There are also other confounding factors that may influence a child's coordination. Rather than a specific deficit of motor control, for example, it is also possible that a child is unable to correctly perceive objects using their visual system. This would likely impact on their ability to coordinate movement if the object is the destination target for a movement, or if the object needs to be avoided. Many coordinated movements require efficient communication between the visual and motor systems in order to integrate information from both modalities. An example of when this would be required is copying down pictures or words from a blackboard into a workbook in the classroom. A child must simultaneously accurately perceive the information on the blackboard while instructing their hands to correctly copy the information into their book. Sometimes children can have difficulties with only one aspect of this pathway, either with visual perception, or problems coordinating movement, or there can be a difficulty in using the information provided by each system together.

The Beery Visual Motor Integration battery (Beery, Buktenica and Beery, 2010) allows investigators to separately assess the different systems required when using both visual and motor systems, and can help disentangle whether problems occur in either in the motor system, the visual system, or in tasks that require integration of information between the modalities.
By combining these coordination assessments with information already collected about the children, such as their DCDQ score and IQ, it was possible to better assess if the 10 children that were assessed in the OT clinic met criteria for developmental coordination disorder, using the DSM5 criteria (see Section 1.9 in the introduction). Therefore, the main aim of this part of

the study was to assess if the children who screened positive for DCD on the questionnaire have severe coordination deficits when assessed using a widely used and standardised measure of coordination. Secondly, we also aimed to investigate if difficulties in visual perception or motor integration might better explain the difficulties seen in these children. I hypothesized that children with 22q11.2DS who had screened positive on the DCDQ would have severe coordination difficulties when assessed using a standardised coordination measure, and deficits in performance on visual motor integration task.

5.5 Methods

5.5.1 Participants and procedure

Ten families with a child with 22q11.2DS aged between 5-16, who had previously screened positive for coordination difficulties on the developmental coordination disorder questionnaire (DCDQ), were invited to attend the Cardiff University Occupational Therapy clinic to take part in occupational therapy assessments. Families were recruited as a sample of convenience, from the larger, national ECHO study sample (http://medicine.cardiff.ac.uk/psychological-medicine-neuroscience/areas-research/copy-number-variant-research/research-projects/).

Inclusion and exclusion criteria for the ECHO study are given in the general methodology section (Section 2.1). As families had to attend Cardiff University to take part in the occupational therapy assessments, those families closest to the University were prioritised. Informed written consent was taken from parents/guardians, or the children themselves where appropriate. The assessments were carried out using funding from the Welcome Trust International Strategic Support Fund (ISSF). As one child was screened using the DCDQ outside its normal range of use (5-15 years), numbers of children scoring below the 5th percentile on the MABC are presented with and without this individual included.

5.5.2 Assessments

Previously collected data on full scale IQ and coordination status was used in this analysis. Data were collected using the assessments described in the General Methodology section as part of the ongoing ECHO study. In brief: full scale IQ was obtained using the Wechsler abbreviated scale of intelligence (WASI) (Wechsler, 1999). The developmental coordination disorder questionnaire (DCDQ) (Wilson *et al.*, 2009) was used to screen for coordination difficulties in the overall ECHO sample of individuals with 22q11.2DS from which the current sample was obtained. Age appropriate thresholds were then applied to indicate if scores on the questionnaire meant an individual was likely to have significant coordination difficulties. Information from these assessments was combined with the following assessments carried out in the OT clinic as a part of this study. Full scale IQ was unavailable for one participant as the child did not successfully complete the WASI. Mean time between assessments was 1.71 years. (s.d.=1.17).

5.5.2.1 Movement ABC

The Movement ABC-2 (Henderson and Sugden, 1992) was used to assess gross and fine motor skills in a subset of children with 22q11.2DS. The MABC comprises eight tasks appropriate for specific age ranges, (3-6, 7-10, and 11-16), covering the domains of manual dexterity, ball skills (aiming/catching) and static and dynamic balance. A total, percentile and standardised score can be obtained for each domain, and, in addition, an overall total or standardised score can be generated by combining scores from each domain. Overall percentile scores below the 5th percentile indicate severe coordination difficulties that would warrant intervention and support. Assessments were carried out by the Occupational Therapists.

5.5.2.2 Beery VMI

The Beery VMI (Beery, Buktenica and Beery, 2010) was used to measure visual motor integration and included the full visual motor integration (VMI) form, and the motor and visual forms separately. The VMI form requires the participant to accurately copy drawings of geometric shapes that get progressively more complex. The supplemental visual perception and motor coordination tasks were also administered after the participant had completed the VMI form. The visual perception form requires the participant to choose a geometric shape from a set of similar choices that matches a target shape. The shapes presented get progressively more complex. The motor form requires the participant to trace the interior of geometric shapes without crossing the border of the shape. This subtest requires fine motor control. Administration of the three subtests allowed for the identification of individuals who may have a relatively isolated deficit in either visual perception or motor coordination. One participant did not complete the visual perception and motor coordination forms due to attentional difficulties and refusal. Beery VMI assessment was carried out by the Occupational Therapists.

5.5.2.3 Statistical analysis

Statistical Analysis was carried out in R version 3.3.3. Relationships between DCDQ, MABC, and scores were assessed using Pearson correlations after checking the distribution of variables. Distributions of MABC scores were explored using histograms and tables with a cut-off of a score below the 5th percentile taken to indicate severe coordination difficulties. I carried out all statistical analysis.

5.6 Results

Table 5-1 Mean age, FSIQ and gender distribution of participants who attended the occupational therapy clinic for assessments. FSIQ was unavailable for three participants.

Mean Age (sd)	**12.53 (2.86)**
Mean FSIQ (sd)	72.22 (9.11)
% Female	40% (4/10)

5.6.1 Movement ABC

When the ten participants who had previously screened positive for coordination difficulties on the DCDQ were assessed with the MABC, we found that eight children had overall scores that fell below the 5th percentile, indicating severe coordination difficulties. Their scores indicated that these children had serious problems in most domains of motor functioning, including fine motor skills, gross motor skills and balance. Four children had scores below the 5th percentile in the aiming/catching domain, five had scores below the 5th percentile in the balance domain, and four had scores below the 5th percentile in the manual dexterity domain. Overlap of children scoring below the 5th percentile in each domain is shown in Figure 5-1. Two children fell below the 5th percentile in both the aiming/catching and balance domains. One child fell below the 5th percentile in both the manual dexterity and balance domains. One child fell below the 5th percentile in all three domains. All children fell below the 15th percentile in overall score, indicating that coordination ability is below average. Of the two children who did not fall below the 5th percentile in overall score, both performed at the 5th percentile for manual dexterity, and one at the 0.5th percentile for aiming/catching. Exclusion of the child who was screened on the DCDQ above the age of 15 resulted in eight of nine children having overall scores below the 5th percentile on the MABC, and three of nine scoring below the 5th percentile on aiming and catching, four of nine scoring below the 5th percentile on the manual dexterity domain, and five of nine scoring below the 5th percentile on the balance domain.

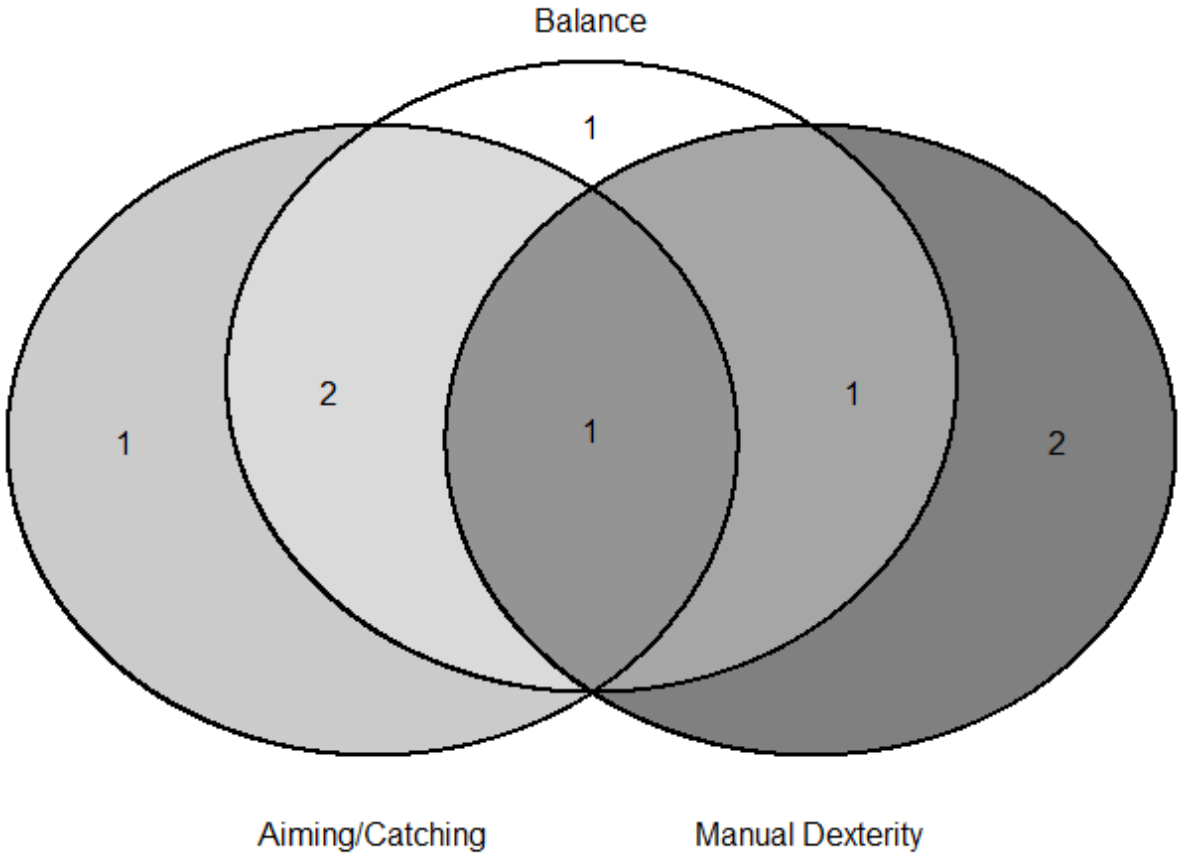
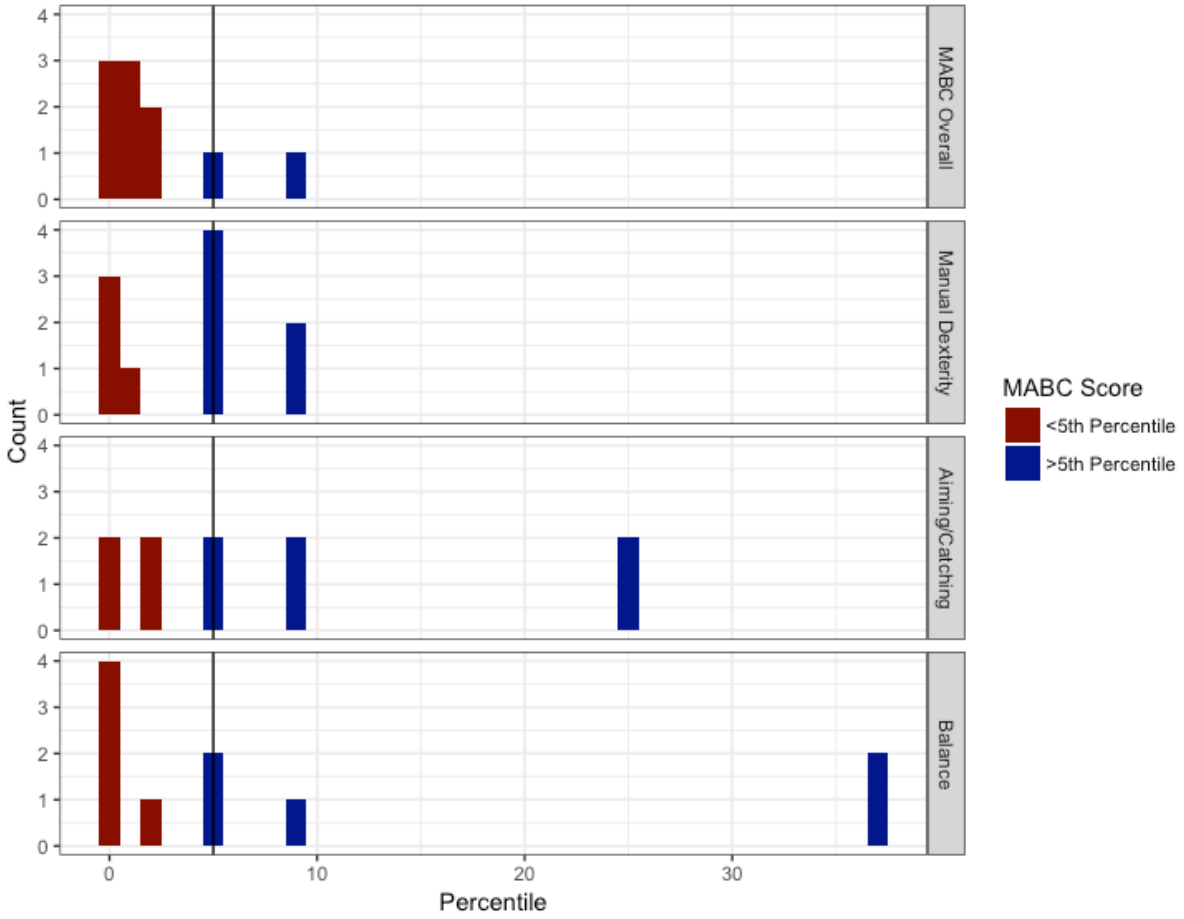


Figure 5-1. Overlap of individuals scoring below the 5th percentile on each of the Movement ABC domains

Table 5-2. Distribution of movement ABC (MABC) percentile scores across domains assessed in children with 22q11.2DS. The black vertical line indicates the 5th percentile.



Movement ABC standard scores and DCDQ scores were associated with each other, such that lower DCDQ scores were associated with lower MABC standard scores (r=0.69 p=0.026). Out of the three MABC domains, only standard scores in the balance domain were associated with DCDQ scores (r=0.79, p=0.007), with lower standard scores in the balance domain being associated with lower DCDQ scores. Standard scores in the aiming/catching (r=0.13, p=0.725) and manual dexterity domains (r=0.30, p=0.401) were not associated with DCDQ scores. MABC standard scores were not associated with the FSIQ of the child (r=0.33, p=0.430).

5.6.2 Beery VMI

Using the Beery VMI to assess visuomotor integration we found that mean visual motor integration and visual perception scores were "low" (more than 2SD below average, 72.5 and

74.1 respectively), while motor coordination scores were “below average” (1-2SD below average, 83.25). The average score for the general population is 100. This would suggest that children with 22q11.2DS have problems in communication between visual and motor systems and that there are deficits in visual perception. In agreement with the MABC data presented in section 0, they also have difficulties with fine motor skill, although to a lesser degree than in visual motor integration or visual perception. The distribution of scores for the three subtests is shown in Figure 5-2. The fine motor skill deficits indicated by the Beery VMI may be in line with what would be expected given lower FSIQ in these participants, as mean IQ is also between 1-2 SD below the general population average. However, in the group of 10 individuals with 22q11.2DS, VMI score was not associated with FSIQ ($r=0.24$, $p=0.565$), nor was motor coordination score ($r=0.59$, $p=0.167$). However, visual perception score was correlated with FSIQ ($r=0.83$, $p=0.020$) and verbal IQ ($r=0.87$, $p=0.005$), but not performance IQ ($r=0.15$, $p=0.715$).

None of the Beery VMI outcome measures were associated with MABC score.

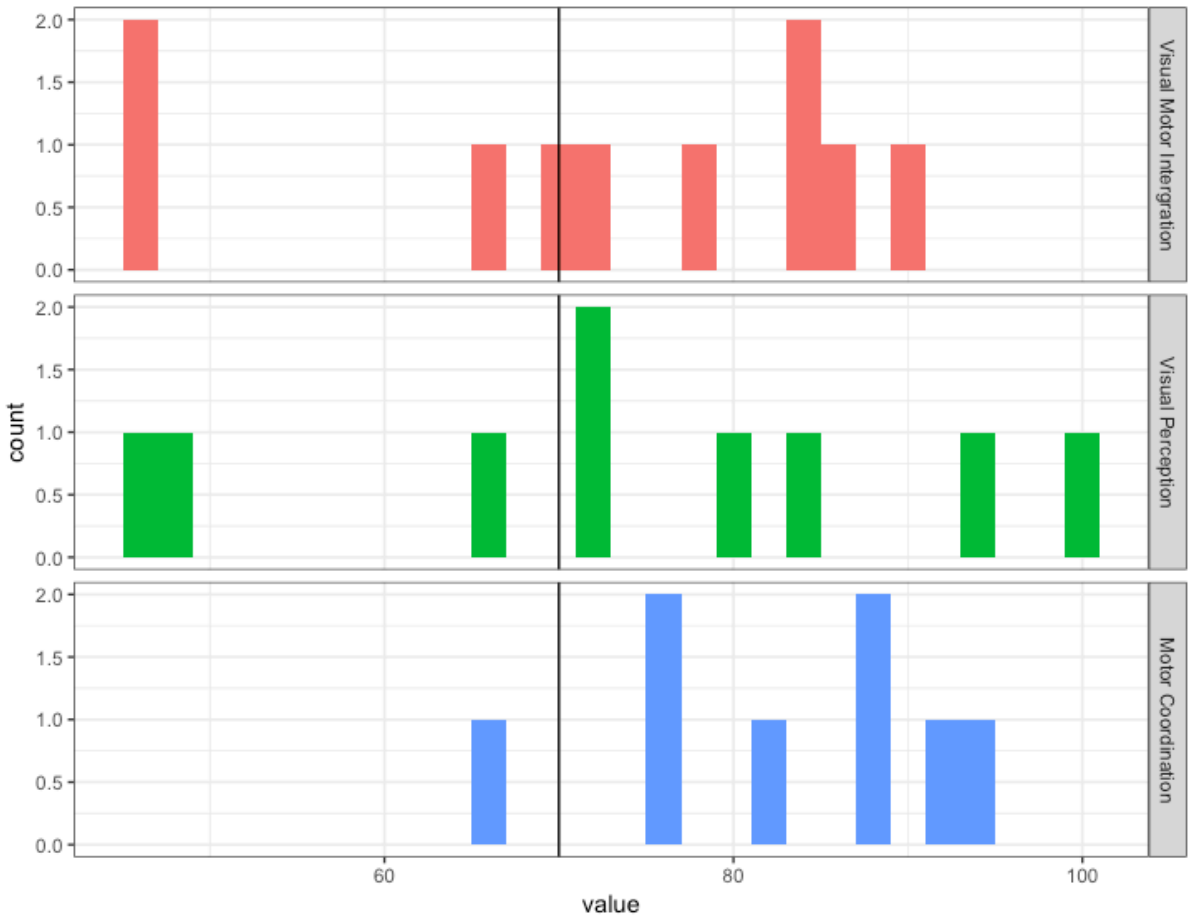


Figure 5-2. Distribution of Beery VMI scores. Black vertical line indicates two standard deviations below average

5.7 Discussion

The current study carried out a detailed assessment of coordination using "gold standard" assessments, in a small sample of children with 22q11.2DS. We found that eight of the ten children assessed using the MABC had overall scores below the 5th percentile, indicating severe coordination difficulties. The remaining two children had MABC scores that fell below the 15th percentile, indicating that their coordination performance was below average. Assessment of visuomotor integration indicated that the children had difficulties with both integration of motor and visual information and visual perception. They also displayed less severe deficits in fine motor coordination using the motor coordination subtest of the VMI.

The results of the MABC support the other evidence in this thesis of coordination deficits in children with 22q11.2DS. They also agree with previous work investigating coordination difficulties in the syndrome, where specific deficits in balance and manual coordination have been found (Van Aken *et al.*, 2009, 2010; Roizen *et al.*, 2011). Our results also found that balance was the most common deficit, as measured by the MABC. However, performance on individual domains of the MABC was variable, with no single domain emerging as consistently affected. This evidence suggests that much like the psychiatric and cognitive phenotype in 22q11.2DS, there is also considerable variability in the motor phenotype.

Importantly, for most participants, coordination performance was below what would be considered given their lower IQ. Mean IQ for the sample assessed was just above the borderline range, between one and two standard deviations below average, while overall scores on the MABC were greater than two standard deviations below average. MABC standard scores were also not correlated with the FSIQ of the child, indicating children with different IQs had similar levels of motor problems. This may suggest that the coordination difficulties are in excess of what would be expected given their IQ, which is one of the diagnostic criteria for DCD according to the DSM-5 (American Psychiatric Association, 2013).

One of the primary aims of these assessments was to investigate if the questionnaire based assessment of coordination, the DCDQ assessment reported earlier in Chapter 3 was adequate in capturing the coordination deficits seen in children with 22q11.2DS. As such, all of the ten participants assessed with the MABC in the current study had screened positive on the DCDQ for coordination difficulties. The high rate of severe coordination difficulties detected by the MABC (8 of 10) suggests that the DCDQ is sensitive to coordination difficulties in this population. In addition, scores on the MABC were well correlated with scores obtained on the

DCDQ, with this relationship mainly driven by scores on the balance domain. Together these results provide evidence for the validity of screening for coordination difficulties in large populations such as patients with 22q11.2DS using this questionnaire. By combining the information obtained on the MABC with the DCDQ scores collected previously, which give a good indication of any impact coordination difficulties are having on daily life, we could conclude that the children screening positive for indicated DCD on the DCDQ are likely to score below the 5th percentile on the MABC.

The assessment of visual motor integration aimed to identify if coordination deficits were purely in the motor domain, or are also influenced by problems with visual perception or being able to combine information from the visual and motor systems. The current results suggest that there are deficits in visuomotor integration and visual perception compared to the general population. Deficits in visual perception have been demonstrated previously in individuals with 22q11.2DS compared to community age and IQ matched controls, using the VMI in one other study (Van Aken *et al.*, 2009), while no deficit in visuomotor integration compared to IQ matched controls was seen in two studies using the VMI in children with 22q11.2DS (Van Aken *et al.*, 2009; Roizen *et al.*, 2011). Thus, children with 22q11.2DS have problems in these domains, but they may not be elevated compared to children with similar levels of intellectual disability. Taking the current results, with evidence from previous studies it would seem likely that difficulties with visual perception and visuomotor integration are influencing problems with coordination to a currently unknown degree, along with deficits in motor control, as demonstrated by the poor performance on the MABC, and sensorimotor tasks as shown in Chapter 4. Similar to the wide range in performance on many other measures in individuals with 22q11.2DS, performance on the VMI was variable, with some individuals showing large

deficits in visual motor integration or visual perception, and others scoring close to the population average (Figure 5-2).

As we were not able to collect information from an IQ matched control group, we cannot directly say if the deficits seen in visuomotor integration and visual perception are broadly in line with what would be expected given the lower IQ of the population. However, both mean visual integration and visual perception scores were more than two standard deviations below the average of the general population, while the mean FSIQ of the group is above two standard deviations below the average. In addition, only the score on the visual perception subtest was associated with full scale IQ, providing supporting evidence that motor coordination and visuomotor integration is not directly related to the child's IQ in this group.

Overall the evidence from the current study shows that the coordination difficulties experienced by children with 22q11.2DS are severe and affect multiple domains of coordination. Concurrent deficits in visual perception and visuomotor integration may also be contributing to these coordination difficulties. Like elsewhere in this thesis, the results also suggest that coordination difficulties are not directly related to the IQ of the child, and may be better considered as a separate aspect of the syndrome.

5.8 Part 2: Pilot intervention for coordination difficulties in 22q11.2DS

In previous chapters and this chapter, I have demonstrated that individuals with 22q11.2DS have high rates of coordination difficulties. In the previous sections, I was able to validate that individuals screening positive for coordination difficulties on the DCDQ are likely to have poor coordination when assessed using the MABC. The DCDQ indicates that individuals have quite severe difficulties in coordination that are likely to affect daily functioning in the domains of productivity, play and social ability. Poor coordination is likely to have a substantial impact on

all aspects of daily life and may compound other difficulties experienced by an individual. In addition, stress can be caused in the family environment as poor coordination increases the amount of attention required for daily care activities from parents. In this thesis, I have shown that ADHD, ASD and anxiety are closely linked to coordination difficulties as measured by the DCDQ, in children with 22q11.2DS, but I have not been able to make inferences on causality. For example, it is unclear if increased anxiety is a result of worry about performance in front of peers due to clumsiness, social exclusion due to clumsiness, or if anxiety causes reluctance to take part in opportunities to practise motor skills, resulting in poorer coordination. Indeed, it may also be that shared brain pathways underlie both coordination difficulties and increased anxiety in children with 22q11.2DS.

If clumsiness is increasing the risk of development of other psychopathology, then interventions to improve confidence and coordination ability may have positive impacts outside of the immediate outcome of improving coordination. Little to no research has been carried out on the design and implementation of interventions to improve coordination in populations with 22q11.2DS or other copy number variant disorders.

If children with 22q11.2DS have coordination difficulties that are very similar to those seen in DCD, then a targeted, patient focused occupational therapy led intervention may be able to have a positive impact on difficulties that are identified by the children and their parents or guardians.

This study had two main aims, to explore the impact of coordination difficulties on everyday life in children with 22q11.2DS and determine the effect of an occupational therapy led intervention in a small group of participants with 22q11.2DS, not only on coordination but also

on concurrent psychopathology (ADHD/Anxiety) and cognitive performance. In order to achieve this, a small group of children with 22q11.2DS were invited to take part in a programme of intervention involving ten, ideally weekly, sessions lasting an hour with occupational therapists. This intervention was designed to identify areas of daily living that the carers/children thought were problematic and design goals to work towards that would improve these areas. Impact on other areas including psychopathology, particularly ADHD and anxiety symptoms, behaviour, executive function, attentional skills, spatial working memory, and fundamental sensorimotor skills were also assessed.

5.9 Methods

5.9.1 Participants and procedure

After completing the initial coordination assessments and being assigned a research diagnosis of DCD, four families with children with 22q11.2DS who took part in the coordination assessments were invited to return to the occupational therapy clinic to attend 10 one-hour sessions of therapy with the occupational therapists, with the aim of improving performance on particular skills. Due to the requirement of being able to attend the university regularly, those families living closest to the university were given priority. Of the four families invited, only two could commit to completing the intervention sessions. Therefore, only two children took part in the intervention. Inclusion and exclusion criteria were the same as the larger ECHO study and are given in the general methodology chapter. The children were both male, aged 9.34 and 13.48 years, with DCDQ scores of 37 and 17 respectively.

5.9.2 Assessments

5.9.2.1 COPM

The Canadian Occupational Performance Measure (COPM) (Law *et al.*, 2014) is a semi-structured interview designed for use by occupational therapists to identify issues that are important to patients and detect changes in perception of functioning and performance in daily life over time. It can also provide the basis for setting goals to work towards during intervention. It is designed to be used as an outcome measure and was therefore administered before and after the intervention to detect any change in daily functioning. The COPM was used to explore difficulties the children experienced due to motor coordination on daily living skills, productivity, leisure and play, and to identify goals that the children and parents thought were important to improve. In addition to the subjective data that the COPM provides, participants can use a rating scale to indicate how well they are performing the skill and their satisfaction with their performance. Change scores can be calculated by comparing ratings before and after the intervention. This can give an indication of the clinical effectiveness of an intervention, with a change score of two points or more considered clinically important (Law *et al.*, 2014). Interviews were conducted in the Cardiff University Occupational Therapy Clinic with the parent/guardian and child simultaneously. All interviews were conducted by the Occupational Therapists Sue Delport and Wendy Cumines, and audio recorded. One audio recording was lost due to a failure of the audio recorder.

5.9.2.2 Movement ABC

The age appropriate version of the movement ABC was administered before and after the ten intervention sessions. In one child (Child A) this meant that the MABC completed after the intervention was appropriate for the next age bracket, resulting in tasks that were slightly more difficult.

5.9.2.3 PEDI-CAT

The Paediatric Evaluation of Disability Inventory, Computer Adaptive Test (PEDI-CAT) (Haley, Coster, Dumas, et.al, 2012) is a computerised questionnaire designed to collect information about daily functioning and disability. It measures ability in three functional domains, daily activities, mobility, and social/cognitive. It also includes a responsibility domain, assessing the extent to which the child or caregiver is responsible for managing tasks in daily life that may be complex. The computerised version of the PEDI uses Item Response Theory statistical models to estimate a child's ability, from the minimum number of most relevant items responded to. Each respondent begins with the same item in each domain, representing the middle of the difficulty range or responsibility range, and the response to this item decides which item will appear next. This allows the questions to be tailored to the child and avoid irrelevant items. The PEDI-CAT was administered to the parent, before and after the ten intervention sessions to measure any changes in disability in the three functional domains or changes in the balance of responsibility taken by the parent and child.

5.9.2.4 Psychopathology assessment

Dimensional psychopathology was assessed using the strengths and difficulties questionnaire (SDQ), to give a broad measure of difficulties, which is sensitive to change, along with ADHD and Anxiety symptoms as assessed by the Child and Adolescent Psychiatric Assessment (CAPA), as these disorders were shown to be associated with coordination as measured by the DCDQ (Chapter 3). A brief description of assessments is given below, with a full description of the CAPA presented in the General Methodology section (Section 2.3).

5.9.2.5 SDQ

The Strengths and Difficulties Questionnaire (SDQ), is a dimensional measure of behaviour containing questions about emotional symptoms, conduct problems, hyperactivity/inattentive symptoms, peer relationship problems and prosocial behaviour. A score for each subscale for these five domains can be obtained, along with a total difficulties score generated by combining the emotional symptoms, conduct problems, hyperactivity/inattention and peer relationship problems together. The SDQ was completed by the parent before and after the ten intervention sessions. In the first instance, the SDQ included an impact supplement. This included questions asking if the respondent thinks the subject of the questionnaire has a problem(/s), and if so asks about how long the difficulties have been present, whether they think they distress the child, if the difficulties impact on daily life, including in home life, friendships, classroom learning and leisure activities, and to what extent the difficulties put a burden on the respondent or family as a whole. Post intervention sessions, we also included a set of follow up questions from the SDQ. These asked if the intervention had reduced problems and if the intervention helped in other ways, for example by providing information, or making problems more bearable.

5.9.2.6 CAPA

As described in more detail in the General Methodology, the Child and Adolescent Psychiatric Assessment (Angold *et al.*, 2009) is a semi-structured interview designed to assess psychopathology in children and enables assignment of research diagnoses. For the intervention study, the ADHD and anxiety sections of the CAPA were completed by the parent before and after the ten intervention sessions in order to assess changes in psychopathology over the time period. These interviews were conducted by myself with the parent and were audio recorded for review and coding purposes. The number of ADHD and anxiety symptoms were calculated before and after the intervention period.

5.9.2.7 Neurocognitive assessment

Aspects of neurocognitive functioning were assessed using The Cambridge Neuropsychological Test Automated Battery. This is a widely used cognitive battery that has norms for children and adults allowing standardised scores to be obtained and is used for neurocognitive data collection in the whole 22q11.2DS sample. Sensorimotor performance was measured using the Clinical Kinematic Assessment Tool (CKAT). This is a sensorimotor battery which allows for detailed assessment of the movement kinematics of participants and is particularly relevant for fine motor skill. This is a short and easy to administer assessment that was used to measure sensorimotor ability in the larger 22q11.2DS cohort.

5.9.2.8 CANTAB

The Cambridge Neuropsychological Test Automated Battery (CANTAB eclipse version 3, Cambridge Cognition Limited, 2006) is a computerised battery of neurocognitive assessments. The children completed the rapid visual processing (sustained attention), spatial working memory and stockings of Cambridge (executive function/planning) tasks pre-and post-intervention in the occupational therapy clinic, in order to assess any changes in cognitive performance after intervention delivery.

5.9.2.9 CKAT

The clinical kinematic assessment tool (CKAT) is a short, portable, computerised kinematic assessment battery that allows measurement of fundamental sensorimotor skills that underlie complex coordinated movements (Culmer *et al.*, 2009). As described in the General Methodology (Section 2.4.2), the CKAT is comprised of three task types, tracking, aiming and steering which probe tracking ability, ballistic movement and force control respectively. The

children completed the CKAT in the occupational therapy clinic pre-and post-intervention to measure any changes in sensorimotor performance after the ten intervention sessions.

Different outcome measures are produced by the different tasks. For the tracking tasks, root mean square error (RMSE) is obtained, which is a dynamic measurement of the distance between the tip of the stylus and the target at any point in time. For the aiming task overall movement time (MT) is measured in seconds, along with the highest peak speed (PS) reached in millimetres per second, the time taken to reach this speed in seconds (TPS), and normalised jerk (NJ) which is a unitless measure of the overall smoothness of a movement. For the steering task, a combined measure of how far away the tip of the stylus is from an idealised reference path, inflated by the percentage deviation in from ideal completion time of 35 seconds called Penalised Path Accuracy (PPA) was calculated (see Section 2.4.2.3 in the General Methodology Section).

5.9.2.10 Statistical analysis

As only two children were able to complete the intervention sessions, statistical analysis is limited to descriptive reporting of scores. For comparison with analysis performed elsewhere in this thesis, RMSE, peak speed, time to peak speed, normalised jerk and PPA were transformed to their reciprocal, and these values are presented in the results.

5.10 Development of the intervention

The COPM interviews completed with the children and carers provided the starting point for identifying goals which the parents and children wanted to work towards. Combined with the information collected as part of the assessment phase, a personalised intervention plan was developed for each child/parent pair. Design of the intervention was based on a logic model

formulated collaboratively with the occupational therapists and Prof. Monica Busse, who helped design the pilot trial structure. Three main categories of evidence based intervention were identified from a review of the literature. Firstly, task oriented approaches which include task specific practice, cognitive orientation and problem-solving. For example, using the Cognitive Orientation to Occupational Performance (COOP) strategy of "goal, plan, do, check" to improve the performance of specific functional goals (Thornton *et al.*, 2016). Second, process orientated approaches – such as identifying and practising some of the underlying motor difficulties, e.g. balance (Sugden, 2007). Third, combined approaches that use aspects of both process orientated and task orientated approaches (Kaiser, 2013). Finally, an additional category was added to the intervention regarding compensatory strategies that were used to improve performance, such as modifying the task, or introduction of aids. Both children attended ten weekly, one-hour occupational therapy intervention sessions at the occupational therapy clinic in order to address the goals that had been identified. The intervention sessions were delivered by experienced occupational therapists, with support from occupational therapy students acting as research assistants.

Using the COPM, four goals were identified for Child A and three goals for Child B. Subsequently, both parents and children, were asked to rate each goal in terms of their importance and current ability to perform the task, using a ten-point rating scale. A rating of one would indicate that the goal was not at all important, or that they were not able to do it at all, while ten would indicate that the goal was extremely important or that they are able to perform it extremely well. Smiley faces were added to the scales to provide an additional visual cue to facilitate the process of rating goals. We attempted to obtain satisfaction ratings from both the parent and child about how well they can perform goals, but the children had difficulty understanding the concept of satisfaction, so these ratings were not recorded.

5.11 Results

After completing the ten intervention sessions, qualitative increases in confidence and problem-solving ability in both children were noted by the occupational therapists delivering the therapy. While objective data were not collected to support this, it is encouraging that the participants both enjoyed the sessions and the families were able to complete the programme of intervention.

5.11.1 COPM improvement

After calculating change scores for each child's goals, I found that Child A had clinically significant change scores (a change in performance score of two or more points) for their goals of "Climb in and out of bath independently" and "Tie own shoelaces" with performance score improvements of nine points and eight points respectively. In addition, Child A's parent indicated a clinically significant change in "do up zips and buttons independently" and "climb in and out of bath independently" with improvements of two and three points respectively.

Child B indicated a clinically significant change in all three of their goals with improvements of seven points for "Tie school tie independently", three points for "play football with family" and seven points for "write legible numbers in maths books". The parent of Child B also indicated clinically significant improvement in all three goals, with improvements of six points for tying school tie, two points for football, and four points for writing numbers. Performance and importance ratings for each child and each goal are presented in Table 5-3.

Table 5-3. Importance and improvement ratings for goals identified using the Canadian Occupational Performance Measure.

	Goal 1		Goal 2		Goal 3		Goal 4	
Child A	Do up zips and buttons independently		Climb in and out of bath independently		Manage toilet hygiene on own		Tie own shoelaces	
	I	**P**	**I**	**P**	**I**	**P**	**I**	**P**
Pre-intervention								
Child Rating	2	1	3	1	1	1	10	2
Parent rating	9	3	10	4	10	1	10	2
Post intervention								
Child Rating	U	2	U	10	U	1	U	10
Parent Rating	9	7	10	3	10	4	10	10
Child B	Tie school tie independently		Play football with family		Write legible numbers in maths books			
	I	**P**	**I**	**P**	**I**	**P**		
Pre-intervention								
Child Rating	10	1	10	5	10	1		
Parent rating	7	3	6	3	9	3		
Post intervention								
Child Rating	7	10	6	8	1	10		
Parent Rating	7	9	7	5	7	7		

P: performance score, I: importance score, U: unable to answer.

5.11.2 Movement ABC improvement

Using the MABC to assess coordination before and after the intervention sessions, we found an increase in the balance domain for both children, with one child improving from the 0.5th percentile to the 16th percentile and the other from the 0.1st percentile to the 0.5th percentile. Child B improved on the overall score from the 1st percentile to the 5th percentile, mainly driven by the increase in balance score. Overall scores remained at or below the 5th percentile for both children suggesting that severe difficulties are still present. Results of the MABC assessments can be seen in Table 5-4.

Table 5-4. Results of Movement ABC assessment pre-and post the 10 intervention sessions. Improvements on the balance task were seen in both children. MD, Manual Dexterity, AC, Aiming/Catching, %ile, Percentile.

Child	Session	Overall Score	Overall (%ile)	MD Score	MD (%ile)	AC Score	AC (%ile)	Balance Score	Balance (%ile)
A	Pre	2	0.5	3	1	6	9	1	0.1
A	Post	1	0.1	2	0.05	3	1	2	0.5
B	Pre	3	1	6	9	5	5	2	0.5
B	Post	5	5	6	9	3	1	7	16

5.11.3 Sensorimotor skill

Sensorimotor skill was assessed using the CKAT battery. This allows for the measurement of ability to track a moving target, make fast ballistic aimed movements and complete a steering task accurately. Child B did not successfully complete the steering task in the pre-intervention assessment session due to difficulties in maintaining attention and refusal to complete the task. Child B had received a research diagnosis of ADHD as a result of the larger ECHO study phenotyping.

For the tracking task, Child A showed increased performance in the medium and fast states when no spatial guide was presented. However, performance in the slow state was better during the pre-intervention assessment than after. Child B showed improvements at all speeds when no spatial guide was presented. When a spatial guide was presented, Child A showed no improvement at Slow or medium speeds but did improve at the fast speed. Child B showed improvements at all speeds when the spatial guide was available. A plot of tracking performance by session and guide state for each participant is shown in (Figure 5-3).

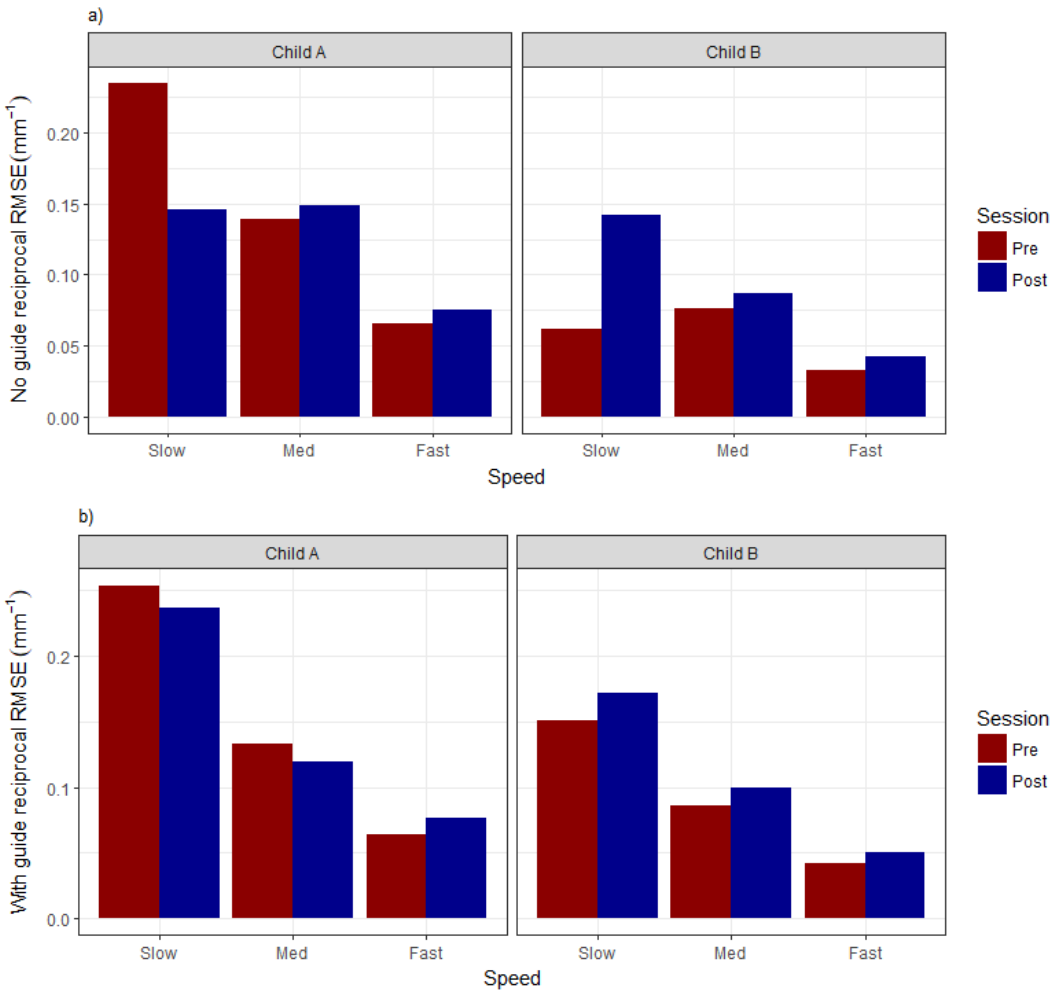


Figure 5-3. Performance on the tracking task of the CKAT for Child A and Child B, before and after intervention sessions. a) shows performance with no spatial guide, and b) shows performance with a spatial guide presented. Higher scores indicate better performance.

In the aiming task, Child A showed higher peak speed, increased reciprocal time to peak speed and increased reciprocal normalised jerk. Combined, these metrics would suggest an increase in the smoothness of the movements made, which may suggest a better ability to make prospective control movements. Child B showed mixed results on the aiming task with, lower post intervention peak speed, but increased reciprocal time to peak speed and reciprocal normalised jerk. In both children, the overall time to make the movements (MT), which can also be taken as a crude measure of performance on the aiming task, decreased in both participants (as evidenced by increased reciprocal movement time). Results are shown in Table 5-5.

Table 5-5. Aiming task performance for Child A and Child B pre-and post-intervention. PS, peak speed, TPS, Time to peak speed, NJ, Normalised jerk, MT, Movement time, SD, standard deviation.

	Session	PS (mm/s)	SD	TPS (s^{-1})	SD	NJ	SD	MT (s^{-1})	SD
Child A	Pre	278.57	327.11	1.82	0.31	0.004	0.004	1.49	0.74
Child A	Post	410.33	262.84	2.17	0.39	0.005	0.005	1.82	0.39
Child B	Pre	425.86	184.20	1.61	0.34	0.003	0.004	1.53	0.68
Child B	Post	382.07	95.35	1.82	0.26	0.004	0.004	1.75	0.56

For the steering task Child, A showed increased performance, with a higher reciprocal PPA. Child B did not complete the steering task during the pre-intervention session due to difficulties with attention, and refusal to complete the task. Post intervention they successfully completed the task.

Table 5-6. Steering task performance for Child A and Child B pre-and post-intervention. Reciprocal PPA is a unitless measure of spatial accuracy, adjusted to standardise for individual variation in speed. Higher values indicate better performance. PPA: penalised path accuracy.

	Session	Reciprocal PPA
Child A	Pre	0.846
Child A	Post	0.971
Child B	Pre	NA
Child B	Post	0.684

5.11.4 Strengths and difficulties questionnaire

Difficulties that the children were experiencing in the domains of emotional symptoms, conduct problems, hyperactivity/inattentive symptoms, peer relationship problems and prosocial behaviour were assessed using the SDQ, before and after the ten intervention sessions. Post intervention, overall difficulties scores decreased in both children, from 27 points to 24 in Child A, and 14 to 12 in Child B. Both children had impact scores in the "very high" range pre-and post-intervention, indicating that the parents thought that the children were still experiencing difficulties and these difficulties were negatively impacting daily life. However, both parents indicated that they thought the intervention sessions had been helpful. This help

was mainly indirect, by providing more information about what could be done and how to help their children.

5.11.5 Neurocognitive testing

Using the CANTAB battery of neurocognitive tests, performance on the stockings of Cambridge, rapid visual processing and spatial working memory tasks were assessed before and after the ten intervention sessions. An increase in the number of problems solved in the minimum number of moves on the stockings of Cambridge task was observed in both participants. This task is an assessment of executive function and planning ability. An increase in spatial working memory task performance, for both between errors and strategy score, was also seen in Child A. Child B did not successfully complete the rapid visual processing task in the pre-intervention assessment session due to difficulties in maintaining attention. They successfully completed the task in the post intervention assessment session.

Table 5-7. Performance on the Stockings of Cambridge, rapid visual processing and spatial working memory tasks for both participants before and after the intervention sessions.

	Session	SOCProb	RVPA	SWMer	SWMStrat
Child A	Pre	0.39	-1.83	-0.46	0.05
Child A	Post	0.69	-2.7	-0.21	0.25
Child B	Pre	-2.01	NA	0.22	-1.11
Child B	Post	-1.52	-1.1	-0.45	-1.11
SOCProb, Stockings of Cambridge, problems solved in minimum moves, RVPA, rapid visual processing, SWMer, Spatial working memory between errors, SWMStrat, Spatial working memory strategy score.					

5.11.6 Pedi-Cat

The PEDI-CAT is a dimensional measure of disability covering the areas of daily activities, mobility, social interaction and responsibilities and was administered to the parents before and after the ten intervention sessions. We observed improvements in the responsibility score in Child B, and increases in the daily activities, mobility and social scores in Child A. Results of PEDI-CAT assessment are shown in Table 5-8.

Table 5-8. PEDI-CAT assessment scores for each child.

	Session	Daily Activities	Mobility	Social	Responsibilities
CHILD A	Pre	52	48	64	47
CHILD A	Post	53	62	65	43
CHILD B	Pre	58	70	65	48
CHILD B	Post	58	66	65	51

5.11.7 CAPA- attention and anxiety Symptoms

The CAPA was completed with the primary carer before and after the intervention sessions in order to assess ADHD and anxiety symptoms. A decreased number of anxiety symptoms were endorsed by the parent of Child A, from 32 to 30 symptoms. In addition, the parent of Child B endorsed one anxiety symptom pre-intervention, and no anxiety symptoms post intervention. The mother of Child B also identified a decrease in the number of ADHD symptoms experienced by Child B, with a decrease from eight symptoms to five symptoms, these symptoms were all inattentive symptoms. The mother of Child A, however, described one additional hyperactivity symptom post intervention.

5.12 Discussion

There is little to no previous research on how to best help children with 22q11.2DS and coordination difficulties. Here I have described the design and implementation of an intervention for coordination difficulties in two children with 22q11.2DS. We selected assessments of functioning, psychopathology, coordination and motor control as these areas are important for daily life and establishment of a diagnosis of coordination difficulties. Qualitative improvements in self-confidence and problem-solving strategies were noted by the occupational therapists working with the children, in addition to improvements in goal performance as indicated by both parents and the children themselves. Both children showed general improvements in tracking ability, particularly at faster target speeds, and one child

showed an improvement in performance at aimed movements. Both children also showed an increase in performance on the stockings of Cambridge task, completing more problems in the minimum number of moves. While the overall scores on the SDQ of difficulties experienced by the children stayed high, parents indicated that the intervention sessions had been helpful by providing information and support on how to better deal with the coordination difficulties that their children experienced. Both parents also endorsed fewer psychopathology symptoms on the CAPA post intervention, which may point towards the intervention helping in areas outside of coordination.

Goal directed therapy allows individuals to work towards improving specific skills that are problematic and have important impacts on daily life or functioning. Overall, the children indicated that they felt they had improved in performance of at least some goals, with change scores above the two-point threshold of clinical significance as described by the COPM manual. However, there was not always agreement between parental and child ratings of performance on tasks, highlighting how different perspectives can influence the perception of performance. For example, one of the goals for Child A was to be able to climb in and out of the bath independently, but while the parent rated this as extremely important with a rating of 10, the child did not feel it was as important and only rated it as three. Subsequently, while the child felt they had improved significantly at this skill, the parent felt there was little change or even a slight decrease in performance. This shows how obtaining ratings, and setting goals with both carers and the children are important. If goals were only set by the parent, the child might not feel they are relevant, or worth working towards, which could hinder engagement with the therapy sessions. Similarly, if only the child is allowed to set goals, more functional skills may not be selected in favour of activities the child enjoys, and the parent may not feel that the therapy is the best use of time.

Using the COPM in this population also presented a few difficulties, mainly around understanding. The children had trouble understanding satisfaction in their ability to perform a skill, so we were unable to obtain satisfaction ratings for the performance of goals. Also, Child A was unable to give importance ratings for goals post intervention, which may mean that their pre-intervention importance ratings are unreliable, as they had difficulty with the concept. Selection of a framework that is inclusive for children of all intellectual levels, or at least can be modified to aid understanding for those with severe learning difficulties may be important. Improvements on the MABC were small, and overall scores remained below the 5th percentile indicating that the children still had severe difficulties with coordination. The intervention sessions were designed to work towards better performance of particular goals or skills. While improving the performance of these skills may involve the parallel improvement of basic skills such as balance, or aiming and catching, these skills may not be directly being practised. As such, the MABC may not be sensitive enough to detect small changes in these skills within individuals.

The pattern of results pre-and post-intervention for sensorimotor skills was also complex. Both participants did not improve on all tasks or outcome measures. Child B showed more consistent improvements across all domains of tracking skill and aiming outcome measures, while Child A showed smaller improvements, or performed worse on some tasks. As is the case with the MABC results, the activities practised as part of the intervention studies are designed with specific tasks and goals in mind, and while improvement in performance of these goals and tasks would be expected, these improvements may not generalise to other more basic skills. There is evidence that training in basic sensorimotor skills does not generalise "upwards" to

more complex tasks, and this is one of the reasons why OT's tend to design interventions around improving performance at specific tasks and goals.

When assessing the difficulties experienced by the children using the SDQ, we found small decreases in overall SDQ scores post intervention, but the parents still felt that the children's difficulties were having large impacts on the children's daily lives. Similarly, although both parents endorsed a slightly decreased number of psychopathology symptoms on the CAPA the overall picture of psychopathology remained the same. Expecting large changes in the psychopathology endorsed was, however, unrealistic in a timeframe of ten weeks. The SDQ is likely a better measure of change in psychopathology in a short timeframe, and had the advantage of including aspects of impact, but is much less specific in the domains of psychopathology.

The parents did indicate that the intervention sessions had been helpful in other ways, particularly in making problems more bearable, or in providing information about how the coordination difficulties can be helped. This stands out as an important outcome of the pilot intervention, that even if direct effects on psychopathology are limited, the intervention process was helpful. Certainly, the children themselves enjoyed the sessions, and the parents found it useful to be able to talk to OT's about the problems difficulties with coordination were causing.

The PEDI-CAT is a dimensional measure of disability including the areas of daily activities, mobility, social interaction and responsibilities. Using this we observed that one child was taking slightly more responsibility after the intervention, as measured by questions asking about the ability to use several functional skills in combination in order to complete tasks of daily life. Examples of this would be remembering to take medication independently, or plan meals. The second child showed small improvements in functioning in daily activities and social interactions. As with the other measures, drawing conclusions from these small changes

is difficult, but may point to some influence of the intervention on areas outside of coordination. As a measure, the PEDI-CAT is easy to use and relatively brief, the parents were able to complete the questionnaire with little assistance. The language used in the questionnaire is quite "American" which proved to be a minor issue, as some questions had limited applicability to the participants.

Performance on the stockings of Cambridge, rapid visual processing and spatial working memory CANTAB task was assessed before and after the ten intervention sessions. Improvements in the number of problems solved in the minimum moves were seen for both participants, and an improvement in spatial working memory between errors and strategy score was seen in Child A. The stockings of Cambridge task is thought to tap into executive function and planning ability, with an improvement in the number of problems solved in minimum moves indicating an improvement in planning ability. Executive function deficits have been demonstrated in non-genotyped individuals with DCD (Wilson *et al.*, 2013), suggesting that coordination and executive functioning may be related. Combined with the qualitative impression of improved confidence and problem-solving ability reported by the Occupational Therapists, this may be an indication that the intervention sessions can have beneficial effects on performance in other areas.

Child A also showed some improvement in the SWM between errors metric, and SWM strategy score. This would suggest some improvement in spatial working memory. Specifically, the between errors metric corresponds to the total number of times a participant touches a box which has already been found to contain a token and indicates how well they have remembered the position of tokens during the task. The strategy score corresponds to how well the participant followed a predetermined heuristic search strategy (Owen *et al.*, 1990). This

strategy comprises following a predetermined sequence by beginning with a specific box and once a token is found, to return to that box to start a new search sequence. Again, working memory deficits have been demonstrated in children with DCD, in both verbal and visuospatial domains (Wilson *et al.*, 2013).

Overall, the pilot intervention showed that it is feasible to use existing strategies for occupational therapy intervention in a population such as children with 22q11.2DS. While we cannot make strong inferences about the effectiveness of the intervention, feedback from the families was highly positive.

5.13 Strengths and limitations of the assessment and intervention phases

As 22q11.2DS is an extremely complex disorder, with many associated symptoms and features, it therefore difficult to identify all individual factors that may contribute to coordination difficulties in individual children. For example, mild skeletal deformities such as club foot or scoliosis may contribute to poor balance or coordination. Similarly, mild neurological problems can also often be seen in these children. Hypotonia is commonly reported in individuals with 22q11.2DS and can persist into adolescence (Bassett *et al.*, 2011). Epilepsy has also been associated with poorer coordination, and there is growing research that children with 22q11.2DS are at increased risk of seizures (Bassett *et al.*, 2011; Kates *et al.*, 2015) and epilepsy (Strehlow *et al.*, 2016). It was not possible to carry out neurological examinations on these children; this means that neurological and other confounding contributions to coordination difficulties cannot be excluded. In addition, there was a gap of 2-3 years between DCDQ screening and assessment of motor difficulties in the OT clinic. In some individuals seen during the assessment phase, parents reported that difficulties had been more severe in the past, but had improved as the children had aged.

The major limitation of the pilot intervention is, of course, the small sample. This highlights some of the difficulty in carrying out research in a relatively rare disorder, most participants in the overall ECHO study do not live within a close enough distance to Cardiff University to allow them to commit to regular travel to the clinic for an intervention. This should be kept in mind for any further development of interventions targeting health issues in 22q11.2DS and other genetic and chromosomal disorders. While the limited results of this pilot are encouraging, it is unlikely that children with 22q11.2DS and coordination difficulties would ever be able to get significant support for coordination problems through the national health service. In addition, it should be noted that all participants in the intervention, along with the occupational therapists carrying out the treatment, were aware that the aim of the sessions was to improve coordination. This means that there may be some bias in the measurements taken by the occupational therapists, or in the parental response questionnaires. However, improvement was seen on the objective computer based tasks, which suggests that bias has not greatly affected the findings of improvement.

Currently, occupational therapy is extremely oversubscribed, with long waiting lists. Groups such as children with 22q11.2DS or other chromosomal disorders are not prioritised for occupational therapy treatment, despite the growing number of identified and diagnosable chromosomal disorders seem to be associated with coordination problems. It may be that any interventions for populations like these will have to be decentralised, with therapists travelling to families, or delivered in a digital or otherwise easily distributable format. This could include online videos of tips and strategies to help with specific skills or information about how to practise component skills such as balance or manual dexterity.

5.14 Conclusions

The results presented in this chapter support the previous evidence of severe motor coordination deficits in children with 22q11.2DS that affect both gross and fine motor skills and have impacts across all domains of daily life. Visual perception and integration of information between visual and motor systems are likely to play a role in the coordination difficulties, but more research should be carried out to identify the specific perceptual difficulties that are experienced by these children. The pilot intervention shows that interventions to help with coordination are possible in populations such as children with 22q11.2DS if designed to respect the complex needs of these individuals. While little firm conclusion can be drawn on the effectiveness of the intervention due to the small sample size, both families greatly appreciated the opportunity to engage with the OT's and discuss the difficulties that their children experience. The children themselves also enjoyed working with the OT's. Future work should focus on expanding intervention studies, ideally with a well-designed trial, to investigate if occupational therapy intervention can have benefits to this population. As a medication free approach, occupational therapy interventions are likely to be popular with families if effectiveness can be demonstrated. Work should also be carried out in finding the best way to deliver the intervention, given the relative rarity of the syndrome and the already high burden of medical appointments that the families have. The number of genetic and chromosomal syndromes that are being diagnosed by genetic services is growing rapidly, and many of these copy number variants have complex phenotypes and carry risk for psychopathology. Therefore, finding efficient and effective ways to help with coordination difficulties will be useful for many patient groups in the future.

5.16 References

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6 Neuroimaging investigation of motor function in 22q11.2 Deletion Syndrome

6.1 Chapter Overview

In the previous chapters I have presented evidence that children with 22q11.2 Deletion Syndrome have coordination and sensorimotor difficulties, that may well form a distinct feature of the 22q11.2 deletion syndrome. While it is difficult to know exactly why these children have coordination and sensorimotor control difficulties, it is likely that it is a result of changes in brain development because of the loss of the 22q11.2 region. This chapter presents a brief overview of the neuroimaging results reported in the 22q11.2DS literature to date and explores structural brain characteristics in our sample of imaged 22q11.2DS children and sibling controls. Using the brain structural analysis program FreeSurfer, relationships between cortex surface area, volume, and thickness and coordination scores are investigated. The volume of motor control relevant subcortical structures in the basal ganglia and cerebellum are also investigated. In addition, diffusion imaging is used to investigate the white matter tracts responsible for motor control and function, and their relationship with coordination. The results show that while our sample of children with 22q11.2 Deletion Syndrome differ in cortical volume and surface area of the parietal lobe, along with having a larger caudate, no relationships are found between coordination scores and cortical or subcortical characteristics. With regards to diffusion imaging metrics, a significantly reduced fractional anisotropy was found in the inferior cerebellar peduncle in children with 22q11.2 deletion syndrome. However, no associations with coordination scores or sensorimotor deficits were found between diffusion measures and coordination measures. These results broadly agree with previous neuroimaging findings in this population.

6.2 Introduction

Many chromosomal disorders are now well recognised to be associated with neurodevelopmental changes and problems. As one of more relatively common, and well-researched copy number variant disorders, there is a wide range of evidence showing that children with 22q11.2DS are at heightened risk for a variety of neurodevelopmental disorders. As mentioned earlier (Section 1.4), approximately 40% of individuals with 22q11.2DS will go on to develop a schizophrenia spectrum disorder. In addition to this, high rates of autism, anxiety and ADHD have been reported in children who carry the 22q11.2 deletion. Less well researched, despite being recognised early after the description of the syndrome, are motor disturbances seen in children with the syndrome. Delays in the attainment of motor milestones are common, along with general clumsiness. These factors can often a result in lack of participation in sports or physical activities. Previously in this thesis, I have provided evidence that these motor difficulties are common, with approximately 80% of children with the syndrome screening positive for indicated developmental coordination disorder (Chapter 3), and that these difficulties can be severe. I have also presented evidence that these children have sensorimotor difficulties in the domains of force control, tracking of moving objects and aimed ballistic movements (Chapter 4). Using gold standard coordination tasks, we also demonstrated deficits in wider domains of aiming and catching, manual dexterity, and particular problems with balance on a small sample of children with the deletion, though no clear fingerprint of deficits emerged (Chapter 5). In the current chapter, I aimed to investigate how structural changes in the brain associated with 22q11.2DS might help explain some of these coordination deficits. This involved using magnetic resonance imaging (MRI) in combination with the motor coordination data collected previously.

6.2.1 Description of imaging methods used

Neuroimaging methods can be complex, and the measures that are produced are often nonspecific and difficult to interpret.

In this chapter, two structural imaging methods are used to investigate the brains of children with 22q11.2DS and unaffected controls. First, brain morphology was analysed using the software package FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) which is documented and freely available to download online. Second, the white matter of the cerebellum was investigated using diffusion tensor imaging and tractography techniques, as disruption to the cerebellar cortex or white matter is known to cause motor symptoms.

FreeSurfer allows for the automated parcellation of the cortex and subcortical structures. For cortical regions, volume, surface area, and thickness can be measured, for subcortical structures, measurements of volume are returned. Other measures are also available, including measures of gyrification, but were not used in the current study. These morphometric measures can then be investigated for relationships with other variables of interest, or differences between groups. While FreeSurfer can investigate white matter volume, a more direct measure of the integrity and characteristics of white matter tracts can be obtained by using diffusion magnetic resonance imaging. In this type of imaging, MRI sequences designed to measure the movement of water molecules are used to measure signal changes due to the diffusion of water in the brain. Usually, magnetic resonance images are produced by applying a radio-frequency pulse to the brain while it is within the homogenous magnetic field generated by the superconducting magnets of the MRI scanner and measuring the resulting signal emitted by hydrogen atoms contained in the water molecules. Diffusion weighted imaging measures the diffusion of water in tissues by applying a magnetic gradient that increases the strength of the

magnetic field in one direction, evenly. This results in the signal emitted by water molecules decreasing as the water molecules move along this gradient, but is unaffected by any motion perpendicular to the direction of the magnetic gradient. The rate of water diffusion can be calculated by comparing the signal when a diffusion weighting gradient is applied, with the signal at the same location when no diffusion weighting is applied. (The no diffusion gradient state is called B=0, where B is the commonly used symbol for magnetic field). The rate of diffusion of water can be measured in any direction, depending on the direction of the magnetic gradient applied. Diffusion tensor imaging uses these principles to measure rates of diffusion in at least six directions, which is then summarized into a "tensor" model for each voxel. The tensor can be thought of as an ellipsoid, with the long axis orientated along the main direction that water is moving in a voxel, or principle diffusion direction, two more vectors describe the diffusion perpendicular to this axis. It is this diffusion tensor that allows for measures of the structure of brain tissue to be inferred.

Diffusion in the brain depends on the local environment of the water molecules. Cells and molecules will create barriers to diffusion, restricting diffusion in certain directions. In a voxel containing only cerebrospinal fluid (CSF), such as in the lateral ventricles, a given water molecule will, on average, be able to move equally in all directions. In a voxel in the cortex, this diffusion will be restricted due to the presence of cells and scaffolding proteins, and the distance that water will be able to diffuse in a given time is likely to be lower. In a voxel in a white matter structure such as the corticospinal tract, the diffusion of water will be restricted by the highly-ordered structure of axon bundles and myelin that make up the tract. In this condition, the distance that water can diffuse will be much greater along the axis of the axon bundles, as compared to perpendicular to the axons, where they will hit the cellular membranes. In a voxel in the CSF, where diffusion is entirely random, and on average equal in all directions,

the diffusion is called isotropic. In a voxel where diffusion is highly restricted along a single direction, the diffusion is highly anisotropic. Measurements of the anisotropy of diffusion in voxels of the brain form the basis of diffusion weighted MRI imaging.

Once you have a measurement of anisotropy in a given voxel, you can use a diffusion tensor to model the principal axis of diffusion and how restricted diffusion is along each direction in that voxel. This information can then be used to reconstruct the white matter tracts of the brain. In the simplest case, this is achieved by propagating lines from voxel to voxel along the principal axis of diffusion.

This study made use of high angular resolution diffusion imaging (HARDI). HARDI imaging consists of measuring diffusion weighted signals in a larger number of uniformly distributed gradient directions than standard diffusion tensor imaging so that a smaller difference in angular frequency features can be distinguished. In this case, instead of the six directions required for DTI modelling, we made use of 30 directions. This helps better resolve fibre orientations in voxels where more than one fibre population is present. Normal DTI techniques are unable to resolve multiple fibre populations in a single voxel.

The diffusion parameters measured can provide some information about the underlying integrity of the white matter bundles. The anisotropy, measured as fractional anisotropy (FA) for a given voxel or tract, can range from one to zero. An FA close to one indicates that the microstructure of that tract or voxel is extremely well ordered (all diffusion is along one principal axis), and high FA values are found in white matter tracts. Low FA, close to zero, indicates that the underlying microstructure is very unordered, and it does not follow one principal axis. Lower FA values tend to be found in the grey matter of the cortex, and in the

ventricles. Disease states are often associated with drops in FA, which may indicate damage to the white matter tracts, though FA is relatively unspecific to the exact type of damage (Feldman *et al.*, 2014).

Two other main metrics can be extracted from the HARDI (and diffusion tensor) models: axial diffusivity and radial diffusivity. These measures are complementary and are products of the three principal eigenvectors of the diffusion model. Axial diffusivity (AD) is equal to Lambda 1 and is the amount of diffusion along the principal axis of diffusion. Radial diffusivity (RD) is a combination of the diffusion perpendicular to the principal axis of diffusion and is usually calculated by adding the Lambda 2 and Lambda 3 eigenvectors and dividing by two. This gives a measure of the amount of diffusion perpendicular to the principal axis of diffusion; it is, therefore, sensitive to states that allow more diffusion through the axon membranes, such as membrane breakdown (Feldman *et al.*, 2014; Tromp, 2016). Mean Diffusivity (MD) is a measure of the distance that water can diffuse in a given time. It is an inverse measure of membrane density, such that in areas of grey or white matter, MD is lower than in the CSF, where water can diffuse more freely. MD is sensitive to the amount of cells in a voxel (more cells, lower MD), oedema and necrosis (both higher MD) (Feldman *et al.*, 2014).

Though these measures can give some information about any changes or damage to the white matter of the brain, they are generally considered to be unspecific markers of damage. While lower FA is usually assumed to be a deleterious state, studies looking at diffusion metrics in patient populations, including neurodevelopmental disorders, have often failed to find a consistent pattern of reduced FA.

Diffusion imaging is also inherently a very noise sensitive and artefact prone technique that requires robust image analysis and quality assurance techniques.

6.2.2 Neuroimaging in 22q11.2DS

Many groups have attempted to use neuroimaging to try and explain the heightened risk for neurodevelopmental disorders in individuals with the 22q11.2 deletion. The earliest studies found gross reductions in brain volume, which were more pronounced in the posterior areas of the brain. Reduced volume of the cerebellum is one of the most consistent findings in 22q11.2DS populations. Midline brain abnormalities are common, along with changes in gyrification. Neuroimaging findings in 22q11.2DS are reviewed in the following sections.

6.2.3 Incidental findings in 22q11.2DS

An incidental finding on MRI is defined as an unexpected, previously undetected, abnormality of potential clinical relevance, that is unrelated to the purpose of the examination (Vernooij *et al.*, 2007). Incidental findings of variable clinical significance are indeed common in the general population, and encompass everything from serious findings such as brain tumours to findings where clinical significance is less clear such as white matter lesions or subclinical vascular changes, which may, but are not always, linked to neurologic events. Though little research on incidental findings has been carried out in 22q11.2DS, an increased rate has been reported, which may reflect neurodevelopmental deficits caused by the loss of genes in the 22q11.2 region.

One of the only studies reporting overall rates of incidental findings in children with 22q11.2DS found a rate of 46.6% (J E Schmitt *et al.*, 2014), including cysts, and ventricular and other CSF abnormalities, as well as vascular white matter and subcortical abnormalities.

This represents an elevation compared with a rate of around 10% found in a typically developing paediatric and young adult population (Gur *et al.*, 2013).

The most common incidental finding in children with 22q11.2 was a cavum septum pellucidium (CSP). This is a normal variant of the brain where there is a CSF filled space between the leaflets of the septum pellucidium that separate the left and right ventricles of the brain. Increased rates of CSP have been found in children with 22q11.2DS, with a tendency to be larger than in the general population (Vernooij *et al.*, 2007; Beaton *et al.*, 2010). A CSP is expected in the foetal brain, but it usually closes soon after birth. Incomplete fusion of these leaflets can manifest as one or two separate fluid filled spaces, either as a CSP or a cavum vergae (CV), the latter being more posterior. A CSP is defined anteriorly by the genu of the corpus callosum, and more superiorly by the body of the corpus callosum. It is bounded posteriorly by the anterior limb and pillars of the fornix and inferiorly by the rostrum of the corpus callosum and anterior commissure. During development, the CSP should close in the direction of the rostrum to the fornix. A more anterior CSP is separated from the more posterior CV by the anterior columns of the fornix. However, if the fornix is insufficiently fused with the corpus callosum, the CSP and CV can form one continuous space.

In 15% of typically developing children, complete fusion of the laminae has occurred within one month after birth, and for the majority (85%) within six months. Estimates of the prevalence of a persisting CSP vary from 2% to nearly 60%. The specific mechanisms that control closure of the septum pellucidium are not completely understood, but fusion of the laminae is related to the development of the surrounding structures, such as the corpus callosum and the hippocampus. Overall brain volume may play a role, with increases in the pressure exerted on the laminae causing closure (Needelman *et al.*, 2006). Overall, the presence of a

wide or large CSP may be a nonspecific marker of atypical brain development (Bodensteiner *et al.*, 1990) either of globally abnormal vertebral growth or of aberrant development of the midline structures. Various studies have reported a CSP/CV rate of approximately 20%-80% in individuals with 22q11.2 Deletion Syndrome (Van Amelsvoort *et al.*, 2001a; Beaton *et al.*, 2010; J E Schmitt *et al.*, 2014), and it is the most common midline brain abnormality described in the syndrome. CSP's have been associated with psychosis in the general population (Landin-Romero *et al.*, 2016). One paper investigated the rate of CSP in individuals with 22q11.2DS and a diagnosis of either schizophrenia or schizoaffective disorder and found that 5/11 individuals had a CSP, though this study lacked a control group to allow statistical tests (Chow *et al.*, 1999). A more recent study provided further evidence for an association between CSP and psychosis within the 22q11.2DS population (J E Schmitt *et al.*, 2014).

Other than CSP, white matter abnormalities have also been seen in children with 22q11.2DS, and have been reported at higher rates than in control populations, however, due to small sample sizes, statistical tests have been insignificant (J E Schmitt *et al.*, 2014). Pathophysiology of white matter hyperintensities (areas of increased signal intensity on an MRI image) is not completely understood, though they seem to occur in regions of gliosis, axonal loss and demyelination, probably as a secondary effect of perivascular damage (Fazekas *et al.*, 1993). Increased white matter abnormality burden is associated with increased risk of dementia, cerebrovascular disease, mood disorders and death (Debette and Markus, 2010).

Other midline abnormalities seen in 22q11.2DS include changes to the hippocampus and disruption of the fornix. (Eliez *et al.*, 2000; Kates *et al.*, 2001; Debbané *et al.*, 2006; Deboer *et al.*, 2007; Deng *et al.*, 2015). Overall, incidental findings in individuals with 22q11.2 Deletion Syndrome are more common than in the general population, though in the general population

rates are likely confounded by differences in reporting between clinicians, due to the unclear relevance of many of these findings. Some of these incidental findings may be non-specific markers of abnormal brain development, reflecting developmental effects of the 22q11.2 Deletion.

6.2.4 Cortical changes in 22q11.2DS

In general, studies on cortical volume in individuals with 22q11.2 Deletion syndrome have found a variety of results of reduced and increased volume of many cortical areas. Global reductions in volume are commonly reported, with a rostrocaudal gradient of effect often observed (Tan *et al.*, 2009). Decreases in cortical volume have been described in the parietooccipital cortex, dorsolateral prefrontal cortex and midline structures (Bearden et al., 2004; Campbell et al., 2006; Eliez et al., 2000; J Eric Schmitt et al., 2014). Increases in volume have been reported in the insula and in frontal lobes (Campbell *et al.*, 2006). A relatively large recent study found increases in cortical thickness in the frontal lobes, lingual gyrus, inferior parietal lobes and medial occipital lobes that were accompanied by reductions in mean surface area (J Eric Schmitt *et al.*, 2014).

A different method of analysing neuroimaging data (or any network data), is graph theory. Applying such models to a sample of individuals with 22q11.2DS aged 8-21 indicated that correlational patterns of networks in the 22q11.2DS group were different to those of healthy controls. Overall, the 22q11.2DS group had reduced mean betweenness, modularity, clustering coefficient, average path length and small-worldness (Schmitt *et al.*, 2016), representing a picture of reduced network efficiency and lower resilience to insult.

In addition to relatively small sample sizes, wide age ranges, and differences in study methods, the lack of agreement of cortical volumetric studies may reflect the general variability of the syndrome. The syndrome is highly variable in its presentation, with some individuals being minimally affected, whereas others experience problems in a range of different psychiatric and neurodevelopmental domains. Similar variability is likely for brain measures.

In addition to effects on cortical volume, thickness and surface area, the 22q11.2 deletion is thought to be associated with changes in gyrification, including polymicrogyria (PMG) and pachygyria. Patients with 22q11.2 deletion syndrome and polymicrogyria and were first described in the mid 90's (Cramer, Schaefer and Krishnamoorthy, 1996; Bingham *et al.*, 1998; Bird and Scambler, 2000; Ghariani *et al.*, 2002; Robin, 2006; Gerkes *et al.*, 2010; Castro *et al.*, 2011). Robin et al. suggested that this PMG is often most severe around the perisylvian region and that it occurred more often on the right hemisphere. They furthermore suggested that this perisylvian PMG may be associated with some of the oromotor dysfunctions seen in the syndrome. PMG in 22q11.2 deletion syndrome remains a rare occurrence, meaning the prevalence is hard to estimate accurately (Robin, 2006).

6.2.5 Subcortical changes in 22q11.2DS

Various subcortical structures seem to be affected by deletion of the 22q11.2 region. One of the most researched is the hippocampus, due to evidence that hippocampal abnormalities are associated with schizophrenia. As mentioned previously 22q11.2DS is associated with reductions in the volume of the hippocampus (Eliez *et al.*, 2000; Kates *et al.*, 2001; Debbané *et al.*, 2006; Deboer *et al.*, 2007; Deng *et al.*, 2015), particularly the body of the hippocampus (Debbané *et al.*, 2006), and reduced hippocampus volume in 22q11.2DS has been associated with lower IQ (Deboer *et al.*, 2007). A longitudinal study of hippocampus volume in

22q11.2DS found that while the hippocampi of individuals with 22q11.2DS were smaller than controls, there was no group-time interaction, indicating no group difference in the trajectory of hippocampal growth (Flahault *et al.*, 2012). Hippocampal malrotation has also been described in the syndrome, and the authors suggested this may contribute to some cases of epilepsy in the syndrome (Andrade, Krings and Chow, 2013).

Changes in the basal ganglia have also been described in patients with 22q11.2DS. Two studies have found larger volumes of the right caudate nucleus in 22q11.2DS compared to controls (Kates *et al.*, 2004; Campbell *et al.*, 2006) while an earlier study found larger volumes of the left caudate head (Eliez *et al.*, 2002). There are also reports of calcification of the basal ganglia in individuals with 22q11.2 deletion syndrome (Sieberer *et al.*, 2005).

One of the most consistent findings in 22q11.2DS are reductions in cerebellar volume (Van Amelsvoort *et al.*, 2001b; Bish *et al.*, 2006; Campbell *et al.*, 2006; Tan *et al.*, 2009), which continue to be present in adulthood (van Amelsvoort *et al.*, 2004). Reductions in the posterior fossa (Eliez *et al.*, 2001) and the cerebellar vermis along with the midbrain and pons (Mitnick, Bello and Shprintzen, 1994) and the volume of the anterior lobe of the cerebellum have also been reported (Bish *et al.*, 2006). Overall these studies contribute to a picture of abnormal cerebellar development in 22q11.2DS, which is likely to contribute to the motor difficulties and other cognitive and psychiatric problems seen in patients with the deletion.

6.2.6 White matter changes in 22q11.2DS

White matter is widely disrupted in individuals with 22q11.2DS. Early studies focused on volumetric changes in white matter. Reductions in white matter volume have been reported in children (Kates *et al.*, 2001; Simon *et al.*, 2005; Campbell *et al.*, 2006), adolescents (Baker *et*

al., 2011) and adults with 22q11.2DS (Van Amelsvoort *et al.*, 2001a; van Amelsvoort *et al.*, 2004). Volumetric results prior to 2009 were analysed as part of a meta-analysis by Tan et al. which concluded that 22q11.2DS is associated with reductions in white matter volume in the temporal, parietal and occipital lobes (Tan *et al.*, 2009). Other reports have also shown reductions in white matter volume in the cerebellum (Campbell *et al.*, 2006), but this finding was not included in the meta-analysis.

More recently, studies have made use of diffusion imaging techniques to probe changes in white matter microstructure that could be relevant to phenotype. Diffusion tensor imaging and related techniques allow for the calculation of metrics that provide information about white matter microstructure. The most widely used metrics are Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD) these are described earlier in the chapter (Section 6.2.1).

Results from diffusion imaging studies in 22q11.2DS have been variable. The first investigation found reduced fractional anisotropy in the frontal, parietal and temporal regions in individuals with 22q11.2DS, and increased FA in the splenium of the corpus callosum, using a voxel based method to compare FA across the whole brain (Barnea-Goraly *et al.*, 2003). This was replicated by Simon et al. in 2005, however, it has been suggested that the increased FA of the corpus callosum may be due to a registration artefact (Ottet *et al.*, 2013), as this finding has not been seen when using improved registration techniques (Simon *et al.*, 2008). In a 2008 study, Simon et al. found clusters of increased FA in bilateral frontal and parietal lobes, with corresponding reduced RD. They interpreted this as a reduction in the number of fibres branching into the cortex from major white matter tracts in 22q11.2DS. Reduced FA was reported by Sundram et al. in 2010, in bilateral areas close to the midline, including the

brainstem, cingulum, internal capsule and corpus callosum, but this study found no areas of increased FA. One of the first studies using the tract based spatial statistics method in 22q11.2DS found a localized reduction of FA and AD in the white matter of the left parietal lobe. In 2012 Radoeva et al. reported changes in diffusion metrics across a wide number of tracts in individuals with 22q11.2DS, using an atlas based method. They reported reduced FA in the uncinate fasciculus, along with reduced AD in the corona radiata, dorsal cingulum, inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), superior cerebellar peduncle, posterior thalamic radiation, internal capsule, external capsule and the sagittal striatum. Interestingly, they also found that AD was correlated with measures of cognition such as IQ and working memory, providing evidence that changes in AD that may reflect changes in axonal integrity are related to the cognitive phenotype in 22q11.2DS. Using the Human Connectome technique to register white matter streamlines with cortical areas, Ottet et al., 2013, found an overall 10% reduction in the number of streamlines in 22q11.2DS compared to healthy controls. They took the number of streamlines as a proxy for the number of fibres in the brain, and so interpreted the reduction in streamlines as a reduction in the number of white matter fibres. This would agree with the widespread reduction of white matter volume that has been reported in 22q11.2DS using volumetric approaches outlined previously in this section. After correcting for this reduction in fibres, they found that connectivity was preserved within the right frontal and parietal lobes, but found reduced connectivity within and between limbic structures. (Kikinis *et al.*, 2013) reported reduced FA in the Inferior fronto-occipital fasciculus (IFOF), and reductions in AD in the IFOF and inferior longitudinal fasciculus (ILF). They reported no changes in RD. In a study looking at DTI metrics in girls with 22q11.2DS, Fragile X, or Turner syndrome, conditions with broad phenotypic overlap, it was reported that the 22q11.2DS group had lower FA than healthy controls (Villalon-Reina et al., 2013). A study in 2014 using tract based spatial statistics (TBSS), reported increased FA in

the internal capsule, corona radiata, body of the corpus callosum and a small region of the left SLF, this study found no areas of reduced FA. Reductions in AD and RD were reported in the body and splenium of the corpus callosum, the anterior thalamic radiation, the SLF and the ILF. Reductions in AD alone were reported in the IFOF, and reductions in RD alone in the left superior corona radiata and upper regions of the corticospinal tract (Jalbrzikowski *et al.*, 2014). Looking specifically at the cingulum bundle, Kates et al. found reductions in FA in the left anterior cingulum bundle, reductions in AD in the left and right anterior cingulum bundle, and reductions in RD in the right superior cingulum bundle and left and right posterior cingulum bundle (Kates *et al.*, 2014). They also found that higher schizophrenia scores were associated with higher FA in the left and right superior cingulum bundle. In another targeted study investigating the connectivity of the hippocampus, Deng et al., found reductions in FA of the fornix, particularly where it emerges from the hippocampus, suggesting changes to the integrity of this important limbic connection. Reductions in FA were correlated with lower FA of the fornix in the right hemisphere (Deng *et al.*, 2015). In a comparison with a population at ultra-high risk for psychosis, patients with 22q11.2DS had higher FA in the corpus callosum and anterior thalamic radiation. The results of this study concluded that overall values for MD, AD and RD were lower, while FA was higher, in 22q11.2DS patients compared to UHR patients, and that healthy control subjects had values for MD, AD, RD and FA, in between that of 22q11.2DS patients and the UHR group. They also found differences between 22q11.2DS patients and healthy controls, with higher FA in the corpus callosum and anterior thalamic radiation compared to controls (Bakker *et al.*, 2016). In the most recent TBSS study carried out in individuals with 22q11.2DS reductions in MD, AD and RD in the corpus callosum, bilateral SLF and bilateral coronal radiata were found. When comparing patients with 22q11.2DS with prodromal symptoms to 22q11.2DS individuals without symptoms, reductions in AD and MD were reported in the prodromal group in the SLF, corona radiata and internal capsule, all in the

right hemisphere. Axial diffusivity of these tracts was associated with psychosis scores (Kikinis *et al.*, 2016). A recent paper using tractography derived from functional (fMRI) activations on a spatial working memory task found various changes in diffusion metrics in the parietal region of the corpus callosum, the middle cerebellar peduncle, genu of the corpus callosum and in the bilateral SLF. These included increased FA of the parietal corpus callosum and the genu of the corpus callosum, along with reductions in MD, AD and RD of the parietal corpus callosum and genu of the corpus callosum, increases in MD and RD in the cerebellar peduncle, and reductions of MD, AD and RD in the SLF. One study has applied a structural connectivity analysis to investigate the default mode network in individuals with 22q11.2DS and found a simultaneous reduction in structural and functional connectivity of the DMN in children with 22q11.2DS. This study used probabilistic tractography to create a connectivity metric, which was lowered in individuals with 22q11.2DS (Padula *et al.*, 2015).

In summary, white matter in individuals with 22q11.2DS seems to be reduced in volume, and generally has reduced integrity, though patterns of findings using DTI metrics are variable. Similar to the results for grey matter volume, results can be variable between studies and groups, which may reflect the extremely variable phenotypic expressivity of the syndrome. Importantly, diffusion imaging metrics are by their nature relatively non-specific and susceptible to noise. When combined with small sample sizes, as is often the case in 22q11.2DS research, this can make consistent results across groups and populations hard to obtain.

6.2.7 Neuroimaging measures and syndrome severity

Various attempts to clarify the relationship between brain structure and syndrome severity, particularly for the presentation of psychotic symptoms, have been made, by measuring white

and grey matter volume and structure in individuals with 22q11.2DS who display prodromal or psychotic symptoms and those that do not.

Regarding white matter structure, changes in diffusion metrics in various white matter tracts across the brain have been found to be associated with scores on measures designed to detect prodromal and psychotic symptoms in individuals with 22q11.2DS (Sundram *et al.*, 2010; Radoeva *et al.*, 2012; Kates *et al.*, 2014; Padula *et al.*, 2015; Kikinis *et al.*, 2016), which may suggest that damage or changes in white matter microstructure or maturation are important in the presentation of these psychiatric symptoms.

Differences in cortical morphology in individuals with 22q11.2DS who display prodromal or psychotic symptoms have also been reported. Increased cortical thickness in the right medial orbitofrontal cortex has been associated with increased numbers of positive prodromal symptoms in 22q11.2DS (Jalbrzikowski *et al.*, 2013). Longitudinal decreases in cortical gyrification of the left occipital lobe have been found to be associated with prodromal symptoms (Kunwar *et al.*, 2012). Similarly, different patterns of development of cortical thickness have been shown to be present in individuals with 22q11.2DS who develop prodromal symptoms, particularly in the frontal lobe (Ramanathan *et al.*, 2016) where a decline in cortical thickness between the ages of 12 and 15 was more severe in those individuals who developed prodromal symptoms. Earlier studies by the same group demonstrated that reductions in surface area of the frontal lobe were associated with worsening psychosocial functioning over time (Kates *et al.*, 2011). This group also demonstrated that longitudinal decreases in the volume of grey and white matter, prefrontal cortex, mesial temporal lobe and cerebellum were associated with increased prodromal symptoms at longitudinal follow up

(Kates *et al.*, 2011). Results such as this suggest that changes in cortical maturation are responsible for some of the severity of symptoms in individuals with 22q11.2DS.

6.2.8 Motor functioning and brain structure

Neuroimaging techniques have been applied to the investigation of many neurodevelopmental disorders, in order to search for a neural signature that may explain associated features. Motor difficulties are by their very nature an extremely complex and heterogeneous group of disorders, that can be caused by many different changes in the central and peripheral nervous systems, or indeed in musculature or the skeleton. They are also often found in combination with other neurodevelopmental difficulties, making separation of causes of comorbidities extremely difficult. Compared to research in other neurodevelopmental disorders, such as ADHD or ASD, very little neuroimaging research has been carried out in populations with coordination disorders specifically. Neuroimaging research assumes that impaired perception and motor function in coordination disorders are due to either insults to the developing brain, or atypical brain development that can be detected using MRI or other imaging modalities. A diagnosis of developmental coordination disorder (DCD) is usually given to children with coordination difficulties that have a severe impact on daily life and are not better explained by a neurological or other cause. From a combination of behavioural, neurological and imaging studies, three main brain areas have been suggested to be compromised in DCD and may contribute to the coordination difficulties seen in the syndrome: the cerebellum, basal ganglia and parietal lobe.

6.2.8.1 Cerebellum

Traditionally the cerebellum has been thought of as a "co-processor" for motor control working alongside the cerebral cortex and basal ganglia and is responsible for automatic processing and

integration of motor and sensory information. Damage to the cerebellum can cause motor control deficits, for example, inflammation or traumatic insult can cause cerebellar ataxia resulting in a loss of coordination (Schmahmann, 2004). While this type of ataxia is usually a result of a lesion or damage to the cerebellum, it follows that neurodevelopmental abnormalities of the cerebellum may cause similar symptoms. As such, research has been carried out to investigate the role of the cerebellum in the symptomatology of developmental coordination disorder. Children with DCD tend to perform poorly on classical tests of cerebellar function, such as finger-nose touching and rapid alternating hand movements (Lundy-Ekman *et al.*, 1991). There are also reports of difficulties with motor adaptation tasks. Motor adaptation is the process by which the brain (dependent on the cerebellum) recalibrates the relationship between sensory input and motor output. In practice, this means that if a motor command has an unexpected outcome or error, the next command will be slightly changed to attempt to minimise this error. Experimentally altering the sensorimotor input allows for motor adaptation to be probed. For example, it has been demonstrated that individuals with DCD perform more poorly at adapting than unaffected individuals when visual input is distorted by a prism (Brookes, Nicolson and Fawcett, 2007; Cantin *et al.*, 2007). Debrabrant et al. found reduced nodal efficiency of the cerebellar lobule IV discriminated between children with DCD and typically developing children (Debrabant *et al.*, 2016), again suggesting that deficits in network connections of the cerebellum are involved in the deficits seen in DCD. Functional MRI studies have found that patterns of activation are different in children with DCD as compared to typically developing children. In a small study comparing functional activation on a fine motor skill trail making task, Zwicker et al. found under-activation of cerebellar and cerebellar-cortical networks compared to typically developing controls (Zwicker *et al.*, 2010, 2011).

6.2.8.2 Basal ganglia

The basal ganglia is also known to play a major role in the control, initiation, automatization and learning of movements. In the early 1990's basal ganglia soft signs were described in clumsy children, that were distinct from those seen in children with cerebellar soft signs (Lundy-Ekman *et al.*, 1991). However, performance of children with DCD on tasks thought to probe basal ganglia function is less consistent than seen in cerebellar tasks. Both positive (Gheysen, Van Waelvelde and Fias, 2011; Biotteau, Chaix and Albaret, 2015) and negative (Lejeune *et al.*, 2013) results for a deficit in serial reaction time and finger tapping tasks have been reported in children with DCD, tasks which are known to recruit the cortico-striatal systems. Neuroimaging studies of children with DCD have found abnormalities in the connectivity of the basal ganglia, including reduced connectivity coefficients between the striatum and parietal cortex (Querne *et al.*, 2008). An fMRI study has found atypical recruitment of the caudate, nucleus accumbens, pallidum and putamen in individuals with DCD and DCD+ADHD (McLeod *et al.*, 2014).

6.2.8.3 Parietal lobe

The parietal lobe is thought to be involved in many motor processes, including processing of visuospatial information, action prediction and observation, and motor imagery. Deficits in visuospatial processing have been shown in children with DCD compared to typically developing children (Wilson and McKenzie, 1998; Wilson *et al.*, 2013). Apart from motor functions, the parietal lobe is also thought to be involved in executive functioning (Wilson *et al.*, 2013), emotional recognition of faces (Cummins, Piek and Dyck, 2005) and response inhibition (Bernardi *et al.*, 2016). These functions are also impaired in DCD, and the combination of cognitive and motor impairments seen in individuals with DCD has led to the conclusion that the parietal lobe may be involved in the aetiology of DCD.

6.2.9 Imaging research in DCD

So far, most neuroimaging research in DCD has focused on task based or resting state fMRI to investigate activation characteristics of the networks of brain areas that are recruited in children with poor coordination. Few studies generally have investigated brain structure either in terms of white matter or grey matter. Those few studies that have investigated white matter have found changes in diffusion metrics in tracts that are thought to be important for motor function such as the corticospinal tract (Zwicker *et al.*, 2012), and for cortico-cortical communication, such as the corpus callosum connecting the parietal lobes and the left superior longitudinal fasciculus (Langevin *et al.*, 2014). Debrabant et al. found reduced FA with a concurrent increase in radial diffusivity of the left retrolenticular limb of the internal capsule. These FA reductions were associated with worse performance on a visuomotor tracing task. They also reported reduced nodal efficiencies of lobule VI of the cerebellum and right parietal superior gyrus as described in Section 6.2.8.1 (Debrabant *et al.*, 2016).

Only two structural MRI studies have been carried out in children with DCD, and both were comparing differences in brain structure in children with DCD alone or with a comorbid disorder, either ADHD or ASD. Langevin et al. found reductions in cortical thickness in children with DCD+ADHD compared to those with ADHD or DCD alone. Children with DCD alone had thinner cortex in the right medial orbitofrontal cortex compared to typically developing children, in addition to the reductions in thickness seen in ADHD and ADHD+DCD groups (Langevin, MacMaster and Dewey, 2014).

Using structural MRI fed into a graph theory analysis, Caeyenberghs et al. found a higher clustering coefficient for the right lateral orbitofrontal cortex in children with DCD compared

to typically developing controls, and concluded that overall, the organisation of networks in children with DCD is relatively intact, as there was little effect of DCD on overall network parameters (Caeyenberghs *et al.*, 2016).

Of 14 neuroimaging studies covered in a recent review of MRI findings in DCD, 11 mentioned the involvement of regions of the parietal lobe in DCD. Most of these studies found differences in activation or connectivity metrics of areas of the parietal lobe compared to typically developing children when completing a trail making task (Zwicker *et al.*, 2010, 2011), go-nogo, tasks (Querne *et al.*, 2008), a tracking task (Kashiwagi *et al.*, 2009), and in motor areas during rest (McLeod *et al.*, 2014). One study using diffusion tensor imaging and graph theory found decreased nodal efficiency of the right parietal superior gyrus in children with DCD compared to typically developing children.

Overall, imaging studies in children with DCD or motor difficulties are relatively sparse, but there is converging evidence to suggest that areas responsible for motor control are compromised in children with motor performance below the norm. It is however unclear if specific problems in areas such as the basal ganglia, cerebellum and parietal lobe are key features of DCD, or if a more general pattern of atypical brain development would better explain the effects on motor performance. In addition, as DCD is often seen to be comorbid with other disorders, and it is extremely rare to find an individual with a "pure" presentation, it is likely that other neurodevelopmental disorders such as ADHD and ASD share underlying neural changes.

6.2.10 What can 22q11.2DS tell us about motor difficulties?

Research focussing on non-genotyped populations of children with coordination difficulties or on children with 22q11.2DS irrespective of the presence of motor problems has found brain abnormalities that may be related to changes in cognition and motor performance. In both populations, changes in the structure of the cerebellum have been observed, with reduced white matter volume and generally reduced size in children with 22q11.2DS, and changes in white matter metrics in individuals with DCD. Both populations also show deficits in balance and high levels of clumsiness, both symptoms of cerebellar dysfunction. As discussed previously (Section 6.2.8.1), the cerebellum is a key structure in motor control and integration of sensorimotor information. In addition to the cerebellum, both lines of research have found evidence to suggest that the basal ganglia or its network of connections may be implicated in deficits of motor control and cognition seen in DCD and 22q11.2DS. As explained previously (Section 6.2.5), calcification of the basal ganglia, along with changes in size, has been reported in 22q11.2DS, while abnormal patterns of connectivity have been reported in individuals with DCD. Finally, deficits in visuospatial skills and spatial working memory are widely reported in both 22q11.2DS and DCD, with potential links to abnormalities of the parietal lobe and its connections to other brain areas. While children with DCD are likely a very genetically heterogeneous population, children with 22q11.2DS represent a more genetically homogenous population, with one putative causative genetic factor of coordination problems. If the 22q11.2 deletion has specific effects on brain structure that are measurable, this may help us understand the mechanisms behind how the brain may be different in individuals with DCD.

While much effort has been undertaken to characterise the changes in brain structure associated with 22q11.2DS, the results remain variable. Consistent patterns of reduced volume of grey and white matter are generally accepted to be seen in individuals with 22q11.2DS, but specific

findings with regards to individual brain regions are often inconsistent. No previous study has investigated cortical or subcortical brain structure in 22q11.2DS specifically with regards to motor control or coordination, nor carried out targeted tractography of the cerebellar peduncles with high-quality diffusion imaging data. Many theorists now expect that sensorimotor control is a fundamental skill of human development, and that good sensorimotor, and by extension, motor coordination skills are required for proper development of other higher order functions and behaviours, such as executive function in infants (Gottwald *et al.*, 2016) and language learning (Rowe, Özçalışkan and Goldin-Meadow, 2008). As such neural deficits caused by the 22q11.2 deletion that affect the development of motor areas such as the cerebellum and basal ganglia, may impact on fundamental sensorimotor skills and therefore have complex effects on the subsequent development of other behaviours. Neuroimaging may allow us to detect these structural, (and functional) changes and when combined with other behavioural and neurological techniques, allow insight into how these deficits are caused and what the cascading impacts on other neural systems might be.

6.3 Aims

In this chapter I aimed to 1) characterise the differences in cortical thickness, surface area and volume in our sample of carriers of 22q11.2 deletion and unaffected controls, over the whole brain, and in targeted regions of motor relevant cortex and; 2) investigate if changes in cortical brain metrics were related to coordination scores using a screening questionnaire for developmental coordination disorder. 3) Characterise differences in motor relevant subcortical structures, including the basal ganglia, and cerebellum, and investigate if changes in subcortical structures are related to coordination. 4) Carry out diffusion tensor tractography of a selection of motor relevant tracts highlighted by research in populations with DCD: the corticospinal

tract and the superior, middle and inferior cerebral peduncles and assess if changes in diffusion metrics are related to coordination performance.

I hypothesised that children with 22q11.2DS will 1) have reduced cortical grey matter volume, particularly in frontal lobes, and corresponding changes in cortical thickness and surface area. In addition, motor relevant cortex (precentral area, superior and inferior parietal lobes) will have reduced volume compared to controls; 2) That children with 22q11.2DS will have changes in cortical brain metrics that are associated with parental reports of coordination ability in daily life (DCDQ); 3) Children with 22q11.2DS will have changes in subcortical brain metrics, namely, larger basal ganglia volumes, and reduced cerebellar grey and white matter volumes, and these volumes will be related to coordination. 4) That children with 22q11.2DS will have changes in diffusion metrics of the corticospinal tract and cerebellar peduncles, namely reduced FA and associated changes in AD and RD, which would suggest damage or disruption to these motor relevant tracts, and that these changes would be associated with poorer coordination.

6.4 Methods

Details of preprocessing steps for FreeSurfer analysis and diffusion tensor imaging analysis are given in the general methodology (Section **2.5**). A summary of the analyses carried out is presented here. We successfully obtained high resolution T1 structural images from 18 child carriers of 22q11.2 deletion and 18 controls. Of these individuals, 18 carriers and 16 controls also had concurrent DCDQ data. We also successfully obtained 30 direction high angular resolution diffusion imaging data on 9 carriers of 22q11.2 deletion and 10 unaffected control siblings. The lower number of diffusion scans was due to the fact that not all participants were able to tolerate staying in the scanner for the entire MRI protocol, as such diffusion scans could

not be collected for some participants. Statistical comparisons using R were carried out in R version 3.3.3 (R Development Core Team, 2011).

6.4.1 Cortical morphometry comparisons

After quality control checks, as recommended by the ENIGMA consortium for cortical segmentation (http://enigma.ini.usc.edu/protocols/imaging-protocols), one sibling scan was excluded due to poor segmentation resulting from motion artefacts. This resulted in a final sample size of 18 children with 22q11.2DS and 17 unaffected sibling controls for the comparisons of cortical volume, thickness and surface area across all brain regions. Cortical surface area and thickness measures were extracted for each of the brain regions parcellated by FreeSurfer and stored.

Initial comparisons of global average total hemispheric surface area, thickness and total intracranial volume were carried out using an analysis of covariance with age as a covariate. Cortical volume was not analysed as it is a product of an individual's overall surface area and thickness.

Comparisons of regional surface area, volume and thickness between groups were carried out using the FreeSurfer's QDEC software. This provides a graphical user interface to the statistics engine of FreeSurfer. Differences in surface area, volume and thickness were examined using age at time of scan as a covariate. Correction for multiple comparisons was carried out using a cluster wise correction. A cluster forming threshold of $p<0.05$ was used for Monte Carlo simulations and a cluster-wise significance threshold of $p<0.01$ was used for visualisation.

6.4.2 Associations between coordination and cortical measures

The association between DCDQ score and cortical surface area, thickness and volume were investigated using general linear models constructed in FreeSurfer's QDEC GUI. Data acquired from the 18 probands were used to investigate the associations. DCDQ score was used as the dependent variable with either volume, surface area, or thickness as the independent variable, and age at time of scan as a covariate. Correction for multiple comparisons was carried out using a cluster wise correction. A cluster forming threshold of $p<0.05$ was used for simulations and a cluster-wise significance threshold of $p<0.01$ was used for visualisation.

6.4.3 Comparisons of motor relevant cortical areas

Comparisons of cortical areas of interest due to motor system involvement were carried out in R Version 3.3.3. Measures of cortical volume, surface area and thickness were extracted for the left and right precentral, superior and inferior parietal lobes. These were imported into R for statistical analysis. Analysis of covariance (ANCOVA) was used to investigate differences in cortical measures between groups in these regions with age at time of scan as a covariate. Plots of each region's cortical surface area, thickness or volume were visually inspected for evidence of an age*group interaction. For cases where there was evidence of such an interaction, an age*group interaction term was added to the original ANCOVA models. The relationship between cortical thickness and surface area was then correlated with DCDQ score residuals, calculated after regressing out the effect of age, using Pearson correlations.

6.4.4 Subcortical morphometry comparisons

After quality control, as recommended by the ENIGMA consortium for subcortical segmentations, (http://enigma.ini.usc.edu/protocols/imaging-protocols), scans from 18 carriers of 22q11.2 deletion and 17 controls were taken forward for comparisons of subcortical

volumes. The volume of each subcortical structures of interest was extracted for each subject. Structures of interest included the putamen, pallidum, caudate, cerebellar white matter and cerebellar grey matter. These values were imported into R version 3.3.3 for group comparisons. Comparisons between the volume of subcortical structures in deletion carriers and siblings were carried out using an ANCOVA with volume of the structure of interest as the dependent variable, deletion status as the group variable and age at time of scan as a covariate. To look for evidence of an age*group interaction, plots of subcortical volume against age were visually inspected. In cases where there was evidence of an Age*group interaction, an age*group interaction term was added to the original ANCOVA models for each structure. The relationship between subcortical volume and DCDQ score was examined using the same method as for cortical regions, using residualised DCDQ score and Pearson correlations.

6.4.5 Tractography metrics

Diffusion tractography was carried out on 9 carriers of 22q11.2DS (mean age=14.44 years sd=2.47) and 10 unaffected siblings (mean age=14.76 years sd= 1.44) (p=0.738). The left and right corticospinal tract along with the inferior, middle and superior cerebellar peduncles were isolated individually in each subject. Details of the tractography methods used to isolate the white matter tracts are outlined in Section **2.5.2** of the general methodology section. Measures of the average FA, MD, AD and RD were extracted for each tract and imported into R for statistical analysis. ANCOVA models were used to investigate effects of group with age as a covariate on diffusion metrics. Plots of each diffusion metric (FA, AD, RD) for each structure were visually inspected for evidence of any age*gender interaction. In cases where there was evidence for an age*gender interaction, an age*gender interaction term was added to the original ANCOVA models.

6.4.6 Tractography correlations with coordination metrics

Extracted diffusion metrics were correlated with coordination measures using a Pearson's rank correlation for each diffusion metric (FA, AD, RD) of each tract against residualised DCDQ score after regressing out effects of age on DCDQ score.

6.5 Results

There was a significant difference in age between the carriers of 22q11.2 Deletion and the unaffected siblings, (22q11.2DS mean age=13.65 sd=2.05, Controls mean age= 14.98, sd=2.05, p=0.048). Mean IQ of the carriers of 22q11.2DS was 75.3 (sd=14.56), and mean IQ of controls was 102 (sd=13.58). Descriptive statistics about the sample are shown in Table 6-1.

Table 6-1. Descriptive statistics of sample

Highest Maternal Qualification		
High (University Degree and/or other higher postgraduate qualification	11%	
Middle (A-Levels/Highers/Vocational Training	11%	
Low (O-Levels/GCSEs)	58%	
No School Leaving Exams	17%	
Unknown	2%	
	22q11.2DS	**Controls**
Participant Age	13.65 (sd 1.86)	14.99 (sd 2.05)
IQ	75.3 (sd 14.56)	102.3 (sd 13.58)
Gender (% Female)	50%	61%
Mother's ethnicity		
European	92%	
Unknown	8%	
Family income		
<=19,999	3%	
£20,000-£29,999	40%	
£40,00-£59,999	33%	
£60,000+	6%	
Benefits	17%	

6.5.1 FreeSurfer cortical comparisons

6.5.1.1 Global hemispheric differences

ANCOVA's for group differences between global cortical metrics found a difference in mean values of surface area in the right and left hemisphere between carriers of 22q11.2DS and controls, with carriers of 22q11.2DS having a lower overall surface area (Table 6-2). There was a significant effect of age on total intracranial volume (ICV) ($F=5.50$, $p=0.025$), with increasing ICV with increasing age.

Table 6-2. Mean values of surface area and thickness for individuals with 22q11.2 deletion syndrome and controls. ICV, intracranial volume

	22q11.2DS (n=18)		Controls (n=17)			
	Mean	**SD**	**Mean**	**SD**	**F**	**P**
ICV	1524174.44	107681.51	1589795.88	165666.06	0.73	0.398
L Surface Area	75084.11	6737.50	81118.84	6523.20	6.25	0.018
R Surface Area	74841.86	7296.79	81625.51	6340.26	7.52	0.010
L Thickness	2.81	0.18	2.72	0.12	2.18	0.150
R Thickness	2.83	0.17	2.76	0.13	1.57	0.219

6.5.1.2 Whole brain cortical analysis

Using the FreeSurfer software to compare cortical surface area, volume and thickness, I found no regions where surface area or thickness differed between carriers of the 22q11.2 deletion and controls, after cluster-wise corrections for multiple comparisons.

6.5.1.3 Comparisons of motor relevant cortex between groups

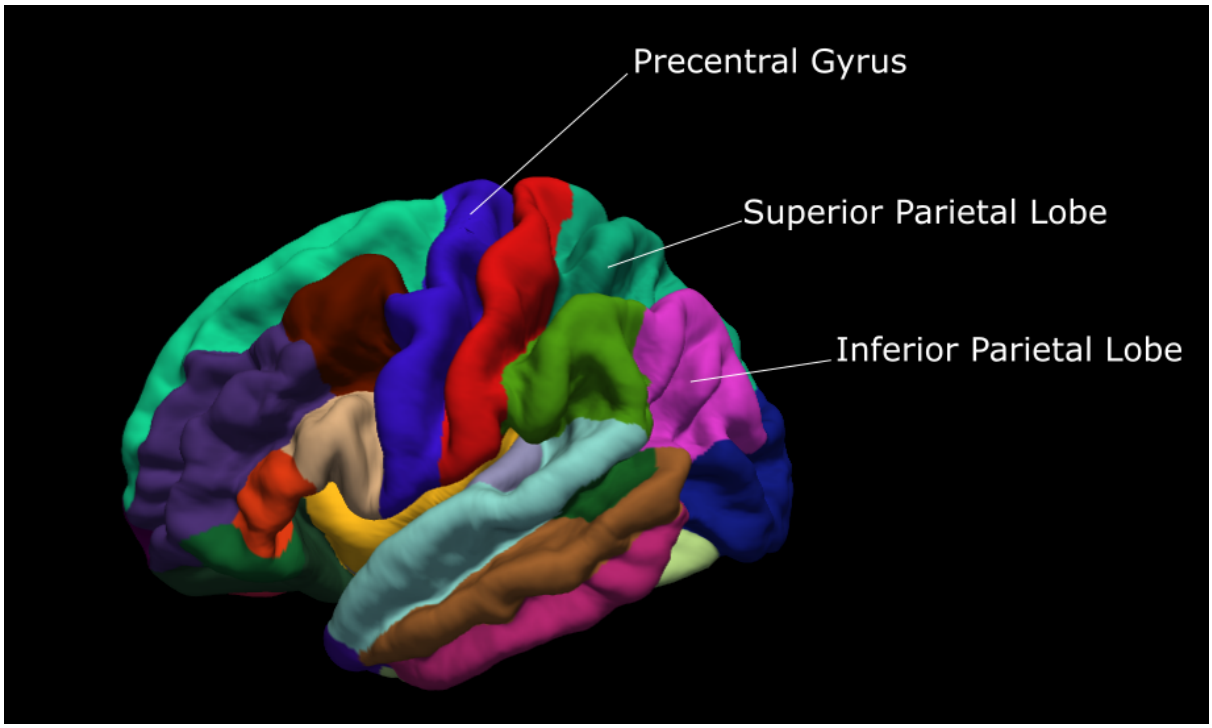

Figure 6-1. Illustration of motor relevant cortical areas used in the analysis, as parcellated by FreeSurfer on an average subject in MNI-305 space.

Table 6-3. Comparisons of motor function relevant cortical areas in individuals with 22q11.2 deletion syndrome and controls.

Surface Area			
	Hemisphere	**F**	**P**
Precentral	**L**	1.20	0.282
	R	0.38	0.542
Superior Parietal	**L**	19.85	0.000
	R	30.78	0.000
Inferior Parietal	**L**	0.81	0.374
	R	0.12	0.728
Thickness			
	Hemisphere	**F**	**P**
Precentral	**L**	2.24	0.144
	R	1.02	0.320
Superior Parietal	**L**	4.60	0.040
	R	5.37	0.027
Inferior Parietal	**L**	0.93	0.342
	R	0.24	0.630
Volume			
	Hemisphere	**F**	**P**
Precentral	**L**	3.63	0.066
	R	1.78	0.191
Superior Parietal	**L**	7.52	0.010
	R	11.49	0.002
Inferior Parietal	**L**	2.24	0.145
	R	0.00	0.944

Children with 22q11.2DS had a lower surface area in the left and right superior parietal cortex (Table 6-3). These changes in surface area were accompanied by changes in volume of the left and right superior parietal areas, with children with 22q11.2 having lower volumes of the superior parietal area. Children with 22q11.2DS also had higher thickness values in the right and left superior parietal lobes compared to controls.

Evidence for age*group interaction effects on cortical surface area were seen for the left and right precentral areas, left and right superior parietal cortex and the left and right inferior parietal cortices. A significant age*group interaction was seen in the left superior parietal cortex for cortical surface area (F=6.29, p=0.017). Cortical surface area of the left superior parietal cortex increases more rapidly in controls compared to individuals with 22q11.2DS (Figure 6-2).

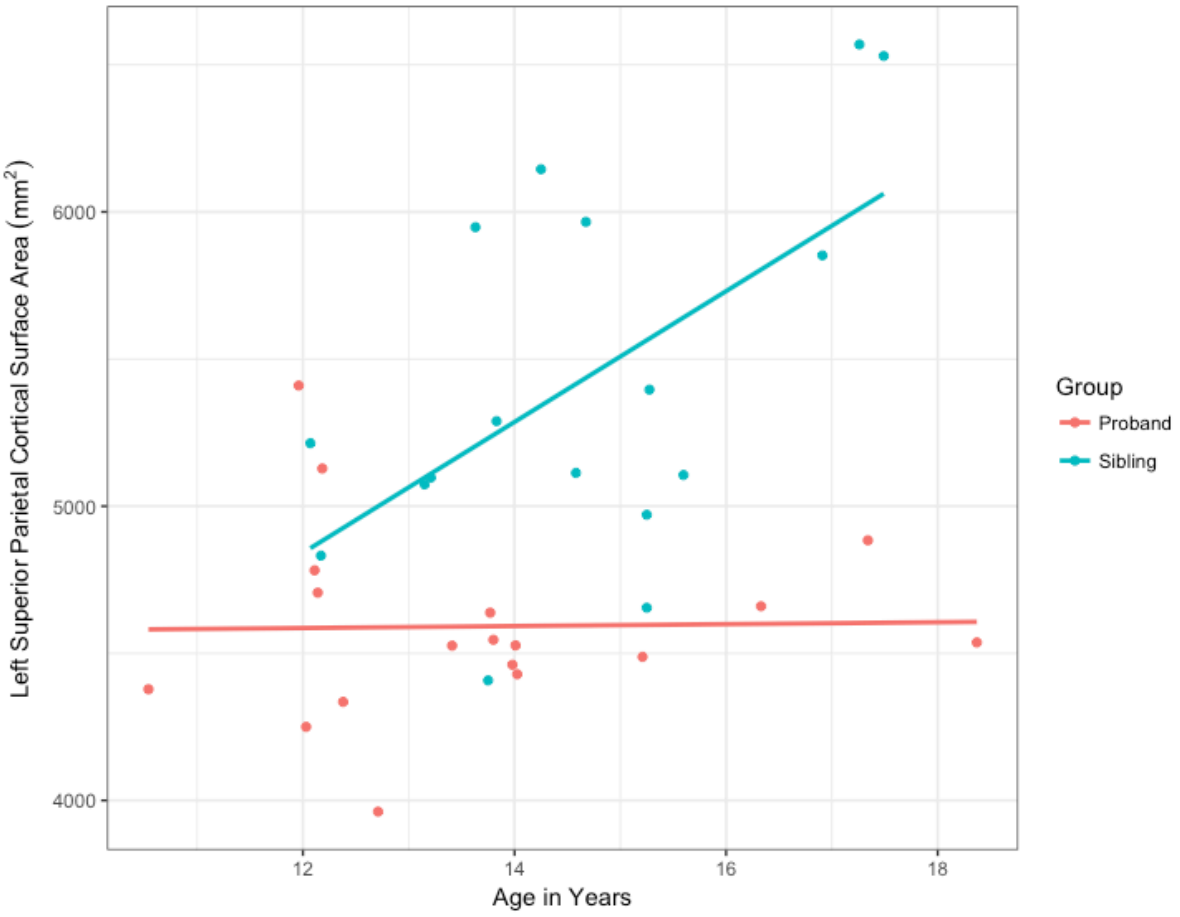

Figure 6-2. Cortical surface area of the left superior parietal lobe in individuals with 22q11.2 deletion syndrome and controls.

Evidence for age* group interaction effects on cortical thickness were seen for all motor relevant cortex regions, but these interaction terms did not meet significance. In addition, visual inspection of plots revealed evidence for age*group interaction effects on cortical volume for

the left precentral area, right superior parietal cortex and left inferior parietal cortex, but these interaction terms did not meet significance.

6.5.2 Relationship between cortical measures and coordination

There were no associations between cortical surface area, thickness or volume with DCDQ total score in the group of children with 22q11.2DS using the whole brain vertex wide approach.

6.5.3 Relationship between motor relevant cortex and coordination

Pearson correlations were conducted for each of the cortical thickness and surface area metrics extracted from the bilateral precentral gyrus, superior parietal lobes, and inferior parietal lobes. There were no significant correlations between residual DCDQ score (i.e., DCDQ score residual after regressing out age) and cortical surface area in the precentral area, superior or inferior parietal lobes. There were no significant correlations between residual DCDQ score and cortical thickness in the precentral area, superior or inferior parietal lobes Table 6-4.

Table 6-4. Results of correlations between regional cortical surface area and thickness and residual developmental disorder questionnaire score.

Surface area		
Region	**r**	**p**
L precentral	-0.11	0.653
R precentral	0.04	0.876
L Sup. Parietal	0.43	0.077
R Sup. Parietal	-0.29	0.251
L Inf. Parietal	-0.05	0.845
R Inf. Parietal	-0.07	0.793
Thickness		
Region	**r**	**p**
L Precentral	-0.22	0.389
R precentral	-0.32	0.196
L Sup. Parietal	-0.03	0.908
R Sup. Parietal	-0.15	0.566
L Inf. Parietal	-0.06	0.813
R Inf. Parietal	-0.05	0.838

6.5.4 Subcortical comparisons

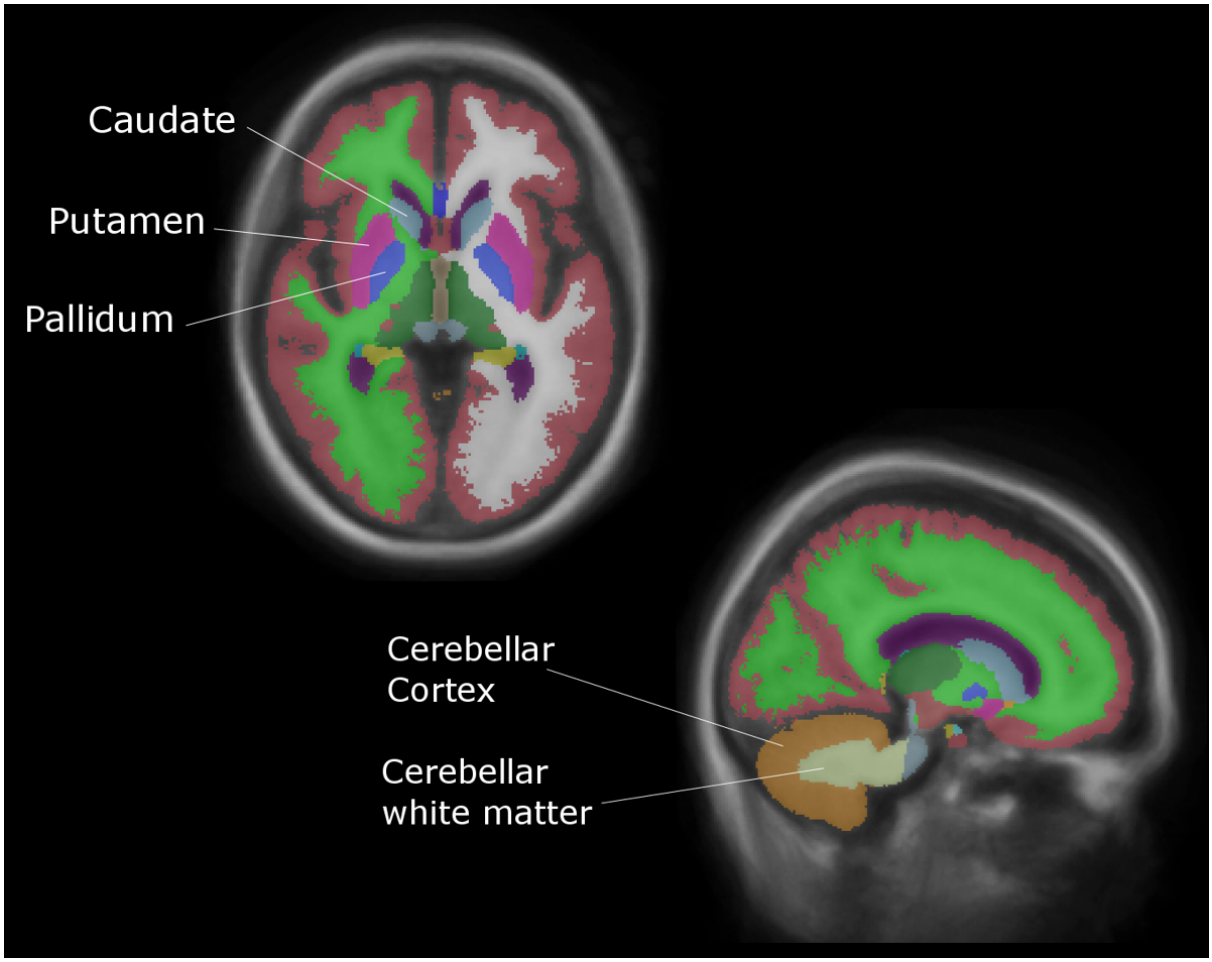

Figure 6-3. Subcortical regions parcellated by FreeSurfer and analysed in this study

Table 6-5. Volume of subcortical structures in individuals with 22q11.2 deletion syndrome and controls.

	22q11.2DS		Controls			
Structure	Mean Volume (mm^3)	SD	Mean Volume (mm^3)	SD	F value	P-value
Left Caudate	3934.150	351.514	3553.494	447.141	11.39	0.002
Right Caudate	3940.078	426.797	3237.747	527.387	22.62	0.000
Left Putamen	5202.911	765.649	5320.171	640.817	0.00	0.956
Right Putamen	5018.406	716.415	5088.429	532.116	0.10	0.758
Left Pallidum	1501.656	274.075	1391.612	233.893	3.37	0.076
Right Pallidum	1408.783	230.476	1376.629	170.555	1.07	0.309
Left Cerebellar White Matter	12765.761	2325.886	15266.671	4061.245	2.03	0.164
Right Cerebellar White Matter	11690.350	1819.628	14558.229	3710.846	4.22	0.049
Left Cerebellar Cortex	52621.161	6761.662	56233.153	6639.429	2.05	0.162
Right Cerebellar Cortex	54769.544	7128.402	58388.741	7416.497	1.79	0.191

Children with 22q11.2 Deletion had a larger caudate bilaterally than controls. Differences were also found in the right cerebellar white matter where children with 22q11.2DS had lower volumes (Table 6-5).

Evidence for age*group interactions were found for all subcortical regions. Significant age*group interactions were found in the left putamen (F=4.69, p=0.039), left cerebellar white matter (F=5.68, p=0.024) and right cerebellar white matter (F=5.19, p=0.030) as shown in Figure 6-4, Figure 6-5, and Figure 6-6.

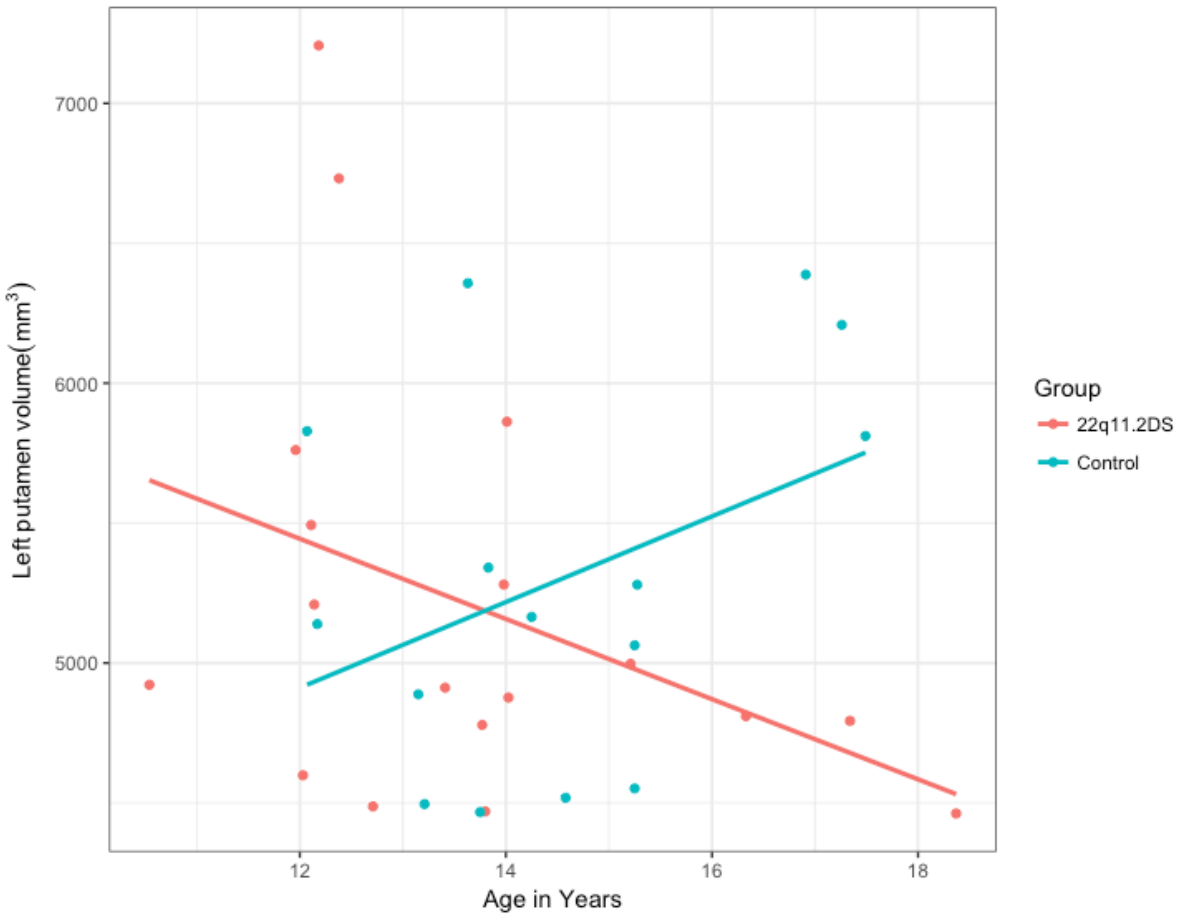

Figure 6-4. Left putamen volume against age in years of individuals with 22q11.2 deletion syndrome and controls.

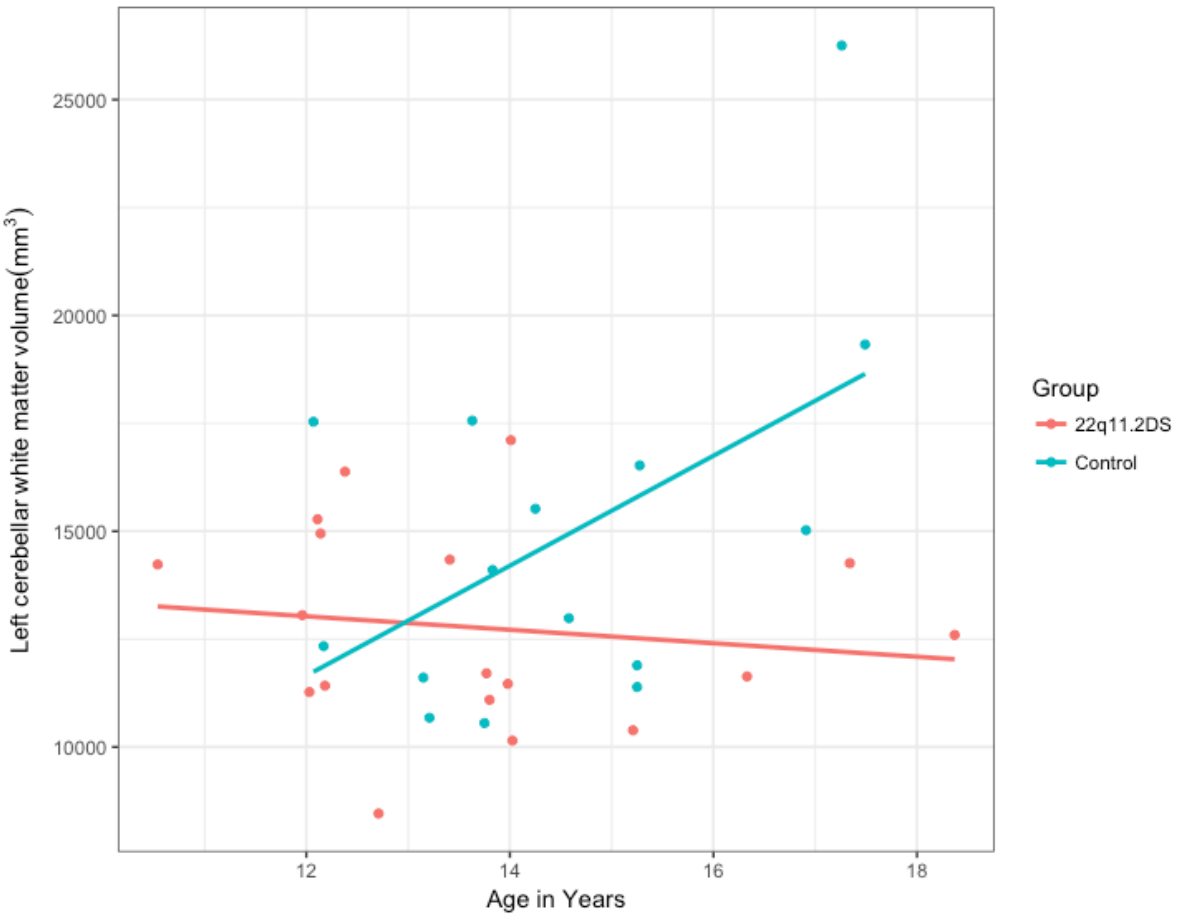

Figure 6-5. Left cerebellar white matter volume against age in years for individuals with 22q11.2 deletion syndrome and controls.

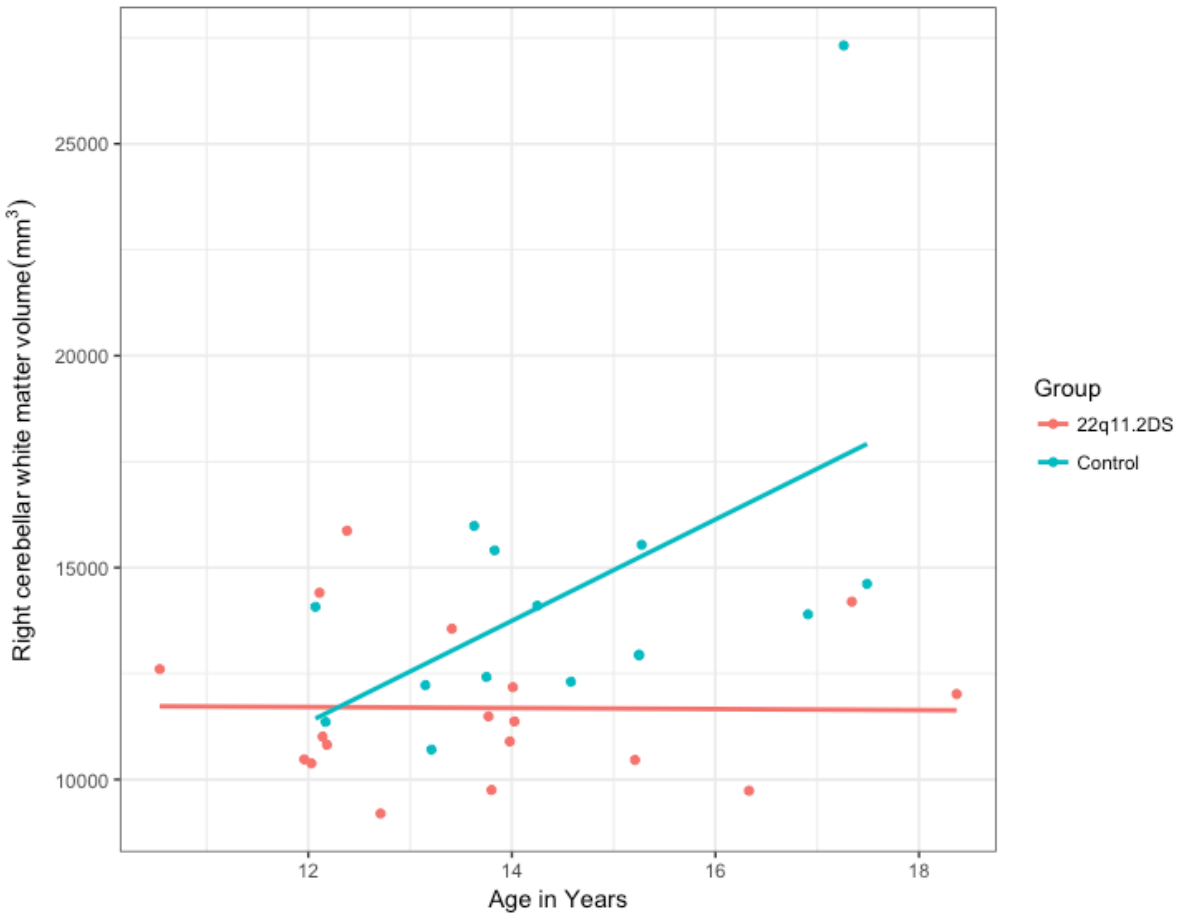

Figure 6-6. Right cerebellar white matter volume against age in years for individuals with 22q11.2DS and controls.

6.5.5 Relationship between subcortical volumes and coordination

Table 6-6. Correlations between subcortical structures and residual developmental coordination disorder questionnaire scores.

Region	r	p
Left caudate	0.06	0.822
Right caudate	0.14	0.588
Left putamen	-0.15	0.540
Right putamen	-0.20	0.434
Left pallidum	0.23	0.357
Right pallidum	-0.08	0.760
Left cerebellar cortex	0.11	0.651
Right cerebellar cortex	0.14	0.585
Left cerebellar white matter	-0.05	0.845
Right cerebellar white matter	0.04	0.871

Pearson correlations were conducted between residual DCDQ score and motor relevant subcortical areas. There were no significant correlations between DCDQ score and subcortical volumes (Table 6-6).

6.5.6 Diffusion imaging of motor tracts

I was able to successfully delineate all tracts of interest in both groups. The tracts delineated are shown in Figure 6-7.

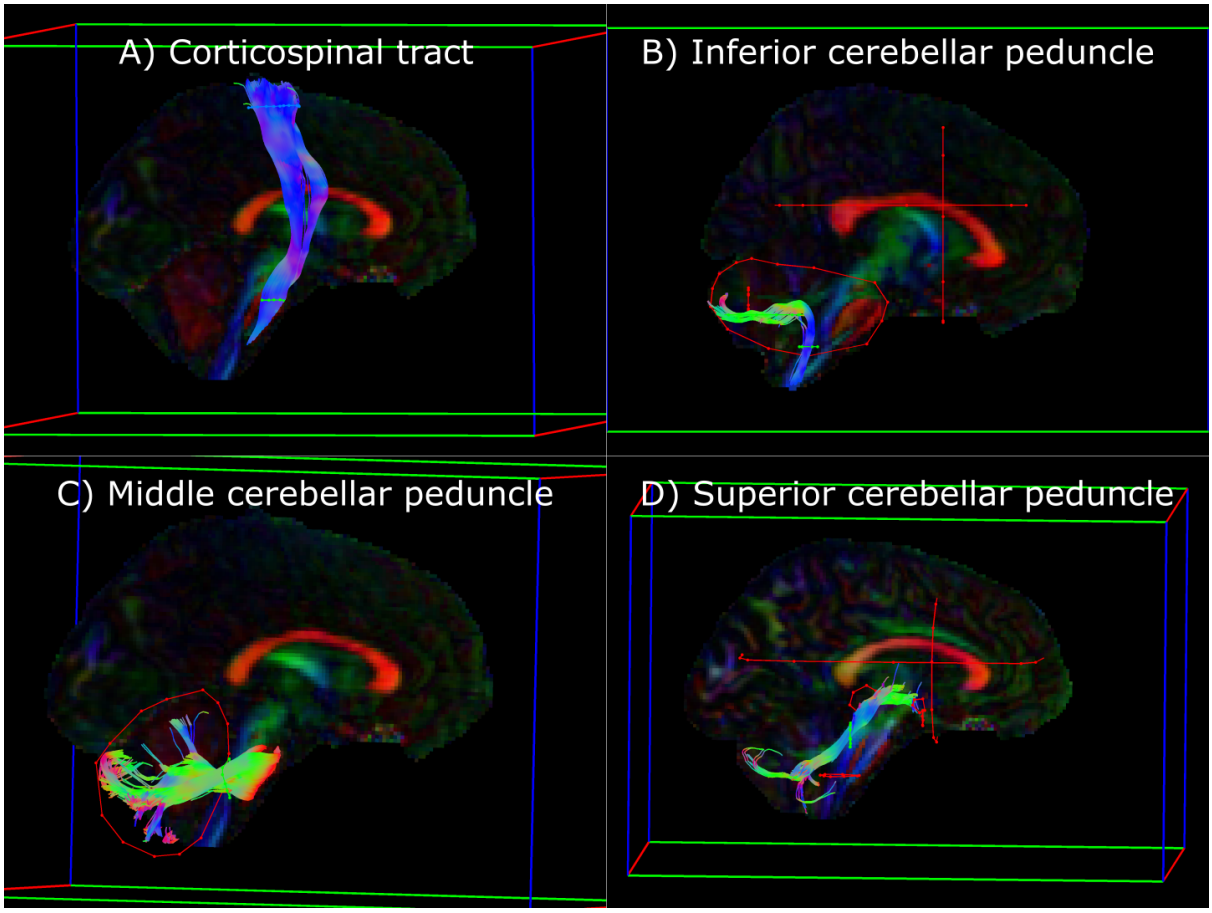

Figure 6-7. The four tracts delineated in children with 22q11.2 deletion syndrome and controls.

Children with 22q11.2 Deletion Syndrome had lower FA in the left inferior cerebellar peduncle. There were no differences in axial diffusivity or radial diffusivity (Table 6-7). Age had a significant effect on FA for the right CST ($F=8.17$, $p=0.011$), left SCP ($F=6.29$, $p=0.018$), and right SCP ($F=11.11$, $p=0.004$).

There was evidence for age*group interactions when investigating FA between groups for all tracts investigated. When age*group interaction terms were included in the original ANCOVA models, a significant effect was found for the MCP (F=4.65, p=0.048, Figure 6-8) and Left ICP (F=19.57, p=0.005, Figure 6-9).

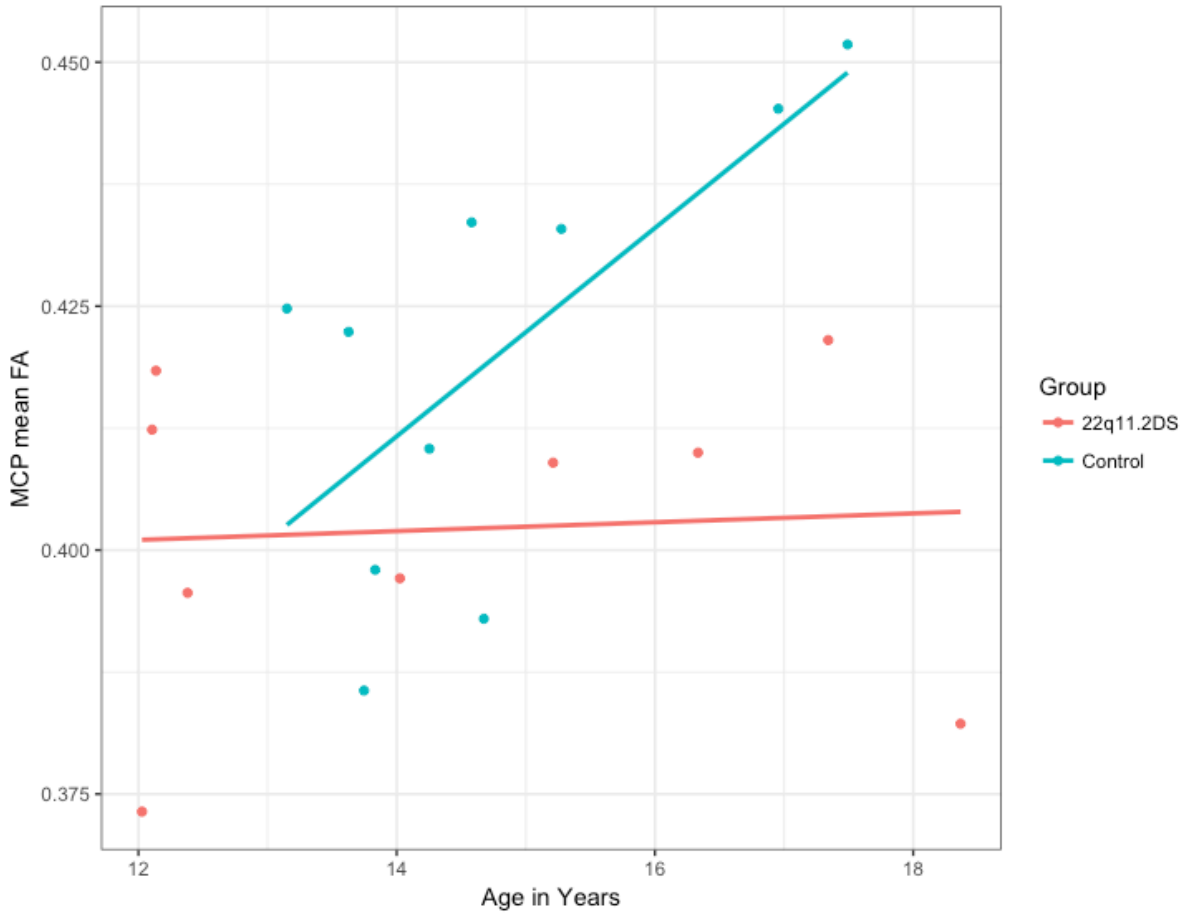

Figure 6-8. Mean fractional anisotropy (FA) for the middle cerebellar peduncle (MCP) in children with 22q11.2 deletion syndrome and unaffected sibling controls.

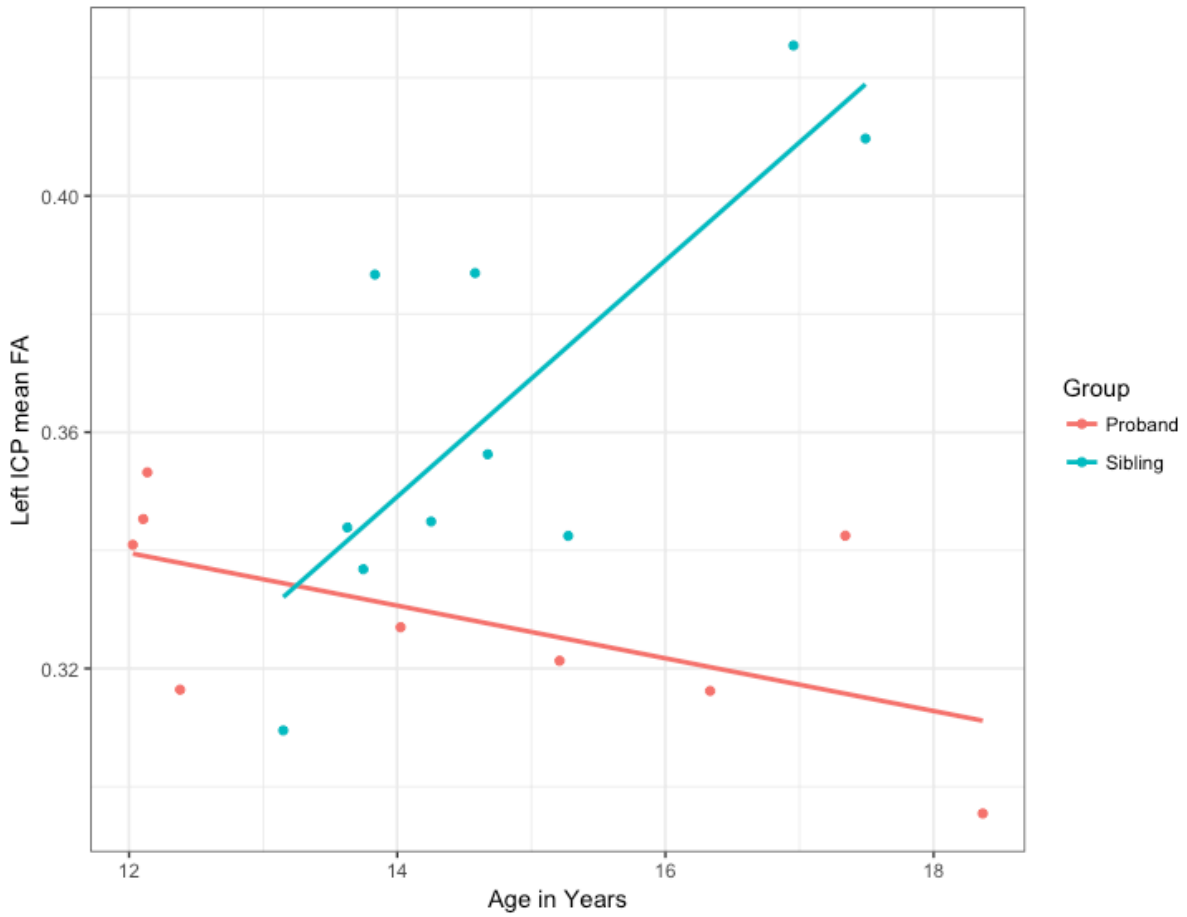

Figure 6-9. Mean fractional anisotropy (FA) in the left inferior cerebellar peduncle (ICP) for children with 22q11.2 deletion syndrome and controls.

Age did not have a significant effect on RD for any tract, but there was evidence for age*group interactions when investigating RD between groups for the Left CST, right SCP, MCP, and left ICP. However, these interaction terms did not reach significance.

Age had a significant effect on AD of the left corticospinal tract (F=5.61, p=0.031). When plotting AD against age for the carriers of 22q11.2 deletion and the controls, evidence for an age*group interaction was found in the right CST, MCP, right SCP and left and right ICP. When an age*group interaction term was included in the original ANCOVA models, there was no evidence of an age*group interaction on AD.

Table 6-7. Diffusion metrics in the tracts delineated. SCP, superior cerebellar peduncle, MCP, middle cerebellar peduncle, ICP, inferior cerebellar peduncle.

	22q11.2D (n=10)		Controls (n=9)			
Fractional Anisotropy						
	Mean	**SD**	**Mean**	**SD**	**F**	**P**
Corticospinal L	0.51	0.04	0.53	0.02	2.27	0.152
Corticospinal R	0.53	0.04	0.55	0.01	0.86	0.369
SCP L	0.31	0.02	0.31	0.03	0.02	0.879
SCP R	0.32	0.02	0.32	0.03	0.02	0.893
MCP	0.40	0.02	0.42	0.02	3.47	0.081
ICP L	0.33	0.02	0.36	0.04	6.41	0.022
ICP R	0.34	0.04	0.36	0.04	2.60	0.126
Radial Diffusivity						
Corticospinal L	5.7E-04	3.0E-05	5.4E-04	2.9E-05	3.11	0.098
Corticospinal R	5.4E-04	4.1E-05	5.2E-04	2.8E-05	0.10	0.761
SCP L	8.0E-04	5.1E-05	8.0E-04	6.9E-05	0.01	0.942
SCP R	7.9E-04	6.8E-05	7.9E-04	5.7E-05	3.57	0.078
MCP	5.9E-04	1.5E-05	5.8E-04	3.4E-05	1.44	0.249
ICP L	8.1E-04	8.1E-05	7.5E-04	9.1E-05	0.03	0.867
ICP R	7.7E-04	6.8E-05	7.2E-04	7.9E-05	0.55	0.470
Axial Diffusivity						
Corticospinal L	1.4E-03	5.2E-05	1.3E-03	3.8E-05	3.58	0.076
Corticospinal R	1.4E-03	4.5E-05	1.3E-03	3.1E-05	4.01	0.063
SCP L	1.3E-03	6.0E-05	1.3E-03	9.7E-05	0.15	0.699
SCP R	1.3E-03	1.2E-04	1.3E-03	6.6E-05	0.00	0.955
MCP	1.1E-03	5.5E-05	1.2E-03	6.8E-05	1.37	0.259
ICP L	1.3E-03	1.5E-04	1.3E-03	1.6E-04	0.03	0.862
ICP R	1.3E-03	1.2E-04	1.3E-03	9.6E-05	0.31	0.587

6.5.7 Relationships between diffusion metrics and coordination

Pearson correlations were conducted for each of the tracts of interest against residual DCDQ scores. There was no evidence for a correlation between any diffusion metrics and residualised coordination scores (

Table 6-8).

Table 6-8. Correlations of diffusion metrics against developmental coordination disorder questionnaire score (DCDQ) in individuals with 22q11.2DS. CST, corticospinal tract, SCP, superior cerebellar peduncle, MCP, middle cerebellar peduncle, ICP, inferior cerebellar peduncle.

	r	p
Fractional Anisotropy		
CST L	-0.18	0.647
CST R	-0.33	0.381
SCP L	-0.01	0.973
SCP R	-0.43	0.251
MCP	0.45	0.228
ICP L	0.32	0.407
ICP R	0.00	0.991
Radial Diffusivity		
CST L	0.22	0.569
CST R	0.26	0.497
SCP L	0.18	0.644
SCP R	-0.06	0.886
MCP	-0.01	0.973
ICP L	0.44	0.240
ICP R	-0.03	0.943
Axial Diffusivity		
CST L	-0.37	0.329
CST R	-0.56	0.121
SCP L	0.22	0.570
SCP R	-0.30	0.438
MCP	0.23	0.544
ICP L	0.51	0.157
ICP R	0.01	0.970

6.6 Discussion

In the current chapter, I have described a structural neuroimaging investigation into brain regions that may be involved in motor deficits seen in children with 22q11.2 deletion syndrome. Using volumetric analysis of motor relevant cortex, differences in surface area and volume of the parietal cortex were found in carriers of 22q11.2 deletion compared to controls, along with increased thickness of the precentral area. However, cortical measures of these regions were not associated with coordination scores in children with 22q11.2DS. I also investigated volume of motor relevant subcortical structures and found that children with 22q11.2DS have a larger caudate bilaterally than sibling controls, after adjusting for age.

Again, there were no associations between the volume of the subcortical structures and coordination scores in children with 22q11.2 deletion syndrome. Using diffusion imaging and targeted tractography of the cerebellar peduncles and corticospinal tracts I found a significant decrease in fractional anisotropy in the left inferior cerebellar peduncle. There were no significant correlations between diffusion metrics of the tracts investigated with coordination scores in children with 22q11.2 deletion syndrome. This is the first study to use tractography of the cerebellar peduncles in this population and to investigate brain structure with regards to motor function in a chromosomal disorder population. This study is the first to demonstrate that it is possible to isolate the cerebellar peduncles using tractography in this syndrome and that the gross appearance of the cerebellar peduncles in children with 22q11.2DS is normal when using tractography techniques. This study is also the first to demonstrate abnormalities of the inferior cerebellar peduncle in the syndrome which provides a plausible mechanism for some of the coordination difficulties seen in the syndrome.

6.6.1 Changes in cortical measures and lack of association with coordination

Whole brain comparisons of average cortical surface area, thickness and volume revealed significant differences in average cortical surface area across both hemispheres with individuals with 22q11.2DS having lower surface area than unaffected sibling controls. Structural differences in the brains of individuals with 22q11.2 deletion syndrome are well documented. Generally, the brains of individuals with 22q11.2DS tend to be smaller, with decreases in grey and white matter volume. In addition, there are reports of increased rates of incidental findings such as cysts, heterotopic grey matter, cavum septum pellucidium and vergae, and changes in cortical gyrification.

However, I did not find any significant regions of difference between individuals with 22q11.2DS and controls using a whole brain wide vertex based approach in FreeSurfer. This is likely due to lack of power in this relatively small sample. Analysis of this type involves many thousands of comparisons being made, and as such requires an extremely stringent correction for multiple comparisons. Therefore, large sample sizes are required to detect differences, unless effects of interest are extremely large. In the literature, similar neuroimaging and analysis methods have found widespread differences cortical morphology in larger samples (Bearden et al., 2004; Campbell et al., 2006; Eliez et al., 2000; J Eric Schmitt et al., 2014). For example, using FreeSurfer, increases in cortical thickness were found in the frontal lobes, lingual gyrus, inferior parietal lobes and medial occipital lobes, with corresponding reductions in cortical surface area (J Eric Schmitt *et al.*, 2014). We are continuing to recruit new participants for the scanning component of the ECHO study, along with carrying out longitudinal scanning of participants who have been scanned previously.

We had aimed to recruit a larger sample of individuals with 22q11.2DS, but the recruitment of clinical samples for MRI research is more challenging than many other samples, including contraindications. 22q11.2DS is a complex disorder with many associated health conditions. Many individuals with 22q11.2DS require surgery at some point in their life due to cardiac defects, skeletal problems, or other complications. This raises the possibility that for individuals who had previously undergone surgery, there may be metal left in the body, which is a contraindication for scanning at the Cardiff neuro-imaging centre, which uses the principle that individuals are not eligible unless it can be definitively proven that there is no risk of metal being present. Other contraindications that prevented some interested participants from being scanned included epilepsy, cochlear implants, along with orthodontic braces and other dental work. Of the individuals who could go in the scanner, many were unable to tolerate the entire

scanning procedure, either due to discomfort, claustrophobia or other reasons. All these difficulties were increased by the fact we were recruiting children, who can find it difficult to tolerate MRI scans in general. Finally, 22q11.2DS is a relatively rare condition, and participants in the parent ECHO study are recruited from all over the UK. Not all families who are interested or able to take part in scanning are able to make the trip to Cardiff for an MRI scan. As such, recruitment for the MRI scanning component was difficult, resulting in a sample that was not as large as we would have hoped.

Within the individuals with 22q11.2DS, I found no associations between coordination scores and FreeSurfer metrics, when analysed using a whole brain, vertex wide approach. Again, this is likely due to having a sample that is underpowered for the type of analysis. However, this could also be due to the relatively non-specific measurement of the DCDQ. While it is extremely sensitive to coordination difficulties at a functional or disability level, it may not be sensitive to specific coordination processes that are more closely related to cortical morphometry. Kinematic measures which allow the investigation of specific motor skills such as aiming, force control and prospective motor control may be more closely related to neuroimaging measures. Unfortunately, the overlap between individuals who had complete MRI scans and sensorimotor data using our kinematic assessments was too small to allow meaningful analysis.

The whole brain approach was complimented by a region of interest based approach focusing on cortical brain areas that are involved with either control of movement or thought to be involved in visuospatial processing. The precentral gyrus, which is included in the precentral ROI is thought to contain the human primary motor cortex. This brain area is responsible for conscious control over many of our muscles and parts of our body. The parietal lobes are

thought to be involved in the dorsal stream of visual processing and have been associated with visuospatial processing. In addition, the parietal lobe is thought to be part of the mirror neuron network in humans and is responsible for storing motor patterns (Rizzolatti and Craighero, 2004). Using this targeted approach, I found differences in surface area and volume in the parietal cortex, where children with 22q11.2DS had lower surface area and volume of the superior parietal cortex in the left and right hemispheres. Reductions in volume of parietal areas are well reported in children with 22q11.2DS and may be related to deficits in visuospatial processing and numerical ability, as both these functions have been associated with the parietal lobe (Bearden et al., 2004; Campbell et al., 2006; Eliez et al., 2000; J Eric Schmitt et al., 2014). Reductions in surface area may signify changes in gyrification of this region. A significant age*group interaction was found in the left superior parietal cortex, where surface area of the superior parietal cortex seems to increase more rapidly with age in controls compared to individuals with 22q11.2DS. However, as controls tended to be slightly older than individuals with 22q11.2DS, this may influence interpretation. However, I did not find any associations between these cortical metrics and coordination as measured by the DCDQ. It may be necessary to use tasks that specifically target functions of the primary motor cortex, such as finger tapping, or the parietal cortex, such as visuospatial rotation tasks to find clearer associations with these cortical metrics and functions.

6.6.2 Subcortical volumes and associations with coordination

I also used FreeSurfer to parcellate the subcortical structures of the basal ganglia and cerebellum that are important for motor control. By comparing the volume of these structures between carriers of 22q11.2DS and controls, I found that individuals with 22q11.2DS had a larger caudate bilaterally than controls, along with individuals with 22q11.2DS having lower volumes of cerebellar white matter in the right hemisphere. The larger caudate in 22q11.2DS

is interesting due to the seemingly increased risk of early onset Parkinson's disease in this population (Zaleski *et al.*, 2009; Boot *et al.*, 2015; Mok *et al.*, 2016), and is a finding that has been previously reported in individuals with 22q11.2DS (Eliez *et al.*, 2002; Kates *et al.*, 2004; Campbell *et al.*, 2006). Larger caudate volumes have been a reported in a large multi-centre study of subcortical volumes in individuals with schizophrenia compared to controls (Okada *et al.*, 2016). However, this finding was not seen in the main ENIGMA consortium investigation into subcortical volume in patients with schizophrenia and controls (van Erp *et al.*, 2016). The Okada paper also demonstrated a greater difference in volume for the right caudate compared to the left between patients with schizophrenia and controls, similar to the greater difference presented here. Elsewhere, larger grey matter volumes in the striatum have been reported in first degree relatives of patients with schizophrenia and patients with schizophrenia themselves (Oertel-Knöchel *et al.*, 2012). Aberrant connectivity of the basal ganglia and parietal lobe has been reported in research into children with DCD. This would follow the same localisation of changes as seen in individuals with 22q11.2DS. Therefore, aberrant cortico-striatal networks may be a mechanism behind some of the deficits seen in 22q11.2DS. This assumption is not however supported by the evidence from correlations between coordination scores and subcortical volumes as which were not found in this study.

6.6.3 Diffusion imaging of the corticospinal tracts and cerebellar peduncles

Using diffusion tensor imaging and tractography I was able to delineate the bilateral corticospinal tracts and cerebellar peduncles in the carriers of 22q11.2 deletion and their unaffected control siblings. Comparisons of diffusion metrics between the two groups revealed a difference in fractional anisotropy of the left inferior cerebellar peduncle, which may be worth investigating further in larger samples. Reduction in fractional anisotropy is a non-specific marker of reduced integrity of a white matter tract and may reflect many different causes. Due

to the lack of other effects in AD or RD, it is difficult to interpret exactly what this change in FA results from.

The inferior cerebellar peduncle (ICP) is primarily concerned with inputs from the rest of the body to the cerebellum. The ICP carries the Spinocerebellar tract, Cuneocerebellar tract, Trigeminocerebellar tract, Olivocerebellar tract and Vestibulocerebellar tract (Michael-Titus, Revest and Shortland, 2010).

Table 6-9. Fibre Pathways of the inferior cerebellar peduncle and their functions.

Fibre Pathway	Function
Spinocerebellar	Proprioceptive and cutaneous sensory information from the torso and legs
Cuneocerebellar	Proprioceptive and cutaneous sensory information from arms and neck
Trigeminocerebellar	Proprioceptive and cutaneous sensation from the face and jaw
Olivocerebellar	Motor skill learning
Vestibulocerebellar	Balance

As Table 6-9 shows, the pathways of the ICP mainly carry proprioceptive and cutaneous sensory information from the body to the cerebellum, where it is integrated with the motor instructions sent from the cortex. Damage to the ICP could, therefore, impact coordination through disruption of the sensory information about the body in space, leading to inaccurate estimations of the motions that must be carried out for a given movement to occur. This would mean that the error correcting function of the cerebellum, which allows smooth movements, would be disrupted, leading to problems with coordination. In addition, the ICP also carries the olivocerebellar tract which is concerned with motor skill learning. A key feature of DCD in

non-genotyped populations is a deficit in the ability to learn new motor skills. If the olivocerebellar tract is disrupted by changes in the white matter microstructure of the ICP, then this could be a basis for some of the motor skill learning deficits in DCD and 22q11.2DS. Finally, deficits in balance have been repeatedly demonstrated in 22q11.2DS, including in my assessments of coordination using the MABC (Chapter 5) (Van Aken *et al.*, 2009; Roizen *et al.*, 2011; McDonald-McGinn *et al.*, 2015). The vestibulocerebellar tract is involved in balance, and again, if disrupted as a part of the changes in white matter microstructure of the ICP, this could be at least partly responsible for some of the balance deficits seen in 22q11.2DS.

6.6.4 Strengths and limitations

Strengths of the current study include a relatively narrow age range. Most other imaging studies in 22q11.2DS have pooled samples across children and adults, resulting in samples that may be confounded by developmental changes that occur throughout development. While our sample has a relatively narrow age range, it still spans early adolescence to young adulthood, a period of significant brain development. We can therefore not rule out the possibility that developmental or maturational processes are influencing different subsamples differently and that this impacts on the results presented. This is also the first study to investigate specific white matter tracts of the cerebellum in this population and to investigate motor ability with regards to neuroimaging metrics. The inclusion of sibling controls is also a strength, as these individuals should be relatively matched on socioeconomic factors and family environment. While some differences in cortical metrics and diffusion metrics were found between individuals with 22q11.2DS and controls, no associations were found with coordination scores. This may be due to the relatively non-specific nature of the DCDQ questions. While the DCDQ is very sensitive to functional coordination deficits, the questions ask about relatively complex coordinated movements. These complex movements are likely to also require significant

cognitive aspects of understanding, in addition to the required level of motor skill. More specific measures of movement kinematics may be more closely associated with brain structural metrics than questionnaire measures such as the DCDQ and should be investigated in combination with neuroimaging metrics in the future.

6.7 Conclusions

There are measurable differences in cortical metrics, volume of the caudate and diffusion metrics of the ICP in children with 22q11.2DS, though it is unclear if these are related to coordination difficulties in this population. Low sample size and a potentially insufficiently process-specific measure of coordination may be obscuring any relationship between coordination and brain anatomy in this study. Further work should be carried out to measure movement characteristics of individuals with 22q11.2DS in more detail, for example relating kinematic measures of sensorimotor skill with brain structure. Using more specific measures of movement may provide clearer insights into the relationships between brain changes associated with 22q11.2DS and difficulties with movement.

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7 General discussion

7.1 Overview

Coordination difficulties can often have a profound impact on daily life. Coordination difficulties in 22q11.2DS are an area of growing research interest, although much remains to be elucidated. Coordination difficulties in non-genotyped populations are commonly seen to co-occur with neurodevelopmental disorders including Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) (Loh, Piek and Barrett, 2011; Travers *et al.*, 2013; Kaiser *et al.*, 2015), but tend to receive less research focus than other aspects of the disorders.

In the first experimental chapter (Chapter 3), I outlined the prevalence of coordination difficulties in a sample of children with 22q11.2DS and unaffected sibling controls. I found that coordination difficulties are common in 22q11.2DS, with around 80% of children meeting criteria for indicated developmental coordination disorder (DCD), compared to 6% of unaffected (control) siblings ($p<0.001$). Furthermore, these scores were related to the number of ADHD, ASD and anxiety symptoms reported by the parents of the children with 22q11.2DS. Indicated DCD was also related to full-scale IQ and visual and sustained attention. This would suggest that the coordination impairment of children with 22q11.2DS can be partially explained by neurocognitive ability.

In the second experimental chapter (Chapter 4), I investigated three fundamental sensorimotor skills that underlie many complex coordinated movements. I assumed that sensorimotor impairment would be related to indicated DCD as well as risk of neurocognitive function and psychopathology. Children with 22q11.2DS performed worse compared to unaffected sibling controls on all three sensorimotor tasks. The only associations found between indicative DCD

and sensorimotor skill were between responses on the "hitting a ball" question of the DCDQ and tracking ability, such that better tracking performance was associated with better ability to hit an approaching ball and between the "bull in a china shop" responses and normalised jerk such that less jerky movements were associated with lower clumsiness. Total score on the DCD screener was however not related to sensorimotor performance in individuals with 22q11.2DS. In addition, sensorimotor performance was not associated with the number of ADHD, ASD or anxiety symptoms, unlike the associations found between indicative DCD and psychopathology. However, sensorimotor performance was related to a range of cognitive abilities including visual and sustained attention, spatial planning and spatial working memory, and tracking performance was related to full-scale IQ,

In Chapter 5, I aimed to expand my studies beyond the DCD screener to obtain a more detailed profile of the difficulties that children with 22q11.2DS have with coordination. The results of the assessments conducted by qualified occupational therapists broadly agreed with the results of the DCDQ, with eight of ten children who previously screened positive on the DCDQ for coordination difficulties, scoring below the 5th percentile on the Movement ABC (MABC). This indicates these children have severe coordination difficulties that would benefit from an intervention. Interestingly, MABC scores were not associated with IQ contrasting with results with our DCD screening instrument. In addition, I found that these eight children had difficulties with visual perception and visuomotor integration raising the possibility visual information deficits play a role in coordination difficulties. The results of the MABC showed wide-ranging deficits, with coordination difficulties spanning all areas of fine and gross motor skills, though balance was the area most commonly affected.

In Chapter 5, I also described a pilot intervention study aiming to support two children with 22q11.2DS and coordination difficulties in improving their performance in goals identified by themselves and their carers. Very little research has been carried out in how best to intervene for children with a complex presentation of coordination difficulties and comorbid problems, as found in 22q11.2DS. Interviews with the children and their carers helped identify areas of daily life affected by the coordination difficulties. Common areas included dressing, bathing, and schoolwork. The interviews also highlighted the extra time and effort that parents of children with coordination difficulties have to invest in day to day activities such as preparing clothes for the day, helping to dress and personal hygiene. While the sample size is too small to draw firm conclusion on the overall effectiveness of the intervention, qualitative improvements were noted by the occupational therapists in confidence and problem-solving ability, and general engagement with problems that the children found difficult. Reductions were also seen in the number of ADHD symptoms endorsed for both children, and small improvements in SDQ scores, though these still remained in the high range. The most important outcome of the intervention pilot was as a proof of concept that existing strategies for interventions into coordination difficulties are feasible in children with a chromosomal disorder such as 22q11.2DS and that the parents described the sessions as useful and helpful. Coordination difficulties in 22q11.2DS represent an under researched and under recognised area and most families are not receiving any support in this area. We found that the parents welcomed the opportunity to talk to qualified clinical staff who could help with advice and support.

In the final experimental chapter (Chapter 6), I investigated how the difficulties with coordination and sensorimotor ability might be related to brain structure. 22q11.2DS has been found to be associated with a number of changes in brain structure, though their clinical

significance needs to be further elucidated. I first examined whether there were any differences in the children with 22q11.2DS, compared to their unaffected siblings, irrespective of their motor difficulties. While this sample is likely underpowered to detect effects across the whole brain, using a region based analysis I identified differences in surface area and volume of the parietal lobe, along with increases in the volume of the caudate and reduced volume of cerebellar white matter. These structural changes are in line with findings that have previously been observed in the 22q11.2DS imaging literature. I also investigated the microstructure of the cerebellar white matter using diffusion tensor imaging, to explore the hypothesis that damage to the integrity of the cerebellar input and output tracts could have deleterious effects on coordination and sensorimotor ability. I found a difference in fractional anisotropy of the inferior cerebellar peduncle, a tract involved in the integration of proprioceptive information from the body. However, the differences I found in cortical and white matter structure in the children with 22q11.2DS were not associated with indicative DCD. As the sample size of our imaging study is still small, power issues are likely to have limited my ability to detect differences between the individuals with 22q11.2DS and sibling controls.

7.2 Bringing the results together

Coordination difficulties seem to be common in children with 22q11.2DS, and I have presented evidence (as presented in Chapters 3 and 4) that cognitive ability is related to the coordination and sensorimotor skills of an individual as both the DCDQ and sensorimotor tasks were found to have links with cognitive processes. Both total scores on the DCDQ and sensorimotor performance were found to be associated with attentional performance which may suggest particular links between attention and motor performance. Evidence of a particularly strong relationship between attention and coordination problems is also supported by the high rates of DCD seen in individuals with ADHD (Kadesjö and Gillberg, 1999; Loh, Piek and Barrett,

2011). Therefore, it seems likely that cognitive and intellectual ability play a role in coordination difficulties but may not explain them entirely.

The coordination difficulties experienced by children with 22q11.2DS are related to psychopathology, particularly ADHD, ASD and anxiety, which may suggest that there are common underlying brain pathways between coordination and these disorders. But, no associations between ADHD, ASD and anxiety symptoms were seen with the sensorimotor tasks. This may be due to either the smaller sample size of children who completed the sensorimotor battery or differences in what the assessments are measuring. It may be that the DCDQ is also sensitive to behaviours associated with psychopathology, while the sensorimotor tasks are a relatively isolated measure of motor ability.

If coordination difficulties are related to psychopathology, then what brain changes could unite the two? There is evidence that damage or changes to the cerebellum are involved in ADHD, ASD, and coordination difficulties (Bledsoe, Semrud-Clikeman and Pliszka, 2009; Becker and Stoodley, 2013; Wang, Kloth and Badura, 2014; Stoodley, 2016). Cerebellar changes have repeatedly been found in 22q11.2DS (Bish *et al.*, 2006) and I was able to demonstrate changes in the cerebellar white matter in children with 22q11.2DS, indicating reduced volume and changes in white matter that may impact accurate motor control in 22q11.2DS. As mentioned in Section **6.6.3**, the inferior cerebellar peduncle primarily consists of input tracts which carry proprioceptive and cutaneous sensory information from the body to the cerebellum. This information is integrated with motor instructions sent from the cortex. Therefore, changes that impact the ICP's ability to transmit information about the body's position in space could cause inaccurate estimations of the body's relative position. This would affect the cerebellum's role in error correction of movement instructions and cause problems with coordination. The ICP

also carries the olivocerebellar tract which is concerned with motor skill learning. Therefore, changes to the ICP could disrupt this tract's ability to transmit signals and cause difficulties with motor skill learning. Finally, the ICP also carries the vestibulocerebellar tract which is involved with balance control. Balance deficits are commonly reported in 22q11.2DS, and changes to the vestibulocerebellar tract that disrupt these balance signals could be a cause of the balance deficits seen in the syndrome (Van Aken *et al.*, 2009; Roizen *et al.*, 2011; McDonald-McGinn *et al.*, 2015).

Another key subcortical structure that is important for movement is the basal ganglia. This has also repeatedly shown to be different in 22q11.2DS, particularly an increased volume of the striatum (Eliez *et al.*, 2002; Kates *et al.*, 2004). The basal ganglia is important for the initiation of movements. Increased volume of the striatum might indicate an "overconnectivity" with other areas of the brain, which could disrupt the balance of input and output signals from the striatum to the Globus Pallidus and Subthalamic Nucleus.

I also found evidence of reduced cortical surface area of the parietal lobe in the children with 22q11.2DS. The parietal lobe is also involved in motor control and is thought to be part of the mirror neuron network in humans, and responsible for storing motor patterns (Rizzolatti and Craighero, 2004). Changes to the cortical surface area of the parietal lobe may suggest that there is a disruption to cortical maturation in this area. If the functions of the parietal lobe are disrupted, this may lead to disruptions in the storage of motor control patterns. The parietal lobe is also thought to be involved in visuospatial information processing and visual perception. Disruption of these functions could also partly account for the coordination and perceptual deficits in 22q11.2DS.

Overall it, therefore, seems that the hemizygous loss of the 22q11.2 region has a detectable, though modest, effect on the structure of at least three motor relevant brain regions, the parietal lobe, striatum and cerebellum. These changes may be involved in the coordination difficulties seen in the syndrome, though more research is required to better understand the pathways behind these deficits.

In Section 3.2 I suggested four potential models for the relationships between cognition, psychopathology and coordination difficulties. As noted in Section 3.2, the results presented here would support the fourth model that was presented (Figure 3-4) as I found that 22q11.2DS affects coordination, psychopathology and cognition, but there are also reciprocal interactions between cognition and coordination difficulties and between cognition and psychopathology. The other models were not supported, for the following reasons. In the first model (Figure 3-1) I suggested that the 22q11.2 deletion had independent effects on the three outcome measures, and that there were no interactions between the outcomes. This model is not supported by the evidence presented here, as coordination was found to be associated with psychopathology and both overall coordination and sensorimotor deficits were found to be related to IQ and neurocognitive performance. In the second model (Figure 3-2) I suggested that the 22q11.2 deletion caused deficits in IQ or cognition that then influence coordination, but psychopathology is not related to coordination or IQ. This model is not supported due to the relationships that were found between coordination and psychopathology. The third model (Figure 3-3) suggested that the 22q11.2 deletion directly caused deficits in IQ, coordination difficulties and psychopathology, but there were also interactions between coordination and psychopathology, but no relationships between cognition and coordination or between cognition and psychopathology. This could be through the fact that that impaired coordination may increase risk for psychopathology and impaired social or environmental interactions may

reduce opportunities for developing coordination skills. This model is refuted by the reported relationships between cognition and coordination difficulties and sensorimotor deficits. However, the current design may not be considered a complete test of these models. To further test the relationships between the three outcomes, and test the mechanisms behind these relationships, a mediation analysis could be carried out.

In Section 1.9, I outlined three potential mechanisms that could explain the coordination deficits that are seen in DCD and potentially 22q11.2DS: an internal modelling deficit, a deficit in automisation and a deficit in the mirror neuron system. The results presented here would support a deficit in internal modelling as being a potential mechanism behind the coordination deficits. This would suggest that the disruption to brain structure and function caused by the deletion, causes a deficit in ability to construct an accurate internal model of the movement of objects and the movements required to appropriately carry out actions. This is supported by the findings of reduced tracking and aiming performance as demonstrated in Chapter 4 in combination with the reduction in volume of the cerebellar white matter and changes in the inferior cerebellar peduncle, as the cerebellum is thought to be a key structure for internal modelling. The hypothesised mechanism of an automisation deficit was not directly tested in this thesis. However, this could be tested using a similar dual task paradigm as employed by Nicholson and Fawcett to assess if cognitive load impacts on motor performance. This is a potential avenue for further research. Similarly, the mirror neuron deficit hypothesis was not directly tested in this thesis. A true test of the mirror neuron deficit this would likely require invasive physiological recordings to identify mirror neurons in humans and any aberrant activity when performing motor tasks. Despite this, some indirect evidence for a mirror neuron deficit is provided by the reduced surface area and volume of the parietal lobe, an area that is thought to be a key node in the mirror neuron network in humans.

7.3 Implications for research

I found an association between FSIQ and coordination ability as measured by the DCDQ and between IQ and tracking performance, but not between the MABC-2 and aiming or steering performance and IQ. This suggests highly specific associations between different aspects as assessed by different measures and IQ, however, the findings need to be interpreted with regards to lack of power, particularly in the MABC-2 sample. Currently, most research on coordination difficulties excludes participants with an IQ in the low or borderline range, under the assumption that in individuals with low IQ, coordination difficulties are best (or most easily) explained by low IQ. However, the mixture of positive and negative associations between IQ and cognitive measures and different measures of motor ability adds to the conflicting literature on the subject. It may be that 22q11.2DS is associated with coordination difficulties that are due to the overall developmental delay associated with the deletion, but also more specific deficits, such as in balance or prospective motor control (tracking and ballistic aiming performance), which have been reported in this thesis and elsewhere (Van Aken *et al.*, 2010a, 2010b). In light of the lack of consensus on the relationship between cognitive ability and coordination performance, further research should be carried out to better understand these relationships in populations like 22q11.2DS and more generally.

Furthermore, the results presented here suggest that coordination difficulties are related to psychopathology. This should be considered when conducting research into children with 22q11.2DS. Coordination difficulties may be a marker for risk in other domains, or a general marker for other neurodevelopmental problems. In particular, attentional processes were found to be associated with both sensorimotor performance and Indicative DCD. Furthermore, ADHD symptomatology, and more specifically the inattention subtype, was also associated

with DCDQ total score. These findings suggest that there is a particularly strong link between attention and coordination, thought the direction of effect is unclear. From the results presented in this thesis, I am unable to say if poor coordination is a secondary result of poor control of attention, or if attentional processes and motor processes are dependent on one another at a more basic (neural) level. Further research should be considered to better disentangle the relationship between attention and coordination difficulties, and the impact poor coordination has on the development of cognitive skills.

Similar to other work using MRI neuroimaging in populations with 22q11.2DS, I found a relatively minor difference between individuals with 22q11.2DS and unaffected sibling controls, despite the potentially severe (bit also varied) phenotypes that are associated with the deletion. This highlights the diffuse effect of these deletions on brain structure.

7.4 Further work

The work outlined in this thesis extends the limited already existing research into coordination difficulties in children with 22q11.2DS and provides further insights into just how common coordination difficulties are in children with 22q11.2DS their wide-ranging impact on daily life and the links with other aspects of the syndrome. However, there is much more research to be done.

Firstly, while I have established that coordination difficulties are common, I was not able to clearly demonstrate that coordination difficulties are not better explained by a neurological, skeletal, or other medical cause. Further research into coordination difficulties in populations such as this should attempt to carry out detailed neurological examinations in order to rule out confounding causes of coordination problems, such as hypo or hypertonia. More research

should focus on attempting to describe the profile of coordination difficulties in 22q11.2DS, as this will provide insight into the systems that are compromised by the deletion. For example, there is some converging evidence that balance is commonly impaired in 22q11.2DS. However, due to the immunological problems seen in the syndrome, many children experience recurrent ear infections (Bassett *et al.*, 2011) which could damage the structures of the inner ear responsible for balance. Therefore, balance deficits could be an indirect result of immune dysfunction rather than any effect of the deletion on neural systems.

I was also unable to investigate if the coordination deficits seen in the syndrome are related to psychosis. While this data is collected as part of the ECHO study, very few individuals had evidence of psychotic experiences in the age range I studied, making an analysis unfeasible. Future work that could be done as part of the ECHO study could explore whether there is a difference in coordination ability between individuals with 22q11.2DS who develop psychotic experiences and those who do not.

Currently, it is unclear if the coordination difficulties in 22q11.2DS persist over time, though there is evidence from non-genotyped populations that suggests that coordination deficits can persist into adulthood (Kirby *et al.*, 2013). Some parents invited to take part in the occupational therapy assessments reported that as their children reached the adolescence and teenage years they found many activities that were previously difficult much easier. In addition, performance on the sensorimotor measures was related to age, with performance increasing as children got older. So far, we have only collected cross sectional data on coordination in our participants and controls, however, as our longitudinal recruitment continues, we will be able to investigate the stability of coordination difficulties over time. In addition, motor disturbances have been described in adults with 22q11.2DS, though mainly with regards to Parkinson's disease, or the

effects of antipsychotic medications. It is not yet clear if there are also clinically relevant disturbances of coordination that are yet to be recognised in adults with the syndrome. Therefore, future work should look to clarify the nature and prevalence of motor disturbances in adults with 22q11.2DS.

While both coordination difficulties and sensorimotor deficits were quite clearly present in children with 22q11.DS I was unable to clearly delineate the relationships between fundamental sensorimotor deficits and problems with coordination at the level of disability and impact on daily life, as the sensorimotor measures and DCDQ were not correlated with each other in 22q11.2DS. Therefore, further work needs to be done on how fundamental sensorimotor deficits are related to impact of coordination difficulties on daily life. Research in populations like 22q11.2DS, where a single genetic factor is the most likely cause of coordination difficulties can provide insight into the specific pathways that link sensorimotor deficits and coordination difficulties. Extending this, there is currently some debate as to whether fundamental sensorimotor skills are in some way required for the development of other cognitive skills, such as executive functioning. Again, populations with a homogenous risk lesion, such as individuals with 22q11.2DS, may provide clearer insight into the relationships between sensorimotor ability and other cognitive domains than potentially genetically heterogeneous populations selected on the basis of the phenotypic presentation of coordination difficulties.

There has been no previous research into interventions for coordination difficulties in individuals with 22q11.2DS or similar chromosomal disorders, despite the clear burden that these difficulties place on both the individual and their carers. While I was able to demonstrate a pilot intervention in two children with 22q11.2DS, further work should be done to investigate

the effectiveness of interventions for coordination difficulties in children with 22q11.2DS and other populations with chromosomal disorders. If coordination difficulties are related to psychopathology an intervention improving coordination, or at least providing strategies to help with skills that children find difficult, might also help with other symptoms. For example, strategies could help by reducing frustration and increasing a child's confidence in their own abilities. Ideally, a well-designed trial looking at the effectiveness of occupational therapy interventions on coordination difficulties, and other domains such as psychopathology or cognition would be carried out.

Though I found evidence for structural differences in the brains of the children with 22q11.2DS that were in agreement with the results found in previous studies, imaging studies in 22q11.2DS, in general, have been limited by low sample sizes. There are currently collaborative efforts to pool neuroimaging data from rare populations such as 22q11.2DS, for example, the 22q11.2DS ENIGMA working group, which will allow increased power to investigate brain-phenotype links, like the relationship between brain structure and coordination or sensorimotor difficulties. While coordination difficulties are not currently a focus of the 22q11.2DS ENIGMA group, this is an area that warrants further investigation.

7.5 Limitations

Aiming for a representative sample, the ECHO study recruits participants with 22q11.2DS from all over the United Kingdom, through the NHS as well as charities and does not exclude any potential candidate. Nevertheless, the sample is slightly skewed towards families from an above average socioeconomic background, who may have more time or freedom to take part in research. In addition, although not studied here, it may be the case that families with children

who are more severely affected by the deletion are more motivated to take part in research. This may impact on the overall generalizability of the findings presented here.

There was no restriction on the type of deletion that participants carried, as long as the "critical region" between LCR22A and LCR22B was deleted. As such, while the majority of participants will carry the typical 3Mb deletion, a small number of individuals will carry a smaller nested deletion. It may be the case that the different deletions have different effects on the outcomes measured here. In the future, it may be better to restrict recruitment to one deletion type in order to limit confounding effects of deletion extent. If sample sizes allow, comparisons of motor symptoms between individuals with the typical deletion and smaller nested deletions may be informative.

With regards to the OT interventions, these two individuals carried out the CKAT and CANTAB tasks multiple times. As such practice effects cannot be discounted in these individuals. Any improvements noted in the intervention phase should therefore be viewed with caution.

As I am not trained in neurology, I was not able to carry out neurological examinations on the individuals that attended the OT clinic for coordination assessments, or those who came to Cardiff for MRI scanning. I am therefore unable to eliminate the possibility that the coordination deficits reported here are not better explained by neurological or other medical causes.

The finding that the questionnaire measures of coordination and objective sensorimotor measures do not correlate with each other, and show different relationships with

psychopathology and cognition is intriguing. While the simplest explanation is that the two measures are simply capturing different processes, it is possible that the DCDQ is actually capturing some aspects of behaviour that are also captured by the CAPA and other psychopathology measures, while the sensorimotor measures are a purer measure of motor deficits.

This thesis focused on the investigation of the cerebellum and it remains true that many of the motor and cognitive symptoms observed could be due to basal ganglia abnormalities. The basal ganglia has been demonstrated to show abnormalities in 22q11.2DS and is therefore a potential target for further investigation with regards to motor difficulties and cognitive problems in 22q11.2DS. Similar to the work carried out here, future research should attempt to investigate the contribution of basal ganglia abnormalities, or abnormalities of the white matter projections of the basal ganglia to the coordination and motor deficits in 22q11.2 deletion syndrome.

Due to the exploratory nature of the work a correction for multiple comparisons was not applied. Therefore, it is likely that some of the significant findings presented here are spurious. If correction for multiple comparisons was applied across the entire thesis it is unlikely that many significant results would survive. As such the results should be viewed as targets for further exploration. However, many of the results follow patterns that would be expected given either research in similar populations, or from previous literature around 22q11.2DS.

7.6 Conclusions

Coordination difficulties are a common feature of 22q11.2DS. Like many other aspects of the syndrome, presentation can be variable, with individual children showing different strengths and weaknesses. The loss of the 22q11.2 region seems to result in changes in cortical and

subcortical brain regions such as the parietal lobe, basal ganglia and cerebellum which provide plausible mechanisms for at least some of the coordination difficulties seen in the syndrome. Coordination difficulties in chromosomal disorders represent an under researched area. Future work should focus on better identifying the patterns of difficulties shown in syndromes like 22q11.2DS, along with their interactions with other neurodevelopmental disorders such as ASD, ADHD and anxiety. This may help us understand how coordination difficulties develop and impact daily life in other populations more generally. Finally, interventions for coordination difficulties in 22q11.2DS should be developed further, as they have the potential to help children with their confidence and behavioural problems.

7.8 References

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