# THE ASSOCIATION BETWEEN GENOTYPE AND COGNITIVE, MOTOR AND BEHAVIOURAL PHENOTYPE IN CHILDREN WITH COPY NUMBER VARIANT DISORDERS.

By

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## Intellectual Property and Publication Statement

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others

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## Abstract

Successful child development is determined by several factors, including a child's genotype. Any deviations to the normal 46 chromosomes, can result in chromosomal disorders or more specifically Copy Number Variant (CNV) disorders. CNV disorders are diagnosed when there is sub-microscopic variance within the chromosomal structure, resulting in either a deletion or duplication to genetic material. The exact implications of CNVs for child development are unknown, although there is good evidence to suggest children are phenotypically developmentally delayed. Alongside this, there is a relatively well-developed understanding of the profiles of more common CNV locations and syndromes. Based on this, it was of interest to understand how CNVs 'in general' impact children's cognitive, motor and behavioural development.

Children and families aged 7-16 years with a diagnosed CNV (via NHS Clinical Genetics collaboration) were recruited and completed a range of standardised assessments (Chapter 2). The feasibility of setting up a clinical project, recruiting a paediatric sample and implementing assessments within the home are discussed in Chapter 3. Chapters 4-6 present a descriptive analysis of the full sample with a range of exploratory investigations. Broadly, children with a CNV present below average cognitive and motor development with elevated behavioural symptoms typical of neurodevelopmental disorders (Chapter 4). A complex profile is found in comparison to unaffected sibling and twin controls (Chapter 5) while approximately 50% show similarities to children with a statement of special educational provision (Chapter 6).

Despite the complex genotype and phenotype relationship, having a CNV irrespective of the: location (CNVs at neurodevelopmental disorder susceptibility loci), type (deletion or duplication), size and number of CNV may risk atypical development. These findings may support awareness and understanding of genetic variance and the impact for a developing child system. This may benefit educational settings, children and families as theoretical and practical implications will be discussed.

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## List of Abbreviations

| | |
|---|---|
| Backwards Digit Recall | BDR |
| Block Recall | BR |
| Clinical Evaluation of Language Fundamentals – 4th edition | CELF-4 |
| Conduct Disorder | CD |
| Copy Number Variant | CNV |
| Core Language Score | CLS |
| Deletion Syndrome | DS |
| Developmental Behaviour Checklist | DBC |
| Developmental Coordination Disorder Questionnaire | DCDQ |
| Expressive Language Index | ELI |
| Forward Digit Recall | FDR |
| Intellectual Disability | ID |
| Manual Dexterity | MD |
| Movement Assessment Battery for Children – 2nd edition | MABC-2 |
| Neuro-Developmental Disorder | NDD |
| Oppositional Defiant Disorder | ODD |
| Perceptual Reasoning Index | PRI |
| Prader-Willi Syndrome | PWS |
| Receptive Language Index | RLI |
| Relationship To Mean | RTM |
| Social Communication Questionnaire | SCQ |
| Strengths and Difficulties Questionnaire | SDQ |
| Vanderbilt ADHD Diagnostic Rating Scale | VADRS |
| Verbal Comprehension Index | VCI |
| Wechsler Abbreviated Scale of Intelligence – 2nd | WASI-2 |
| Williams Syndrome | WS |
| Wisconsin Card Sorting Task | WCST |
| Working Memory | WM |
| Working Memory Test Battery for Children | WMTB-C |

# Chapter 1 - General Introduction

## 1.1 Introduction

The human genome contains information that determines how we will develop as humans, which is organised into 46 chromosomes as 23 pairs (Health Education England, 2014). Any deviations or variance to the normal genome arrangement, can occur numerically or structurally. Numerical abnormalities result in changes to the number of chromosomes present in the genome. Examples of this include Downs Syndrome in which there is an extra copy (trisomy) of chromosome 21 and Fragile X Syndrome where there is loss (monosomy) of the X chromosome (National Human Genome Research Institute, 2016). In contrast, structural abnormalities result in changes within the chromosome. These include chromosomal duplications, deletions, inversions, insertions, and translocations. Unbalanced changes within the chromosome that result in losses (deletions) or gains (duplications) of genetic material, are termed Copy Number Variants (CNVs) (Ionita-Laza et al, 2009) and it is these that are the focus of this thesis.

CNVs have been found to increase the risk of human disease and are involved in a range of health conditions (Cook & Scherer, 2008; Crawford et al, 2019; Feuk, Carson, Scherer, 2006; Henrichsen, Chaignat & Reymond, 2009; McCarroll & Altshuler, 2007). In relation to child development, CNVs are risk factors for neurodevelopmental disorders (e.g. intellectual disability and developmental delay) (Coe et al, 2014; Feuk, Carson, Scherer, 2006; Grayton, 2012; Mitchell, 2015) and are implicated in common genetic syndromes: Williams Syndrome (7q11.23 deletion), 22q11.2 Deletion Syndrome, Prader-Willi, and Smith-Magenis Syndromes (Thapar & Cooper, 2013).

This thesis is concerned with understanding how genetic variance impacts children's development. There are complexities surrounding the genotype and phenotype relationship as CNVs can be a source of normal human variation or CNVs can have a multi-systemic impact leading to a range of physical, health and psychiatric difficulties. There is emerging evidence that CNVs are a risk factor for neurodevelopmental disorders, but there is a limited understanding of the specific implications for cognitive, motor and behavioural development. Alongside this, there is well developed understanding of more common CNV syndromes, however there is limited understanding of less common variants and those not associated with a specific syndrome.

This chapter will explore the literature on CNVs and children's cognitive, motor and behavioural development. This is followed by the methodological approach employed in investigating these abilities (Chapter 2), a discussion of the challenges of conducting clinical research with a paediatric patient population (Chapter 3), followed by the research investigations (Chapter 4-6) and a general discussion (Chapter 7).

## 1.2 Copy Number Variants

### 1.2.1 Biological Background

The human body is made up of trillions of cells which contain our hereditary information in the form of 'deoxyribonucleic acid' (DNA). DNA information is stored as a code made up of 4 chemical bases, and the sequence of these bases determine how an organism will function. Specific DNA bases pair up with each other to form units called 'base pairs'. Each base is also connected to a sugar molecule and a phosphate molecule and these exist within a spiral arrangement (double helix). The structure of the DNA molecule is similar to a ladder, whereby the rungs of the ladder represent the base pairs, and the sugar and phosphate molecules are the parallel side structures (Genetics Home Reference, 2020).

Within the nucleus of each cell, the DNA molecule is packaged into structures called chromosomes. Each cell normally contains 46 chromosomes arranged in 23 pairs, and half (of each chromosome pair) are inherited from each parent. Chromosomes 1-22 are referred to as autosomes as they look the same in males and females, whereas the 23$^{rd}$ pair differs between males and females and determines the sex of the individual (Health Education England, 2014). A chromosome is made up of hundreds and thousands of genes, whereby a gene contains a small section of DNA. Genes are responsible for coding specific proteins that are critical for functions of the body such as cells and body tissue structure, function and regulation (Feuk, Carson & Stephen, 2006). Most people have two copies of the gene, one from each parent. However, 'Copy Number Variant' (CNV) disorders occur where there are changes to the number of copies of genes present within the chromosome. This can occur via a deletion or duplication to the genetic material in the chromosome, whereby a deletion results in an individual having only one copy of the genes in that region, whereas duplication results in having three copies (i.e. 2 on the affected chromosome and 1 on the other) (Gershon & Alliey-Rodriguez, 2013).

### 1.2.2 Identification

CNV's can be identified via a range of microarray detection methods and techniques including fluorescence in situ hybridization, array comparative genomic hybridization, and next generation sequencing technologies (Duan et al, 2013; Zarrei, MacDonald, Merico & Scherer, 2015).

In the first instance, referrals to the clinical genetics service can occur due to a variety of reasons. For example, if there is a family history of a genetic disorder then clinical genetics can explore the risk to other family members. Alternatively, a child with a pre-existing diagnosis such as developmental delay or learning difficulties can be referred to investigate whether an underlying genetic basis is contributing to the condition (Bradley-Smith, Hope, Firth & Hurst, 2010). Further family samples may be investigated (from parents and siblings) as the variant can be inherited from a parent, either paternally or maternally or as a new 'de novo' variant (National Human Genome Research Institute, 2016; Nowakowska, 2017).

Following genetic analysis, an individual's genetic profile is described as their 'karyotype'. There is a standard way of reporting this variance (i.e. cytogenetic location) which provides the address of the variant. The specific location of the CNV is referenced by the chromosomal number, the arm (e.g. short (p) or long (q)) and the specific band/s (position) affected (see Figure 1.1) (Conrad et al, 2010; Unique, 2008). The further away from the centre of the chromosome (centromere) the number increases. For example, 14q21 is closer to the centromere than 14q22 (Genetics Home Reference, 2020).

Once a CNV is detected, it can be grouped into one of three main categories: benign, pathogenic, or VOUS. Firstly, 'benign variants' are often reported in the literature and found in the normal population. Secondly, 'pathogenic variants' are well documented in the literature, and are found to have clinical significance with variable outcomes (i.e. varied phenotypical outcomes among carriers of the same CNV). Finally, 'Variants of Uncertain Significance' (VOUS) include CNVs which are not pathogenic or benign as there is limited evidence surrounding their clinical significance (Nowakowska, 2017).

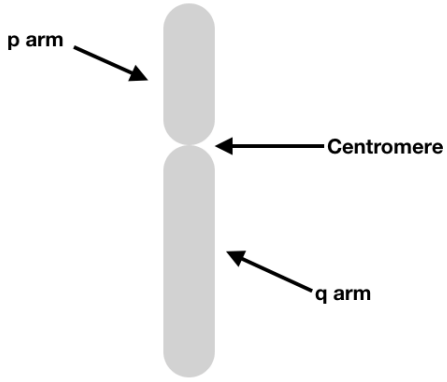


**Figure 1.1: Diagram presenting the structure of a chromosome. Reproduced from The Genomic Education Programme (2014)**

CNVs have been implicated within a range of health conditions with complex phenotypic outcomes (D'Angelo et al, 2013; Preiksaitiene et al, 2014). In relation to child development, there is good evidence surrounding the phenotypical outcomes associated with CNVs that reside within common genetic syndromes (Thapar & Cooper, 2013). These are diagnosed when an individual presents the symptomology typically associated with that genomic loci (Lee & Scherer, 2010). There are well-defined genetic syndromes which are due to copy number variance. These include Angelman Syndrome and Prader-Willi Syndrome (15q11-13 deletion); Williams Syndrome (7q11.23 deletion); Smith-Magenis Syndrome (17p11.2 deletion) and DiGeorge Syndrome/Velocardiofacial syndrome (22q11.2 deletion) (Bradley-Smith, Hope, Firth & Hurst, 2010).

In the case of Velo-Cardio-Facial syndrome or Di George syndrome, this is caused when there is missing genetic material from one copy of chromosome 22. As presented in Figure 1.2, the long arm (q) of the 22$^{nd}$ chromosome and band 11.2 is partly or entirely affected (see red line) and intellectual, developmental and psychological difficulties are typical phenotypical outcomes (McDonald-McGinn & Sullivan, 2011). In the case of less common CNVs, or those not associated with a specific syndrome there is the challenge of systematically defining the significance of the variant. This may be due to limited knowledge of the clinical manifestations associated with more rare variants which are impacted by the factors in the section to follow.

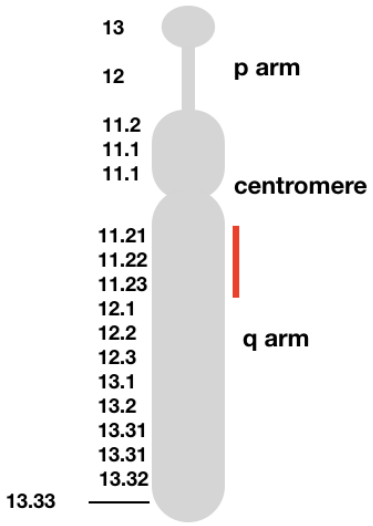


**Figure 1.2: Diagram presenting CNV variance to location 22q11.2. Reproduced from Unique Rare Chromosome Disorder Support Group (2008)**

### 1.2.3 Considerations

Once identified there are factors which may impact how the CNV can influence phenotypical outcomes. These include the CNV type (i.e. deletion or duplication), clinical manifestation (e.g. penetrance and expressivity) the number and loci of the variance.

#### 1.2.3.1 CNV type

Copy number variance can result in either losses (deletion) or gains (duplication) to genetic material at specific loci. Both these variances are important and can subsequently result in diverse phenotypical outcomes, as found in CNVs to 16p13.11 (Nagamani et al, 2011); 17q12 (Rasmussen et al, 2016) and 16p11.2 (Bernier et al, 2017). For example, Abbas, Cox, Smith and Butler (2016) reviewed the literature of the phenotypical symptoms in individuals with a 7q11.23 duplication and the reciprocal deletion (Williams Syndrome). Whilst there were some overlapping phenotypical features, the duplication group were found to suffer from social anxiety with contrasting profiles of overfriendliness in the deletion group. Alongside this, genetic variance may also impact developmental processes differently. For example, macrocephaly (larger brain size) has been reported for individuals with a 1q21.1 duplication in contrast to microcephaly (smaller brain) in deletion carriers (Bernier et al, 2016; Brunetti-Pierri et al, 2008).

#### 1.2.3.2 Expression and penetrance

Genetic variance will manifest itself differently across individuals. 'Variable expression' and 'incomplete penetrance' are factors that can explain the complex relationship between genetic variance and phenotypic outcomes.

Individuals with the CNV may present clinical symptoms that range from severe to entirely absent (Butler et al, 2017; Grayton et al, 2012; Moreno-De-Luca et al, 2013). This highlights the difficulty of defining the genotype and phenotype relationship, as CNVs work in a probabilistic and variable manner. 'Penetrance' refers to the proportion of people that show the phenotypical outcomes associated with the genetic condition. If people do not show the signs or features of the disorder, then this could suggest 'reduced or incomplete penetrance' (Genetics Home Reference, 2020). Not all individuals with a deletion or duplication will present shared phenotypic symptoms as the genetic variance will manifest itself differently in individuals (Grayton, Fernandes, Rujescu & Collier, 2012). This issue of variable expressivity has been detailed across a range of CNV locations. For example, a complex phenotype consisting of developmental delays, dysmorphic features and neurological abnormalities have been reported across patients with a deletion to 15q11.2 (Hashemi et al, 2015). Similarly, individuals with the 16p11.2 CNV have been found to present a range of difficulties including developmental delays, brain size alterations, psychiatric outcomes and congenital abnormalities (Shinawai et al, 2010). Based on the issues discussed above, a child may have a variant at a specific locus but may not present the clinical features typical of the associated syndrome.

#### 1.2.3.3 CNV location

Neuro-Developmental Disorders (NDDs) are caused by atypical brain development, which can result in difficulties with cognition, social interaction, language or motor control (Mitchell, 2015). CNVs have been to associate with NDDs, with variance to specific loci increasing this risk (Hill & Maughan, 2015; Malhotra & Sebat, 2012).

There are well defined neurodevelopmental syndromes which are associated with specific chromosomal abnormalities (e.g. Williams Syndrome) with emerging understanding of some specific CNV regions which increase the risk: 1q21.1; 3q29; 15q13.3; 15q11.2; 16p11.2; 16p12.2 16p13.11 and 22q11.2 (De Wolf, Brison, Devriendt & Peeters, 2013; Grayton, Fernandes, Rujescu & Collier et al, 2012; Kendall et al, 2017; Rosenfeld et al, 2013; Srebniak et al, 2014; Torres, Barbosa & Maciel, 2015).

#### 1.2.3.4 Size and number

CNVs are often diagnosed when there is a segment of DNA that exists at variable number at the size of 1 kilobase (Kb) to several megabases (Mb) in comparison to a normal reference genome (Feuk, 2006; Grayton et al, 2012). CNVs of a larger size (1 Mb or larger) would often warrant medical attention (Lee & Scherer, 2010) but very small CNVs have also been found to be have clinical consequences (Barber, 2005). Alongside this, having more than one CNV has been found to lead to an increase in difficulties. The 'two-hit hypothesis' suggests the presence of second CNV can cause a more profound phenotype (Gillentine & Schaaf, 2015; Girirajan et al, 2010; Kumar, 2010). However, ultimately it is hard to detect or predict how these factors interact and impact phenotypical outcomes due to the various biological processes involved (Rosenfeld et al, 2013).

## 1.3 Theoretical frameworks

CNVs have been identified as being a contributing factor to the onset of Neuro-Developmental Disorders (NDD). NDDs collectively refer to a group of diseases that involve impairments to the growth and development of the brain with an onset during early development, resulting in cognitive, neurological or psychiatric difficulties (Merner, Dion & Rouleau, 2015; Van Den Bossche et al, 2012). NDDs include diagnoses of intellectual disability, developmental delay, speech and language disorders, attention deficit hyperactivity disorder and autism spectrum disorder (Cooper et al, 2011; Morrow, 2010; Mitchell, 2015; Pescosolido, Gamsiz, Nagpal & Morrow, 2013; Sanders et al, 2011). There is evidence of developmental delays and intellectual impairments in individuals with CNVs at specific loci including 16p13.11 (Nagamani et al, 2011), 16p11.2 (Snyder et al, 2016); 15q/15q11.2/15q11q13 (Distefano et al, 2016; Gillentine et al 2017; Von der Lippe, 2011), 1q21.1 (Bernier et al, 2016) and 22q11.2 (Gur et al, 2014; Jonas, Montojo & Bearden, 2014).

To help situate our understanding of how genetic variance may lead to developmental difficulties, we can firstly consider the role of genes. In the case of CNVs, there is a change to the number of copies of genes in that segment. There are approaches that aim to explore how genes directly impact behaviour, such as quantitative behavioural genetics, computational modelling and molecular genetics. Although plausible, there is a need to further assess the role of specific genes and how these contribute to phenotypical outcomes in more detail (Gray, Karmiloff-Smith, Funnel & Tassabehji, 2006). Related to

this, Fisher (2006) argues it is too simplistic to assume direct genotype and phenotype associations of genes and behavioural outcomes. To understand atypical development as characterised in NDDs, the complexity of the biological system needs to be considered. Genes are implicated in the signaling and production of biological processes, but they work in a complex manner, interacting with other networks modulated by environmental variables. Therefore, the various pathways from gene to cognitive and behavioural outcomes need to be considered to explore the genotype - phenotype relationship.

To understand this complex relationship, there is a general consensus that a multidisciplinary, multifactorial and multilevel viewpoint is valuable. This involves considering the various stages involved in development from biological underpinnings (e.g. genes), brain development to behavioural outcomes. Such approaches have been devised to understand typical and atypical development (NDDs) (Cicchetti & Dawson, 2002; Morton & Frith, 2001; Pennington, 2009; Scerif & Karmiloff-Smith, 2005); Williams Syndrome (Jarvinen-Pasley et al, 2008; Nikitina, Medvedeva, Zakharov & Savvateeva-Popova, 2014); 22q11.2 developmental neuropsychiatry (Hiroi et al, 2013); communication disorders (Bishop, 2009) and child development and psychopathology (Cicchetti & Blender, 2004; Reiss & Dant, 2003; Rutter & Sroufe, 2000). To explore these multidisciplinary perspectives further, theoretical frameworks can be considered. These frameworks support the idea that development is complex, and there is an interaction between factors which produce outcomes at a behavioural level. The following section will briefly discuss three relevant theories:

### 1.3.1 The Multiple Deficit Model

The Multiple Deficit Model approach to developmental disorders by Pennington (2006) helps us to understand the complex interaction between etiologic (genetic and environmental), neural, and cognitive factors, and how these factors contribute to the behavioural phenotype (see Figure 1.3).

In contrast to single-deficit approaches, this model takes a multifactorial viewpoint, considering the complexity surrounding the genotype and phenotype link. At each level of the model, the arrows are bidirectional, which emphasise the within-level interactions.

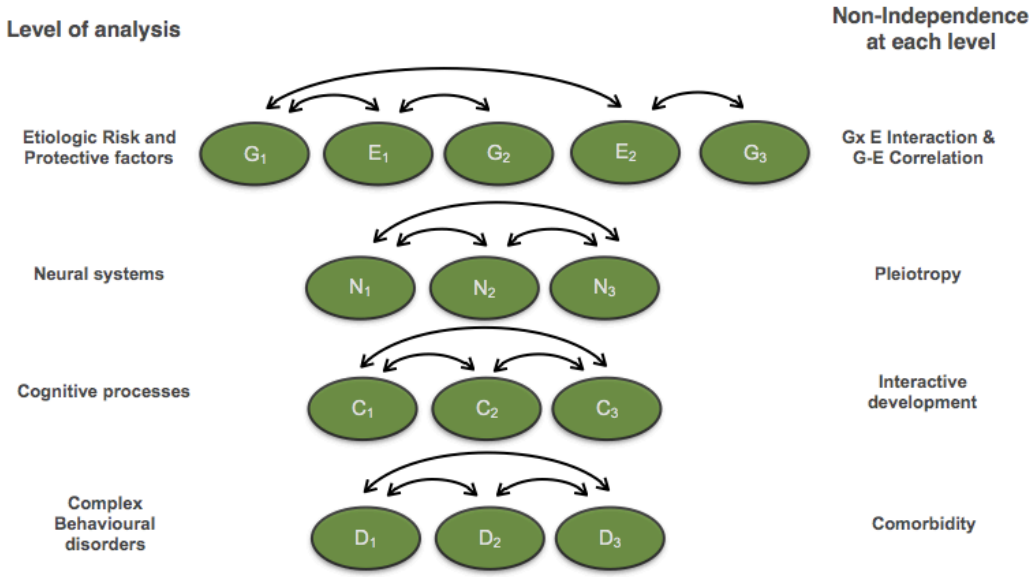


**Figure 1.3: Multiple Deficit Model (adapted from Pennington, 2006)**

Firstly, development is influenced by a series of etiologic risk or protective factors. These factors take the form of genetic abnormalities (G) or environmental factors (E) that interact and alter the development of neural systems. At the neural level, these genetic factors can impact various neural systems and brain development. Often, a CNV location encompasses genes that result in multiple phenotypical outcomes (Willcutt et al, 2005). As a result of these neural changes, there will be changes to the developmental trajectory resulting in atypical outcomes at the cognitive level. As cognitive development is interactive, this can impact various cognitive domains, which lead to varied behavioural symptoms. This final level can lead to phenotypical outcomes that meet the diagnostic criterion of more than one NDD (i.e. comorbidity) (Pennington, Willcutt & Rhee, 2005). Support for co-morbid and/or co-occurring developmental difficulties have been reported. For example, Willcut et al (2010) found overlapping cognitive deficits in reading disorder and ADHD and report that there is no single cognitive deficit that is specific to each disorder, but that there are overlapping features typical in both groups. Alongside this, McGrath et al (2008) report an increased risk of ADHD for children with speech sound disorder and specific language impairment. Similar findings are reported in other studies (August & Garfinkel, 1990; Willcutt & Pennington 2000; which demonstrate how children are at risk developing of more than one NDD.

Alongside this, evidence from the CNV literature can support the pathways presented. There is evidence that copy number variance has been linked to brain malformations or structural changes (Baker, Chaddok, Baldeweg & Skuse, 2011; Kariminejad et al, 2011; Maillard, 2015; Lin et al; 2017; Stein, 2015; Qureshi et al; 2014) and these link to psychiatric symptoms (Ramanathan et al, 2017). This can be explored in the 22q11.2 deletion which encompasses the COMT gene. This gene is involved in prefrontal functions and the reduced gene dosage due to the deletion can subsequently risk deficits to cognitive functions and contribute to psychiatric disorder (Gothelf, Schaer & Eliez, 2008). Finally, links between gene variance, the brain and behavioural outcomes have been reported by Chang et al (2016). They found associations between brain alterations and cognitive and behavioural impairments in 16p11.2 CNV carriers.

### 1.3.2 Intergenerational Multiple Deficit Model

An extension of Pennington (2005) is presented by van Bergen, van der Leij and de Jong (2014) (see Figure 1.4) in the Inter-generational Multiple Deficit Model. This model also focuses on generational influences on development through parental genetic and cultural transmission.

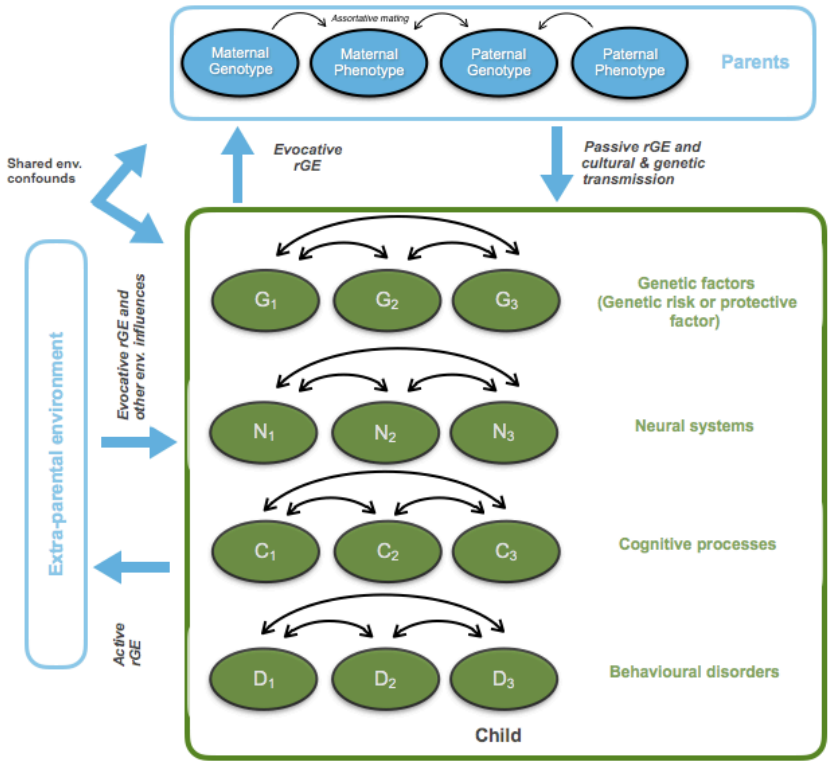


**Figure 1.4: The Intergenerational Multiple Deficit Model (adapted from van Bergen, van der Leij and de Jong (2014)**

The Pennington model (2006) principally focuses on the role of the child. In contrast, the intergenerational model also considers parental characteristics and how these contribute to the child's phenotype. Parents pass on their genes to their children and this determines the child's genetic make-up. In addition to this, parents can influence children's phenotype via 'cultural transmission'. This transmission is linked to the environment children are situated in by their parents and parental characteristics (e.g. parental cognitive phenotype). These parental factors have been implicated in developmental disorders (Pennington et al, 2009) and speech, language and literacy development (McGrath et al, 2007). This model also considers the similarities children can have with their siblings, due to shared parental environmental and genetic factors. In addition to parental factors this model also accounts for the wider environmental influences that can impact developmental outcomes (e.g. extra-parental outcomes) and the interaction with wider environmental influences (see Figure 1.4, blue, left).

This model can be applied to the CNV literature, as work has discussed the role of parental influences on child phenotypical outcomes (Moreno-De-Luca et al, 2015). Earhart et al (2016) report a family of five (1 father and 4 children) who all had a 7q11.23 duplication. They all suffered with language and intellectual delays and met the criteria for Autism Spectrum Disorder. Related to this, Klaassen (2016) investigated the effect of parent's academic attainment on children's cognitive impairments due to 22q11.2 deletion syndrome. They found a significant association between the parent's education level and child's intelligence scores. The authors argue that this supports the idea that parental phenotype can have a modulating effect on their child's phenotype. Finally, Olszewski et al (2014) found significant correlations between IQ scores for 22q11.2 deletion carriers and their relatives which was found to be stable across late childhood to early adulthood. The authors suggest this finding could be attributed to genetic factors (excluding the 22q11.2 locus) and/or environmental influences.

### 1.3.3 Neuroconstructivism

The Neuroconstructivist perspective complements the models discussed above as it adopts a dynamic approach to understanding development by considering the multidirectional interplay between genes, the brain, cognitive processes and the environment (Karmiloff-Smith, 2006; 2009).

This approach challenges those theories that suggest NDDs are characterised by domain-specific impairments (e.g. Nativist approach) and those that aim to directly map genes on to cognitive and behavioural outcomes. For example, Karmiloff-Smith, Scerif and Thomas (2002) reviewed approaches that aim to clarify the association between genes and phenotypical outcomes and found there was not a clear, causal link, but a complex relationship. They found varied phenotypic outcomes for different genetic syndromes which spanned several developmental domains. Rather than interpreting NDDs via the framework of an innate cognitive modular system (Baron-Cohen, 1998; Karmiloff-Smith, 1998), the neuroconstructivist framework highlights the need to consider the various factors at play in a developing system (i.e. the child), and how the components interact and impact on phenotypical outcomes (see Figure 1.5).

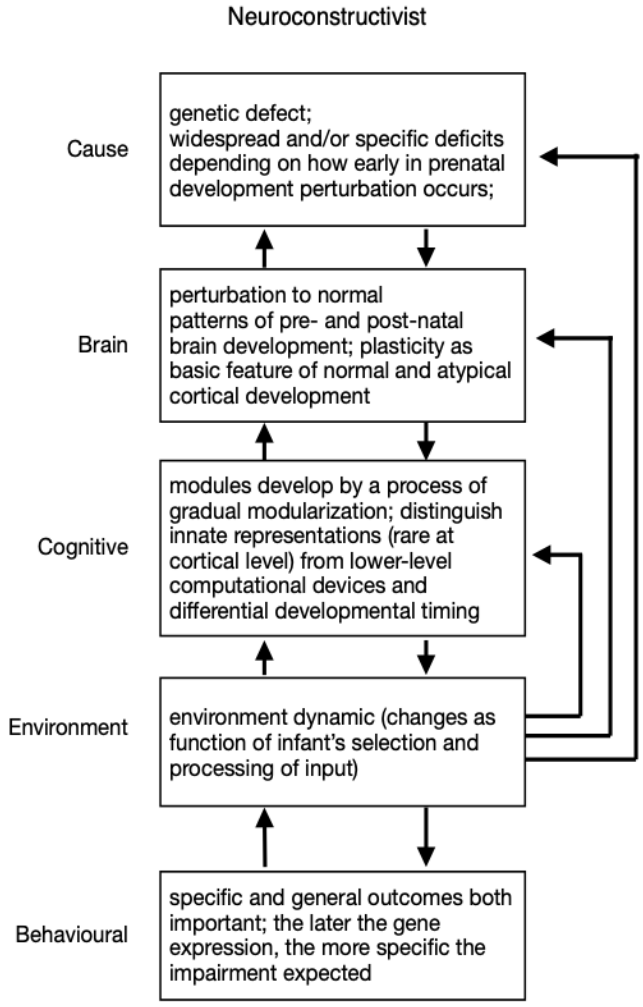


**Figure 1.5: Neuroconstructivist perspective reproduced from Karmiloff-Smith (1998)**

In support of this, Westermann et al (2007) argue that cognitive development is based upon multiple factors that allow children to adapt to their environment through 'mental representations'. These representations take the form of neural activation patterns that allow individuals to respond to the environment. There is a dynamic relationship between the neural system and cognitive development. As children interact with the environment this contributes to brain development and its processing capacity and ability.

Developmental constraints can influence mental representations and impact cognitive development. These limitations exist from the gene to environmental level, and atypical development can be due to altered constraints that influence the developmental trajectory. Karmiloff-Smith argues that phenotypical symptoms that are typical of NDDs emerge from altered trajectories (Oliver, Johnson, Karmiloff-Smith & Pennington, 2000), which can be influenced by genetic mutations, neuronal factors, and other biological factors in combination with environmental adaptions which have widespread effects on the developing system and contribute to atypical behavioural outcomes (Karmiloff-Smith, 1998). For example, parental expectations of their child with a genetic variant may impact the learning and exploration opportunities they create for them, which may influence developmental outcomes from an early age (Massand and Karmiloff-Smith, 2015; Karmiloff-Smith, 2012). As a result of these complex developmental processes, individuals can exhibit phenotypic symptoms that span different NDDs. The effects do not impact behaviour in a neat, clearly defined manner, so some children may show profiles that consist of impairments across developmental domains, with some domains relatively preserved or intact (Karmiloff-Smith, Scerif and Ansari, 2003).

Evidence from the CNV literature can support this perspective. Riley et al (2015) report that individuals with variance at chromosome 2 present a range of phenotypical outcomes which span medical, psychological and physical development (e.g. speech delays, ADHD, short stature, dysmorphic features and feeding difficulties) thus emphasising how genetic variance can span and impact multiple developmental domains and trajectories. Findings by Bernier et al (2017) may support this. They found the number of diagnoses present in children with a 16p11.2 CNV, were greater than the number of children in the sample due to multiple diagnoses per child. This can show the cascading impact of genetic variance across developmental domains. Alongside this, it is difficult to control for shared biological processes and the resulting developmental outcomes as Martin et al (2014)

suggest there are significant shared biological processes affected by copy number variance that coexist within the neurodevelopmental conditions, ADHD and ASD.

Overall, these perspectives provide insight into the complex interaction of factors that are influential for child development. Firstly, genetic abnormalities can have a cascading impact on developmental processes leading to atypical behavioural outcomes. This can explain comorbidity and overlapping phenotypical symptoms present in some NDDs (Pennington, 2006). Extending this, factors external to the child (e.g. parental phenotypes and the environment) can impact phenotypical outcomes (Van Bergen, van der Leij & de Jong, 2014). Finally, the dynamic neuroconstructivist approach (Karmiloff-Smith, 2009) provides understanding of how genetic variance can impact the developmental process and lead to multiple difficulties which span various developmental domains in a unique manner (e.g. domain general or specific patterns).

These perspectives provide an insight into the complex relationship between genotype and phenotype. This project is concerned with understanding how genetic variance influences phenotypical outcomes in more detail. CNVs can contribute towards health risks, neurodevelopmental disorders, and developmental delays. However, of specific interest are these 'delays', and how they can impact children's cognitive, motor and behavioural development with a focus on domain *general* and *specific* outcomes.

## 1.4 Copy Number Variants and cognitive development

Successful psychological development is characterised by a range of cognitive, motor and behavioural skills that allow children to process information, interact with the world and with others. These developmental domains and their associated skills are of focus as they provide the foundations for learning and development (Early Years Foundation Stage, 2012).

### 1.4.1 Cognitive domains

The next section outlines the cognitive developmental domains of focus in this thesis – Intellectual Ability, Working Memory, Cognitive Flexibility and Language ability. These will be discussed in line with their impact for successful child development.

#### 1.4.1.1 Intelligence

Intellectual ability refers to the skill that allows us to reason, solve problems, plan, and reflect on our acquired knowledge (Gottefredson, 1997). Performance is typically assessed by tasks investigating verbal and non-verbal ability which tap into crystallised and fluid abilities respectively. Crystallised intelligence assesses acquired knowledge while fluid reasoning assesses skills of abstract thinking and problem solving (Carroll, 2003). Average performance is at 100, with IQ scores below 70 (2SDs below) suggesting severe intellectual impairment (Gathercole & Alloway, 2008; Neisser et al, 1996).

Higher intellectual ability is advantageous as it supports everyday demands (Gotteredson, 1997), better learning ability (Calero et al, 2007) and is linked to reduced criminal, alcohol and psychological problems (Zettergren & Bergman, 2014). In contrast, lower IQ scores have been linked to a range of outcomes including increased ill health risks, psychological difficulties and delinquent behaviour (Batty, Shipley, Gale, Mortensen & Deary, 2008; Gottfredson & Deary, 2004; Leech, Day, Richardson & Goldschmidt, 2003; Zammit et al, 2004).

IQ ability can have implications for occupational, income, and educational outcomes. In relation to academic achievement and school grades, the role of IQ has been confirmed across a range of studies (Colom & Flores-Mendoza, 2007; Deary, Strand, Smith & Fernandes, 2007; Freberg et al, 2008; Lemos et al, 2014; Roth et al, 2015; Kaufman, Kaufman, Liu & Johnson, 2009). Fergusson, Horwood and Ridder (2005) found low IQ scores at middle childhood were linked to higher rates of unemployment, lower income and welfare dependency in adulthood. In contrast, higher IQ was associated with increased academic achievement (i.e. degree attainment and post-school qualifications).

#### 1.4.1.2 Working Memory

Working Memory (WM) refers to a limited-capacity system that stores information for a short duration (seconds) and is key to learning, cognitive development and academic achievement (Cowan, 2014). Theories exist such as the ‘Embedded-processes’ model by Cowan (1997) whereby information requires attentional resources for successful manipulation or processing. WM is embedded within two levels consisting of long-term memory store (unlimited capacity) and a focus of attention (limited capacity) extended by narrower focus of attention for more selective processing (Oberaurer, 2002).

Of focus in this thesis is the multi-component model proposed by Baddeley and Hitch (1974). This model and its three components have been discussed and investigated extensively (Baddeley, 1996; 1996; 2002; 2003; 2010, Repovs & Baddeley, 2006). The domain general 'Central Executive' (CE) is proposed to support the manipulation of information in relation to the domain specific subcomponent slave systems: the 'Visuospatial Sketchpad' (VS) and the 'Phonological Loop' (PL) which store visuospatial and verbal information respectively. Simple WM (storage) ability is assessed via tasks that require the successful *storage* of information until errors are made. These include the forward digit span (verbal) and block recall (visuospatial) (Gathercole, 1999; Pickering, 2006; Milner, 1971; Corsi 1972). Complex WM tasks assess the *storage* and *manipulation* of information which rely on the CE and either the PL *or* the VS (e.g. backwards digit recall) (Alloway, Gathercole & Pickering, 2006; Alloway et al, 2008). Performance on the WM (simple and complex) have been found to be influential for mathematics, language comprehension and literacy achievement across a range of studies (De Jong, 1998; Gathercole & Pickering, 2000; Gathercole, Pickering, Knight, & Stegmann, 2004; Gathercole, Alloway, Willis & Adams, 2006; Nation, Adams, Bowyer-Crain, & Snowling, 1999).

Performance on WM assessments have been found to be a good predictor of children with poor academic achievement. Children with lower academic achievement on key areas of the national curriculum have been found to perform poorly on complex WM tasks during primary school and secondary school (Gathercole & Pickering, 2000; Gathercole, Pickering, Knight & Stegmann, 2004; St Clair-Thompson & Gathercole, 2006). WM tasks (simple and complex) have been found to relate to mathematics (Amico & Guarnera, 2005; Ashcraft & Kirk, 2001; McLean & Hitch, 1999; Holmes, Adams & Hamilton, 2008; Imbo, Vandierendonck & Vergauwe, 2007) and reading ability (Carretti, Borella, Cornoldi & De Beni, 2009; Daneman & Merikle, 1996; Dawes, Leitão, Claessen & Nayton, 2015; Gathercole & Baddeley, 1990; Jong, 1998; Pham & Hasson, 2014; Seigneuric, Ehrlich, Oakhill & Yuill, 2000; Swanson & Berninger, 1995).

WM is crucial to support learning and academic progress as it supports the basis of acquiring knowledge (e.g. child's capacity to learn) (Alloway & Alloway, 2010). Within the classroom setting, children with WM difficulties may subsequently face challenges and demands that can impact this progress. Tasks include following the teacher's instructions (e.g. content, order and number of instructions); engaging in learning

activities that require the storage and manipulation of content and keeping track of work and current progress (e.g. place keeping errors) (Gathercole & Alloway, 2008; Holmes, 2012). Children with poorer WM have been reported by teachers to have shorter attention spans; more likely to be distracted; less likely to monitor their work effectively and are less efficient at problem solving (Alloway, Gathercole, Kirkwood & Elliott, 2009). Similarly, poorer complex WM has been found to be associated with social impairments (peer rejection and less social competence), and less efficient conflict resolution skills and increased aggression (McQuade, Murray-Close, Shoulberg & Hoza, 2013).

#### 1.4.1.3 Cognitive flexibility

Cognitive Flexibility (CF) (or set shifting) refers to the ability to adjust, adapt and switch our behaviour in response to changes in the environment (Diamond, 2014; Jurado & Rosselli, 2007). CF is assessed by tasks that require individuals to successfully adapt their behaviour, such as card sorting tasks that require participants to switch the rules by which they sort the cards (Anderson, 2002; Kirkham, Cruess & Diamond, 2003). Early reports of CF suggest this skill emerges from the age of three to four years on simple tasks (Epsy, 1997) and there are developmental changes to proficiency of this skill. Throughout childhood and adulthood there is considerable improvement from the age of approximately 7 years to adolescence (Anderson, 2002; Crawford & Channon, 2002; Crone, Ridderinkhof, Worm, Somsen, & Van Der Molen 2004; Daigneault, Braun & Whitaker, 1992).

CF has been found to predict academic achievement in reading and mathematics (Cartwright et al, 2007; 2010; Clark, Pritchard & Woodward, 2010; Cole, Duncan & Blaye, 2014; McClelland et al, 2014; Purpura, Schmitt & Ganley, 2017). In relation to social skills, CF has been found to link to children's understanding of others and their own mental states (theory of mind). Muller, Zelazo, and Imrisek (2005) propose that the skills required during a card sorting task parallel that of shifting between cognitive perspectives when understanding others. Alongside this, better performance on CF tasks have been found to link to better problem solving. For example, Bonino and Cattelino (1999) found children with higher CF were more capable of solving conflict during a social task that assessed cooperative and competitive behaviour. Those with better CF engaged in more turn-taking and less competitive behaviour.

#### 1.4.1.4 Language

Language development focuses on four domains: phonology (production and discrimination of sounds); grammar (language rules); semantics (meaning of words) and pragmatics (communication competence) (Toppelberg & Shapiro, 2000). This PhD explores how well children combine these language domains to communicate effectively, with a focus on how well children understand (receptive) and articulate (expressive) language (Law, Charlton & Asmussen, 2017). Performance in these areas in infants as young as 10 months of age has been associated with cognitive and educational outcomes 10 years later (Bleses et al, 2016; Hohm, Jennen-Steinmetz, Schmidt & Laucht, 2007).

In relation to educational outcomes, difficulties with language can impact how well children can learn, interact with classmates, understand the teacher, access the school curriculum and classroom activities. This is discussed by O'Keefe and Farrugia (2016). Children with receptive language difficulties may struggle with auditory processing (e.g. recognising and interpreting sounds); short term auditory memory (processing and retaining verbal information or instructions) and vocabulary development (e.g. building on previous knowledge). Expressive language difficulties may result in children presenting disordered language (e.g. sentences are hard to understand, lack of grammatical rules) and delayed language (e.g. immature short sentences) (O'Keefe & Farrugia, 2016).

Poorer language skills and disorders have been linked to behavioural problems (Beitchman et al, 1996; Van Daal, Verhoeven & Balkom, 2007) and have been found in children with disruptive behaviour disorders (e.g. Attentional Deficit Hyperactivity Disorder, Oppositional Defiant Disorder) (Gremillion & Martel, 2014). These language difficulties can also lead to social and behavioural difficulties as Menting, Lier and Koot (2011) found children with poor receptive language showed increased externalising behaviours and were also at risk of being rejected by peers. Similar difficulties are reported longitudinally by Levickis et al (2018). Children with language disorder showed associations with hyperactivity/inattention and conduct problems at 4, 5 and 7 years and peer problems at 4 and 5 years.

Language competence allows children to understand others and express their own needs effectively (Keenan & Shaw, 1997). These social aspects of language are known as

pragmatic skills, which allow individuals to use language competently in social/cultural contexts to communicate their intentions, convey meaning, understand other people's intentions and engage in common conversational behaviours (e.g. greeting, turn taking and shared conversation topic) (Adams, 2002; MacWhinney, 2005). These can be nonverbal (e.g. eye gaze or gestures) or verbal (e.g. jokes or figurative language) (Baird & Norbury, 2016). Difficulties with pragmatic abilities can play a role in emotional and behavioural difficulties (Law, Rush, Clegg, Peters & Roulstone, 2015) and have social implications such as social exclusion and difficulty maintaining friendships (Cummings, 2011).

### 1.4.2 Copy Number Variants and cognitive outcomes

The following sections will review studies that explore the cognitive abilities of children with Copy Number Variants with a focus on intelligence, working memory, cognitive flexibility and language.

#### 1.4.2.1 Intelligence

There has been limited work on CNVs and intelligence in children. In relation to adults, MacLeod et al (2012) found no evidence for an association between IQ and rare CNVs and in their large non-clinical sample (over 3,000 elderly participants). However, they did report that CNVs implicated in neuropsychological disorders (at specific loci) were associated with fluid intelligence. Similarly, no associations have been found for rare CNVs and IQ in an adolescent sample (n=800, 15.7-28.9 years) by McRae et al (2013) suggesting the presence of rare CNVs do not account for variations in adolescent IQ. However, the authors discuss that the findings may be limited due to recruitment decisions (taking the individual with the most extreme IQ measure) and the accuracy and detection rate of the microarray testing technique.

Previous work has mainly focused on samples of adults *and* children and those who have genetic variance at specific CNV locations and/or implicated in syndromes. Osorio et al (2012) assessed children, adolescents and adults (7-29 years, (n=15) with a deletion to chromosome 17p11.2 (Smith-Magenis Syndrome) in comparison to controls (n=15). Employing the Wechsler Intelligence Scales (Child and Adult scales) to explore general cognitive functioning, they found clear differences as all but one of the deletion group fell into the mild to moderate intellectual disability range. Similar findings are reported by Hippolyte et al (2016) in their investigation of the cognitive abilities of children and

adults (aged 4.8-59 years) with a 16p11.2 CNV. They found lower scores of the duplication (n=44, FSIQ = 75) and deletion (n=62, FSIQ = 72) in comparison to family controls (n=71, FSIQ=98) employing a range of measures of overall cognitive functioning (Wechsler Intelligence Scales, Wechsler Abbreviated Scale of Intelligence and Differential Ability Scales–2nd Edition).

The intellectual profiles of children with well-defined CNV syndromes have been reported. *Domain general* impairments to intellectual ability have been found in individuals with Williams Syndrome (WS) which is diagnosed by a deletion to the long arm of chromosome 7 at 7q11.23 and is characterised by a distinctive health, developmental and cognitive profile (Donnai & Karmiloff-Smith, 2000). Reviews report Full-Scale IQ (FSIQ) ranges from 40 – 100 (average = 55) (Marten, Wilson & Reutens, 2008). Alongside this, there is increasing evidence on the cognitive outcomes of children with the 22q11.2 Deletion Syndrome (DS) which is characterised by a range of clinical and medical outcomes. In contrast to a typical developing population whereby IQ levels range from 85-115 (mean=100), intelligence has been reported to be approximately 70 (McDonald-McGinn et al, 2015). For example, based upon age-appropriate Wechsler Intelligence Scales, De Smedt et al (2007) found FSIQ ranged from 50-109 (M=73.48, around 2SD below mean) in children (n=103) with only a small number (15/103) in the normal intellectual development range (FSIQ > 85).

Related to this, there has been reports of domain *specific* intelligence profiles for individuals with these syndromes. In children and adolescents with 22q11.2 DS, Lajiness-O'Neill et al (2006) found significantly better verbal IQ than performance IQ (non-verbal). In comparison to controls (n=8), the deletion group (n=14) had lower FSIQ (M=102 vs M=70.0) and verbal IQ (M=107.5 vs M=76.7), however performance IQ was worse (approximately 2SDs below controls) (M=96.4 vs M=67.90) on Wechsler scales. This specific profile of higher verbal IQ than performance IQ (non-verbal) for individuals with the 22q11.2 deletion has been previously reported using standardised measures (De Smedt et al, 2007; Jacobson et al, 2010; Moss et al, 1999; Oskarsdottir, Belfrage, Sandstedt, Viggedal & Uvebrant, 2005; Swillen et al, 1999; Woodin et al, 2001).

A *domain specific* intelligence profile has also been discussed for individuals with WS. Sampaio et al (2009) conducted analysis of intellectual ability (Wechsler Scales) in a group of children and adults (n=17, 7-31 years). Significantly poorer intelligence scores

were found across all subtests (full scale, verbal and non-verbal) in comparison to controls. Although non-significant, the authors report relatively preserved skills in verbal ability, due to better scores on the verbal tasks (digit span mean = 4.43, similarities mean = 3.59) in comparison to severe impairments on the non-verbal IQ tasks (block design mean = 1.29). This domain specific profile has been previously been discussed (Merla, Brunetti-Pierri, Micale & Fusco, 2010; Nunes et al, 2013), with some reporting only slight differences in verbal and non-verbal IQ (Howlin, Davies & Udwin, 1998).

#### 1.4.2.2 Working Memory

In line with the Baddeley and Hitch (1974) model, simple WM tasks refer to those that require maintenance of information in the corresponding slave systems (storage), whilst complex tasks require recruitment of the slave system and the central executive (manipulation).

A *domain specific* WM profile has been reported for children with 22q11.2 DS consisting of impairments to spatial WM (Bearden et al, 2001). In children (5-12 years) Wang, Woodin, Kreps-Falk and Moss (2000) found verbal simple WM was within the normal average range (M=9.1, SD=3.0), while visual-spatial ability fell below average (M=7.0, SD=2.5) (population mean=10). In relation to visuospatial complex WM, Wong, Riggins, Harvey, Cabaral and Simon (2014) found children with 22q11.2 DS (n=47) made more spatial and temporal errors in comparison to controls (n=49) in a computerised task requiring children to recall the location of a frog that appeared sequentially at different locations on the screen.

Related to these domain *specific* weaknesses, similar findings have been reported children with WS. There has been a profile of poor performance on visuospatial memory tasks such as the Corsi span task (simple visuospatial WM) in relation to controls (Conners, Moore, Loveall & Merrill, 2011; Vicari et al, 1996; Vicari, Bellucci & Carlesimo, 2003). For example, Rhodes et al (2011) aimed to extend this previous research, by exploring complex WM performance in children and adults (n=14, 11-29 years). In relation to typically developing controls, the WS group were impaired on the verbal tasks (simple and complex WM) and the complex visuo-spatial WM task. A contrasting profile was found for simple visuospatial WM, as no effect was found for group differences in remembering spatial locations.

These findings suggest that children with WS are impaired on spatial tasks that require information to be held and subsequently manipulated. Vicari, Bellucci and Carlesimo (2006) found children with WS were impaired on a task that required mental rotation in contrast to a simple mental visualisation. The authors discuss this in relation to poor executive function deficits, which could be contributing towards the impairments in manipulation (Menghini et al, 2010; Rhodes et al 2010; Rhodes et al, 2011).

#### 1.4.2.3 Cognitive Flexibility

Previous work has been conducted in children with more commonly known CNV syndromes. Osorio et al (2012) assessed executive functions in children and adults (n=17, 9.6-29.3 years) with WS. The CNV group performed significantly worse than controls across executive function tasks. In relation to performance on the shifting task (Wisconsin Card Sorting Task, WCST) the deletion group had a higher average rate of perseverative errors (M=40.1, SD=17.9) in contrast to controls (M=15.5, SD=24.5).

There are clear difficulties faced by children with 22q11.2 DS on tasks assessing cognitive flexibility. Poor WCST performance has been reported for children (Lajiness-O'Neill et al, 2006) and for children and adults on a set-shifting task (Campbell et al, 2010). Related to this, Shapiro, Wong and Simon (2013) investigated the development of response inhibition in children with 22q11.2 DS by administration of a Go/No-Go paradigm. Two component processes were assessed: proactive (anticipatory) and reactive (actual stopping). Proactive stopping required slowing down in preparation for a stimulus, which involved effective monitoring of the task content. In comparison to controls, the CNV group performed worse on reactive stopping than proactive stopping. This finding highlights difficulties in inhibitory behaviours in deletion carriers compared with controls. Overall children with this CNV have been found to exhibit difficulties on tasks that require flexible thinking and manipulation of information (Chawner et al, 2017; Shapiro, Tassone, Choudhary & Simon, 2014).

#### 1.4.2.4 Language

In relation to copy number variance and language outcomes, Owns and Beatty-DeSana (1981) reported expressive language difficulties in four patients (3 children, one adult) with a duplication to 9p. Severely affected language skills have also been reported for children, adolescents and adults with chromosome 4 syndrome (deletion to 4p). The sample presented significant difficulties in communication and expressive language

skills, which fell below the 36-month age developmental functioning level (Marshall, 2010). Although there is emerging evidence of the language skills in individuals with less common CNVs, there is a greater understanding of common CNV syndromes.

*Domain general* language difficulties are prominent within WS (Brock, 2007; Mervis & Becerra, 2007) with deficits suggesting a distinctive developmental path (Karmiloff-Smith et al, 1997). Joffe and Varlokosta (2007) explored the language abilities of 10 children with WS. On standardised measures of receptive and expressive language, the WS group performed at or below 2 SDs below the mean for receptive grammar, expressive vocabulary, expressive semantics and expressive grammar, and performance across all language tasks was lower than typically developing controls (n=10).

Children with WS have been found to have difficulties in communication and pragmatic language ability (Asada, Tomiwa, Okada & Itakura, 2010; Hoffmann et al, 2013; John, Dobson, Thomas & Mervis, 2012; Stojanovik & James, 2006; Stojanovik, 2006). This can include difficulties expressing what they mean (Asada et al, 2010) and interpretation of sarcasm and metaphors (Godbee & Porter, 2013) as identified in early development (toddlers) (Laing et al, 2002). Language development in the context of WS have been found to follow an atypical developmental trajectory which can link to difficulties in responding and asking for information (Stojanovik, 2006). These difficulties may be due to the underdevelopment of receptive and expressive language in individuals with WS, which may impact proficiency of pragmatic skills (Van Den Heuvel, Manders, Swillen & Zink, 2016).

Related to this, children with WS have been found to have difficulties with conversational and communication skills (Asada, Tomiwa, Okada & Itakura, 2010; John, Rowe & Mervis, 2009) which can further impact their social communication skills (Alfieri et al, 2017). For example, Van Den Heuvel and colleagues (2017) compared children with WS (n=8, ages 6–12) and 22q11.2 DS (n=8, ages 7–13) and found both groups showed impairments in conversational ability. The WS group showed difficulties in managing the topic of a conversation and tended to dominate the conversation which contrasted to a less dominating role observed in the 22q group. In relation to this, general socio-communicative and specific pragmatic language difficulties have been reported for children with 22q11.2 DS. These include difficulties grasping implicit meanings,

adapting language appropriately to the environment and using contextual information adequately (Heuvel, Manders, Swillen & Zink, 2017).

Related to the 22q11.2 DS, there have been reports of language difficulties and delays reaching speech and language milestones for children from reviews (Ousley et al, 2007) and language and communication investigations (Persson et al, 2006; Solot et al, 2000; Solot et al, 2001). This language phenotype may be specific to this CNV group as Rakonjac et al (2016) compared children with the 22q11.2 DS to two control groups. One group had a phenotype resembling that of 22q11.2 DS (e.g. facial appearance, heart malformations) and the other were age-matched typically developing controls. The authors suggest a significant effect of genotype as speech and language delays were found in the deletion group in comparison to both control groups. Similar difficulties have been reported using standardised language measures (Clinical Evaluation of Language Fundamentals, CELF). Moss et al (1999) found low scores across expressive language (M=66.4, SD=14.7); total language (M=66.9, SD=14.9) and receptive (M=70.6, SD=16.3) domains. Similarly, using the same measure, Glaser et al (2002) reported overall language functioning in the 'moderately delayed' to 'severely delayed' range' (M=70.4, SD=18.5) in children and adolescents (n=27).

There have been language difficulties reported for children with Prader-Willi Syndrome (PWS). This syndrome is characterised by a deletion to 15q11-13 (paternally inherited chromosome), which contrasts to Angelman syndrome (maternally inherited chromosome) (Buiting, 2010). Dimitropoulos, Ferranti & Lemler (2013) explored the language functioning of children and adults (n=35, 7-44 years) with PWS using the Clinical Evaluation of Language Fundamentals-4. They found significant impairments to core language ability in the very low range (scores of 70 or below) and low receptive (M=57.19, SD=11.1) and expressive language (M=60.54, SD=13.3) scores.

Overall in relation to CNVs and cognitive outcomes, previous work has focused on both children and adults with investigations of the domain general and specific profiles of more commonly known CNV syndromes (e.g. Williams Syndrome and 22q11.2 DS). A range of deficits have been reported but there has been limited work on how copy number variance in general (regardless of loci or syndrome) impacts cognitive development.

## 1.5 Copy Number Variants and motor development

The following section describes outlines the motor skills of focus in this thesis – fine motor and gross motor ability. These will be discussed in line with their impact for successful child development and in relation to the CNV literature.

### 1.5.1 Motor domains

Motor competence is essential for our interactions with the world as it enables us to successfully respond to environmental demands (Adolph, 2008). Within early settings (e.g. preschool), children spend a vast amount of their time engaging in activities that require adequate motor skills to help them learn and explore (Marr, Cermak, Cohn & Henderson, 2003). These skills are linked to educational (Bart, Hajami & Bar-Haim, 2007) and social (Livesey, Mow, Toshack & Zheng, 2010) outcomes.

Movement difficulties can impact activities of daily living, eating skills, activity participation and academic achievement (Magalhaes, Cardoso & Missiuna, 2011; Prunty, Barnett & Plumb, 2013; Jolly & Gentaz, 2014; Kirby, Sugden & Purcell, 2013; Schoemaker et al, 2013; Summers, Larkin & Dewey, 2008; Wang, Tseng, Wilson & Hu, 2009; Zwicker, Missiuna, Harris & Boyd, 2012). In relation to academic achievement, individuals with motor problems have been found to have poorer school progress and motivation (Cantell, Smyth & Ahonen, 2003), risk of learning difficulties (Dewey, Kaplan, Crawford & Wilson, 2005) and lower aspirations (Cantell, Smyth & Ahonen, 1994). Alongside this, coordination difficulties can risk negative social, emotional and psychological outcomes. This includes being bullied (Piek et al, 2005); reduced perceptions of self-worth (Piek, Baynam & Barrett, 2006) and negative mental health and wellbeing (Cairney, Veldhuizen & Szatmari, 2010; Green, Baird & Sugden, 2006; Kirby, Williams, Thomas & Hill, 2013). These difficulties can lead to social isolation as children with coordination difficulties have been found to have lower levels of participation (play, leisure and social activities) and enjoyment levels (Bart, Jaurs, Erez & Rosenberg, 2011; Cairney et al, 2005; Mandich, Polatajko & Rodger, 2003; Skinner & Piek; 2001); face isolation in the playground (Smyth & Anderson, 2000) and have fewer social hobbies and past-times (Cantell, Smyth & Ahonen, 1994).

Such movement difficulties are a major diagnosing factor of Developmental Coordination Disorder (DCD). This disorder can emerge in children and persist throughout development and impact other developmental domains (Cousins & Smyth, 2003; Geuze

& Borger, 1993; Losse et al, 1991). It is broadly manifested by *domain general* (e.g. poor fine and/or gross) motor skills (Sugden & Wade, 2013; Visser, 2003). In relation to these skills, impairments can occur *domain-specifically* where performance is impaired on specific motor domains such as balance tasks in comparison to manual dexterity tasks (Dewey & Kaplan, 1994). The following sections will discuss these in detail.

#### 1.5.1.1 Fine motor

Fine motor skills include the recruitment of smaller muscle groups, as required during tasks that require manipulation, reaching or grasping (Payne & Isaacs, 2016). During childhood, these skills are essential for children to learn, interact and explore the environment and gain independence (e.g. eating, fastening buttons and tying shoelaces). Fine motor competence can link to mental health and wellbeing (Hill et al, 2016); perceptions of self-worth (Piek, Baynam, & Barrett, 2006) with links to later academic achievement (Grissmer et al, 2010) and risk of educational underachievement (Stoeger, Suggate & Ziegler, 2013).

In relation to academic achievement, children with learning difficulties have been found to present movement difficulties (Vuijk et al, 2011). Fine motor skills are key for handwriting (Feder & Majnemer, 2007) with children of poorer ability presenting errors in writing and letter size judgment (Feder & Majnemer, 2007; Volman, Schendel & Jongmans, 2006). Fine motor competence has also been linked to early maths skills, as successful exploration and manipulation of objects can facilitate knowledge acquisition and learning (Luo, Jose, Huntsinger & Pigott, 2007; Pagani & Messier, 2012).

#### 1.5.1.2 Gross motor

Gross motor skills encompass the use of large muscle groups which are involved in actions that stabilise the body. These skills are essential for development and are as important as fine motor skills to support activity and interaction with the environment (Cools, De Martelaer, Samaey & Andries, 2009). Actions include balance, sitting and walking which are supported by a postural control system (Payne & Isaacs, 2016). Delays to the development of this system can result in impairments and constraints to the skills that support mobility, reflexes, and effective coordination, resulting in abnormal postural movements and adaptation in response to everyday demands (Shumway-Cook & Woollacott, 2007).

Poor gross motor ability has links to low academic achievement and future achievement (Knight & Rizzuto, 1993; Lopes, Santos, Pereira & Lopes, 2013; Son & Meisels, 2006). For example, Westendorp et al (2011) found that children with learning difficulties scored significantly lower on tasks assessing gross motor ability, in comparison to a typically developing sample. They also report a significant link between locomotor skills and reading performance, with an increased lag in learning to read linked to poorer locomotion (e.g. running, hopping, jumping). Further to this, poor gross motor skills have been linked to less peer acceptance in play settings (Livesey, Mow, Toshack & Zheng, 2010) and greater likelihood of being bullied (Bejerot, Plenty, Humble & Humble, 2013).

### 1.5.2 Copy Number Variants and motor outcomes

There has been limited work on how *copy number variance* impacts motor development specifically, as the majority of work has focused on CNV locations and syndromes. CNVs have been found in 26% of subjects (n=82) with Developmental Coordination Disorder (DCD) (Mosca et al, 2016). Alongside this, impaired motor development (e.g. hypotonia and abnormal motor agility) and movement difficulties have been reported in case studies (Pebrel-Richard et al, 2012; Lindstrand et al, 2010; Willoughby, Favero, Mochida & Braaten, 2014). The following will discuss more common syndromes.

*Domain general* impairments to motor abilities have been reported for children and adolescents with Angelman Syndrome (AS) (deletion to maternal 15q11-13 chromosome). These consist of delays reaching motor milestones and immature fine and gross motor movements which parallel early developmental motor skills (Beckung, Steffenburg & Kyllerman, 2004; Clayton-Smith & Laan, 2003). Motor delays have also been reported in 90-100% of children with Prader-Willi Syndrome (PWS) (deletion to the *paternal* chromosome) (Cassidy, Schwartz, Miller & Driscoll, 2012). This syndrome is characterised by short stature, health problems, developmental delays, obesity and hypotonia in early development (Greenswag, 1987; Cassidy, 1997). Children have been reported to perform poorly on standardised motor performance assessments (Carrel, Myers, Whitman & Allen, 2002; Lam et al, 2016) with *domain specific* motor impairments to gross motor skills. These gross motor skills may link to the major characteristic of hypotonia (low muscle tone and muscle strength) and obesity in this syndrome, which may result in difficulties reaching motor milestones, (Goelz, 2006; Reus et al, 2011).

Motor delays have also been described for children with Williams Syndrome (WS). These exist as *domain general impairments* to motor functioning and development across the lifespan (Carrasco et al, 2005; Chapman, du Plessis & Pober, 1996; Gagliardi, Martelli, Burt & Borgatti, 2007; Tsai, Wu, Liou & Shu, 2008). A *domain-specific* profile for school aged children (n=38) with WS has been presented by Wuang and Tsai (2017) consisting of fine motor skill impairments relative to gross motor skills. The authors suggest this could be attributed to the demands placed on the frontoparietal network during tasks assessing manual dexterity. The difficulties may be due to inadequate development of this system, which could also relate to the developmental delays and cognitive difficulties present within this group (Davare et al, 2006; Martens, Wilson & Reutens, 2008; Wuang & Tsai, 2017).

In relation to children with 22q11.2 DS, there have been reports of movement difficulties which continue throughout development. Sobin et al (2006) administered the Movement Assessment Battery for Children and found 94% of children had marked deficits. They analysed performance longitudinally and found difficulties to motor skills emerge early in development (from 4 years) and continue throughout school age. Related to this, Van Aken et al (2007) explored the motor development of primary school aged children (n=37) with 22q11.2, and a control group (n=34). All the children in the control group scored above the 15th percentile (i.e. no signs of movement difficulty) in contrast to only 8 in the CNV group. These motor difficulties have been found to emerge in early development. Swillen et al (2005) assessed the motor development of children with 22q11.2DS with the presence of a heart defect (n=11, mean age=41months) in comparison to those without the deletion but with a heart defect (control group) (n=19, mean age=46months). They found significantly lower performance of the CNV group, with a specific profile of performance deficits on the gross motor measures. These tasks assessed locomotion and stationary ability, which require children to balance and coordinate movements successfully relying on cerebella structures. These performance difficulties could link to the early health complications of hypotonia (low muscle tone and strength) in this CNV group (Boot et al, 2015; McDonald-McGinn et al, 2016; Swillen et al, 1999).

There has also been a *domain specific* motor profile reported for children with 22q11.2 DS by Van Aken et al (2009), consisting of difficulties in manual dexterity, visual perception and motor coordination. For example, Van Aken et al (2010) explored the

underlying processes that may link to the motor deficiencies in this CNV group. They investigated this using a visuo-motor task which assessed the accuracy and stability of participants' arm movements. The CNV group moved faster than controls to reach the target point, and then struggled to make corrective movements to locate the target effectively. When reaching a target point of interest, there is usually an initial movement stage followed by corrective movements to reach the target. If the initial stage is performed with excessive velocity, then more precision movements are required to help reach the target effectively. The lack of this precision effect in the deletion group can be attributed to differences in feedforward planning, which involves an understanding of the motor movement before it is executed. These *specific* motor difficulties in children with 22q11.2 DS may be due to inadequate predictions of the consequences of their motor actions, which may relate to the difficulties with cognitive flexibility as previously discussed (Antshel, Fremont & Kates, 2008; Woodin et al, 2001).

This section has discussed literature on the motor profiles of children with CNVs. At present the work has mainly explored groups of children with more common genetic syndromes (e.g. 22q11.2DS, WS and PWS). Within these syndromes' *domain general* and *specific* motor profiles have been discussed, but there is still limited understanding of how *general* structural variance impacts motor development.

## 1.6 Copy Number Variants and behavioural development

### 1.6.1 Behavioural development

In line with the theoretical frameworks discussed, genetic variance can have a cascading impact on phenotypical outcomes. Children can present a range of behavioural difficulties which span or lead to neurodevelopmental disorders.

Social communication difficulties that affect how children interact and understand others can be manifested within Autism Spectrum Disorder (ASD). ASD encompasses difficulties across three domains: social interaction; verbal and nonverbal communication and restricted/repetitive interests or activities (Charman, 2003; Plomin et al, 2013; Reid, Lannen & Lannen; 2016). Socially, children with autism show fewer behaviours relating to joint attention and social interaction (Griffith, Pennington, Wehner & Rogers, 1999) but with relatively intact understanding of other's intentions (Carpenter, Pennington & Rogers, 2001). Communication and language problems include acquisition delay,

difficulties in responding, sustaining and initiating communication and repetitive or stereotyped use of language (Frith, 1989). Individuals who are affected often have other comorbid difficulties that impact mental health, sensory domains, eating, sleeping daily living and motor functioning (Couteur & Szatmari, 2015) with intellectual disability most commonly co-occurring (Matson & Shoemaker, 2009).

Difficulties with attention that impact home and school functioning can give rise to Attention Deficit Hyperactivity Disorder (ADHD) these difficulties can be predominately inattentive, predominately hyperactive-impulsive, or combined (inattentive and hyperactive) (Said, Huzair, Helal & Mushtaq, 2015; Rowland et al, 2008). Attentional and impulsivity difficulties can impact social situations (e.g. having fewer friends, being unpopular or social rejection) (Nijmeijer et al, 2008) and risk poor academic achievement and educational progress (Loe & Feldman, 2007) with adverse long-term outcomes (e.g. higher school dropouts, absenteeism and having to repeat an entire school grade) (Barbaresi et al, 2007). In relation to life outcomes, ADHD has been linked with increased risk of: injury (Merrill, Lyon, Baker & Gren, 2009; Pastor & Reuben, 2006), driving-related problems in adulthood (Thomas, Molina, Pelham & Gnagy, 2007); sleep problems (Spruyt & Gozal, 2011); delinquency (Meier, Perrig & Koenig, 2012) and the development of substance and alcohol abuse problems (Charach, Yeung, Climans & Lillie 2011; Lee, Humphreys, Flory, Liu & Glass, 2011).

Commonly comorbid (30-50%) with ADHD are disruptive behavioural disorders: Oppositional Deficit Disorder (ODD) and Conduct Disorder (CD) (Burns et al, 2001; Ghosh & Sinha, 2012; Loeber, Burke & Lahey, 2000) which are characterised by antisocial or violent behaviours (Soppitt, 2016). During early development, children typically learn behavioural and emotional control, however some may face difficulties acquiring these skills and defiant and disruptive behaviours may emerge and persist (Egger & Angold, 2006). These impairments may link to the development (neural and structural) and functioning of frontal brain regions involved in empathy and emotional regulation (Blair, 2001; Popma & Vermeiren, 2008) and to the emergence of violent behaviours (Davidson, Putnam & Larson, 2000). Children with ODD are found to have more aggressive solutions to peer social problems than controls (Coy, Speltz, DeKlyen & Jones, 2001) and face difficulties on cognitive tasks (Speltz et al, 1999). These disorders can risk negative future outcomes (e.g. developing major depression; smoking, psychoactive substance misuse, being fired from a job and school expulsion) (Biederman

et al, 2008) along with major costs to society based factors of social exclusion, crime and social economic status (Scott, Knapp, Henderson & Maughan, 2001).

Emotional competence relates to how children successfully regulate and overcome negative emotions (Huppert, 2009). Competence in this behaviour has been linked to school readiness and school success (Raver, 2003) and children who find this difficult are found to be less productive in the classroom, struggle with learning tasks and are less accurate during their work assignments (Graziano, Reavis, Keane & Calkins, 2007). Difficulties in emotional regulation can manifest within emotional or mood disorders such as anxiety and depression (Ladouceur et al, 2005; Leyfer, Gallo, Cooper-Vince & Pincus, 2013). Children with depression have been found to present social difficulties, low self-esteem, low confidence, decreased self-worth and cognitive difficulties (Kaslow, Rehm & Siegel, 1984; McClure, Rogeness & Thompson, 1997). Related to cognitive outcomes, individuals with depression have been found to perform poorly across tasks of executive function (e.g. attention shifting and memory) (Beats, Sahakian & Levy, 1996; Matthews, Coghill & Rhodes, 2008; Nebes et al, 2000; den Hartog et al, 2003; Grant, Thase & Sweeney, 2001; Tsourtos, Thompson & Stough, 2002).

### 1.6.2 Copy Number Variants and behavioural outcomes

The following section describes outlines the behavioural symptoms of focus in this thesis – Social Communication, Behavioural Difficulties, Psychological and Emotional and Attentional Difficulties. These will be discussed in line with their impact for successful child development and in relation to the CNV literature.

#### 1.6.2.1 Social communication

CNVs are implicated in neurodevelopmental disorders that encompass behavioural difficulties relating to social communication and interaction, such as ASD (Marshall et al, 2008; Heil & Schaaf, 2013). CNV variance has been found to influence ASD susceptibility (Weiss et al, 2008) and ASD diagnoses and symptoms have been reported in case reports and small groups of less common CNVs: duplications to xp11.22-p11.23 (Edens et al, 2011); 18q12.1-q12.2 duplication (Wang et al, 2013); 12p13.33 deletion (Silva et al, 2014); 14q32.2 deletion (Babovic-Vuksanovic, Merritt, Jalal & Barbaresi, 2004); 2q23.1 deletion (Mullegama, Alaimo, Chen & Else, 2015) and 19p13.2 deletion (Welham et al, 2015).

There is more evidence for social communication profiles of children with CNV syndromes. For example, 90% of children (n=20, 4-18 years) with Smith-Magenis Syndrome (17p11.2 deletion) were found to have scores that fell in the autism range (Laje et al, 2010). Alongside this, children with 22q11.2 DS have been reported to have: poor social competence (Campbell et al, 2011); difficulties on experimental tasks that require understanding of mental states (Ho et al, 2012) and impairments to social skills, social cognition and social functioning (Vangkilde et al, 2016). Studies have shown that children with 22q11.2 DS present behaviours that are symptomatic of ASD which span: reciprocal social interaction; communication; repetitive and restricted behaviour and interests (Angkustsiri et al, 2014; Fine et al, 2005; Kates et al, 2007). In their review, Bertran, Tagle and Irarrzazaval (2018) reported that 20%-50% of individuals with 22q11.2 DS met the DSM-IV diagnosis for ASD. Based upon the social communication difficulties and repetitive behaviours found in children, adolescents and young adults with this deletion, it has been suggested that individuals with 22q11.2 DS should be screened for ASD in early development (Ousley et al, 2017).

Similar social communication and interaction difficulties have been reported for children with WS. Klein-Tasman, Mervis, Lord and Phillips (2007) found 50% of children showed socio-communicative deficits that paralleled ASD. This was characterised by restrictive/repetitive behaviours, communication deficits, and difficulties with reciprocal social interaction. Adolescents with this CNV have been shown to find it difficult to know the difference between lies and jokes, which can subsequently impact peer relations and social situations & interactions (Sullivan, Winner & Tager-Flusberg, 2003). These social difficulties can extend into adulthood and impact interpersonal interactions, friendships and the ability to handle conflicts (Fisher & Morin, 2017). Although some individuals with WS have been found to exhibit ASD behavioural symptomatology, other studies have shown an alternative profile of social difficulties in this CNV group which are more socially orientated (Lincoln, Searcy, Jones & Lord, 2007). Children with WS have been reported to have less stranger anxiety and interact inappropriately with unfamiliar individuals. For example, Dodd, Porter, Peters and Rapee (2010) conducted an experiment to see if children would engage with a stranger when the face was seen (social) or when it was covered (non-social). Compared to controls, children with WS were more likely to engage with the stranger in both conditions. Therefore, whilst there

are overlaps with ASD in relation to some behavioural symptoms in this group, the social behaviors can also be characterised by 'hyper-sociability' (Jawaid et al, 2012).

Social communication difficulties encompassing ASD-like profiles and diagnoses have been reported for individuals with Angelman Syndrome (AS) and Prader-Willi Syndrome (PWS) (Bennett, Germani, Haqq & Zwaigenbaum, 2015; Dimitropoulous & Schultz, 2007; Dimitropoulous, Ho & Feldman, 2013; Peters, Beaudet, Madduri & Bacino, 2004; Veltman, Craig & Bolton, 2005). Children and adults with PWS have been found to show difficulties with social behaviour (theory of mind) and high rates of ritualistic, rigid and repetitive behaviours (Clarke et al, 2002; Lo, Siemensma, Collin & Hokken-Koelega, 2013; Greaves, Prince, Evans & Charman, 2006).

#### 1.6.2.2 Behavioural difficulties

There have been reports of the behavioural profiles of children with less common CNVs. This includes maladaptive behaviours in 22q13 deletion carriers (Shaw, Rahman & Sharma, 2011) and behavioural difficulties (repetitive, obsessive attachments to objects; self-injurious behaviour; stubbornness and clumsiness) in children with a 5p12 deletion (Cri du chat syndrome) (Cornish & Pigram, 1996).

In relation to more common CNV locations, there is understanding of the behavioural patterns of children with AS. Difficulties include aggression; non-compliance; repetitive and stereotyped behaviour (Summers, Allison, Lynch & Sandier, 1995). There is a particular pattern of 'food-related' behaviours present in this CNV group which included chewing; mouthing objects; eating non-food items; gorging food and an increased appetite (Berry, Leitner, Clarke & Einfeld, 2005). Similar behavioural difficulties are reported by Walz and Benson (2002). They also commented on the cheerful disposition of children with AS in contrast to anxious and overly sensitive profile of those with PWS.

Individuals with PWS have been found to present similar behavioural difficulties during childhood and adulthood of temper tantrums; difficulties with routines; skin picking; lying and aggression (Cassidy, 1997; Cassidy & Driscoll, 2009; Clarke et al, 1996; Dykens & Cassidy, 1995; Dimitropoulos, Feurer, Butler & Thompson, 2001; Holland et al, 2003; Holm et al, 1993). These difficulties are present within school or group settings as self-aggressive acts (e.g. head banging, biting), temper tantrums and impulsiveness (Poisson et al, 2015). In contrast to controls, Einfeld et al (1999) found children with PWS have been found to present higher levels of antisocial behaviours on the

Developmental Behaviour Checklist (e.g. lying, stealing, hiding and lighting fires). Although not significantly different, the PWS group also scored higher on the communication disturbance; anxiety; social relating; disruptive and self-absorbed scales.

#### 1.6.2.3 Psychological and emotional difficulties

There has been reports of CNV variance in individuals with Major Depressive Disorder (Degenhardt et al, 2012) and emerging evidence of the psychological development of less common CNVs such as children and adults with chromosome 18 variance (Zavala et al, 2010). However, there is more information available on the psychological development of individuals with more common syndromes.

Emotional and psychological difficulties have been reported for PWS (Reddy & Pfeiffer, 2007) with adolescence and young adulthood as key developmental periods for increased difficulties (Steinhausen, Eiholzer, Hauffa & Malin, 2004). In comparison to controls, Skokauskas et al (2012) found children (N=24, Mean age=9.92) with PWS had higher internalising problems on the Child Behaviour Checklist consisting of withdrawn-depressed behaviours. Using the same assessment measure, van Lieshout et al (1998) found the emotional and behavioural profiles of children with PWS were comparable to children attending Mental Health Centres. In contrast to non-clinical controls, both groups scored within the clinical range presenting attentional problems, delinquent behaviour and withdrawn symptoms.

There is also evidence of the psychological phenotype of children and adolescents with 22q11.2 DS which commonly consists of withdrawn behaviour, anxiety and depression (Jolin et al, 2009; Kelley, Sanders & Beaton, 2016). Children with 22q11DS are at risk of anxiety and depression in contrast to typically developing controls (Stephenson et al, 2015). In this CNV group depression has been found to occur in 12-29% of individuals and anxiety disorders in 39% (Bertran, Tagle & Irarrzazaval, 2018).

#### 1.6.2.4 Attentional difficulties

Attentional difficulties have been reported for children with more commonly investigated CNV syndromes such as Williams Syndrome (Klein-Tasman et al, 2015; Klein-Tasman & Lee, 2017; Leyfer et al, 2006); Prader-Willi syndrome (Wigren & Hansen, 2005) and Smith-Magenis Syndrome (deletion to 17p11.2) (Gnanavel, 2014) and children with 22q11.2 DS.

Attention difficulties (ADHD) are found to be commonly co-occurring with the 22q11.2 deletion, (Bertran, Tagle & Irarrzazaval, 2018; Schneider et al, 2014) with a *domain-specific profile*. For example, Jolin et al (2009) found the inattentive ADHD subtype was most common (78%) of their child and adolescent sample who presented ADHD (9/24). This specific profile of inattentive ADHD subtype has been previously reported for children with the 22q11.2 CNV (Antshel et al, 2007; Niarchou et al, 2015).

In conclusion, this section has discussed various behavioural outcomes present within children with CNVs. The findings suggest behavioural difficulties that span neurodevelopmental disorders, with more understanding of the domain *general* and *specific* (e.g. inattentive subtype for 22q11.2 deletion carriers) profiles of children with more well-defined CNV syndromes (e.g. SMS, 22q11.2 DS and WS). However, there is limited understanding of how genetic variance (in general) may influence behaviour.

## 1.7 Copy Number Variants and cognitive, motor and behavioural development

Performance on cognitive tasks closely link with motor development (Burns, O'Callaghan, McDonell & Rogers, 2004; Gottwald et al, 2016; McDonell & Rogers, 2004; Murray et al, 2006; Leonard & Hill, 2014; Piek, Dawson, Smith & Gasson, 2008; Wassenberg, 2005). This relationship can be explored by considering the role of brain mechanisms involved in both domains. The prefrontal cortex and its development and function are key to cognitive *and* motor processes (i.e. executive control and motor control respectively) (Diamond, 2000). This concurrent motor and cognitive development can have implications for behavioural outcomes as exemplified in NDDs which encompass difficulties to these developmental domains (e.g. ADHD and ASD) (Liu & Breslin, 2013; Pitcher, Piek & Hay, 2003; Sugden & Wade, 2013). Based upon this, the following section will discuss research that reports on a combination of cognitive, motor *and* behavioural development of children with CNVs. This is useful in understanding the cascading impact of genetic variance on development and provides insight into whether variance impacts the phenotype in a uniform manner leading to domain-general difficulties or in a unique domain-specific fashion.

In relation to previous work on CNVs, there has been work investigating the *two* developmental domains rather than the *three* of interest. This includes the *behavioural* and *motor* development of children and adults with a 4p16.3 deletion (Wolf–Hirschhorn

Syndrome (Nag et al, 2017) and 9q34.3 deletion (Kleefstra Syndrome) by Schmidt et al (2016). They found signs of muscular hypotonia, ASD symptomology and low adaptive behaviour (to daily living skills, socialisation, motor skills and communication) in all participants (n=8, 2-27 years). *Behavioural* and *cognitive* difficulties have been reported for children with the 2q37 deletion (Fisch et al, 2016), 4p16.3 deletion (Fisch et al, 2010) and 16p11.2 deletion (Hanson et al, 2015). In relation to the duplication, Synder et al (2016) found a significantly higher number of current DSM diagnoses which spanned cognitive and motor domains (DCD and intellectual disability most frequent).

In relation to *cognitive*, *motor* and *behavioural* assessments, there has been previous work conducted in a range of CNV locations, although these commonly consist of few assessments per developmental domain. Bernier et al (2016) investigated the behavioural, neurological and medical profiles of children and adults with 1q21.1 variance. They used cognitive, motor and behavioural measures, although the cognitive assessments were limited (e.g. only intelligence and phonological short-term memory). Similarly, Mahr et al (1996) investigated the neuropsychiatric profiles of individuals with the 18p deletion. They used a comprehensive cognitive and motor battery but with only one behavioural measure. Finally, limited assessments (one behavioural and one cognitive) have been used by Zwanenburg and colleagues (2016) in their assessment of the developmental functioning of children with a 22q13.3 deletion.

A spectrum of phenotypical features which *span* cognitive, motor and behavioural domains have been reported for individuals with the 15q11.2 deletion from case studies (Von der Lippe, Rustad, Heimdal & Rodningen, 2011), clinician reports (Vanlerberghe et al, 2015) medical reviews (Hashemi et al, 2015) and literature reviews (Cox & Butler, 2015). The 15q11.2 region is implicated within the Angelman syndrome (AS) and Prader Willi Syndrome (PWS) which occur due to deletions to the 15q11-q13 location (15q11.2 is also implicated with this). In relation to these syndromes there is limited understanding of *specific* cognitive, motor and behavioural development, as there have been a limited number of assessments conducted per domain (Micheletti et al, 2016) with some studies only investigating *cognitive* and *behavioural* domains (Gillentine et al, 2017; Gross-Tsur et al, 2001; Peters et al, 2004).

There have been reports of the *cognitive*, *motor* and *behavioural* profiles of common CNV syndromes such as Williams Syndrome (WS) from reviews (Martens, Wilson & Reutens, 2008). In relation to cognitive and behavioural functioning, Greer et al (1997)

found children and young adults (n=15, 4-18 years) presented IQ scores in the moderate range to low average range, with relative strengths in non-verbal reasoning. Behavioural assessments reveal relative strengths in the development of socialisation and communication skills while daily living skills and attention problems were of clinical significance in the majority. However, a limited number of assessments were used per developmental domain (e.g. IQ measure, two behavioural measures and no motor measure). Similarly, previous work has only focused on two domains (Rossi & Giacheti, 2017; Saad, Abdelrahman, Abdallah, Othman & Badry, 2013; Udwin & Yule, 1991).

There is knowledge of the *cognitive*, *motor*, *behavioural* and *psychological* development of children with more well-defined CNV syndromes, such as 22q11.2 DS from reviews (Kates, Tang, Antshel & Fremont, 2015; Ousley et al, 2007) and neuropsychological assessments (Niklasson et al, 2002; Swillen et al, 1999). These broadly report movement delays, IQ scores 1SD below the mean and ASD and ADHD-like behaviours (Niklasson & colleagues, 2001; 2009). For example, Cunningham et al (2018) focused on the association between movement difficulties (indicative DCD), neurocognition and psychopathology in children with the deletion (n=70) and sibling controls (n=32). The authors suggest children with a 22q11.2 CNV are at high risk of DCD with co-morbid neurocognitive deficits and mental disorders (anxiety, ADHD, ASD) as they presented: poorer cognitive performance; signs of at least one psychiatric disorder and higher signs of DCD (81.4%, n=57) in contrast to controls (6.3%, n=2).

In summary, this section has discussed research that has explored the cognitive, motor *and* behavioural development of children with CNVs. Often research has only explored two domains in contrast to the three of focus. Alongside this, work has been conducted on more commonly investigated CNV syndromes which provides an understanding of the phenotypical outcomes of specific CNV locations but does not provide insight into how copy number variance can impact development in general. Finally, the studies employing measures to assess all three domains, have used an inconsistent number of assessments per domain which subsequently mainly focus on one domain in contrast to the other.

## 1.8 Research aims and approach

The literature review has discussed studies that explore the cognitive, motor and behavioural profiles of children with a range of CNVs. Sections (1.4-1.6) presented studies that explored these developmental domains separately. The final section (1.7)

discussed research that investigated cognitive, motor and/or behavioural development. The work presented in these sections was mainly based on children with more well-defined CNV syndromes (i.e. Williams Syndrome, 22q11.2 Deletion Syndrome). Often this work was conducted in both children and adults, without a specific focus on a developmental population. Although a range of standardised assessments were employed, there were often a small number of assessments used per domain and these mainly focused on cognitive and behavioural outcomes or on one domain in contrast to the other.

To our knowledge there is no study that has specifically explored the impact of copy number variance on children's cognitive, motor and behavioural development. Although work has been conducted on more common syndromes, there are various genetic loci which are variants of unknown significance as these are rare or there is limited evidence concerning their clinical significance. We know that CNVs risk developmental delay or neurodevelopmental disorders, however there is still limited understanding of how having a CNV in *general*, may *specifically* impact cognitive, motor and behavioural domains. These developmental domains are key for successful child development and provide the foundations for interacting with the world, learning and communicating.

The theoretical frameworks discussed in section (1.3) supply useful perspectives on the project. The three theories suggest development is complex, and genes interact in multifaceted ways leading to a range of phenotypical outcomes. Firstly, the Multiple Deficit Model by Pennington (2006) helps us to think about the cascading impact of genetic variance on phenotypical outcomes and how children can present a range of behavioural outcomes that span different developmental domains. This project explored this by recruiting children with a range of CNVs and administering cognitive and motor assessments. Behavioural data was gathered via questionnaires completed by caregivers. To extend this, the Intergenerational Multiple Deficit Model by van Bergen et al (2014) allows an insight into how environmental and genetic factors can contribute to phenotypical outcomes. Based upon this, non-affected sibling controls took part in the same assessments. Finally, the Neuroconstructivist perspective (Karmiloff-Smith, 2006; 2009) discusses the complex interplay between genetic, environmental, brain and cognitive processes and how these factors can interact and alter the developmental trajectory. Considering this, the data will be discussed in relation to domain-general and domain-specific developmental profiles. For example, a child may show difficulties to

one domain in particular (i.e. domain-general). Alternatively, they may present strengths and weaknesses within a developmental domain (i.e. domain-specific).

Based upon this, the project aimed to investigate the following research questions:

*(1) How does having a Copy Number Variant impact cognitive, motor and behavioural development?*

This project involved working in collaboration with NHS Clinical Genetics, in particular the Yorkshire Regional Genetics service. All patients had a diagnosed CNV and were visited in their home to complete the assessments. A single case approach was adopted, as each child has a unique karyotype (genetic profile) and this supports the detailed phenotyping conducted during this project. To understand these areas a comprehensive assessment battery which consisted of a range of standardised cognitive (n=4), motor (n=2) and behavioural assessments (n=7) were administered.

Children aged 7-16 years and their non-affected siblings were recruited. The project methods and assessment battery are discussed in Chapter 2. In relation to the research question, Chapter 4 will discuss overall group patterns with an exploration of the whole sample, including investigations by the type (deletion and duplication), location (neurodevelopmental susceptibility loci), number of variants (child with 2 CNVs) and the manifestation of CNVs within the same family (3 siblings, role of variable expressivity).

*(2) How do children with a Copy Number Variant perform in comparison to an unaffected sibling?*

It is of interest to explore how unaffected siblings perform on the same tasks as those with a diagnosed CNV and this is discussed in Chapter 5. Controls have been recruited across a range of studies and based upon this, unaffected biological siblings were recruited (where present) to help support our understanding of how genetic variance manifests phenotypically across patients and siblings.

*(3) How do children with a Copy Number Variant perform in comparison to children from a Special Educational Needs' School?*

Developmental deficits and delays have been reported for children with a range of CNV disorders. Children have been found to present behaviours typical of neurodevelopmental disorders and present below average performance on standardised assessments. Based upon this, it was of interest to understand how the developmental profiles of children with

copy number variance compared to children with Special Educational Needs and Disabilities (SEND). Children with SEND provision and support have difficulties that span cognitive, motor and behavioural domains in line with the Special Educational Needs and Disability Code of Practice: 0 to 25 years (Department of Education, 2015).

Related to this, anecdotal evidence from the clinicians involved in the current project can support this. There is currently an increasing number of parents who are fighting for additional support from their local school or council (e.g. Education, Health and Care Plan) to help their child who has a CNV diagnosis (see Page 72-73 for details of this). Investigating the specific developmental outcomes associated with genetic variance may have beneficial implications for health professionals and families. Based upon this, children from a SEND school with no known genetic aetiology were matched to the patients and underwent the same cognitive and motor assessments. This is discussed in Chapter 6.

## 1.9 Chapter summary

In summary, the literature review suggests there is evidence of the cognitive, motor and behavioural profiles of children with specific CNVs in more well-defined CNV syndromes (e.g. Williams Syndrome, 22q11.2 Deletion Syndrome). However, this project explored how copy number variance (in general) impacts children's cognitive, motor and behavioural development. The aim was to understand how changes within the chromosome (structural variance) such as losses and gains to genetic material (deletions and duplications respectively) can influence development employing a comprehensive assessment battery. As genes are responsible for critical biological processes, it was of interest to explore how genetic changes contribute to development, and whether this leads to atypical development for the whole child system or whether this has a more localised impact resulting in a phenotype of relative strengths and weaknesses.

Additional research questions were explored to understand how children with a CNV perform in comparison to control subjects. Chapter 5 provides insight into the potential role of shared genetics and environmental factors as the closest aged non-affected sibling was approached to take part and both group and single case comparisons are explored. Of those recruited, two families included twin siblings (i.e. patient's twin sibling and siblings who are twins). It was also of interest to understand how the current sample performance in comparison to children who have a standard statement of educational difficulties. The

patient sample was matched as close as possible (age and gender based) to a sample of students from a special educational provision. This exploration in Chapter 6 provides an insight into the extent of developmental difficulties present in children with a Copy Number Variant.

# Chapter 2 – Methodology and Assessment Battery

This chapter gives an overview of the project method and a description of the assessments employed. The battery of tasks included a range of standardised measures of cognitive and motor functioning which were all administered by the researcher (Joyti) at a time most suitable for the family and often these were conducted across more than one visit to the family home. Alongside this, a booklet consisting of standardised questionnaires were completed by parents to gain an understanding of children's behavioural symptoms.

## 2.1 Participants and procedure

This PhD project was based on a collaboration between the University of Leeds, School of Psychology and Clinicians from NHS Clinical Genetics. The clinicians screened the Yorkshire Regional Genetics Clinic paediatric database for patients who met the eligibility criteria: patient, diagnosed Copy Number Variant (duplication or deletion) and aged between 7-16 years. This screening process took place at several different time points across the project, with a variable number of eligible patients identified by the clinician in each batch. Once screened, the clinician signed and addressed a project invitation letter to the parent/carer of the patient. Once a batch of letters were ready these were enclosed, alongside information packs provided by the researcher, and mailed to participants. The information packs included: parent information sheets; child information sheets (primary and secondary aged); permission to contact letters and a prepaid envelope - which were all NHS ethics approved. Families were asked to respond on the permission to contact form with their contact details to find out more, which were addressed to the researcher at the School of Psychology. Within a week of receiving the permission to contact letter, the families were contacted to discuss the project. If they chose to take part, home visits were arranged at a time most suitable for them. At this point any questions were answered and siblings were recruited where possible. A discussion of the factors involved in the project initiation stage and recruitment process are detailed in Chapter 3 (feasibility assessment).

On the home visit, the consent procedure was conducted first. For children aged 7 to 12 years, verbal consent was taken, and parents completed the consent form. For children aged 13-16 years, written consent was taken, with the parent present. Following the consent procedure, the assessments began. The assessments took up to 3 hours to complete and often these were conducted across multiple visits (1-3) to the family home.

The assessment battery consisted of standardised cognitive, motor and behavioural measures that were reliable, valid and appropriate for the age and ability ranges in the sample (Cicchetti, 1994). The specific details of the scoring procedures per task are detailed in the following sections. These were administered in the same order across participants, although there were often deviations to this due to the multiple visits and the issues involved in conducting assessments in the home setting (see Chapter 3). As a broad overview, the cognitive and motor assessments provided an understanding of atypical or typical performance in relation to children of the same age, as a standardised score and a percentile rank was generated. Alongside this, a range of standardised clinical questionnaire measures were used to assess behavioural symptomology typical of neurodevelopmental disorders. The specific scoring and analysis procedure of each questionnaire is detailed in the sections to follow, with thresholds used in scoring broadly based on behaviours that met clinical cut-off scores, or scores that fell within ranges where further clinical investigation would normally be recommended.

Finally, control groups of unaffected children were also recruited (i.e. no genetic abnormality). Parents and the closest aged sibling of the patient were invited to take part, to investigate the role of phenotypical outcomes and shared family environment (e.g., socio−economic status, parental upbringing practices). There was initially limited uptake from parents, so recruitment was stopped, however 5 siblings were recruited. Of interest, all 5 siblings were younger, one of which was a patient's twin and two were twin siblings of the patient. This group took part in the cognitive, motor and behavioural assessments and findings relating to group and single case comparisons are discussed in Chapter 5. Alongside this, to understand the extent of developmental difficulties in children with CNVs, children were recruited from a Special Educational Needs school (see Chapter 6) and took part in the cognitive and motor assessments. The cognitive and motor assessments were administered by the researcher in the home/school setting and the behavioural data was collected via a parental response to the standardised questionnaires used. The following sections discuss the assessment battery (2.2 – 2.4).

## 2.2 Cognitive assessments

The following measures are standardised assessments of cognitive function and support an understanding of performance in relation to children of the same age. Based on this, it was of interest to understand whether children have face difficulties across cognitive

functions (in general) or whether there is a specific pattern of domain-specific strengths and weaknesses. Broadly the cognitive tasks provide an overview of general cognitive functioning (Intellectual Ability), how well children can store and manipulate information (Working Memory), flexible thinking (cognitive flexibility) and the ability to understand and express language (language functioning).

### 2.2.1 Intellectual functioning

General, verbal and non-verbal IQ were assessed using the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-2) (Wechsler, 2011). The WASI-2 is a shorter version of the full Weschler Intelligence Scale batteries (30 minutes, 6-90 years), making it beneficial for use in the home setting and for clinical populations (Irby & Floyd, 2013). The Weschler scales and the abbreviated version have been reported in a range of studies involving children with genetic syndromes as reported in Chapter 1 (De Smedt et al, 2007; Lajiness-O'Neill et al 2006; Osorio et al, 2012; Hippolyte et al, 2016). Based on this and given practical considerations (time considerations and the number of assessments in battery) the WASI-2 was employed in the present work.

General cognitive functioning was assessed via performance across four subtasks, which generate a Full-Scale IQ (FSIQ) score. This score is comprised of performance on two non-verbal and two verbal tasks that map onto a Perceptual Reasoning Index (PRI) and Verbal Comprehension Index (VCI), respectively. These broadly explore verbal IQ (i.e. crystallised intelligence - stored factual knowledge) and non-verbal IQ (i.e. fluid intelligence - abstract thinking). Performance on all tasks was assessed against the WASI-2 norms in relation to the participant's age.

The PRI consists of two tasks: block design and matrix reasoning. These tasks investigate the ability to analyse and synthesise abstract visual stimuli, fluid thinking and visual intelligence. Firstly, within the block design task the participant was shown a 2D picture of a red and white design and was asked to recreate the design using 3D blocks within a specific time limit. The blocks sides were either red, white, or half white and half red. Scores were generated from the time participants take to complete the task, with a higher score given for a faster time. The matrix reasoning task consisted of an incomplete matrix and/or series and participants were required to select the correct design to complete the sequence matrix. Performance was scored as either correct or incorrect (1 or 0 respectively).

The VCI tasks explored crystallised intelligence, word knowledge and verbal and abstract reasoning. In line with the manualised scoring criteria, responses to these tasks were scored as either 0, 1 or 2, according to the level of detail. The vocabulary subtask required participants to name the object presented visually (picture items) and define words (visual and oral presentation). Secondly, the similarities subtask required participants to select an image that shares a common characteristic with a target stimulus for the picture items. For the remaining verbal items, the participant was presented with two words (common objects or concepts) and asked to describe how they were similar (e.g. child and adult).

Scores were calculated by:

- Calculating raw scores based on the scoring procedure for each task.
- Then these were totalled and converted into standardised T-scores
- The T-scores are then combined to generate a composite score:
    - Perceptual Reasoning Index: Block Design and Matrix Reasoning task T-scores were summed
    - Verbal Comprehension Index: Vocabulary and Similarities task T-scores were summed
    - Full Scale-4: The T-scores from all 4 subtasks were totalled
- The Full-Scale score was then used to make a qualitative classification of IQ functioning (Wechsler, 2011) into one of five categories: Very Superior (130 & above); Superior (120-129); High Average (110-119); Average (90-109); Low Average (80-89); Borderline (70-79) or Extremely Low (69 & below).

### 2.2.2 Cognitive flexibility

The Wisconsin Card Sorting Task (WCST) (Heaton et al, 1993) was administered to assess set-shifting ability, cognitive flexibility and perseveration. The WCST is a well-established task, for application in ages 6.5-89 years and takes 20-30 minutes to administer. It has been used in various clinical populations including patients with autism (Ozonoff, 1995), those with Developmental Coordination Disorder (Wuang, Su & Su, 2011) and Williams syndrome (Osorio et al, 2012).

The task included three stimuli cards that were distinguished by three features: Colour, Form and Number, and two decks of 64 response cards. Participants were instructed to consecutively match the response cards to the stimuli cards with no information about the

sorting rule. Participants were only told if the match was right or wrong. Once the participant correctly matched the cards in line with the active sorting rule across 10 consecutive trials then the sorting rule was changed to a different distinguishing feature, without any warning being given to the participant. The order of the features by which cards were to be sorted were: *colour, form, number, colour, form and number*. This task continued until all categories were completed or all cards were used. The aim was for participants to think flexibly and to correctly recognise the switch in the sorting rule. This ability was referred to as 'set shifting/cognitive flexibility' and was assessed by the number of perseverative errors. These errors are the number of times the participant persisted in responding to an incorrect sorting rule.

Perseverative errors were calculated as:

- The total number of perseverative errors (raw scores), as defined according to the scoring criteria in the manual (Heaton et al, 1993).
- This raw score was then corresponded to the participants age in the appendix to yield a standard score
- This standard score was used to determine a diagnostic category the participant's score fell within, based on the WCST's classification system. These categories were: Above-average range (≥ 107); Average (92-106); Below-average (85-91); Mildly impaired range (77-84); Mildly-to-moderately impaired range (70-76); Moderately impaired range (62-69); Moderately-to-severely impaired range (55-61) or Severely impaired range (≥ 54).

### 2.2.3 Working Memory

Subtasks from the Working Memory Test Battery for Children (WMTB-C) (Pickering & Gathercole, 2001) were used to investigate simple and complex WM. The battery itself is based upon the components of the Baddeley and Hitch Working Memory (WM) model (1974) and it has previously been implemented in primary and secondary aged children (5-15 years) (Gathercole, Pickering, Ambridge & Wearing, 2004; Gathercole & Pickering, 2000). The tasks and the associated scoring technique were as followed:

Firstly, the Forward Digit Recall (FDR) task was administered to assess verbal simple WM. This explores how well the child can hold verbal information for a short amount of time, which is useful when listening to instructions in the classroom or remembering directions. In this task participants were asked to recall a sequence of digits in the same

order as they were verbally presented by the researcher (in an even monotone, at a rate of 1 per second). The practice trials consisted of three sequences, which increased in length by 1 digit from 1 to 3 (e.g. 1st trial recall "2"; 2nd trial recall "1, 5" and 3rd: "7, 4, 8"). Following this, the test trials were administered. There were 9 blocks, each consisting of 6 sequences of equal length. Block 1 consisted of a digit span of 1 and the sequences in each block increased by 1 up to a digit span of 9. For example, in the 2nd block they were asked to correctly recall 2 digits and so forth. Correct responses were scored as 1 and incorrect responses were scored as 0. If 3 or more errors were made within a block (i.e. 3 incorrect trials out of 6), then the task was discontinued. The total number of correct responses were totalled to generate a 'Trials Correct Score'. This score was then corresponded to the participants age (in year and month band) to yield a standard score and percentile rank for their age.

Secondly, visuospatial simple WM (storage) was assessed using the Block Recall (BR) task. A block recall board was placed in front of the participant and the side visible to the researcher was numbered, but the side facing the participant was blank. The researcher tapped out a sequence on to the board (at a rate of one per second) and the participant was required to reproduce this sequence in the correct order. Consistent with the methodology in the FDR task, practice trials were administered (digit span starting at 1, then increasing to 3), there was 9 blocks (digit span 1-9) comprised of 6 trials and the scoring and discontinue rules were the same.

Following a similar procedure to the FDR task, the Backwards Digit Recall (BDR) task assessed the storage *and* manipulation of verbal information (complex verbal WM). A sequence of digits was presented orally by the researcher, but participants were required to recall the list in the reverse order (i.e. 1, 2, 3 would be 3, 2, 1). Four practice trials were conducted (span length 2-3) and the task consisted of 6 blocks of 6 trials that increased in digit span from 2 to 7, with the same scoring procedures followed as previous described for other tasks within the WMTB-C.

### 2.2.4 Language

Language ability was assessed using the Clinical Evaluation of Language Fundamentals – Fourth Edition (CELF-4) (Semel & Wiig, 2006). The CELF-4 is a flexible screening tool used to identify and evaluate language and communication difficulties in children (5 – 16 years). It takes around 30 – 60 minutes to administer (Paslawski, 2005). The CELF

has been administered in a range of clinical populations including children with developmental language impairment (Webster et al, 2006), ADHD (Cordier, Munro, Wilkes-Gillan & Docking, 2013), ASD (Akbar, Loomis & Paul, 2013), WS (Joffe and Varlokosta, 2007), 22q11.2DS (Glaser et al, 2002; Moss et al, 1999) and PWS (Dimitropoulos, Ferranti & Lemler, 2013). The CELF-4 has an assessment model consisting of four levels, see Figure 2.1. The language assessments used aligned with this structure.

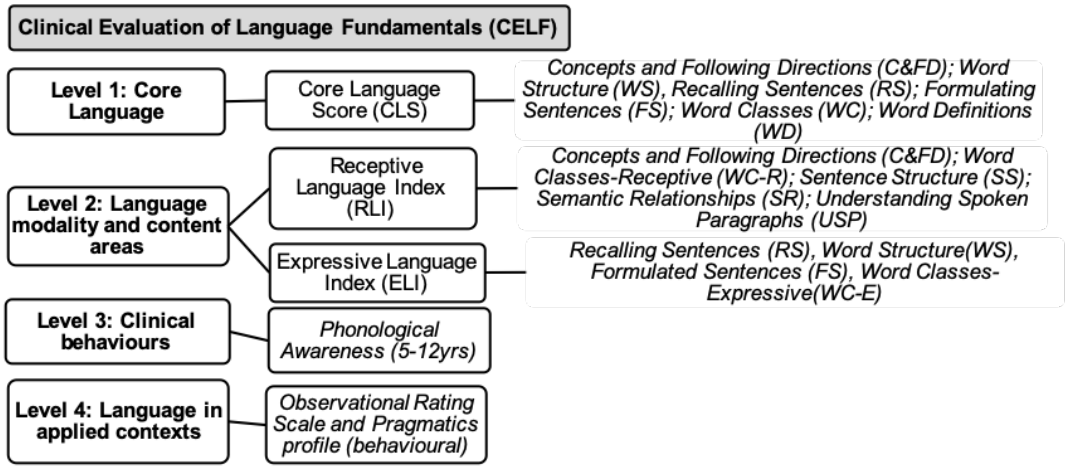


**Figure 2.1: Overview of the tasks and assessment levels from the CELF-4**

#### 2.2.4.1 Level 1

The level one tasks are designed to identify the presence of a language disorder and determine the eligibility of the child for relevant support services. Although diagnoses were not made in the present work, this measure was used to understand general language ability as these allow a Core Language Score (CLS) to be generated. The CLS is a composite score comprised of 4 subtasks, which vary in administration based upon the participants age. As a broad overview, these assess how well children perform on receptive and expressive tasks that require: instructions to be understood and followed (C&FD); successful recall of lengthy and complex sentences (RS); application and knowledge of word structure rules (WS); understanding of words and their relationship (WC); word meanings (WD) and the ability to generate coherent sentences based on target stimuli (FS).

CLS Scores were generated by:

- Calculating the raw score for each subtask based upon the total number of correct item scores.

- Converting these raw scores into standardised scaled scores corresponding to age band in years.
- Summing the scaled scores of the relevant subtasks and converting these into a standardised composite score, and a percentile rank for the CLS.
- Performance was also classified by the 'Guidelines for describing the severity of a language disorder' within the CELF-4. The classifications were: Above average (CLS score of 115 & above); Average (86 to 114); Marginal/Borderline/Mild (78 to 85); Low range/moderate (71 to 77) or Very low range/severe (70 & below).

If the CLS is 85 or below, the manual suggests further testing (at other levels) is warranted because these additional levels best discriminates the performance of children with and without the presence of a language disorder. In the present work, all children underwent the same assessments at each level as diagnoses were not being made, but nevertheless CLS score remained a useful measure to obtain, indicative of general language strengths and weaknesses.

#### 2.2.4.2 Level 2

The Level 2 assessments focus on modality and content areas. Age-relevant subtasks that comprise the Receptive Language Index (RLI) and Expressive Language Index (ELI) were administered to understand language strengths and weaknesses, see Figure 2.1. The RLI included tasks that measured auditory and listening comprehension. These assessed how well children: understand and follow lengthy sentences (C&FD); understand word and their associated classes (WC-R); interpret sentences of increasing length and complexity (SS); understand how words are semantically related (SR) and engage in critical thinking and understanding of spoken content (USP). Meanwhile, the ELI is a measure of overall expressive language skills. Age dependant tasks were administered within this domain, which explored the ability to: correctly recall sentences of increasing length and complexity (RS); successfully apply word structure rules (WS); formulate coherent sentences (FS) and correctly describe the relationships between associated words (WC-E). The scoring procedure for each of these composites was the same as already described for the CLS.

#### 2.2.4.3 Level 3

In line with the Level 3 assessments, one short task was administered in children under the age of 12 years. The 'Phonological Awareness' task was used, as children with phonological difficulties have been found to face difficulties with tasks such as spelling and reading. This task assessed the ability to understand and manipulate sounds (i.e. syllables, rhyming, phoneme blending). The total number of correct item responses were compared to a criterion-referenced score in the manual, after adjusting for the participant's age. Performance was then quantified as: "meets criterion for age" or "does not meet criterion for age".

#### 2.2.4.4 Level 4

To explore the participants language and communication in applied contexts, the Pragmatics profile (PP) and the Observational Rating Scale (ORS) questionnaires were used. These were provided to parents in the questionnaire booklet (see Appendix A & B).

The PP is a checklist developed for use by teachers and parents of children, teenagers and young adults (Reidy et al, 2013; Senner, 2011), which helps to identify verbal and non-verbal behaviours that may negatively impact on academic and social-based communication. The questionnaire explored language behaviours that are required in social contexts (e.g. conversational skills; asking, giving and responding to information and knowledge of implicit social rules). The questionnaire contained 52 items, split into 3 sections. These sections group statements that ask how well the child engages in (1) Ritual and conversational skills, (2) Asking for, Giving and Responding to information and (3) Nonverbal communication skills. Parents were asked to respond with a rating that best describes how often the child demonstrates that skill (1=never, 2=sometimes, 3=often or 4=always). If the skill is Not Observed, this was indicated by a "NO" response and if the skill was not applicable this was scored as "NA". Responses were totalled and this raw total score was assessed against an age-based criterion score in the manual. If the participant met this score, then this was indicated by "Meets", whereby pragmatic development appears appropriate for their age. However, if they scored lower than the criterion score this was described as "Does Not Meet", which suggests delays or weaknesses to the development of pragmatic skills.

The ORS was used to understand *where* and *when* language difficulties occur as these can vary by the context and the situation. Difficulties at school can impact learning (e.g.

understanding of relevant materials, learning strategies and during classwork) and at home they may affect how well children can articulate their needs or understand others. The ORS has previously been used by teachers or parents, but is also commonly used by Clinicians or Language professionals at clinics to support intervention planning and provide further understanding of language functioning (Massa et al, 2008; Purse & Gardner, 2013). The ORS explored language functioning in four main areas: learning, speaking, reading and writing. There were 40 statements in total, each describing a specific behaviour, and parents were asked to rate how often each behaviour occurs. Responses included: never, sometimes, often or always. In reference to the manual, problems that occur most frequently are of greatest concern. As language difficulties are not being diagnosed in the present work, nor are we intervention planning, the descriptive information from the questionnaire was used to provide further understanding of the participants language functioning. Based upon this, language and communication difficulties that occurred most frequently (i.e. always) were used as additional descriptive information.

## 2.3 Motor assessments

### 2.3.1 Fine and gross motor assessment

To explore motor functioning the Movement ABC, Second Edition (MABC-2) was used (Henderson, Sudgen & Barnett, 2007). This measure is widely used to assess children's movement competence in specific age bands (3-6, 7-10 and 11-16 years) and takes approximately 20-40 minutes to complete (see Figure 2.2). The MABC-2 has been used to assess the motor performance of children from various clinical groups, including children with ASD (Liu & Breslin, 2013), ADHD (Pitcher, Piek & Hay, 2003), and those with Developmental Coordination Disorder (Wuang, Su & Su, 2012).

Age-appropriate subtasks were administered to assess fine (manual dexterity) and gross motor skills (dynamic and static balance). As per instructions in the MABC-2, practice trials were given for each task and performance on subtasks was scored in relation to the child's age in years.

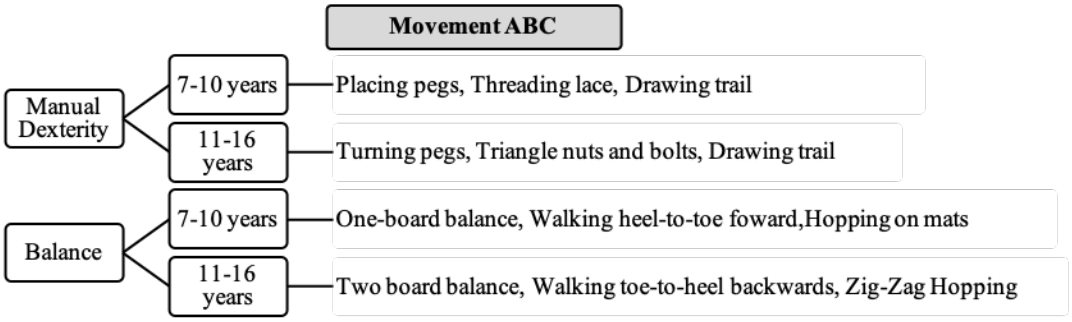


**Figure 2.2: Subtasks from the Movement ABC-2**

#### 2.3.1.1 Manual Dexterity tasks

The Manual Dexterity (MD) tasks required hand and eye coordination; coordinated and complementary hand movements and precise and accurate movements faced with speed demands (see Figure 2.2). For 7-10-year olds, in the placing pegs task participants were instructed to use both their preferred and non-preferred hand to place 12 mushroom pegs into a peg board as quickly as possible whilst timed. They were also asked to hold the box of pegs steady with the other hand. Both hands were tested, and a score was generated based on how long it took to complete the task. The manual defines a failed trial as one where the participant drops a peg out of reach, changes hands throughout the trial or picks up more than one peg at a time. The threading lace task required the child to thread a lace through a lacing board. This trial was defined as 'failed' if the participant laced around the edges or missed a hole. Performance was assessed by accuracy (failed trial criteria) and speed. Finally, the drawing trial task required the child to draw a single continuous line on a narrow trail without crossing the boundaries. Accuracy was assessed in line with the manuals scoring criteria and a score was given based upon the number of errors.

In the versions of the MD tasks designed for 11-16-year olds: the turning pegs task consisted of 12 pegs (half yellow and red) which were inserted into a peg board. The participant was required to successfully invert the pegs as fast as they could, so the other colour was showing. A trial was defined as 'failed' here if the participant repositioned the pegs externally (e.g. on the table, on their body or the peg board), changed hands, dropped a peg out of reach or if they left any pegs unturned. Both hands were tested and scored in relation to speed. In the triangle nuts and bolts task, completed participants instead of the threading lace task, participants were required to construct a triangle using 3 yellow strips and 3 loose nuts and bolts. Speed and accuracy were assessed (failure was defined as producing an incorrect arrangement; resetting the pieces or knocking/dropping an item

out of reach). Finally, the drawing trial was similar to the one discussed for 7-10 years, only with a more complex design trail to trace through.

#### 2.3.1.2 Balance tasks

The static and dynamic balance component measured children's ability to effectively control and stabilise their body. Tasks assessed how well children can: hold a specific position; engage in slow and accurate movements, and move their body effectively in fast, explosive movements - see Figure 2.2.

For Ages 7-10, the One-Board Balance task was administered. Participants were required to balance (statically) on a balance board on each leg, and were assessed for up to 30 seconds. Timing was stopped when a fault occurred (e.g. tilting the board so side touches the floor, touching the floor with the free foot, touching the balance board with the free foot, or touching the supporting leg with the free foot). Scores were generated based on time for the best leg (i.e. balanced for longest time) and other leg (i.e. shortest time). Secondly, the Walking Heel-to-Toe Forwards (dynamic balance) task required the child to walk along a straight line, placing the heel of one foot against the toe of the other with each step. According to the manual, the line should be 4.5m and used in a clinic or gym hall setting, however due to the nature of the current project (i.e. home visits so limited space) a 90cm line was used and participants were asked to walk along this 5 times (equates to 4.5m/450cm). The number of correct consecutive steps taken from the beginning of the line were assessed, without leaving a space, stepping off the line, touching the surrounding floor with the free foot to gain balance or readjusting the foot once on the line. The maximum number of steps obtainable were 15, and a score was given based upon the number of steps completed. Finally, the Hopping on Mats subtask (dynamic balance) consisted of six floor mats that were lined-up adjacent to each other. Participants were asked to complete 5 continuous hops in a forward direction, from one mat to the next, stopping on the last mat. They were required to stay in the boundary of each mat, hop on each mat in sequence and keep the free foot from touching the ground. Both legs were tested and the number of successful hops out of 5 was assessed for the best (highest) and other leg (lowest).

The versions of these subtasks for use with 11-16 year olds were similar. Firstly, Two-Board Balance replaced One-Board balance as the static balance task, it consisted of 2 balance boards joined together. Participants were required to successfully balance heel-

to-toe for up 30 seconds and the timer was stopped if a fault occurred. Faults were described as lifting either foot off the board, touching the floor with either foot, shifting the boards to alter the alignment or touching the base of the board with sides of shoes. Secondly, the Walking Heel-to-Toe backwards task (dynamic balance) followed a similar principle to the task described for ages 7-10 years. Participants were required to walk with the heel of the leading foot at the start of the line, placing the toe of the trailing foot against the heel of the leading foot with each step. A maximum score of 15 steps could be obtained, and deviations from this score were due to the same faults already described. Finally, the Zig-Zag Hopping task was similar to the hopping mats task it replaced, only this time the mats were lined in a zig-zag formation, rather than in a straight row. Both legs were tested (best and other) and participants were required to make 5 continuous hops diagonally from one mat to the next.

Scores were calculated by:

- Converting the raw scores for each task into standard scores, based upon normative data corresponding to the child's age in years in the MABC manual.
- The relevant standard scores for each subtasks were summed to generate Manual Dexterity and Balance component scores, in relation to the scoring procedure in the manual (i.e. taking into account the best and other leg scores)
- The component scores have a mean of 10 and standard deviation of 3 and motor functioning was then described by the classifications given in the MABC-2, in the form of a traffic light system: At or below the 5$^{th}$ percentile: Significant Movement Difficulty, Between the 6$^{th}$ – 15$^{th}$: At risk of Movement Difficulty and Above the 15$^{th}$ percentile: No signs of movement difficulty.

### 2.3.2 Kinematic assessment

The Clinical Kinematic Assessment Tool (CKAT) (Culmer et al, 2009; Flatters et al, 2014) was used to provide kinematic recordings of a participant's uni-manual coordination whilst performing a series of tablet-based tasks. It took around 15 minutes to complete. CKAT was presented on a portable tablet device, which required the participant to interact with a touchscreen using a hand-held stylus pen which was used to report end-point kinematics for their hand movements whilst they interacted with visual stimuli presented on screen (tablet: Toshiba Portege M700-13P tablet, screen: 303x190 mm, 1200x800 pixels, 60 Hz refresh rate). This assessment investigated how well

children engaged in object manipulation (i.e. controlling a stylus pen), manual control (providing adequate control and force) and visual manual control (hand-eye coordination). This was administered in ages 7-11 years because this age corresponds with normative data available from the Born in Bradford project for CKAT (see https://borninbradford.nhs.uk/what-we-do/schools/primary-school-years/) which was referred to in order to generate a percentile rank for each task within this battery. The 3 subtasks and their associated output measures were as followed:

#### 2.3.2.1 Tracking

This required participants to keep the stylus tip as close as possible to the centre of a dot (10mm diameter) as it moved around the screen in a 'figure 8' pattern at increasing speed. This task assessed the spatial and temporal accuracy of the participant's performance in two conditions. In the 'No guide' condition the target dot was presented alone, while in the 'With guide' condition a black guideline was presented underlying the dot, which indicated the direction that the path it would take whilst moving. The outcome from this task was tracking error, which refers to the average distance (mm) between the stylus tip and the centre of the dot at each sampled time point.

#### 2.3.2.2 Aiming

During this task participants produced a series of aiming movements with the stylus, to reach targets that were presented sequentially and positioned at various locations on screen. Fifty target dots were presented and participants were required to slide their pen across the screen moving from target-to-target as quickly and accurately as possible. The median movement time for these 50 aiming movements was assessed. Movement time was defined as the time it took to arrive at each target after exiting the previous target.

#### 2.3.2.3 Tracing

Participants had to trace along paths between designated start and finish points whilst staying within a set boundaries (5mm in width). As they were drawing, an on-screen trial was presented, similar to ink from a real pen. There was a total of 6 trials, which comprised of 2 identical paths (A and B) which were mirrored being presented 3 times. There was also a pacing box presented on top of the path, which participants were asked to remain within to standardise their speed. Penalised path accuracy was derived from this task, which assessed how well the participant traced the midline of the trail they were

asked to follow, adjusting this score based on how deviant they were from an optimal completion time of 36 seconds. Accuracy was calculated as the average distance between the stylus tip and an idealised reference path at each sampled time point.

## 2.4 Behavioural assessments

Behavioural assessments were used to explore a range of behaviours, see Figure 2.3. These took the form of standardised questionnaires that was provided in a booklet to parents for them to complete and return. There were 7 questionnaire measures in total, parents were asked to complete all 7 for the Patients (see Appendix A) but only 6 for the siblings, with the Developmental Behaviour Checklist unnecessary in this reference group (see Appendix B).

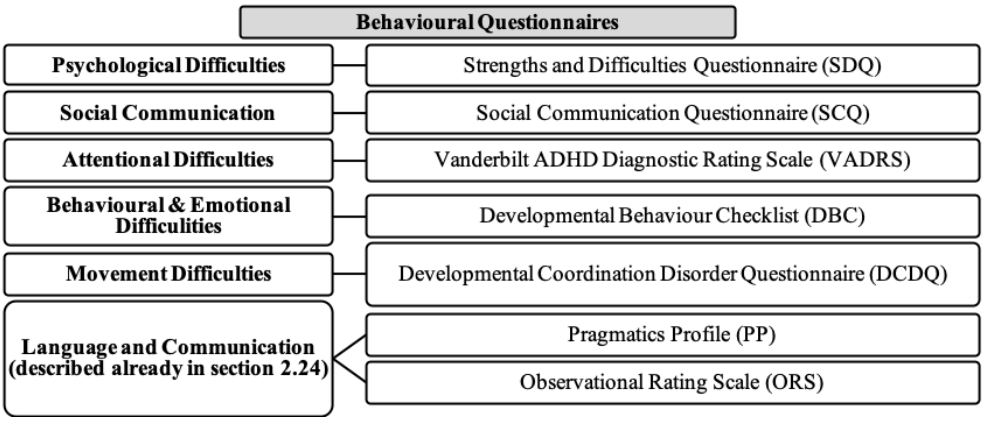


**Figure 2.3: An overview of the questionnaires used to assess behavioural symptoms.**

### 2.4.1 Psychological difficulties

The Strengths and Difficulties Questionnaire (SDQ) is a measure of psychopathology for children and adolescents (Goodman, 1997). It comprises of 25 items in total, which assess behaviours across the following subscales: (1) Emotional symptoms; (2) Conduct problems; (3) Hyperactivity/ inattention; (4) Peer relationship problems and (5) Prosocial behaviour. Scales 1-4 are summed to provide a "Total difficulties score" that is a measure of psychological strengths and difficulties. Based upon normative data from a large UK based community sample, performance was classified into one of 4-band system: close to average (80% of the expected population); slightly raised (10%); high (5%) and very high (5%) (Youth in Mind, 2020). A higher total difficulties score suggests an increased risk of difficulties as children with higher 'total difficulties' have been found to be at an increased risk of diagnosis with a clinical mental disorder (Goodman & Goodman, 2009).

### 2.4.2 Attentional difficulties

The Vanderbilt ADHD Diagnostic Rating Scale – Parents version (VADRS-Parent) (Wolraich et al, 2003) was used to screen for attentional difficulties. This measure provided an initial assessment of ADHD symptomology, as defined by the 18 DSM-IV criteria considered when diagnosing ADHD (3 subtypes) as well as additional items assessing symptoms associated with co-existing conditions: Oppositional Defiant Disorder (8 criterion), Conduct Disorder (12 criterion), Anxiety and Depression (7 criterion) (Austerman, 2015).

Questions assessed *symptom domains* (i.e. inattention and anger) and *performance* domains in line with the in DSM-IV criterion (Wolraich et al, 2003). For the symptom domain, parents were asked to rate the severity of each behaviour on a 4-point scale Likert scale: never (0); occasionally (1); often (2) and very often (3). The performance domain consisted of questions which relate to academic performance (overall school performance; reading, writing and mathematics) and relationships with others (peers, parents, siblings and participation in organised activities) with responses being instead graded on a 5-point Likert scale (excellent, above average, average, somewhat of a problem and problematic). If the participant obtained at least 6 responses of 2 or 3 (i.e. often or very often) on the symptom measures, or 4 or 5 (somewhat of a problem or problematic) in the performance domains this suggested positive signs of ADHD. Specific scoring on certain criteria then were indicative of possible subtypes. A similar scoring process was used to identify the presence of ODD, CD and anxiety and depression difficulties.

### 2.4.3 Social communication

To screen for Autism Spectrum Disorder (ASD) behaviours, the Social Communication Questionnaire (SCQ) Lifetime Form (Rutter, Bailey & Lord, 2003) was used. The SCQ was used to identify signs of ASD symptomology. The questions explored the child's entire developmental history with a focus on: social interaction; communication and restricted, repetitive and stereotyped patterns of behaviour. The SCQ takes around 10 minutes to complete and consists of 40 items that each required a 'yes or no' response. The statements had associated scores of 0 or 1, and these were summed to generate a total score. A total score of 15 or above suggests positive behavioural symptoms that align with ASD. Diagnoses were not being made in the current work, but this score

recommends that further assessment or a follow-up is necessary (Chandler et al, 2007; Eaves, Wingert, Ho & Mickelson, 2006).

### 2.4.4 Behavioural and emotional difficulties

The Developmental Behaviour Checklist for Parents, 2nd edition (DBC-P) (Einfeld & Tonge, 2002) was used to assess emotional and behavioural difficulties. This tool is used for individuals aged 4-18 years with intellectual disability or developmental delay (Einfeld & Tonge, 2002). As CNVs have previously been associated with developmental delay and neurodevelopmental disorders, it was only included in the Patient but not Sibling questionnaire booklet. The DBC consisted of 96 questions across 5 subscales: (1) Disruptive/antisocial behaviour, (2) Self-absorbed, (3) Communication disturbance, (4) Anxiety and (5) Social relating. Responses required a response of either 0 (not true), 1 (somewhat true) and 2 (certainly true) and these were summed to generate a Total Behaviour Problem Score (TBPS). This score quantified the severity of the behavioural and emotional disturbance across the 5 scales. A TBPS greater than the clinical cut off described in the manual indicates a "definite psychiatric case" or "major" behavioural/emotional problems.

### 2.4.5 Movement difficulties

The Developmental Coordination Disorder Questionnaire (DCDQ) (Wilson et al; 2007, 2009) was used to screen for coordination difficulties that are typical of DCD. The DCDQ consisted of 15 statements which map onto motor strengths and weaknesses in 3 main areas: 'motor control during movement' (6 questions), 'fine motor and handwriting' (4 questions), and 'general coordination' (5 questions) for children aged 5-15 years. Parents were asked to rate the statements, comparing the degree of coordination their child displays with that of other children of the same age. Ratings were made on a 5-point Likert scale: not at all (1); a bit (2); moderately (3); quite a bit (4) and extremely (5) - like your child. The responses were totalled to yield a total score, with a maximum score of 75. Following this, if a child was between 5-7 years of age a Total score in the range of 15-46, was then defined as 'Indicative of, or Suspect for DCD'. In children aged 8-9 years old the range this definition applied to was adjusted to 15-55, and in 10-15 year olds the range shifted again to span from a total score of 15 up to (and including) 57.

# Chapter 3 – The feasibility, evaluation and impact of conducting research in a paediatric patient sample in the home setting.

## 3.1 General introduction

This project was initiated to investigate the phenotypical profiles of children with genetic variance (i.e. Copy Number Variant, CNV). CNVs are a specific type of genetic mutation which result in deletions or duplications to chromosomal material. Previous evidence suggests CNVs are associated with variations in ability and are implicated in neurodevelopmental disorders (Grayton, Fernandes, Rujescu & Collier et al, 2012; Mitchell, 2015). Alongside this, the majority of previous work has explored the profiles of children with more commonly known CNV syndromes (e.g. Williams Syndrome and 22q11.2 DS) or the outcomes associated with variance at specific chromosomal locations. To present knowledge, there has been limited work conducted on how CNVs in *general* (i.e. rare variants or not associated with a syndrome) influence developmental outcomes.

The cognitive, motor and behavioural strengths and weaknesses of children with a diagnosed CNV were investigated using a range of assessments. The assessment battery consisted of standardised assessments that were selected because they are well-established and have demonstrated reliability and validity in other studies of children and across intellectual ability ranges. Participants were recruited via our collaboration with NHS Clinical Genetics and assessments were conducted in the family home across various visits. This chapter discusses the feasibility of conducting this type of project, with evaluation and recommendations for future projects. The following sections explore the procedures, issues and barriers of initiating a NHS based project (i.e. gaining NHS ethics and relevant approvals), identification and recruitment of a paediatric patient population (i.e. working with a NHS clinician and clinical sample) and conducting research (i.e. assessments) within the home setting.

## 3.2 Project evaluation approach

This project involved recruiting a paediatric patient sample and administering psychological assessments in the home setting. There were various challenges and issues faced during the project's initiation and implementation, and this chapter discusses the feasibility of conducting this type of work. Feasibility studies can be designed to address whether a project can work, does work, or will work and considers factors such as

practicality, recruitment, data collection procedures, acceptability, appropriateness and implementation (Bowen et al, 2009; Orsmond & Cohn, 2015). Assessing implementation success enables evaluation of whether the project works in real-world settings (Peters, Adam, Alonge, Agyepong & Tran, 2013) and can lead to measurable impacts on patient level or service level outcomes (Proctor et al, 2011). Based upon this, a feasibility assessment and evaluation criteria were devised to address to two main objectives:

Objective 1: To discuss and evaluate the feasibility of **conducting research in a developmental patient sample in the home setting** in relation to:

**1.1 Setting up an NHS project:** This project collaborated with NHS Clinical Genetics and various approvals were required prior to implementation. The issues and challenges faced during the project initiation stage are discussed in section 3.3.1 with recommendations for future work.

**1.2 Recruiting a developmental patient population**: Patients were recruited via our NHS collaboration. Section 3.3.2 discusses the factors and issues involved in the identification, recruitment and retention of paediatric patients.

**1.3 Conducting psychological assessments in a paediatric patient population:** Data was collected using standardised assessments in the home setting. Section 3.3.3 will discuss the feasibility of obtaining data and implementing research in the home setting.

Objective 2: Preliminary assessment of project impact.

It was of interest to explore how the project may have impacted families. An initial questionnaire measure was used to investigate this.

On completion of the assessments, parents and the clinician received a performance feedback booklet which summarised the patient's performance on the standardised assessments. Following this, (after 3 months) evaluation questionnaires were sent out to parents to assess how the project supported their understanding of their child's overall, cognitive, motor and behavioural development and if they used the feedback booklet to support their child. The findings from this are discussed in section 3.3.4.

## 3.3 Findings and discussion

### 3.3.1 Setting up an NHS project

This research was conducted as part of a PhD project in collaboration with the University of Leeds, School of Psychology and clinicians from NHS Clinical Genetics. The project was funded between October 2016 and October 2019. In October 2016, the application form was started by the researcher and an initial project meeting took place with the researcher, the clinician and the main PhD supervisor to discuss the project in general. The main outcome was to start work on gaining the relevant approvals. As the work involved NHS patients, several NHS approvals and procedures were required prior to project initiation (see Figure 3.1, Project Start).

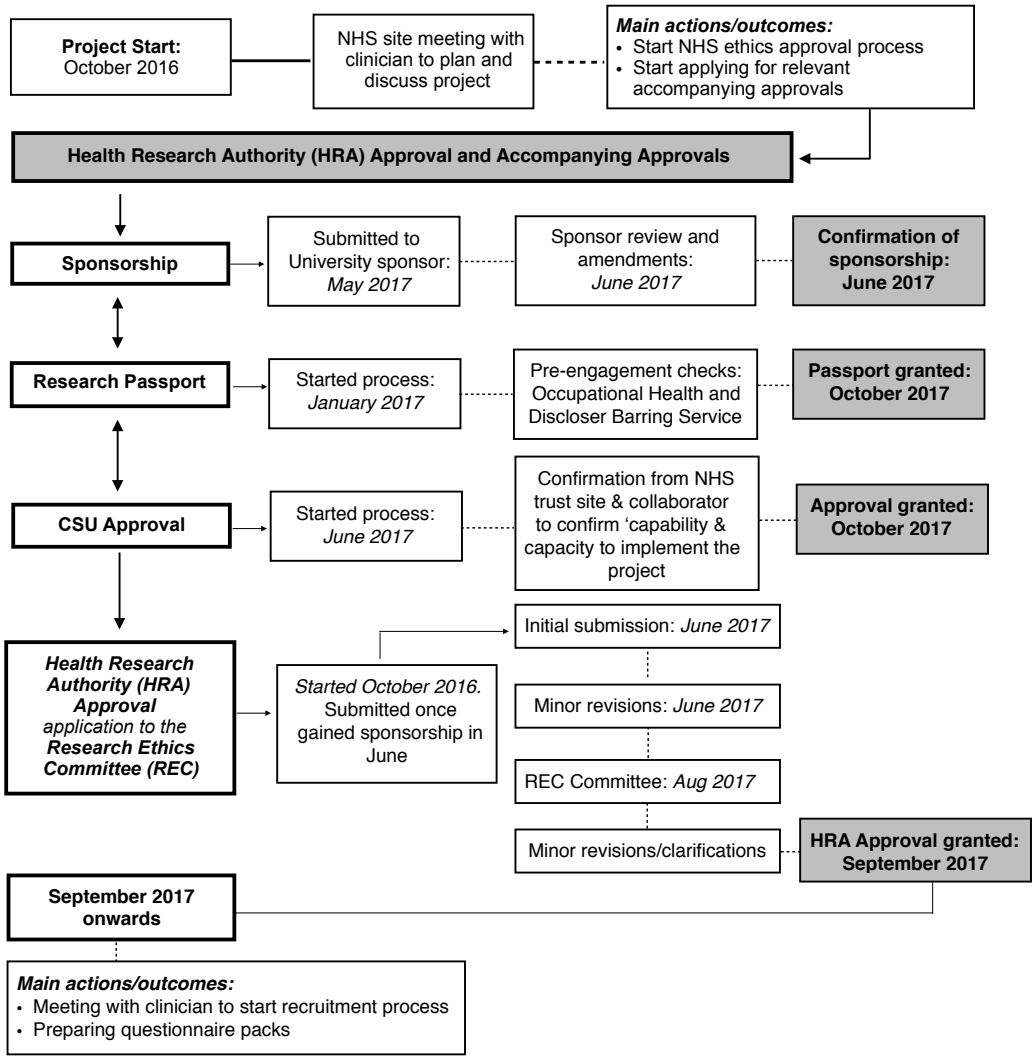


**Figure 3.1: Flow diagram presenting the stages involved in setting up an NHS based project.**

To implement an NHS based research project, various approvals must be in place prior to any research work. These approvals are in place to ensure the research will be implemented in a safe and ethical manner in line with NHS guidelines on both a project and researcher level (see Figure 3.1).

The main NHS ethics approval was obtained from the Bradford Research Ethics Committee (REC) in the form of Health Research Authority Approval (HRA approval). The application for this was completed online on the Integrated Research Application System (IRAS). The core project documentation was required which included: project information (research protocol, participant information sheets, consent forms, letters of invitation, validated questionnaires); finance documentation (letter from sponsor); investigator information (CV for student, supervisors and chief investigator) and other project documents (risk assessment and statement of activities letter).

Various accompanying approvals were required along with the HRA application and these were uploaded on the IRAS with the project documentation once secured. Firstly, a project sponsor (ours was the University of Leeds) was compulsory to ensure responsibility for indemnity and liability for the project. The university sponsorship team conducted a comprehensive review of the HRA application and documentation and responded with amendments and clarifications. Alongside this, approval was required from the collaborating NHS site to ensure the site and clinician had the capacity and capability to support the project (CSU approval). Finally, the PhD student was required to have a Research passport to permit work within the NHS and with NHS patients. To obtain this, an occupational health check and Disclosure and Barring Service check were completed, and relevant training was completed online (Good Clinical Practice) (see Figure 3.1).

Following multiple revisions of the HRA application and project documents, and once all the accompanying approvals were secured, the full application was submitted on the IRAS. The REC staff completed an initial application assessment, and this was followed by a panel review where members of the supervisory team and researcher attended. The panel asked various questions and suggested minor amendments to the project documentation and IRAS form. Following this process, successful HRA approval was gained in September 2017.

Overall, the project initiation phase took a year in total. This involved project planning, the completing the HRA application, devising and revising all the project documents and gaining the accompanying approvals required to work with NHS patients.

#### 3.3.1.1 Evaluation and recommendations

The following will discuss and evaluate setting up an NHS project followed by potential recommendations:

**Clinician support on NHS ethical approval documents:** Although the approvals were completed by the PhD student working on the project with support from the research team (supervisors), often specialist knowledge was required from the clinician. Due to the clinician's workload, it was challenging to get in contact to discuss the approval process or arrange meetings, which subsequently impacted the project timeline. For example, CSU approval was a key requirement to progress the application and it was difficult to liaise and contact the clinician to secure this. The clinicians had specialist knowledge and experience, but as the main research team were based in Psychology, we were unaware of the NHS based support we were eligible to apply for. This took the form of the NHS portfolio, which places the research project on a wider network of projects within the NHS and allows additional research support from the NHS site.

Reflecting on these issues, in relation to external clinical collaborators, it is useful to plan a clear project outline or timeline at the start of the project with all members and highlight the key dates for each stakeholder. Effective communication between all parties at the project initiation phase can reduce the likelihood of a delayed application and would also be beneficial in gaining information on collaboration-specific procedures or requirements (e.g. NHS portfolio). Within the project team, it is useful to have: a project application strategy in place, details of key application review dates or pre-scheduled meetings devised. This ensures that there is an effective communication in place and each project member is aware of the approvals required and the associated timeline and specific requirements of these.

**Length and detail of the IRAS application and associated documents:** The HRA application required a detailed project protocol which included a literature review, project description, and consideration of ethical issues and barriers. There were various additional project documents (e.g. protocol, project information sheets and consent

forms) that were key to gaining HRA approval. These documents took several months to produce with multiple drafts sent between the PhD supervisory team.

In line with the previous section, due to the high level of detail required in these approvals it is recommended that a clear project plan is initially devised and discussed with all stakeholders. Within the project team it is essential to plan key submission dates for all members of the team and keep a thorough record of the application form amendments prior to the first formal submission. For example, throughout the setting up a project stage there were application form amendments from individuals within the project team (e.g. various checks by members of supervision team), the sponsorship team (e.g. around 2 versions here) and REC committee (e.g. initial screening prior to meeting). Alongside this, it may be beneficial to create a question plan which consists of all the questions in the application and strategise whose expertise is required at different time points. The application consists of questions which require lengthy, detailed answers so it may be useful to allocate specific questions to different project members to utilise their expertise and save time where possible. Some of the IRAS questions required: a summary of the main issues (e.g. ethical, legal or management and how these will be addressed); methodology, design and the scientific justification. Based on these questions, it may be suitable to allocate these questions to project members who have previous experience working with the NHS, clinical populations or children.

Overall the NHS ethical approval process is time consuming (Jamrozik, 2004) and starting this as early as possible is beneficial. The whole approval process took a year in total, with this length of time not unusual based on previous reports (Koshy & Clark, 2016). Key to the project start up is effective communication between all project members to prevent delays to the application process, limit any potential difficulties and ultimately avoid failure (e.g. rejection or request for major revisions, which would add more time to the preparation of a project) at the REC committee (Koshy & Clark, 2016). Finally, it is beneficial to look at past, successful applications and utilise the documentation support and training available on the NHS website.

### 3.3.2 Recruiting a paediatric patient population

Factors concerning the identification, recruitment and attrition of a developmental patient population are now discussed, followed by an evaluation and recommendation within each section:

### 3.3.2.1 Patient identification

Once the relevant approvals were gained (in September 2017) the recruitment stage was initiated from October 2017, see Figure 3.2. Based upon work within individuals with diagnosed genetic syndromes (see Chapter 1) and a power analysis, we planned to recruit a sample size of 30-60 patients. Although this number was not achieved (given the issues to be discussed in this chapter) the relatively small sample size provided the opportunity to conduct a range of detailed single case and group based exploratory investigations.

Recruitment was conducted via a clinician who was based in a Hull hospital and who made occasional clinic visits to a Leeds NHS site, where project meetings were held with the researcher. The clinician screened the Yorkshire Regional Genetics Service paediatric database for eligible patients (aged between 7-16 years, with a diagnosed Copy Number Variant (deletion or duplication)). This age range was decided based upon the age ranges referenced in the standardised measures employed in the assessment battery. This age range is also useful as it provides an understanding of the developmental profiles of children in both primary and secondary education. Once patients were identified, the clinician printed and signed the committee approved invitation letters on NHS letterheads. Following this, the researcher enclosed the letter with the remaining project documentation (parent information sheet, child information sheets and permission contact form with prepaid envelope) and posted these. This process continued at five time points during the recruitment stage, with 83 potential recruits approached in total (see Figure 3.2, number of letters sent out).

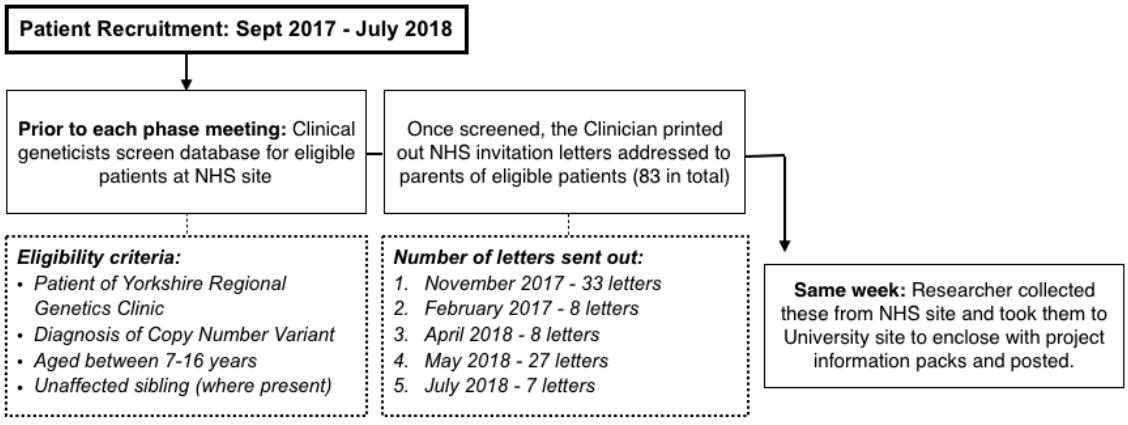


**Figure 3.2: Flow diagram presenting the patient identification stage**

**Clinician's workload and involvement:** The clinician's involvement was key to this stage. The clinician was effectively a bottle-neck for the recruitment phase as they were required to screen the database for eligible participants and then print out the letters addressed to the family. Conducting this in batches was effective for the clinician, although the number of letters in each batch was not consistent (Figure 3.2: 33, 8, 8, 27 and 7) which may have influenced the number of children recruited. Alongside this, the clinician mainly identified eligible patients from their case load which may have also contributed to the lower numbers. In some cases, the Clinician also discussed the project at the clinic visits with the patients.

As previously discussed, to improve the recruitment strategy in future projects the NHS based support should be utilised or explored where possible (i.e. NHS portfolio). In this instance, additional research staff may have supported the clinician in screening the patient database. Alongside this, broadening the recruitment strategy may be beneficial for future projects. Advertising the project via wider networks of clinicians or via genetic charities, may attract a wider number and be less time consuming for one clinician alone. Finally, while a performance feedback report was given upon assessment completion, if more incentives were offered for participation this may have improved the response rate.

#### 3.3.2.2 Patient recruitment

Enclosed with the project invitation letter was a permission to contact form which was addressed to the researcher at the University of Leeds. Families responded to this with their contact details to find out more. In total, 30 forms were returned (conversion rate, 37%) during the recruitment stage which was rolling from November 2017 to July 2018 - see Figure 3.3 for details. On the day or week received, the researcher contacted the families to discuss the project. Often multiple attempts were made to contact the family, and some families were also chased up months later if there was no answer. Of the 30 contacted, 100% booked in a home visit for their child to complete the cognitive and motor assessments and agreed to have the questionnaires sent via post and collected on the visit. The researcher was flexible to accommodate the family, so visits were offered at various times (e.g. after school, weekends and during school holidays) at a time most suitable for the family to complete the assessments which took up to 3 hours. Non-affected siblings were also recruited at this stage.

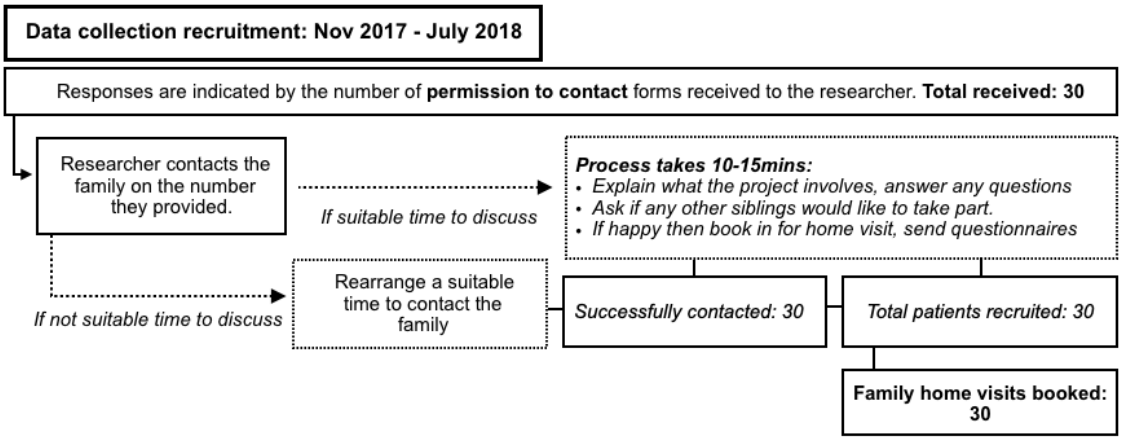


**Figure 3.3: Flow diagram presenting the patient recruitment process**

**Response rates:** Based on this two-stage process, it is useful to be mindful that the low conversion rates at the point of first contact from the clinician likely (i.e. 83 letters and 30 responses). However, based upon the response rate, it is likely that once families are engaged (i.e. contacted by the research team to discuss the project) there's a high probability of converting this into booking a home visit.

#### 3.3.2.3 Patient attrition

Of the 30 home visits booked, 28 were successfully conducted - see Figure 3.4. The 2 uncompleted visits were due to cancellation prior to the home visit due to family illness. Attempts were made to reschedule but there was no response. Of the 28, successful data was collected for 23 patients (discussed in the following section). Although the project was made as flexible and as accommodating as possible for families, patient attrition (n=5) was due to various reasons, see Figure 3.4. In one case, the parents were keen for their child to take part in the project but on the home visit the patient refused. The parents said they would send the questionnaires to the researcher, although after multiple communication attempts this was unsuccessful. Multiple cancellations on the home visit or on the morning itself, occurred most often (n=4) due to: parent illness, child illness, child making plans, child asleep or lack of sleep.

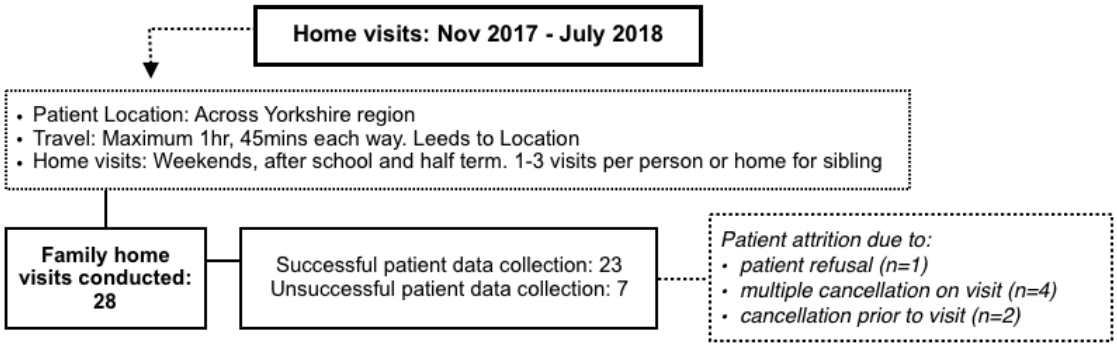


**Figure 3.4: Flow diagram presenting participant recruitment and attrition levels**

**Patient personal factors and family circumstances:** In relation to recruitment, often circumstances of the individual patients (e.g. psychological difficulties and learning difficulties) or their family influenced whether they continued with the project or whether full data was obtained. In one case, the parents made three cancellations prior to the scheduled home visit due to child anxiety and social difficulties but the researcher arranged to have the behavioural questionnaires via post instead of direct assessment. Unfortunately, the parents did not send the questionnaire back after two sets. Alongside this, two children had learning difficulties consisting of language delay and physical disability. Behavioural data was returned successfully for one child, but for the other multiple questionnaires were given (n=3), but these were not returned. This child's sibling was also a patient who was scheduled to take part, but the parent cancelled three times on the day of the visit and the questionnaires (multiple mentioned above) were not returned. Based on this, during the recruitment phase, it is essential to offer flexible arrangements for home visits and the type of data obtained (i.e. just questionnaires instead of direct assessment).

Alongside this, it is key to be aware of any potential family circumstances. Two families cancelled on the morning of the scheduled visit twice which may be due to the comorbid health difficulties and diagnoses the parents mentioned on the initial phone call. Second attempts were made to reschedule, but personal circumstances were taken into account and a third attempt was not made. Based upon this, it is recommended the number of times the family has been contacted for recruitment and any participant-specific details are clearly logged. This can ensure the family and their circumstances are respected and they are not pressured into taking part.

Overall, in relation to recruiting a patient population, the clinician's involvement and the personal and family circumstances of children with a genetic disorder need to be considered.

### 3.3.3 Conducting psychological assessments with a paediatric patient population

The following section will discuss the feasibility of conducting psychological assessments in a patient population in relation to data outcomes, appropriateness of assessments and issues of the home setting. In relation to Figure 3.5, the home visits were booked at a time most convenient to the family and conducted by the researcher. On arrival of the home the consent procedure was conducted with the parents and the child. At this point, the next home visit was also arranged (to complete assessments), the questionnaires were collected or parents were provided with a pre-paid envelope to send them back in later.

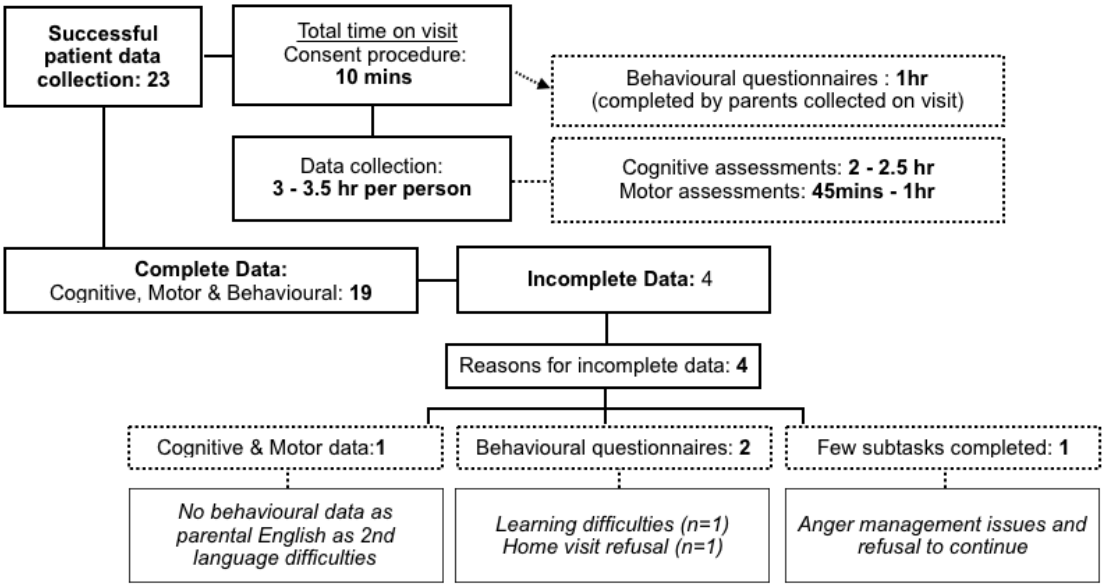


**Figure 3.5: A flow diagram presenting information on the data collected.**

Information on the data collected are presented in Figure 3.5. Full cognitive, motor *and* behavioural data was collected for 19 children, cognitive *and* motor data was collected for one child and only *behavioural* data for two. One child refused to continue with testing, so only a few cognitive subtasks were completed. The assessment battery consisted of reliable and valid standardised assessments that are well described in the

literature and are suitable for the age and intellectual ability range of the sample. The cognitive and fine motor assessments required a small amount of space, preferably a table top whilst the gross motor tasks required more space as they are commonly for use in gym settings. Due to this, adaptations were made to accommodate the more limited space available in the home setting, see Chapter 2 – Methodology.

#### 3.3.3.1 Evaluations and recommendations

**Incomplete data:** there was difficulty obtaining full data for 4 patients (Figure 3.5, reasons for incomplete data). Firstly, for one child cognitive and motor data was received, but the behavioural questionnaires were not received as the parents struggled to complete the booklet due to limited English language proficiency. For two children only behavioural data was collected. Of these children, one had learning difficulties and the other child refused a home visit multiple times due to anxiety and social difficulties. Finally, one child only managed to complete a few cognitive subtasks due to severe anger management difficulties on the home visit. This led to project withdrawal as they refused to partake in the next scheduled home visit.

Overall in relation to data collection, adaptions were made where possible to gain data. To achieve this, the researcher was flexible and accommodating around the family's commitments and conducted multiple visits. In relation to data outcomes, when cognitive and motor data could not be collected, parents were asked if they could complete the behavioural questionnaires. In some cases, the extent of the genetic disorder can lead to a disabling condition or the patient may present psychological difficulties. Based upon these phenotypical outcomes, it is essential to consider the potential project adaptions that can be made to support families to make them feel at ease where possible. In this project, for the children who faced social difficulties, parents were offered the option to only complete the behavioural questionnaires. This helped avoid direct contact with the researcher themselves (i.e. child doesn't have to meet new people) and the family would still gain some feedback information.

**Resources and space in the home:** The cognitive and fine motor tasks (besides gross motor) required relatively small space and the participant was required to face the researcher. In the majority of homes this was feasible, but in a few cases it was hard to accommodate this (i.e. no dining table). In such situations accommodations were made, by sitting on the floor or using a fold away table. It was challenging to implement some

of the balance tasks from the MABC-2 as these are commonly carried out in large open spaces (e.g. gym halls or clinic settings). Adaptions were made where reasonable to suit a living room space and to minimise risk of injury to the child (i.e. length of the line to walk on).

To ensure data was collected in a safe and standardised manner on each visit, adaptions were made to the accommodate the spacing issues faced in some homes. Recommendations would include taking a fold-away table which would be adequate for the home setting. Although home visits are convenient for the family, it would also be beneficial to also offer parents the opportunity to conduct the assessments in a University laboratory or in a clinic setting and offer to reimburse travel. This option may also increase the number of families that sign up for the project, and work well for those who have other child commitments, family circumstances or limited space in the home setting.

**Distractions**: As the assessments were conducted in the home setting with other family members present, it was difficult to minimise the noise levels or external disruptions. This took the form of distractions by other family members, electronic devises and pets. Although it was highlighted on several occasions that a quiet space is required to successfully complete the tasks, it was often challenging to relay this to some family members and to control for these factors.

In conclusion, when conducting psychological assessments in a developmental patient population it is beneficial to reassure the family you can accommodate their needs by being flexible and accommodating where possible. To ensure families are respected and children feel comfortable any particular requirements or child-specific difficulties should be discussed during the initial phone call. This was demonstrated in this project as multiple visits were made for a patient who had behavioural and social difficulties, and this helped to improve familiarity with the researcher. Similarly, on a home visit a child with parental reports of concentration and attentional difficulties was given multiple breaks (to play on their phone and with pet) to keep them interested and motivated to engage in the tasks.

### 3.3.4 Project impact and benefit assessment

Following completion of the assessments, we were interested in understanding the views of the families who took part. This was a small step in understanding the potential impact of the project, which may inform future projects with larger sample sizes.

Once the data was collected and analysed, parents were sent a feedback report which summarised the findings in a user-friendly booklet (see Appendix C for an example). This booklet detailed the patient's performance on the cognitive and motor measures as a percentile on a number line, using a traffic light system (e.g. below average, average and above average performance). Questionnaire data was reported in relation to behaviours typical of a neurodevelopmental disorder, whereby symptomology above or below a specified cut off indicated behavioural difficulties. Following this, a short evaluation form (see Appendix D) was sent out to 22 families. Although data was collected for 23 patients, one participant only completed two subtasks of the cognitive battery so they were not sent a feedback form (as we decided not to send a performance report due to insufficient data and concerns over compliance with task instructions due to conduct problems).

Of the 22 forms sent, 11 were returned (50% response rate). The first question asked parents how the project has helped them understand more about their child's development. Responses to each question were indicated on a Likert scale ranging from strongly disagree to strongly agree, see Figure 3.6 and 3.7.

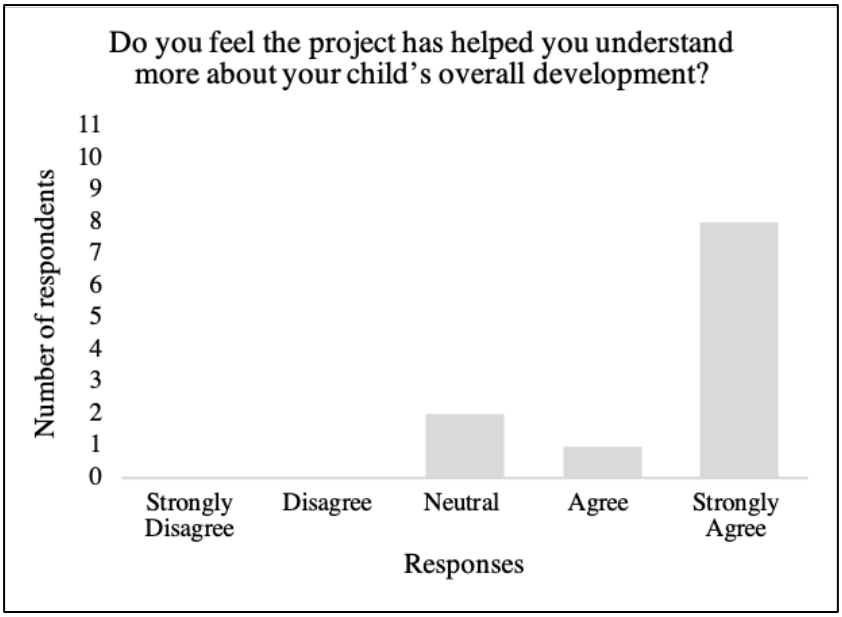


**Figure 3.6: Parental responses to understanding of their child's overall development**

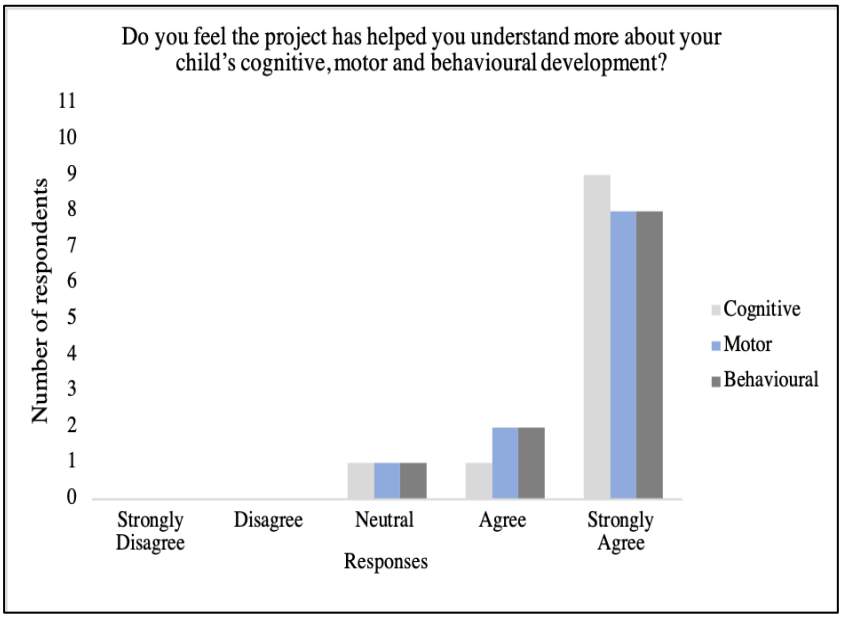


**Figure 3.7: Parental responses to understanding of their child's cognitive, motor and behavioural development**

Parents were also asked if they used the feedback booklet in any way to support their child (yes or no, with space for further detail if yes). The majority (9/11, 82%) indicated that they had used the feedback to support their child. Qualitative responses for this question reveal that 7 parents used this feedback to send to school. It was also indicted that the report was used as evidence for the Disability Living Allowance (n=1) and in support of their child's Education, Health and Care Plan (EHCP) (n=3). One family indicated that the report provided encouragement for their child to partake in more learning exercises at home and one said that the report has supported their understanding.

Based on anecdotal information from the clinician working on the project, families often ask clinicians to write letters of support for their child's for EHCP application. An EHCP is a legal document which details the child's developmental (educational, health and social care) strengths and difficulties and details the support or services that will be provided to help address their specific needs. Based upon the present evaluation's findings, the provision of the performance feedback reports may be beneficial for families who require additional support for their child and need evidence to support an application for such assistance (e.g. EHCP, DLA).

In relation to the data from the clinician on the ECHP status of the full sample (n=23). EHCP provisions were underway for 35% (8/23), with 3 at a SEND school, 3 with EHCPs in place in mainstream schooling and 2 with EHCP applications in progress. Of the

remaining 15 patients, 3 had informal extra educational support in class (School Action/ Plus level) but 17% (4/23) had EHCP application requests by parents being resisted by their schools. Of these cases, who had their request resisted, the Clinical Genetics Consultant had provided 2 with letters of support to council for an EHCP application. Lastly, the remaining 35% (8/23) had no provisions: this either constituted no educational support (n=4) or no support as yet because the child was too young to fairly assess for support (i.e. just started school with 'emerging ID') (n=4).

These findings highlight the potential value of the current project. We aimed to explore the impact of general copy number variance (i.e. not syndrome specific or location specific) on phenotypical outcomes. At present, CNVs are found to be implicated in neurodevelopmental disorders or associated with developmental delay. However, there is relatively less understanding of how general variance impacts variation in cognitive and motor ability and behavioural symptomology among carriers. Based on the evaluation data, the majority of parents reported an improved understanding of their child's development and they used the report to help their child. For 65% (15/23) of the sample, an ECHP was not in place, which may place the child at risk of poor educational progress given the risk of developmental delay and/or neurodevelopmental disorders related with copy number variance.

## 3.4 Conclusions

In summary, setting up a project with the NHS is a time-consuming process. It is beneficial to start the application form early, explore previous successful applications and have a detailed preliminary project meeting with all members to support a collective understanding of the site-specific requirements and protocols (e.g. University and NHS). Alongside this, it is beneficial to clarify *who* is responsible for each part of the process (e.g. CSU approval) and *when* draft documents are required, so the project team can collectively improve and amend these. Finally, it is useful to contact the relevant departments involved in the process in advance (e.g. sponsorship department, REC committee) so there is a clear understanding of what approvals are necessary later in the application process and the associated timeline. Overall, key to securing NHS ethics is having a clear understanding of the documentation required, the accompanying approvals and utilising the support available.

In relation to identification and recruitment of a developmental patient population, it can be challenging to reach the desired sample size for clinical research due to the recruitment strategy working with clinical samples sometimes necessitates. In the present project, eligible participants were identified by the clinician working on the project and a varied number of invitations were sent out to families. In future projects, it would be useful to be aware of other NHS research avenues (e.g. NHS portfolio) which can better support such projects, including contacting other research groups to enlist other clinicians on the project or recruiting participants externally. It may also be advantageous to offer incentives to take part. Finally, in relation to recruiting a patient population, it is essential to be aware of the specific features of patient population itself as children with CNVs are at risk of neurodevelopmental disorders. In the present work, some children faced learning difficulties and social difficulties. In these cases, it is beneficial to make project adaptations (e.g. offer parent-reported questionnaire-based assessments where direct cognitive and motor assessment is not feasible) to ensure they can still partake.

Finally implementing research within the home setting can be challenging due to extraneous variables (e.g. space of the home, distractions and resources). To minimise the impact this can have, it is useful to discuss the data collection requirements in advance of the visit, so adjustments can be made in due course (e.g. taking a fold away table) and to ensure a clear understanding of any patient specific factors (e.g. attentional or social difficulties). It is essential to be considerate of any family specific details discussed on the initial phone call, so these can then be taken into account on the home visit or if the family decides to cancel (e.g. patient or sibling health difficulties). Finally, to avoid the potential difficulties associated with home visits, it would be valuable to offer the assessments in controlled university laboratory or clinic setting as an alternative.

Despite the relatively small sample size, detailed phenotyping was successfully conducted in the majority (23 out of 30 who contacted the research team). Based upon preliminary analysis of the impact of the project, the evaluation data shows the project supported parents understanding of their child's overall, cognitive, motor and behavioural development and that they made use of feedback reports to support their child. Patients in the present sample were undergoing various stages of securing external provisions to support their child (e.g. DLA and EHCP) and some detailed that they shared the findings from this project with their child's school, and in support of these applications. These

findings may highlight the potential benefit, impact and contributions of offering such assessment to families of children affected by copy number variation.

# Chapter 4 – Exploring the cognitive, motor and behavioural development of children with Copy Number Variants.

## 4.1 Chapter overview

Copy Number Variants (CNVs) have been associated with the risk of developing a neurodevelopmental disorder. Previous work has investigated the developmental profiles of children with more commonly known CNV syndromes (e.g. Williams Syndrome, 22q11.2 Deletion Syndrome). It remains unclear however, how CNVs in *general* (regardless of loci) influence specific developmental outcomes. Based upon this, the present chapter explores the cognitive and motor abilities and behavioural symptoms of the full patient sample (section 4.3). These developmental domains and their associated skills provide the foundation for successful learning, interaction with the world and with others. Alongside this, exploratory investigations were conducted of groups of children with a variant at a specific location (section 4.4: neurodevelopmental susceptibility); by the type of genetic variance (section 4.5: deletion and duplication), the role of genetic variance among family members (section 4.6: three patients with the same CNV) and of multiple variants (section 4.7: a child with two variants).

## 4.2 General method and materials

### 4.2.1 Participants and procedure

The current chapter is based on patients recruited from the Yorkshire Regional Genetics clinic. This includes 23 children (Mean age=10.39, SD = 2.41) with a diagnosed CNV aged between 7-16 years. Presence of a CNV was confirmed via standard methods (e.g. FISH/microarray) at medical genetics laboratories. The recruitment and data collection procedures were conducted following the protocols approved by the NHS Research Ethics Committee and accompanying bodies. Table 4.1 provides a description of the participant sample. This information is taken from the patient's cytogenetic report which is issued by the genetic laboratory and provided by the Clinical Geneticist for the purpose of this project. This report details the patients karyotype which is based on the results of the genetic screening (microscopic investigation of the chromosome), interpretation of the findings in relation to the clinical profile, any information of further tests required and any further advice. Consent was obtained from participating children (verbal or written) and parent/carers on the home visit.

**Table 4.1: Clinical characteristics of the whole patient sample**

| Patient | Age | CNV | Type | Clinical summary from cytogenetic report |
|---|---|---|---|---|
| 23 | 9 | 1q21.1-1q21.2 | Dup | Developmental delay, pathogenic, lies within the 1q21.1 microduplication SL which is associated with a broad phenotypic spectrum. The clinical features in this patient are consistent with those associated with duplication of this region so it is probable that the duplication is contributing to phenotype. |
| 17 | 12 | 3q26.1-3q26.2 | Dup | Developmental Delay, auditory processing disorder, dysplastic hip. Due to size and gene content of imbalance therefore it is likely to be the cause of patient's clinical features. |
| 12 | 8 | 7q11.23 | Del | Williams Syndrome diagnosis |
| 9 | 13 | 10p15.3-11.21 & Xq25-Xq28 | Dup / Del | Developmental delay, Microcephaly. Imbalances likely cause of phenotype and associated clinical features. |
| 11 | 11 | 12p13.32-12p13.31 | Del | Developmental delay. Although limited data on the phenotypic/genotypic association for this region the large size and high gene content of imbalance mean it is possibly contributing to patient's phenotype. |
| 4 | 10 | 15q13.3 | Dup | Unexplained mild learning difficulties, ?ASD, region of variable penetrance. Tentative evidence of CHRNA7 gene as risk factor for neurobehavioral disorders. |
| 18 | 13 | 15q11.2 | Dup | Coordination difficulties, learning difficulties, speech language difficulties and SEN statement. Lies within the 15q11.2 SL which is associated with a broad phenotypic spectrum. The coordination difficulties and speech difficulties seen in patient have previously been reported in patients with a duplication to this region, therefore it is possible this duplication may be contributing to phenotype. |
| 25 | 7 | 15q13.3 | Dup | Undergoing ASD assessment, speech delay, repetitive hand movements (at present limited literature surrounding the phenotypical outcomes associated, tentative evidence of CHRNA7 gene implicated in neuro-behavioural disorders. |
| 16 | 7 | 16p11.2 | Del | Autistic trait, emerging learning difficulties, TIC disorder. Del lies in the 16p11.2 BP2-BP3 and region |

| | | | | |
|---|---|---|---|---|
| | | | | predisposes to DD and ID therefore possible contribution towards phenotype as consistent with the learning difficulties in patient. |
| 1 | 10 | 16p11.2 | Dup | Social communication difficulty, learning problems, CNV within Susceptibly Loci for microduplication syndrome. Dup linked to variable phenotype and variable penetrance – consistent with patient and likely cause of phenotype. |
| 8 | 7 | 16p12.2-11.2 | Dup | Developmental delay (gross motor disproportionally delayed) CNV consistent with16p11.2-16p12.2 microduplication locus associated with variable phenotype. CNV is likely cause of patient phenotype. |
| 15 | 10 | 17p12 | Dup | Statemented, associated health difficulties and clinical features of Hereditary Motor and Sensory Neuropathies. Charcot-Marie-Tooth hereditary (Muscle weakness, mild-moderate sensory loss, high arched feet). Features in this sample are consistent with those for duplication of this region, therefore it is likely contributing to phenotype. |
| 20 | 15 | 16p12.2 | Del | Joint hypermobility and motor delay. CNV lies within 16p12.2 microdeletion risk locus for neurodevelopmental disease (broad phenotypic spectrum). CNV likely cause of patient's phenotype. |
| 21 | 10 | 16p11.2 | Dup | Behaviour problems and clinical features. CNV lies within 16p11.2 microduplication Susceptibly Loci. The behaviour problems and mild dysmorphism evident in patient align with duplications of this region, so it is possible imbalance is contributing to phenotype. |
| 22 | 12 | 16p12.2 | Dup | Suspect ASD; Coordination Difficulty; Episodic Rage; Falls into NDD loci. Duplication associated with a broad phenotypic spectrum. |
| 29 | 9 | 16p12.2 | Del | Learning difficulties and social communication difficulties. CNV lies within 16p12.2 microdeletion risk locus for neurodevelopmental disease (broad phenotypic spectrum). CNV likely cause of patient's phenotype as consistent features reported for this deletion. |
| 30 | 7 | 16p11.2 | Del | General developmental delay. 16p11.2 microdeletion syndrome. CNV likely cause of phenotype due to general developmental delay. |

| | | | | |
|---|---|---|---|---|
| 28 | 12 | 17p12 | Dup | Duplication associated with Charcot-Marie-Tooth hereditary (Muscle weakness, mild-moderate sensory loss). Patient presents some early features consistent with Hereditary Motor and Sensory Neuropathies. |
| 5 | 10 | 20 p12.3-p12.2 | Del | Neuro-behavioural problems. Emerging evidence of PLCB1 gene to neuro-behavioural disorders, but at present not conclusive. |
| 6 | 14 | 20 p12.3-p12.2 | Del | Autistic features, behavioural problems, macrocephaly. Emerging evidence of PLCB1 gene to neuro-behavioural disorders, but at present not conclusive. |
| 7 | 13 | 20p12.3-p12.2 | Del | Neuro-behavioural problems. Emerging evidence of PLCB1 gene to neuro-behavioural disorders, but at present not conclusive. |
| 3 | 8 | 22q11.21 | Del | Developmental delay and various health difficulties. Phenotype and genotype align with DiGeorge syndrome. |

The assessments were conducted in the home setting at a time and day most suitable for the family across multiple visits (see Chapter 2 for detailed description of the method and assessment battery). The cognitive and motor assessments took around 2-3 hours to complete, and around 1 hour for the questionnaire booklet (see Appendix A). Children completed the cognitive and motor assessments administered by the researcher on the home visits. Caregivers completed a questionnaire booklet to obtain data on behavioural symptoms. The cognitive battery included measures of: intellectual functioning (WASI-2, Wechsler, 2011); cognitive flexibility (WCST, Heaton et al, 1993); Working Memory (WMTB-C, Pickering & Gathercole, 2001) and language functioning (CELF-4, Semel & Wiig, 2006). The motor assessments included the tasks that comprise the Manual Dexterity and balance components from the Movement ABC-2 (Henderson, Sudgen & Barnett, 2007) and kinematic assessment for some children (CKAT, Culmer et al, 2009; Flatters et al, 2014). The questionnaire battery included screening measures of: language functioning (PP and ORS, Semel & Wiig, 2006); social communication (SCQ, Rutter, Bailey & Lord, 2003); movement (DCDQ, Wilson et al; 2007, 2009); psychological (SDQ, Goodman, 2001); attentional (VADRS-Parent, Wolraich et al, 2003) and behavioural and emotional difficulties (DBC, Einfeld & Tonge, 2002).

### 4.2.2 Analysis

The sections to follow describe the cognitive, motor and behavioural data from children with a CNV. Group averages and the Relationship To Mean (RTM) are discussed for each section, which are based on z-scores calculated for the respective assessment. This classification was inspired by the CELF-4 language battery as this provides clear understanding of performance in relation to the normal distribution of scores. The MABC-2 standard scores have a mean of 10 and standard deviation of 3, while the remaining measures have a mean of 100, standard deviation of 15. Section 4.3 explores the data from the full sample, while the sections 4.4 and 4.5 present group comparisons.

T-tests were conducted where possible (parametric) but often based on the small sample size and the unequal number of children in both groups the assumption of normality was violated, therefore analysis was conducted using the Mann-Whitney U test (non-parametric) (de Winter, 2013; Fay and Proschan, 2010; Goss-Sampson, 2019) using JASP (JASP Team, Version 0.10.2, Computer software, 2019). JASP reports the Mann-Whitney U-statistic as a W, as it is an adaptation of Wilcoxon's signed rank test. Alongside this, a Bayesian Independent Samples T-Test was used to generate a Bayes Factor (BF). A BF below 1 suggests evidence for the null hypothesis (e.g. no difference between having a CNV that situates in an NDD susceptibility loci) whilst a BF above 1 provides evidence in favour of the alternative hypothesis (e.g. children with an NDD are at increased risk of poor performance than those without). The factor score is classified as providing anecdotal (BF between 1-3), moderate (BF 3-10), strong (10-30), very strong (30-100) evidence (Quintana & Williams, 2018; Wetzels, van Ravenzwaaij & Wagenmakers, 2014). However, as the sample size is very small, great caution will be required when looking at the statistical results.

## 4.3 Copy Number Variance and overall cognitive, motor and behavioural outcomes

### 4.3.1 Background and sample

In this section, the data from the full patient sample will be discussed. The sample characteristics of these participants are presented in Table 4.1 above. As discussed in the feasibility chapter (Chapter 3) it was often challenging to obtain full cognitive, motor and behavioural data for all participants due to varying reasons. Based upon this, the data

obtained will be discussed where relevant. Each section (i.e. cognitive, motor and behavioural) will discuss findings from the associated subdomains, followed by a discussion of the developmental domain in relation to literature on CNVs.

### 4.3.2 Cognitive assessments: findings and discussion

This section will discuss the findings from the Intelligence (IQ), Working Memory (WM), Cognitive Flexibility (CF) and language assessments.

#### 4.3.2.1 Intellectual functioning (IQ)

Children completed the WASI-2 assessment which generated a measure of verbal IQ (Verbal Comprehension Index, VCI), non-verbal (Perceptual reasoning, PRI) and overall intellectual functioning (Full Scale IQ, FSIQ), see Table 4.2.

**Table 4.2: WASI-2 performance of the full sample**

| WASI-2 Composite | Verbal IQ (VCI) | Non-Verbal IQ (PRI) | Full scale IQ (FSIQ) |
|---|---|---|---|
| n | 21 | 21 | 21 |
| Mean | 85.76 | 79.62 | 81.10 |
| S. D | 13.88 | 15.01 | 14.14 |
| Relationship to the mean | -0.95 | -1.36 | -1.26 |

In relation to Table 4.3 which presents the number of children in each classification for VCI (range: 58-113), the group average situated in the “low average” classification. When considering the number of participants in each classification band, the majority (12/21) of the sample presented “low average” performance or below. In comparison, a smaller number of children gained scores in the “average” (8/21) and “high average” (1/21) classification. The PRI average (range: 56 – 107) was the lowest across all IQ measures (M=79.62, SD=15.01) and situated in the “low average” classification. The findings were similar to the VCI measure, as the majority (16/21) gained scores which placed them in the “low average” classification and below, with fewer in the “average” range (5/21). Similarly, FSIQ (range: 59-108) situated in the “low average” classification (M=81.10, SD=14.14) and the majority (16/21) presented “low average” and below performance,

with only a small number (5/21) in the "average" range. These findings show that the majority of children present poor intellectual functioning for their age.

**Table 4.3: WASI-2 qualitative classifications for the full sample**

| WASI-2 Composite | | Verbal IQ (VCI) | Non-Verbal IQ (PRI) | Full scale IQ (FSIQ) |
|---|---|---|---|---|
| Classification | Standard scores | n | n | n |
| Extremely Low | 69 & below | 2 | 5 | 4 |
| Borderline | 70 – 79 | 5 | 7 | 8 |
| Low average | 80 – 89 | 5 | 4 | 4 |
| Average | 90 – 109 | 8 | 5 | 5 |
| High Average | 110 – 119 | 1 | 0 | 0 |
| Superior | 120 – 129 | 0 | 0 | 0 |
| Very superior | 130 & above | 0 | 0 | 0 |

The WASI-2 provides an assessment of estimate of general intellectual functioning which is a combination of performance on verbal (VCI) and non-verbal (PRI) assessment, which map onto crystallised and fluid (PRI) skills respectively. The tasks that assess crystallised intelligence assess acquired, factual knowledge in contrast to fluid intelligence which explores how well children engage in problem solving, deal with novel situations and process and synthesise information (Gotteredson, 1997). To explore the relationship between these subdomains a paired samples t-test was conducted. This revealed a significant difference between the VCI (M=85.76, SD=13.88) and PRI (M=79.62, SD=15.01) index ($t(20)= 2.38$, $p = .027$). To explore this domain specific pattern in more detail, percentile ranks for each patient are presented in Figure 4.1.

In relation to performance on the VCI, PRI and FSIQ measures, it is clear that the majority (12/21) of participants presented domain *general* difficulties across all subdomains. These findings suggest that these children struggle on tasks that require language skills, abstract thinking, factual knowledge (VCI subtasks), alongside difficulties in problem solving, pattern recognition and attention to detail (PRI subtasks). Such difficulties may have implications for academic achievement (Neisser et al, 1996) with future risks for employment, income and the levels of qualification obtained in adulthood (Fergusson,

Horwood & Ridder, 2005). Seven out of the 21 children presented a mixed profile. This consisted of 4/21 children (Patient: 1, 16, 20, 23) obtaining two scores that fell below the 25th percentile and one between the 26-50th percentile. Three of these children showed relatively better performance on the VCI measure as this situated between the 25-50th percentile. Alongside this, 3/21 children (Patient: 15, 21, 22) obtained one or more scores that ranked between the 50-75th percentile alongside a score that fell below the 50th percentile. Finally, the remaining 2 participants (Patient: 4 and 6) scored above the 50th percentile across all 3 measures, which may suggest relatively intact intellectual abilities.

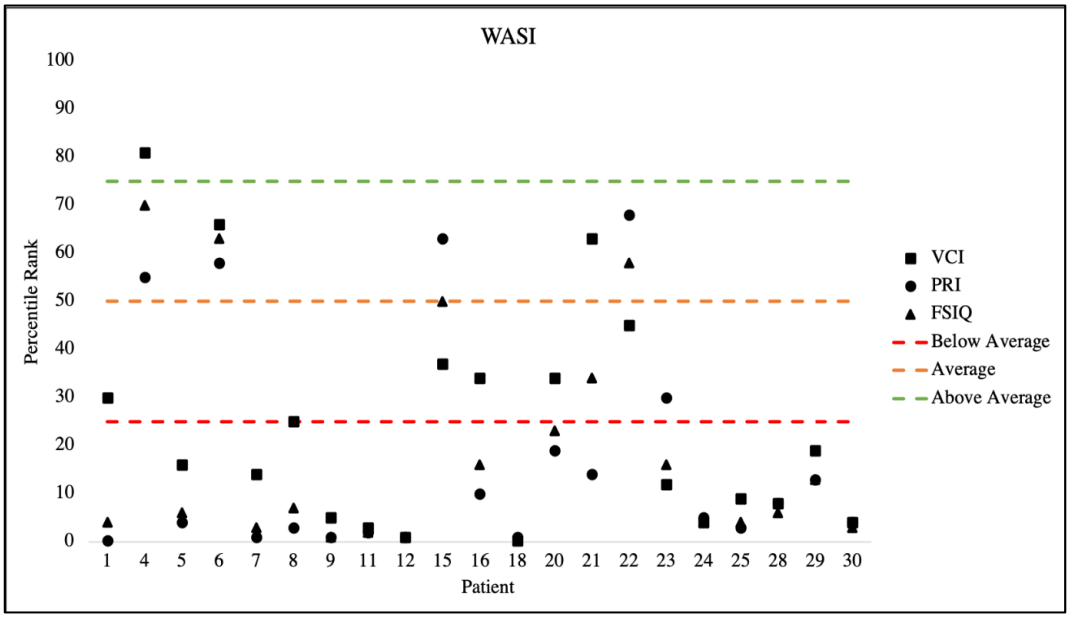


**Figure 4.1: WASI-2 percentile rank performance of the full patient sample**

In relation to IQ and *general* copy number variance, there is limited understanding. Previous work has investigated the *association* between CNVs and intelligence (McRae et al, 2013) and in samples of older adults (MacLeod et al, 2012). At present there is more understanding of the intellectual profiles of children with specific CNVs residing within well-known CNV syndromes. For example, in children with Williams Syndrome (WS), Full Scale IQ (FSIQ) has been reported to range from 40 – 100, with an average of 55 from a range of studies (Marten, Wilson & Reutens, 2008). A similar profile has been reported for children with Prader-Willi Syndrome (PWS), whereby FSIQ situates between 55-70 (Dykens, Hodapp, Walsh, & Nash, 1992) and in children with Smith-Magenis Syndrome (SMS) (deletion to 17p11.2). For example, Osorio et al (2012) conducted cognitive assessment of children, adolescents and adults (7-29 years) and

reported an average of 52.78 (SD=12.90) with similar findings from Madduri et al (2006) at 50.33 (SD=12.91).

In studies of children with 22q11.2 DS, FSIQ has been reported to fall 2 SDs below the mean (i.e. 70) across a range of studies (Cunningham, 2018; Lajiness-O'Neill et al, 2006). Moss et al (1999) reported full scale IQ was 71.2 (SD=12.8) in 33 patients (6-27 years). Niklasson et al (2001) found average FSIQ was 70 (SD =24.7) in 30 children and adults assessed on Weschler scales (5-33 years). Relatedly, Woodin et al (2001) completed a range of neuropsychological assessments in children (n=50, 6-17 years) and FSIQ averaged at 76 (SD = 12.70). Finally, Swillen et al (1999) assessed neuropsychological abilities and academic skills in 9 children aged between 6-12 years and FSIQ situated at 74 (SD=3.70). The FSIQ profile of the current sample (M=81.10) contrasts to that of children with 22q11.2 DS, as it fell -1.26 SD below the mean (low average classification).

In the present work, sample averages for the FSIQ, VCI and PRI measures situated in the low/borderline classification. In relation to classifications for FSIQ, the majority (15/21) obtained a score of 85 or less and borderline Intellectual Difficulties (ID) were most common (8/21). These findings are similar to De Smedt et al (2007) who found FSIQ ranged from 50-109 (M=73.48) in their sample of children with 22q11.2 DS (n=103, 4-17 years). Only a small number (15/103) scored within the normal intellectual development range (FSIQ > 85) which is similar to the present work (5/21), while the majority scored below this. Forty-seven subjects presented borderline intellectual functioning (between 70 – 85), 37/103 had scores in the mild ID range (55-70) and 4 obtained a score below 55 (moderate ID). In relation to the present work, the findings suggest that on average, this group of children present poor intellectual functioning in comparison to children of the same age. On a group level the severity of these difficulties do not extend as low as that reported for children with specific diagnosed CNV syndromes such as WS, PWS or 22q11.2DS, but based upon the qualitative classifications the majority (15/21) scored below 85. Alongside this, 4/15 presented difficulties that aligned with that reported for those with genetic syndromes (FSIQ=70).

In line with previous work in children with genetic syndromes, this project found a domain-*specific* profile consisting of statistically significant differences between performance on the verbal IQ (M=78.66) and non-verbal IQ (M=72.64) measures. This discrepancy of relatively less impaired verbal IQ has previously been reported for individuals with 22q11.2DS (Jacobson et al, 2010; Moss et al, 1999; Niklasson et al,

2001; Lajiness-O'Neill et al 2006; Oskarsdottir, Belfrage, Sandstedt, Viggedal & Uvebrant, 2005; Swillen et al, 1999; Woodin et al, 2001). This profile has also been reported in children with WS (Merla, Brunetti-Pierri, Micale & Fusco, 2010; Nunes et al, 2013). In children and adults (n=17, aged 7-31 years), Sampaio et al (2009) found a profile consisting of severe impairments on the non-verbal IQ tasks (e.g. block design subtest) with relatively preserved skills in verbal ability (e.g. digit span and similarities).

#### 4.3.2.2 Working Memory (WM)

To assess WM ability, participants completed 3 tasks from the WMTB-C: Forward Digit Recall, FDR (verbal simple WM); Block Recall, BR (visuospatial simple WM) and the Backwards Digit Recall, BDR (verbal complex WM). Data from these assessments are presented in Table 4.4. Across all 3 tasks average performance fell near to 1 SD below the mean. Performance was lowest for visuospatial simple WM, followed by verbal complex WM and then verbal simple WM. In line with Gathercole and Alloway (2006), the group presented "moderate to severe impairment" for VS simple WM (more than -1.33 below the mean) with "mild impairments" on the verbal complex WM measure (more than -1SD below the mean). In relation to group classifications in Table 4.5, the majority of the sample situated below average.

To explore these findings in more detail, Table 4.6 presents the number of participants who had scores of at least 1SD below the mean. The majority obtained standard scores that fell 2SDs below the mean. There was also a higher number of children (FDR = 10/14; BR = 9/15 and BDR = 5/14) who exceeded more than 2SDs compared with those who fell below between -1 and -2 below the mean (excluding those who did not complete). These findings are comparable to the profiles of a sample of children with special educational needs (Pickering & Gathercole, 2004) and developmental disorders (Alloway, Rajendran & Archibald, 2009) where learning difficulties are prominent. WM supports the learning and the acquisition of knowledge as it provides the basis for storing and manipulating verbal and visual information (Gathercole & Alloway, 2006). Children with poor WM are reported to be more likely to be distracted, less efficient at monitoring their work and at solving problems (Alloway, Gathercole, Kirkwood & Elliott, 2009). Therefore, poor performance on tasks assessing WM can impact how well children learn and subsequently perform on educational measures (Gathercole & Alloway; 2008; Alloway, Gathercole, Kirkwood & Elliot, 2009). For example, poor verbal complex WM (as found in the present sample) has been closely linked to academic progress (Gathercole

& Pickering, 2000) and complex activities such as reading whereby information is to be successfully integrated and coordinated (Alloway & Gathercole, 2005).

Table 4.4 presents the data from children who obtained a standard score. However, for some participants (n=6) a standard score was not available in the manual on the FDR and BR as the total number of correct responses they obtained was extremely low for their age. Alongside this, 5 children did not complete the BDR task as they found the concept and task too challenging to understand. The support stimuli included in the assessment battery (number line from the WMTB-C) was used to aid understanding of the task, although this was unsuccessful for the children in question. Table 4.7 presents the sample average when these children were given a score of 0. Performance extends 2SD below the mean for the BR and BDR, which indicates severe WM impairments.

**Table 4.4: WMTB-C exclusions data of the full sample**

| Task | Simple Verbal (FDR) | Simple VS (Block recall) | Complex Verbal (BDR) |
|---|---|---|---|
| N completed | 19 | 17 | 16 |
| Mean | 86.84 | 78.24 | 83.44 |
| S. D | 15.27 | 19.14 | 15.35 |
| Relationship to the mean | -0.87 | -1.45 | -1.10 |
| Task too difficult | 0 | 0 | 5 |
| No standard score available | 2 | 4 | 0 |

**Table 4.5: WMTB-C performance classifications for the full sample**

| Classification | Simple Verbal (FDR) | Simple VS (Block recall) | Complex Verbal (BDR) |
|---|---|---|---|
| | N | N | N |
| Below Average (85) | 14 | 15 | 14 |
| Average (100) | 1 | 0 | 0 |
| Above Average (115) | 4 | 2 | 2 |

**Table 4.6: WMTB-C number of participants performing below average**

| Relationship to the mean | Simple Verbal (FDR) | Simple VS (Block recall) | Complex Verbal (BDR) |
|---|---|---|---|
| N | 14 | 15 | 14 |
| 78 to 85 (-1 to 1.5) | 0 | 2 | 3 |
| 71 to 77 (-1.5 to -2) | 2 | 0 | 2 |
| 70 & Below (-2 & below) | 10 | 10 | 5 |

**Table 4.7: WMTB-C inclusions data of the full sample**

| Task | Simple Verbal (FDR) | Simple VS (Block recall) | Complex Verbal (BDR) |
|---|---|---|---|
| N | 21 | 21 | 21 |
| Mean | 78.57 | 63.33 | 63.57 |
| SD | 29.87 | 35.83 | 38.77 |
| Relationship to the mean | -1.43 | -2.44 | -2.43 |

To understand how the scores from the present sample placed in relation to individuals of the same age, percentile ranks were explored, see Figure 4.2. Nine out of twenty participants (43%) presented clear domain *general* difficulties all on three tasks as their score was situated below the 25$^{th}$ percentile (Patient: 8,9,12,18,23,24,25,29,30). Of these 9 children, 2 scored so poorly that no percentile rank was available for their age on the FDR and BR and they found the BDR task too challenging to complete (Patient: 12,18). Alongside this, no score was available on the block recall (Patient 9) and the BDR (Patient: 8, 25). This can highlight that these children face difficulties in both storing *and* manipulating information, which provide the basis for learning and knowledge acquisition (Alloway & Alloway, 2010). The majority of these 9 participants presented "moderate to severe impairment" across all WM tasks as they ranked below the 9$^{th}$ percentile on all measure (8/9) (Gathercole & Alloway, 2006). The remaining participant presented "moderate to severe" verbal simple and complex WM impairment (>9$^{th}$) with "mild" visuospatial simple WM impairment (>16$^{th}$) (Patient 30).

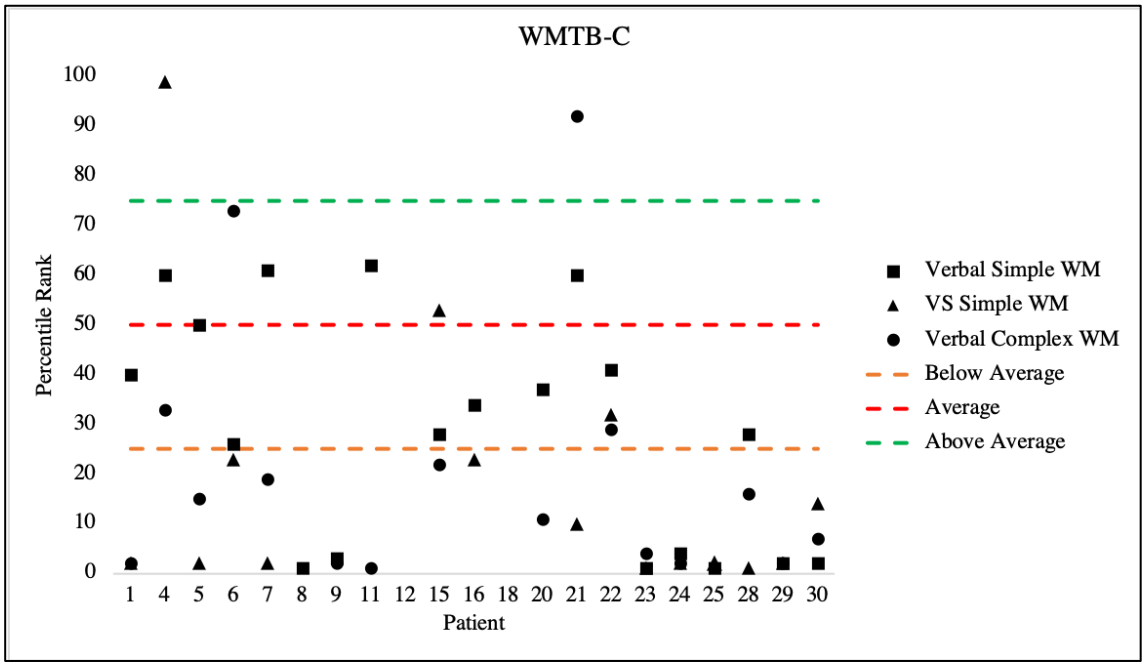


**Figure 4.2: WTMB-C percentile rank performance of the full sample**

In comparison some children presented profiles of relative strengths and weaknesses. For example, 7/21 (33%) gained scores which situated both below the 25th percentile and between the 26th and 50th percentile. Of these, one child (Patient 7) scored below the 25th percentile across two tasks (block recall, BDR) while in the 50th – 75th range for FDR. Related to this, some children (Patient: 1, 5, 16, 20, 22, 28) presented a particular profile of relatively better performance on the FDR task (verbal STM) in contrast to the BR and BDR tasks. The remaining 24% (5/21) (Patient: 4, 6, 11, 15, 21) presented mixed performance as they gained scores that situated in both the 26-50th band and 50-100th band. In summary the findings may suggest that the sample present below average WM functioning, with relative strengths in simple verbal WM.

In relation to the genetics literature, there are reports of the WM profiles of children with more commonly known syndromes. Overall these detail domain *general* difficulties with a *specific* pattern of relative strengths and weaknesses. A profile of 'non-verbal learning' deficits have been reported in children with 22q11.2 DS. This consists of relatively intact verbal simple WM with impairments to visuospatial ability (simple and complex) (Antshel, Kates, Roizen, Fremont & Shprintzen, 2005; Oskarsdottir, Belfrage, Sandstedt, Viggedal & Uvebrant; Sobin et al, 2005; Swillen et al, 1999). For example, in children (n=36, 5-12 years), Wang, Woodin, Kreps-Falk, and Moss (2000) found performance on the visual-spatial simple memory task (spatial memory) ability fell 1SD below average

(M=7.0, SD=2.5) (average=10, SD=3). Whereas, performance for the number recall task (verbal simple WM) was within the normal average range (M=9.1, SD=3.0). Similarly, in 50 children (aged 5-17 years), Woodin et al (2001) found relative strengths on the verbal learning and memory task in contrast to relative weaknesses on the visual-spatial design memory and complex verbal memory task. The authors suggest that this group of children appear to be impaired on tasks that require more fluid abilities (e.g. executive functions) which are utilised during complex memory tasks and tasks that require abstract thinking (e.g. non-verbal tasks such assessing visual spatial skills). In contrast they presented relatively intact skills on tasks that rely on stored, factual knowledge and the ability to retain information (verbal IQ or verbal simple WM). These difficulties in visual spatial memory were linked to difficulties in arithmetic, which may have subsequent outcomes for learning (e.g. multiplication and division) and academic progress (Bearden et al, 2001). This profile of difficulties has also been found to extend to complex verbal WM (Maeder et al, 2016; Wong, Riggins, Harvey, Cabaral & Simon, 2014).

Domain general WM difficulties have been reported for children and adults with WS (Sampaio, Sousa, Fernandez, Henriques & Goncalves, 2008), although a domain specific profile is more commonly reported. Similar to individuals with 22q11.2 DS this consists of relatively persevered verbal simple WM skills in contrast to impairments in visuospatial abilities (Conners, Moore, Loveall & Merrill, 2011; Gathercole & Alloway, 2006; Jarrold, Baddeley, Hewes & Phillips, 2001) and spatial cognition (Bellugi et al, 2000; Vicari, Bellucci & Carlesimo, 2003). For example, in 16 patients with WS (mean age: 10.12), Vicari et al (1996) found performance on the digit span task (simple verbal WM) was comparable to controls, while performance on the block tapping task (visuospatial simple WM) was significantly lower. This profile of relatively intact verbal abilities has been found to extend to complex verbal WM, based on performance on backwards digit recall tasks (Mervis et al, 2000; Robinson, Mervis & Robinson, 2003).

#### 4.3.2.3 Cognitive flexibility

Cognitive flexibility is a higher cognitive executive function which supports the skill of switching behaviours and adapting to changes in the environment (Diamond, 2014; Jurado & Rosselli, 2007). Difficulty in this skill may impact performance on academic subjects, such as mathematics (Snowling & Hulme, 2015) and reading (Cartwright et al, 2007) and on tasks that require flexible thinking or problem solving. In relation to social development, this skill can relate to how well children can shift their perspective to

understand others (Müller, Zelazo, & Imrisek (2005) and solve social conflict (Bonino & Cattelino, 1999).

This skill was assessed using the WCST and the number of perseverative errors (i.e. persistence to incorrect sorting rule) were analysed. Of the 21 participants who completed the cognitive assessments, 16 successfully completed the WCST. The remaining 5 found the task too challenging and did not want to continue. For the children who managed to complete the task, the sample mean situated in the "below average" classification (see Table 4.8). Alongside this, below average and lower (10/16) functioning was most common, with a smaller number of children (6/16) gaining scores in the average classification (see Table 4.9). To explore the data further, Table 4.10 presents the data with the other 6 participants assigning a score of 0. In this case the sample score situated in the "moderately impaired" classification (M=65.33; SD = 38.02, RTM: -2.31).

**Table 4.8: WCST exclusions data of the full sample**

| WCST Perseverative Errors | | | |
|---|---|---|---|
| N | Mean | S. D | RTM |
| 16 | 85.75 | 12.11 | -0.95 |

**Table 4.9: WCST diagnostic classifications for the full sample**

| WCST Classification | Standard scores | n |
|---|---|---|
| Above average | > 107 | 0 |
| Average | 92 – 106 | 6 |
| Below-average | 85 – 91 | 4 |
| Mildly-impaired | 77 – 84 | 3 |
| Mildly to moderately impaired | 70 – 76 | 0 |
| Moderately impaired | 62 – 69 | 3 |
| Moderately to severely impaired | 55 – 61 | 0 |
| Severely impaired | > 54 | 0 |

**Table 4.10: WCST inclusions data of the full sample**

| WCST Perseverative Errors | | | |
|---|---|---|---|
| N | Mean | S. D | RTM |
| 21 | 65.33 | 38.02 | -2.31 |

To explore the data further, Figure 4.3 presents the percentile ranks of the sample.

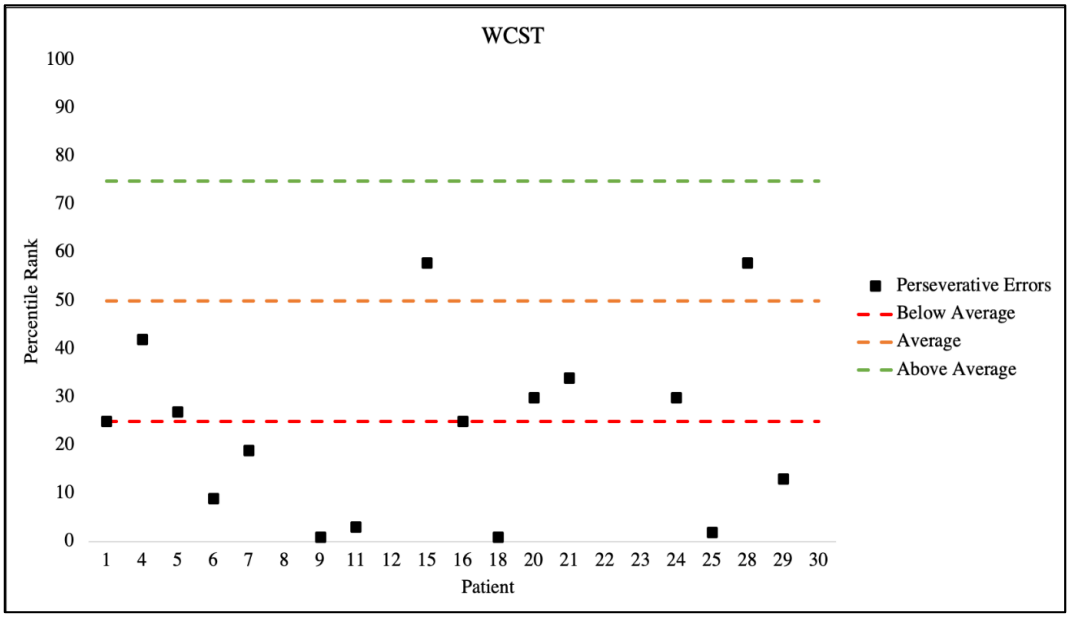


**Figure 4.3: WCST percentile rank performance of the full sample**

In line with the WCST percentile classifications, 6/16 situated in the average classification with a higher number (10/16) performing below average or worse. This can indicate that these children may have difficulties performing tasks that require information to manipulated or require flexible thinking.

In relation to the genetics literature, the findings are similar to that of children with well-known CNV syndromes. Children with 22q11.2 DS have been found to perform worse on tasks of higher cognitive control such as response inhibition, working memory and cognitive flexibility in contrast to typical developing controls (Shapiro, Tassone, Choudhary & Simon, 2014). In relation to tasks of cognitive flexibility (e.g. WCST), poor performance in comparison to sibling controls has been reported (Chawner et al, 2017; Cunningham et al, 2018; Niarchou et al, 2014). For example, Lajiness-O'Neill et al (2006) found average performance for 14 children and adolescents on the WCST was

lower (M=85.4) than sibling controls (M=102.4). Similarly, in children and adolescents old enough to partake in the WCST assessment, Oskarsdóttir et al (2005) found the majority (6/9) faced challenges shifting categories and concepts. These findings show that these children have an inflexibility in their problem-solving approach.

Similar findings have been reported for children with WS. This consists of executive function deficits across tasks of working memory, attention set-shifting and planning (Menghini, Addona, Costanzo & Vicari, 2010; Rhodes et al, 2010). Osorio et al (2012) found difficulties in abstract and flexible thinking in children and adults (n=16, aged 9 – 29 years) as they had a higher number of perseverative errors (M=40.1, SD= 17.9) in contrast to controls (M=15.5, SD=24.5). Performance on tasks that require higher executive functions (e.g. complex WM, shifting) are linked to progress in academic subjects (St-Clair Thomson & Gathercole, 2006) and these difficulties may risk future challenges as Howlin and Udwin (2006) report lower levels of educational and employment attainment in individuals with WS.

#### 4.3.2.4 Language

Language assessment was conducted using the CELF-4 in line with the 4 assessment levels described in Chapter 2. These include (1) overall language functioning (core language) (2) language strengths and weaknesses (receptive and expressive language) (3) underlying clinical behaviours (phonological awareness) and (4) language in context (pragmatics profile). Twenty children successfully completed this, as the remaining child who was included in the other assessments refused to continue (Patient 22).

In relation to Level 1 (see Table 4.11) core language was within -1.5 to 2SD below the mean suggesting both receptive and expressive language difficulties. This score situates within the “low range/moderate” range of guidelines for describing the severity of a language disorder. In line with the CELF-4, a standard score of 85 or below recommends further testing is required as this score best discriminates the performance between children with typical or atypical language development (Semel & Wiig, 2006). Based upon this, the majority of the sample may be at risk of poor overall language functioning or risk language disorder, which is also evident by the classifications in Table 4.12.

**Table 4.11: CELF-4 core language performance of the full sample**

| Core Language | | | |
|---|---|---|---|
| N | Mean | S. D | RTM |
| 20 | 72.00 | 21.80 | -1.87 |

**Table 4.12: CELF-4 core language classifications for the full sample**

| Core Language | | | |
|---|---|---|---|
| Standard scores | Relationship to the mean | Classification | N |
| 115 and above | +1SD | Above average | 1 |
| 86 to 114 | Within + or – 1SD | Average | 6 |
| 78 to 85 | Within -1 to 1.5 SD | Marginal/Borderline/Mild | 2 |
| 71 to 77 | Within -1.5 to 2 SD | Low range/Moderate | 2 |
| 70 & below | -2SD and below | Very low range/Severe | 9 |

Similar difficulties are presented from the Level 2 assessments (nature of the disorder-modality and content areas) (see Table 4.13) as receptive and expressive language group averages situated in the "low range/moderate" language difficulties classification. The subtasks that comprise these indices vary per age band (i.e., 5-8; 9-12 and 13-16 years). The Receptive Language Index (RLI) broadly consists of subtasks that require children to understand, interpret and act on instructions of increasing length (e.g. concepts and following directions); express how words associate and are semantically similar to each other (e.g. word classes and semantic relations) whilst understand spoken sentences and engage in successful critical thinking and abstract reasoning (e.g. sentence structure and understanding spoken paragraphs). The Expressive Language Index (ELI) subtasks require adequate knowledge and expression of word rules and pronouns (e.g. word structure); successful recall of complex and lengthy sentences (e.g. recalling sentences); successful articulation of the relationships and connections in meanings (e.g. word classes-expressive) and the ability to formulate sound spoken sentences (i.e. semantically and grammatically) when given a target word and illustration (e.g. formulated sentences).

**Table 4.13: CELF-4 language strengths and weaknesses of the full sample**

| Language Strengths and Weaknesses | | | | |
|---|---|---|---|---|
| Modality & Content area | n | Mean | S.D | RTM |
| Receptive language | 20 | 70.75 | 17.81 | -1.95 |
| Expressive language | 20 | 75.70 | 21.39 | -1.62 |

In line with Table 4.14, the majority gained scores that fell more than 1 SD below the mean for receptive (16/20) and expressive (12/20) language which may suggest difficulties in the aforementioned skills in comparison to children of the same age. Work by the Specific Language Impairment Consortium (2004) defined language difficulties if expressive or receptive language composite scores were 1.5 below the average for the age. Although diagnoses are not being made in the present work, the scores in the sample can suggest this sample is at risk of language difficulties across both modalities.

**Table 4.14: CELF-4 language strengths & weaknesses classifications for the full sample**

| Language Strengths and Weaknesses | | | | |
|---|---|---|---|---|
| Standard scores | Relationship To Mean | Classification | Receptive (n) | Expressive (n) |
| 115 and above | +1SD | Above average | 1 | 1 |
| 86 to 114 | Within + or – 1SD | Average | 3 | 7 |
| 78 to 85 | Within -1 to 1.5 SD | Marginal/Borderline/Mild | 3 | 2 |
| 71 to 77 | Within -1.5 to 2 SD | Low range/Moderate | 1 | 1 |
| 70 & below | -2SD and below | Very low range/Severe | 12 | 9 |

To assess underlying clinical behaviours, the Level 3 – Phonological Awareness task (see Table 4.15) was completed by children aged 7-12 years (age dependent task). The majority presented “adequate” processing at the level of phonology for their age. This which suggests the child has adequate knowledge of sounds structures and how to manipulate sounds which is key for pre-reading, reading and spelling tasks.

**Table 4.15: CELF-4 underlying clinical behaviours classifications for the full sample**

| Classification | n=15 | % of sample |
|---|---|---|
| Meets criterion score: adequate processing at the level of phonology | 9 | 60% |
| Doesn't meet criterion: inadequate processing at the level of phonology | 4 | 27% |
| Task too difficult to complete | 2 | 13% |

Finally, the Level 4 questionnaire assessments (see Table 4.16) completed by parents reveal the majority of participants had "inadequate" pragmatic abilities based on their age. This finding suggests this sample of children are at risk of difficulties in social situations whereby an understanding of others and successful expression of one's own needs are required (Keenan and Shaw, 1997). These behaviours can be verbal (e.g. jokes) and/or nonverbal (e.g. eye contact) and difficulties with pragmatic skills may lead to friendship difficulties or social exclusion (Cummings, 2011).

**Table 4.16: CELF-4 language and communication in context classifications for the full sample**

| Questionnaire | Classification | n=20 | % of sample |
|---|---|---|---|
| Pragmatics Profile | Meets criterion: Adequate communication abilities in context | 2 | 10% |
| | Doesn't meet: Inadequate communication abilities in context | 18 | 90% |

To explore domain general and specific patterns of language performance, Figure 4.4 presents the distribution of scores based on percentile rank. The majority (14/20) presented domain general language difficulties as they scored below the 25$^{th}$ percentile across all measures (CLS, RLI and ELI). A smaller number of children 4/20 presented a mixed profile whereby they had one or two scores that situated below the 25$^{th}$ percentile (Patient: 4, 7, 15, 21). Specific to this group is that all these children fell below the 25$^{th}$ percentile for receptive language. Finally, only 1 child (Patient 6) presented relatively

intact language functioning as they scored above the 75th percentile across all measures. Based on qualitative interpretations of the participants during testing, attentional difficulties during were of particular concern as this assessment consisted of the lengthiest subtasks. Alongside this, one child had English as a second language (Patient 11) which could explain the profile of consistent difficulties.

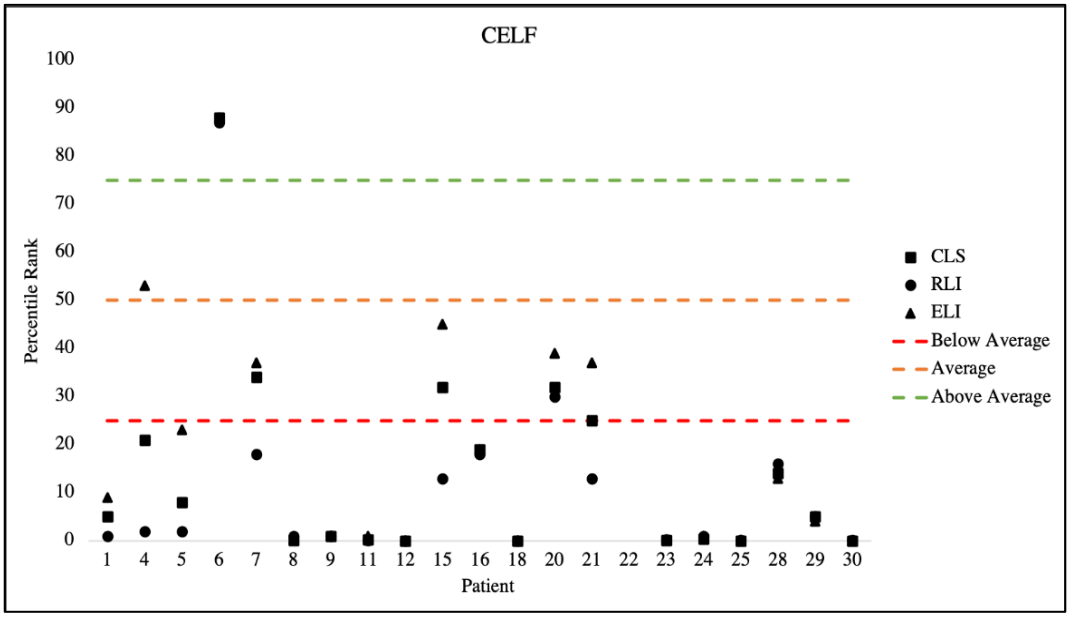


**Figure 4.4: CELF-4 percentile rank performance of the full sample**

These findings suggest the majority of children in the sample present language difficulties. In relation to receptive language, this assessed listening and auditory comprehension. Comprehension difficulties may result in the child facing challenging understanding what different words mean, keeping a memory of instructions or understanding specific grammatical markers. Expressive language difficulties may result in challenges recalling new words, and using the correct grammar, words and sentence structure to articulate meaning. These speech and language difficulties can negative implications for reading, spelling and literacy proficiency (O'Keefe & Farrugia, 2016).

In relation to the CNV literature, there is greater understanding of the language skills of more common CNV syndromes. The language skills of children with WS are reported to present a unique, domain specific developmental trajectory (Karmiloff-Smith et al, 1997). Children with WS have been reported to have relative strengths in their verbal simple WM ability, which has been found to link to relatively persevered phonology and vocabulary (Grant et al, 1997). Taking into account the cognitive deficits of children with

WS, speech production has been reported to be relatively intact (Bellugi, Wang & Jernigan, 1994). This unique expressive language profile in individuals with this CNV (Bellugi et al, 2000; Brock, 2007) has been found to relate to the high rates of sociability and desire to communicate and interact with others (Bellugi, Lai & Wang, 1997; Fishman, Yam, Bellugi & Mills, 2011).

Language difficulties have been reported for individuals with PWS, consisting of language delays (Cassidy & Driscoll, 2009). Receptive language is relatively intact in comparison to expressive language. These difficulties may relate to the poor oral motor skills in this CNV group which may impact articulation skills (Lewis, Freebairn, Heeger & Cassidy, 2002). Relatedly, language difficulties may be linked to the characteristics of this syndrome including intellectual disability, abnormal development of mouth anatomy and functioning of the speech organ, obesity and cerebral development (e.g. left hemisphere) (Akefeldt, Akefeldt & Gillberg, 1997). For example, Dimitropoulos, Ferranti and Lemler (2013) used the CELF to investigate language functioning in 35 children and adults (7-44 years) and found performance situated in the 'very low range/severe classification' for describing a language disorder. Performance fell more than 2SDs below the mean on the core (M=60.37, SD=13.8), receptive (M=57.19, SD=11.1) and expressive language composites (M=60.54, SD=13.3).

Within samples of children with 22q11.2 DS language delays have been reported (Antshel et al, 2005; Rakonjac et al (2016); Solot et al, 2000; Solot et al, 2001) with mixed findings for receptive and expressive language. Using the CELF-R, Moss et al (1999) found language performance fell 2SDs below the mean for 20 children (aged 6- 27 years) across total language (M=66.9, SD=14.9); receptive (M=70.6, SD=16.3) and expressive language (M=66.4, SD=14.7). Whereas, Glaser et al (2002) found the reverse. They used the Clinical Evaluation of Language Fundaments-3 to investigate language functioning of 27 children and adults (ages 6-19 years) and controls. Overall language functioning situated in the "moderately delayed to severely delayed" range (M=70.4, SD=18.5) with significant differences between receptive (M=69.0, SD=17.3) and expressive language (M=74.0, SD=20.9). Overall, the findings show poor language ability which extends more than 2SDs below the mean in CNV groups.

The majority of the current sample did not present adequate pragmatic language skills. These findings are comparable to children with 22q11.2 DS (Van Den Heuvel, Manders,

Swillen & Zink, 2017) and WS (Asada, Tomiwa, Okada & Itakura, 2010; Hoffmann et al, 2013; John, Dobson, Thomas & Mervis, 2012; Stojanovik & James, 2006; Stojanovik, 2006) whereby children have been found to struggle to express what they mean, respond and ask for information and present adequate conversational skills. Despite a (typically) highly sociable personality, individuals with WS have been found to face challenges in conversations and when understanding the requirements of the conversational partner (e.g. turn-taking or producing an adequate response) (Brock, 2007)

#### 4.3.2.5 Findings and discussion from the full cognitive assessment battery

In relation to the standard scores from the children who participated in all 4 cognitive assessments (n=20, see Figure 4.5) the majority of the sample (13/20, 65%) performed at or below average across all measures. Of these children, 5/20 (Patient: 9, 12, 18, 25, 30) had consistently low performance across all measures. This included gaining scores of 85 or below on the WASI-2 (across FSIQ, VCI and PRI); WMTB-C (FDR, BR and BDR); WCST (including the children who found this too difficult to complete) and language (core, receptive and expressive measures). Of the remaining children (8/20) had a mixed profile consisting of scores that situated both below 85 and between 85-100 (Patient: 1,5, 8, 16, 20, 23, 24, 29). Alongside this, 7/20 the children had some scores that situated below average and some that were above average (Patient: 4, 6, 7, 11, 15, 21, 28). However, none of the children performed consistently above average. These findings show that this group of children with copy number variance fall below average in relation to peers of the same age across cognitive tasks. These children are at risk of poor cognitive functioning, but the severity of these difficulties vary by individual.

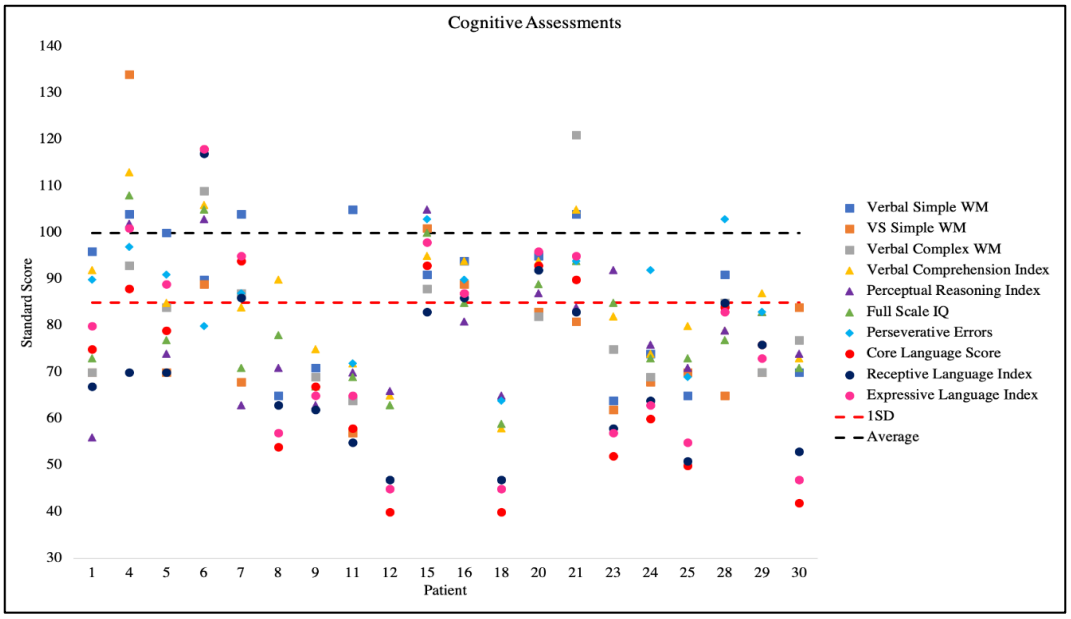


**Figure 4.5: Standard score distribution of the full sample across cognitive measures**

In relation to the intellectual assessment, FSIQ for the present sample was more than 1 SD below average and this finding contrasts to that of children with diagnosed CNV disorders. For example, the average IQ for children with WS has been reported to be situated around 55 (Marten, Wilson & Reutens, 2008), with similar findings for children with SMS (Osorio et al, 2012). The IQ for children with 22q11.2DS is slightly higher around average is 70 (Woodin et al, 2001). Formal diagnoses of intellectual disability are diagnosed when IQ scores fall two or more standard deviations below the mean and there are significant impairments in adaptive functioning (Simonoff, 2015). Although diagnoses are not being made in the current project, a small number (4/21) presented scores aligning with this, thus displaying signs of severe intellectual impairment (Gathercole & Alloway, 2008; Neisser et al, 1996). Although the present group findings did not extend as low as this (-2SD) it did still extend below average (-1.26) which can indicate the children are at risk of general intellectual difficulties. There was a particular profile found of relatively intact verbal IQ, in contrast to non-verbal IQ and this domain specific profile has been previously reported for children with 22q11.2 DS and WS.

To explore this domain specific profile further, the tasks that comprise the VCI score assess crystallised intelligence (i.e. stored factual knowledge) in contrast to the PRI tasks which assess fluid abilities (i.e. abstract reasoning and logical thinking). The domain specific profile may parallel that reported for children with WS (Sampaio et al, 2009) and

22q11.2 DS (Moss et al, 1999) whereby a profile of 'non-verbal learning difficulties' have been reported with children showing difficulties on tasks assessing non-verbal functions (e.g. abstract reasoning, non-verbal reasoning and visuospatial abilities) (Antshel et al, 2005). For example, Woodin et al (2001) reported this profile in their sample of 80 children with 22q11.2 DS. The sample had strengths in their ability to learn and retain verbal information but presented difficulties on the tasks that required more fluid abilities such as complex processing and executive functions (i.e. verbal complex WM and visual spatial design memory). Related to this, the findings from the WM and CF assessment may parallel this. Average group performance on the FDR was relatively intact in comparison to the other two tasks. The FDR task required participants to store verbal information for immediate recall, without any explicit requirements for complex processing. This finding combined with that of the relatively intact verbal IQ performance (i.e. stored, factual crystallised knowledge) may highlight that this sample of children may instead struggle to engage in more complex forms of information manipulation (i.e. abstract reasoning and fluid intelligence).

The findings from the WM assessments and CF task may parallel the profile reported for children with 22q11.2 DS whereby difficulties on tasks of higher cognitive functions and visuospatial ability have been reported (Woodin et al, 2001). For example, Maeder et al (2016) conducted a longitudinal design and found children with 22q11.2 showed a profile of atypical development on executive function domains (i.e. WM and CF). In the present work, the block recall task was used to assess simple visuospatial WM, whilst the BDR assessed verbal complex WM (storage and manipulation). Considering the number of children who found the BDR task too challenging (giving a score of 0 extends average to more than 2SDs below the mean) and for those children who did not obtain a standard score as their score was so low highlights the difficulties the sample may face. Similarly, the findings from the WCST may support this. There was a number of children who could not complete this as they found the concept too challenging and outcomes with them included in the analysis extended more than 2 SDs below the mean, whilst without this the average fell close to 1 SD below. This task assesses higher cognitive functions of planning, flexible thinking and problem solving whereby poor performance on this task may indicate deficits in complex thinking, planning strategies and successful execution. These difficulties can have implications for learning and academic progress, as children with poor verbal complex WM and cognitive shifting ability have been found to make

errors in learning tasks as they face challenges keeping track of their work, planning the next words in a sequence, monitoring their work and completing the task required (St Clair-Thompson & Gathercole, 2006).

WM and CF functioning can have implications for language development and performance on language tasks (Archibald, 2017; Baddeley, 2003). For example, poor performance on tasks assessing executive function (e.g. CF) can impact a child's ability to successfully plan an effective response and which may impact their ability to generate an appropriate language response (Semel & Wiig, 2006). Similarly, children with language impairments have been found to have poor complex verbal WM, whereby they face problems keeping words in memory (Montgomery, 2000; Gillam, Cowan & Marler, 1998; Weismer, Evans & Hesketh, 1999). Related to this, the findings for the language assessment reveal overall language functioning for the sample situated between 1.5 to 2 SD below the mean. According to the assessment battery a score below 85 would warrant further assessment as this score discriminates children who are at risk of language disorder. Therefore, this may highlight that the sample are at risk of language difficulties in relation to children of the same age. In relation to receptive and expressive language modalities, the sample performed -1.5 to 2 standard deviations below the mean, which situated into the low range/moderate of describing the severity of a language disorder.

As previously discussed in the language assessments section, the findings may relate to the structure of tasks that comprise these composites whereby critical thinking and abstract reasoning skills (e.g. sentence structure and understanding spoken paragraphs) and executive resources are required (e.g. concepts and following directions and formulating sentences). The findings from the language assessments are similar to that of findings from children and adults with 22q11.2 DS. For example, Glaser et al (2002) found the sample average was relatively better for the expressive language composite (M=70.4) in comparison to receptive language. This is similar to the present work (M=75.70). Alongside this, the present core language score (M=72.0) was also similar to that reported by Glaser et al (2002) (M=70.4) which may suggest children with a CNV present a language profile comparable to children with a diagnosed genetic syndrome.

In summary, findings from the cognitive assessments show that this group of children present a domain general profile of cognitive difficulties (below average performance across all measures), although there is a specific pattern of strengths and weaknesses within each cognitive domain. In relation to IQ, scores are in the low average range across

all measures, with relative strengths in verbal IQ in contrast to non-verbal IQ. This profile of relatively preserved verbal functioning (without complex processing) was clear on the verbal simple WM task, with relative weaknesses on the visual spatial simple WM task and the complex WM task. The executive function element required during the complex WM task links to the cognitive flexibility measure as the average score was close to 1 SD below average. This shows children may struggle to problem solve, engage in abstract reasoning and flexible thinking. The findings from the language assessment reveal a profile of overall language difficulties, which span both receptive and expressive subdomains. Although there was slightly better performance on the expressive language (language articulation) measures in contrast to receptive tasks (listening and auditory comprehension) the scores still situated in the moderate language difficulty classification which suggests this sample group present impaired language functioning on a day to day basis and in relation to children of the same age.

These findings parallel the phenotype reported for children with common genetics syndromes such as 22q11.2 DS and WS whereby difficulties with general cognitive ability, higher cognitive functions and language functioning have been reported. For IQ functioning there was a domain specific pattern of relatively better verbal IQ than non-verbal IQ which was similar to that reported for WS and 22q11.2 DS. A similar pattern was observed for the complex WM components which further highlight the difficulties that these children may face on tasks that require more abstract and complex thinking opposed to those that rely on more stored factual knowledge (i.e. simple verbal WM). These strengths in simple verbal WM may also relate to the relatively better expressive language profile identified in the group which may link to preserved phonological skills, which have been reported for children with WS, but also parallel the difficulties in task that require complex problem solving or manipulation (i.e. complex WM or flexibility).

### 4.3.3 Motor assessments: findings and discussion

#### 4.3.3.1 Fine and gross motor

Movement behaviour was assessed using the Movement ABC-2 and the tasks that comprise the Manual Dexterity (MD) and Balance components were administered. A total of 20 children completed the assessment, as one patient did not wish to continue with the assessment (Patient 22).

The sample mean for both components, see Table 4.17, fell below average (MABC-2 mean=10). In line with the MABC-2 manual (Henderson, Sugden & Barnett, 2007), scores which fall 1 or 2SDs below the mean are used as critical cut of points: a standard score of 3 (-2SDs) would indicate that the child is at need of support, whilst a score that falls 1SD below the mean suggests monitoring is required as the child is "at risk" of difficulties. In line with this, there was a domain specific pattern consisting of performance deficits on the MD subtask (over 2SD below mean) with a profile of "at risk" of difficulties on the balance tasks (static and dynamic) (1 SD below mean).

**Table 4.17: MABC-2 performance of the full sample**

| Movement ABC | | | | |
|---|---|---|---|---|
| Component | n | Mean | S.D | RTM |
| Manual dexterity | 20 | 3.5 | 2.33 | -2.17 |
| Balance | 20 | 7 | 4.63 | -1 |

The MD tasks of the MABC-2 assess both spatial and temporal demands. These demands require children to make precise and accurate movements (e.g. threading lace, keeping pen through narrow boundary) whilst working under pressure (i.e. tasks were timed). The balance tasks require children to maintain static balance and subsequently maintain control over their body parts (e.g. on balance board keeping a straight posture, control over arms and legs) whilst the dynamic balance assess accurate movements met with spatial restrictions (e.g. walking heel to toe straight on a line, hopping within a mat). In relation to Table 4.18, the majority of the sample presented clear manual dexterity difficulties (80%) in comparison to balance where the number was equal across groups.

**Table 4.18: MABC-2 classifications for the full sample**

| Percentile | Classification of movement difficulty | MD (n) | Balance (n) |
|---|---|---|---|
| At or below 5$^{th}$ | Significant | 16 | 9 |
| Between 6$^{th}$ – 15$^{th}$ inclusive | At risk– monitoring required | 1 | 1 |
| Above 15$^{th}$ | No signs | 3 | 10 |

Figure 4.6 presents the distribution of percentile classifications by participant which aligns with the traffic light system detailed in the manual. There are two main profiles found within the sample.

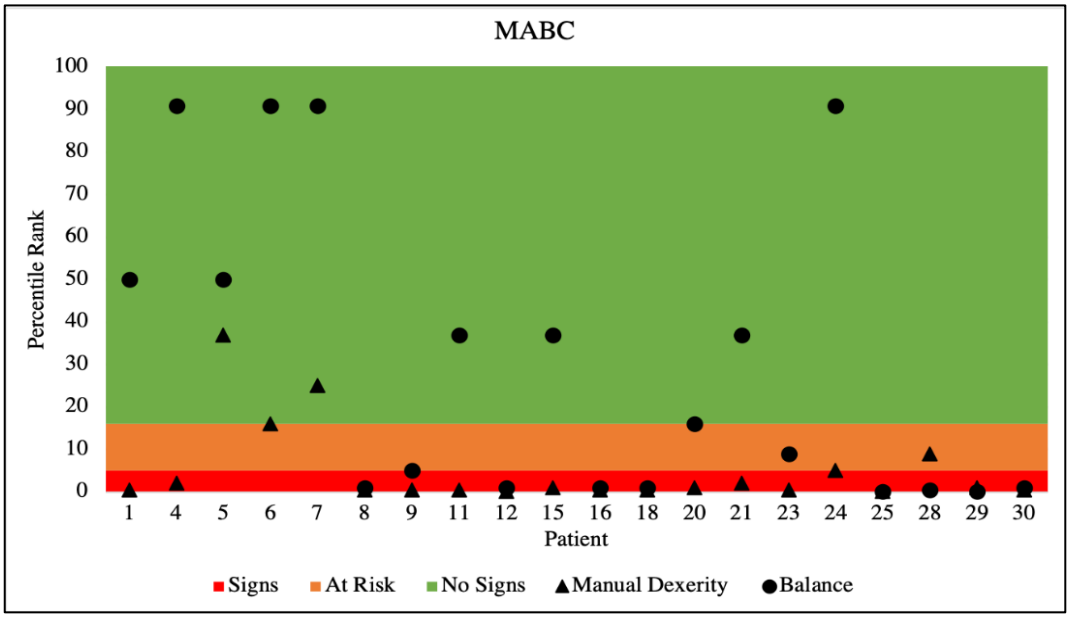


**Figure 4.6: MABC-2 percentile rank performance of the full sample**

Firstly, the majority (8/20, 40%) presented domain *general* difficulties whereby performance on both components was at or below the 5$^{th}$ percentile, indicating significant fine and motor difficulties. Motor competence is essential for gaining academic, social and cognitive skills, with children lacking this at risk of academic underachievement and social difficulties (Dewey & Kaplan, 1994). Fine motor skills are key to knowledge acquisition, as children use their hands to learn (e.g. painting, drawing, feeling, pouring). The children with poorer scores may struggle with tasks that require one hand to support the other (e.g. writing tasks), tasks that require coordinated movements (e.g. tying shoelaces) and when faced by time pressure. Similarly, the fine motor skills can impact engagement levels in learning activities and exploration with the world (Marr, Cermak, Cohn & Henderson, 2003) which can risk educational (Bart, Hajami & Bar-Haim, 2007) and social (Livesey, Mow, Toshack & Zheng, 2010) difficulties. Related to this, the balance performance may suggest risks to poor gross motor competence. These tasks require the recruitment of large muscle groups, which may subsequently impact how effectively children may respond or adapt to environmental demands (Adolph, 2008).

Secondly another dominant group (7/20, 35%) consisted of those children who presented a profile of domain *specific* strengths and weaknesses (Patient: 1, 4, 11, 15, 20, 21, 24). They had relatively intact gross motor skills (balance tasks) (i.e. scores above the 15$^{th}$ percentile so no signs of difficulty) but with significant impairments in manual dexterity (at or below the 5$^{th}$ percentile). In these cases, these children may face challenges on essential tasks that require the recruitment of smaller muscles such as reaching, manipulating objects or grasping (Payne & Isaacs, 2016). Fine motor competence skills lay the foundations for interacting, exploring the world and gaining independence (e.g. for eating, tying shoelaces, self-care). Alongside this, these skills are essential for academic subjects such as handwriting (Feder & Majnemer, 2007) and maths skills as they allow the exploration and manipulation of objects to support learning (Luo, Jose, Huntsinger & Pigott, 2007; Pagani & Messier, 2012).

Finally, a smaller number of children (2/20, Patients 23 and 28) presented a mixed profile consisting of "at risk" and "significant" difficulty. Participant 23 presented significant difficulties on the manual dexterity measure, with a reverse profile in Patient 28. Alongside this, only a small number of children (3/20) (Patient: 5, 6, 7) showed no signs of difficulty as performance across both domains was above the 15$^{th}$ percentile.

In relation to the CNV literature, there has been work conducted on children with CNV syndromes. Children with 22q11.2 DS have been found to present general movement difficulties which are present early in development (pre-school) are reported to continue throughout school age (early and middle childhood) (Gerdes et al, 1999; Sobin et al, 2006). For example, in relation to controls school aged children (n=37, 5-14 years) with 22q11.2 DS had poorer performance on standardised assessments of fine and gross motor skills (Van Aken et al, 2007). Similarly, the majority of children (8/9, Mean age= 12.05) were found to have poor overall motor functioning (MABC-2), which denotes significant difficulty (Cunningham et al, 2018). There has also been a specific profile of prominent gross motor impairments reported for children with this CNV (Antshel et al, 2005). These difficulties have been found to emerge early in development (n=14, 2-5 years) as Swillen et al (2005) found in comparison to controls the CNV group presented marked deficits for locomotion and stationary ability. Similarly, difficulties with balance have been reported by Roizen et al (2010) in their assessment of motor function of children aged 9-15 years. There was a common feature of hypotonia (low muscle tone and muscle strength) in children with this CNV, which may be a contributing factor to the profile of

gross motor difficulties in comparison to controls (Boot et al, 2015; McDonald-McGinn et al, 2015; Swillen et al, 1999).

Similar motor delays have been reported for children and adolescents with a deletion to 15q11.2-q13. These have been reported for individuals with Angelman Syndrome (AS) (Beckung, Steffenburg & Kyllerman, 2004; Clayton-Smith & Laan, 2003) and Prader-Willi Syndrome (PWS). Motor problems are prominent in PWS (Reus et al, 2011). For example, general motor delays are prominent in 90-100% of children (Cassidy, Schwartz, Miller & Driscoll, 2012) with a domain specific profile of gross motor difficulties which can relate to the major characteristics of obesity and hypotonia in this syndrome.

Similarly, children with WS have been reported to show domain general motor impairments in comparison to children of the same age (Tsai, Wu, Liou & Shu, 2008) with similar reports of hypotonia (Bellugi et al, 1990). In their report of the clinical characteristics of infants, children and adolescents, Carrasco et al (2005) report significant deficits meeting motor milestones. In 24 individuals (2-30 years), Chapman, du Plessis and Pober (1996) found fine-motor, gait, tone and reflex abnormalities were evident early in development and continued into adulthood, whilst hypotonia was evident in early childhood but improved with age. Similar fine and gross motor difficulties are reported by Gagliardi, Martelli, Burt and Borgatti (2007) in their investigation of the neurological (e.g. cerebella signs, sensory functions) features of 47 children and adults (3-30 years). They suggest the cerebellar impairments found in the sample can link to the poor balance control and fine motor difficulties faced by individuals with this CNV. These cerebellar dysfunctions may result in challenges in motor skill learning (e.g. learning to ride a bike) and on tasks requiring complex fine motor control.

Overall on a group level fine motor difficulty appear to be more prominent than balance impairments. These findings parallel that of children with CNV syndromes (e.g. Williams Syndrome) and may relate to the cognitive impairments discussed in the previous section.

#### 4.3.3.2 Kinematic assessment

The Clinical Kinematic Assessment Tool (CKAT) (Flatters et al, 2014) was used to assess fine motor control or pen skills. The device is a portable tablet in which the participant was required to use a stylus to complete. The stylus is similar to a pen which requires precise force to control the movement of the pen during three tasks: tracking (tracking a

moving dot with and without a spatial guide), aiming (draw between a series of dots) and tracing (draw along an abstract path keeping within the boundary). These tasks assess basic sensorimotor control processes. Visual stimuli were presented, and the participant was required to process and interact with this information and generate a movement response and the resulting behavioural output from the motor system was assessed. Children aged between 7-11 years completed this measure (as normative data were available for this age range) and findings are presented in Figure 4.7.

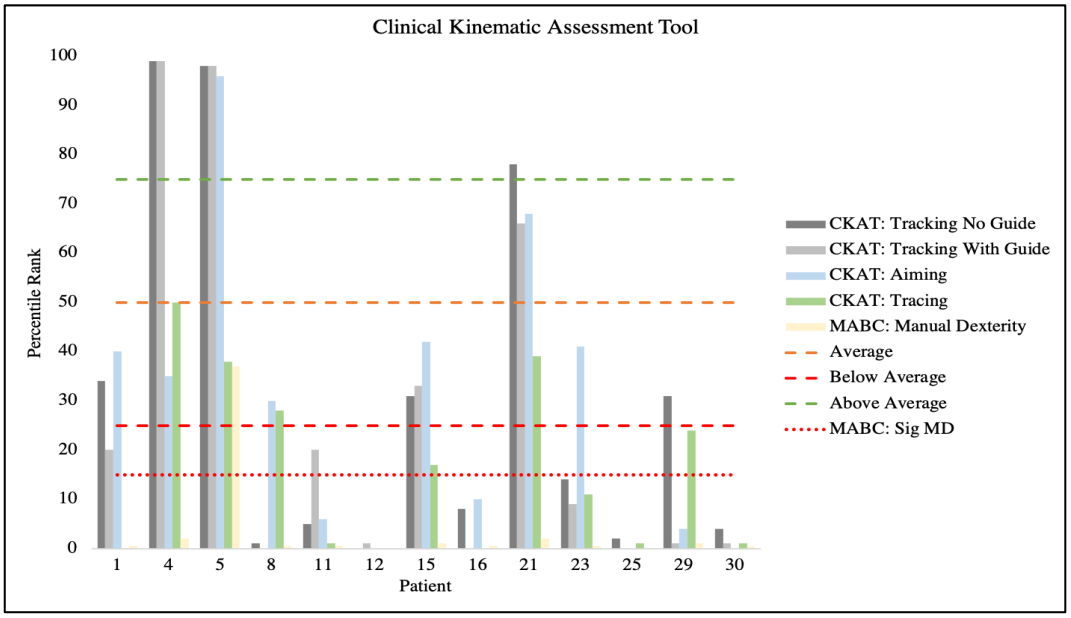


**Figure 4.7: CKAT percentile rank performance**

In relation to children of the same age, none of the children gained consistent scores that situated in the above average range. Three children (Patient: 4, 5, 21) presented a mixed profile which consisted of performance of above average on some tasks and performance which extended below the 50$^{th}$ percentile, but not as low as the 25$^{th}$. In comparison, the majority of children (10/13, 77%) presented scores across all 3 tasks that fell below average (below 50$^{th}$ percentile). Of these children, 5/10 (Patient: 1, 8, 15, 23, 29) performed both below the 25$^{th}$ and between the 26$^{th}$ – 50$^{th}$ percentile, although there was no specific pattern observed within these individuals. Finally, the remaining children 5/10 had scores that fell consistently below the 25$^{th}$ percentile (Patient: 11, 12, 16, 25, 30). Alongside this, all 10 presented significant difficulties on the MABC-2 MD task.

The tracking task required a slow-moving target dot to be followed as closely as possible and the spatial location of the dot has to be predicted. The resultant score is an assessment of both spatial (error and distance from the centre of the dot and tip of stylus) and temporal

accuracy. The findings from this task show the majority of children may struggle with tasks that require the successful coordination of movement when interacting or faced with a moving target (e.g. moving ball). Secondly, the aiming task required the participant to draw a line to a series of dots presented at different spatial locations both quickly and accurately. Comparable to the previous task, the majority of the sample presented difficulties in accurately planning and implementing fast aiming movements to reach a target. This movement behaviour may link to difficulties in reaching out to grasp an object. Finally, during the tracing task the participant was required to maintain good force control to keep within boundary lines whilst drawing along an abstract path. On the path was a box which moved across the path, and participants were instructed to try and keep the speed of their tracing within this box. Accuracy was assessed by the deviation (mm) the made from the reference path. Therefore, this group of children may face difficulties on tasks requiring precision force and control (e.g. drawing, writing and grasping objects).

There is limited work conducted on the visuo-motor development of children with CNVs in general. There have been reports of visuomotor coordination deficits and movement planning in adults with WS (Hocking, Rinehart, McGinley, Moss & Bradshaw, 2011). However, the present findings parallel those reported for children with 22q11.2 DS. For example, Van Aken, Caeyenberghs, Smits-Engelsman and Swillen (2009) found in comparison to age and IQ matched controls (n=28) school aged children (n=28) showed specific difficulties on the MABC manual dexterity task (Henderson & Sugden, 1992) and the visual perception and motor coordination tasks from the BEERY assessment (Beery, Buktenica & Beery, 1997). The visual perception task assessed integration of visual and motor skills, whilst the motor coordination task assessed how well children can trace a figure without deviating outside the path lines. The authors suggest these difficulties could be attributed to the profile of non-verbal learning difficulties (as previously discussed, i.e. relative difficulties in visuospatial memory and non-verbal IQ) in children with this CNV. Similar visuo-motor difficulties have been found by Van Aken et al (2010) who found school aged children engaged in ‘young ballistic movement strategy’ (maximum velocity and acceleration) when completing a visuo-motor tracking task. This group found it challenging to predict the outcome of their movement behaviour (e.g. speed) as they engaged in fast movements to reach the target and then subsequently faced difficulty engaging in successful corrective movements to locate the target.

#### 4.3.3.3 Findings and discussion from the motor assessments

In summary, findings from the MABC-2 reveal the children in the sample are at risk of difficulties for gross motor abilities (static and dynamic balance) whilst showing significant fine motor (manual dexterity) deficits. In relation to percentile ranks, two main groups were identified. This consisted of children who presented domain general motor deficits, and those who presented relatively intact gross motor skills in contrast to significant fine motor difficulties. Following this, a number of children completed the CKAT assessment, whereby the majority of children fell below average on tasks requiring sensorimotor control. Alongside this, all individuals in this group presented significant difficulties on the manual dexterity component of the MABC-2. In comparison to children of the same age, these children may find it challenging to engage in and accurately perform a range of tasks. These tasks may require manual manipulation (e.g. reaching and grasping), coordinated hand movements (e.g. tying shoelaces) and accurate and timely movement decisions (e.g. interceptive time). Alongside this, these difficulties may impact functioning during academic tasks (e.g. writing or drawing), daily living tasks or those requiring precision movements (e.g. fastening buttons, using knife and fork).

These difficulties found in motor skills in the present sample are similar to the difficulties found in children with genetics syndromes. The domain general patterns of motor deficits as identified in a number of children in the present sample is similar to that of children with 22q11.2, WS and PWS. Although the group averages reveal a domain specific pattern of “at risk” of gross motor difficulties the profile of “significant” fine motor difficulties does parallel that of children CNV syndromes. For example, Van Aken et al (2010) found children with 22q11.2DS found it difficult to predict the potential consequences of their motor actions and then subsequently engage in corrective movements. A potential explanation for this finding is difficulty with feedforward planning, whereby the ability to form a successful motor action plan is comprised, thus resulting in inaccurate movement behaviour. This may relate to the findings from the CKAT whereby the majority of the sample performed poorly on tasks assessing temporal and spatial accuracy. Related to this, in a different study, Van Aken et al (2010) found children with 22q11.2 DS faced challenges anticipating the movement of a target during a visuo-motor tracking task. They suggest this could be attributed to difficulties in cognitive flexibility. This finding may parallel the difficulties discussed in the cognitive section in relation to the WCST and complex WM task performance.

### 4.3.4 Behavioural assessments: findings and discussion

The following section explores the data from the questionnaires completed by parents. In total there were 21 respondents and Table 4.19 presents the findings.

**Table 4.19: Frequency of behavioural symptomology for the full sample**

| Questionnaire | Classification | n=21 | % |
|---|---|---|---|
| Developmental Coordination Disorder Questionnaire | Indication of, Suspect DCD | 20 | 95% |
| | Probably not DCD | 1 | 5% |
| Strengths and Difficulties Questionnaire | Close to average | 2 | 10% |
| | Slightly raised | 4 | 19% |
| | High | 1 | 5% |
| | Very high | 14 | 67% |
| Social Communication Questionnaire | Signs | 14 | 67% |
| | No Signs | 7 | 33% |
| Vanderbilt ADHD Diagnostic Rating Scale | Predominantly Inattentive | 4 | 19% |
| | Predominantly Hyperactive/Impulsive | 0 | 0% |
| | Combined Inattentive/ Hyperactive | 10 | 48% |
| | Oppositional Defiant Disorder | 13 | 62% |
| | Conduct disorder screen | 5 | 24% |
| | Anxiety/ Depression screen | 8 | 38% |
| Developmental Behaviour Checklist | Above clinical cut off | 17 | 81% |
| | Below clinical cut off | 4 | 19% |

#### 4.3.4.1 Movement difficulties

To extend the discussion of motor abilities as explored above, the Developmental Coordination Disorder Questionnaire (DCDQ) (Wilson, 2007) was completed by parents. The DCDQ consists of 15 questions, which asks questions about children's movement

behaviour in relation to 3 factors: ‘control during movement’ (a moving object or while child is moving); ‘fine motor and handwriting’ and ‘general coordination’.

A total score was calculated which was then assessed in relation to the child’s age to evaluate whether the child showed: “indication of, or suspect for, DCD” or “probably not DCD”. The maximum score on the questionnaire is 75 and the sample average was 35.67 (S.D. 11.97). Although the present work was not intended to diagnose DCD, the majority (95%) of the sample were found to show signs of this disorder. This may suggest the majority of the sample are at risk of movement difficulties that are common of children with DCD. DCD can encompass difficulties with fine motor, gross motor, sensory integration, motor planning or visual perception (Matheis & Estabillo, 2018) which can impact activities of daily living, learning and academic achievement.

As previously discussed in the motor section, children with genetic syndromes (e.g. WS, PWS and 22q11.2 DS) have been reported to experience motor difficulties and delays. In relation to DCD, Cunningham et al (2018) investigated the movement behaviour of 70 children with 22q11.2DS and 32 controls. Administering the DCDQ, indicative DCD was found in the majority of the sample 81.4% (n=57) in contrast to only 2 children in the control group (6.3%).

#### 4.3.4.2 Psychological difficulties

Findings from the Strengths and Difficulties Questionnaire reveal the majority (67%) of the sample showed “very high” total difficulties. The numbers were lower for “high” (5%); “slightly raised” (19%) and “close to average” (10%) categories. The overall sample mean was 23.24 (SD = 7.37) which fell into the ‘Very High’ category on the SDQ (20-40 = Very High). This may highlight the psychosocial problems that children may be at risk of across emotional, conduct, hyperactivity and peer domains (Stone et al, 2015). Alongside this, this sample may be at risk of mental health difficulties as children with higher total difficulties have been found to have greater rates of mental disorder (Goodman & Goodman, 2009).

In relation to work conducted in samples with CNVs, Rhodes et al (2010) employed neuropsychological measures alongside the SDQ in 19 individuals aged 11 to 29 years with WS. They found the majority of the sample presented psychological difficulties as 90.9% gained scores in the abnormal range on the SDQ, with a smaller number in borderline range (9.1%). Alongside this, in contrast to controls, children and adolescents

with 22q11.2 DS have been found to be at risk of psychological difficulties. They have been found to present profiles of anxiety, depression and withdrawn behaviour (Jolin et al, 2009; Kelley, Sanders & Beaton, 2016; Stephenson et al, 2015).

#### 4.3.4.3 Social communication

On the Social Communication Questionnaire (SCQ), scores of 15 or higher are indicative of possible ASD. The average score for the sample was 18.29 (SD=9.67) which exceeds the cut off. Alongside this, the majority of the sample (67%) presented behaviours that align with an ASD diagnosis, although further evaluations are required to confirm this. As a result of these symptoms, this group of children may face challenges with social interaction; verbal and nonverbal communication and daily functioning, interests or activities (Charman, 2003; Plomin et al, 2013; Reid, Lannen & Lannen; 2016).

CNVs have been implicated as risk factors for neurodevelopmental disorders (Thapar & Cooper, 2013). The majority of the sample presented signs of ASD align with previous findings of literature concerning children with CNV syndromes and less common CNVs such as variance to 2q23.1 (Mullegama, Alaimo, Chen & Elsea, 2015); 12p13.33 (Silva et al, 2014); 18q12.1-q12.2 (Wang et al, 2013); 14q32.2 (Babovic-Vuksanovic, Merritt, Jalal & Barbaresi, 2005); and 19p13.2 (Welham et al, 2015).

In relation to children with CNV syndromes, ASD appears to be commonly reported. For example, Laje et al (2010) found 90% of children (n=20, 4-18 years) with Smith-Magenis Syndrome (SMS) presented scores that fell into the autism range on the Social Responsiveness Scale. Similarly, autism-like behaviours have been reported for individuals with PWS and AS (Veltman, Craig & Bolton, 2005). For example, in children with AS, Peters, Beaudet, Madduri & Bacino, (2004) found 8/19 children (aged 5 months to 11 years) met the DSM-IV criteria for autism. The remaining 11 children did not meet the diagnosis criteria but presented autistic behavioural characteristics such as stereotyped hand or body mannerisms, difficulties with play skills and deficits to language development. In individuals with PWS, reviews highlight the phenotypical similarities between PWS and autism, including social communication impairment and restricted and repetitive behaviours, with some reports presenting behaviours comparable to children with an ASD diagnosis (Bennett, Germani, Haqq & Zwaigenbaum, 2015; Clarke et al, 2002; Dimitropoulous & Schultz, 2007; Dimitropoulous, Ho & Feldman, 2012). In relation to social functioning, Lo, Siemensma, Collin and Hokken-Koelega,

(2013) assessed 'Theory of Mind' in 66 children (9-14 years) and found a third of children screened positive for ASD in comparison to healthy controls. However, there was a domain specific profile in this group consisting of maladaptive behaviour and routines. Similarly, Greaves, Prince, Evans and Charman (2006) found children with PWS and autism had similar profiles of repetitive and ritualistic behaviours.

Alongside this, 20%-50% of individuals with 22q11.2 DS have been reported to meet the DSM-IV diagnosis for ASD (Bertran, Tagle & Irarrzazaval, 2018). Children have been reported to have behaviours that are symptomatic of ASD such as difficulties with social interaction and communication; and repetitive and restricted behaviour and interests (Fine et al, 2005; Kates et al, 2007). Angkustsiri et al (2014) administered both the Autism Diagnostic Observation Schedule (ADOS) and social communication questionnaire in 100 children (7-14 years). Many children appeared to be socially competent, though ASD-like behaviours were evident in the sample (e.g. weaknesses in theory of mind, taking perspectives, communication, non-verbal communication and repetitive behaviours). However, this profile may be due to other comorbidities evident in children with this deletion such as developmental delay, anxiety or attentional deficits which may lead to social interaction difficulty or poor cognitive control which may in turn lead to difficulty regulating obsessive compulsive behaviours.

A similar profile has been reported for children with WS (Klein-Tasman et al, 2009). For example, Klein-Tasman, Mervis, Lord and Phillips (2007) found 50% of young children (29 aged 2.5 to 5.5 years) presented ASD-like socio-communicative deficits. These difficulties may extend to adolescence (Sullivan, Winner & Tager-Flusberg, 2003) and adulthood (Fisher & Morin, 2017) which may impact how well individuals manage social interactions, conflicts and situations. Although social communicative difficulties have been reported, there is a specific socially oriented profile described for individuals with this CNV consisting of reduced stranger anxiety and hyper-sociability (Lincoln, Searcy, Jones & Lord, 2007; Jawaid et al, 2012; Jones et al, 2000).

#### 4.3.4.4 Attentional difficulties

In relation to the Vanderbilt ADHD Diagnostic Rating Scale (VADRS-Parent), attentional difficulties were evident in almost 50% of the sample. The majority (48%) presented a profile which aligned to Combined Inattentive/Hyperactive subtype, in contrast Predominantly Inattentive (19%) or Hyperactive/Impulsive (0%) profile.

Alongside this, behavioural and emotional difficulties were clear as 62% displayed signs of Oppositional Defiant Disorder and 38% presented signs of anxiety and depression.

Attentional difficulties consisting of combined inattentive/hyperactive behaviours were most common in the sample (10/21, 48%) in contrast to inattentive or hyperactive/impulsive subtypes. This combined profile of hyperactive and distractible behaviours can subsequently lead to social problems and academic difficulties (Hill, 2003; Milich, Balentine & Lynam, 2001; Said et al, 2015). Commonly co-occurring (30-50%) with ADHD are disruptive behavioural disorders. Present findings reveal 13/21 (62%) of children presented signs of Oppositional Defiant Disorder which may result in violent and aggressive behaviours (Coy, Speltz, DeKlyen & Jones, 2001). These behaviours can risk negative outcomes in the future (e.g. substance misuse, school and work dismissal) (Biederman et al, 2008).

In relation to the CNV literature, there is evidence of attentional difficulties (ADHD) in children with genetic syndromes. For example, in children with WS some reports have found ADHD to be the most prevalent psychiatric disorder (Leyfer et al, 2006). Rhodes, Riby, Matthews and Coghill (2010) compared children 19 children with ADHD, WS and typically developing controls and assessed behavioural symptoms (Conner ADHD rating scale) and neuropsychological functioning. Both the WS group and ADHD group presented similar cognitive and behavioural profiles. This included scores in the clinical range for ADHD, similar hyperactive, cognitive problems, inattentive behaviours, working memory and short-term memory functioning. Alongside this, almost half of the children in the WS presented oppositional behaviour difficulties. The authors discussed this finding in relation to the profile of hyper sociability which is previously reported in children with this CNV. They suggest children with WS have difficulties with social-cognitive signals, theory of mind and forming friends which may subsequently result in impaired social understanding which may be interpreted as oppositional-like behaviours.

Attentional difficulties have been reported in children with 22q11.2 DS (Bertran, Tagle & Irarrzazaval, 2018; Schneider et al, 2014). A domain specific profile of the inattentive subtype has been commonly reported (Antshel et al, 2007; Zagursky, Weller, Jessani, Abbas & Weller, 2006) alongside a profile that is different to children with idiopathic ADHD (unknown cause). For example, Niarchou and colleagues (2015) compared the ADHD phenotype of children with and without 22q11.2DS. The 22q11.2 DS (n=44, 6-14 years), presented a different ADHD phenotype in comparison to controls consisting

of higher prevalence of the ADHD inattentive subtype (61%) and a higher rate of anxiety (generalised anxiety disorder).

#### 4.3.4.5 Behavioural and emotional difficulties

The Developmental Behaviour Checklist (DBC) (Einfeld & Tonge, 2002) is a questionnaire measure used to assess the severity of emotional and behavioural disturbances in children with intellectual disability or developmental delay. Children with intellectual disability are three to four times more likely than non-affected children to experience difficulties in these areas (Dekker, Koot, van der Ende & Verhulst, 2002). Based on this, this measure was employed as the current patient population are at risk of developmental delay. Findings from the DBC reveal the majority (81%) 17/21 had a total behaviour problem score (TBPS) that exceeded the clinical cut off percentile which indicates that the subject would be a "definite psychiatric case" or has "major behavioural/emotional problems". The TBPS is a sum of scores across emotional and behavioural areas including disruptive/antisocial behaviours, self-absorbed, communication disturbance, anxiety and social relating domains. Alongside this, the group average was 70.14 (SD=32.22) which also exceeds the cut off.

In relation to the genetics literature, emotional and behavioural disturbances have been reported for children with WS within both home and school settings. For example, Udwin and Yule (1991) found 85% of their sample (20 children, 6–14 years) scored above the cut-off for behavioural difficulties. Alongside this, work in samples of children with PWS suggests elevated emotional and behavioural difficulties. Using the DBC, Einfeld et al (1999) found 46 children (mean age 17.7) with PWS scored higher (M=51.7) than controls with intellectual disability (n=454) (M=42.3). The PWS group presented a specific profile of increased antisocial behaviour problems (e.g. steals, hides, lies and lights fires). Alongside this, children and adolescents with PWS have been found to have clinically elevated psychopathological disturbances (e.g. externalising, internalising conduct problems, anxiety) in contrast to controls with only intellectual disability (Reddy & Pfeiffer, 2007). Similar difficulties have been reported by van Lieshout et al (1998). They found the emotional and behavioural profiles of children with PWS were similar to children attending Mental Health Centres as both groups gained scores in the clinical range across attentional problems, delinquent behaviour and withdrawn symptoms.

#### 4.3.4.6 Findings and discussion of all the behavioural assessments

Questionnaire data was received from 21 participants. Figure 4.8 presents the number of children who scored above the clinical cut off on one or more questionnaires. In total there were 7 questionnaires completed, 5 are discussed below and the remaining 2 questionnaires were discussed in the language section from the CELF-4.

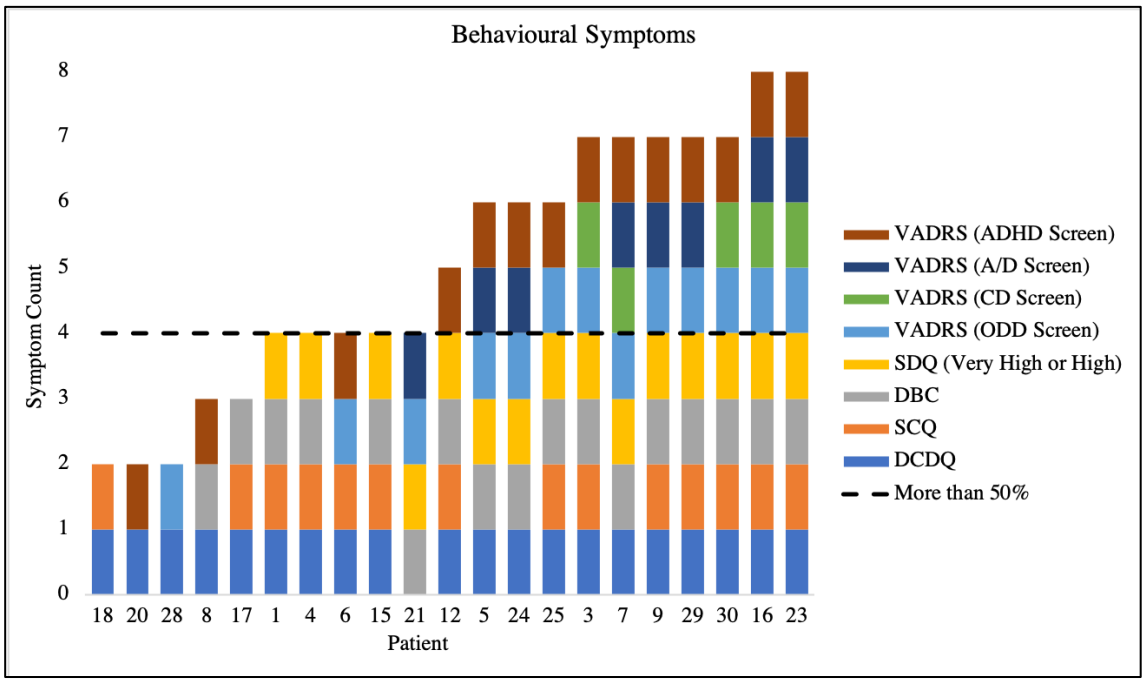


**Figure 4.8: Number of behavioural symptoms per patient in the full sample**

Each patient presented behavioural difficulties as their scores exceed the clinical cut off score on the respective measure. The majority of the sample (16/21) presented consistent difficulties across 50% of the measures. These participants had signs of movement difficulties (DCDQ), social communication difficulties (SCQ), very high or high psychological difficulties (SDQ), attentional difficulties (either inattentive, hyperactive or combined) (VADRS), and major behavioural and emotional difficulties (DBC). Of the remaining 5 children, they all presented movement difficulties but a less consistent pattern of emotional and behavioural and ASD-like and ADHD-like symptomology.

Children in this sample present behavioural symptoms which align with behaviours typical of neurodevelopmental disorders as more than 50% presented difficulties across each questionnaire. Psychological difficulties were prevalent as the majority of the sample gained scores in the very high total difficulties category of the SDQ which may place these children at risk of developing a mental health disorder. This can also be supported major emotional and behavioural difficulties as identified by the DBC. The

social communication difficulties (i.e. behaviours typical of ASD) were evident in more than 50% of the sample, which may impact how well children communicate and interact with others. Children in this group present clear movement difficulties in contrast to children of the same age, as 95% were found to show signs of DCD. These motor difficulties may subsequently impact how well these children respond to situations in the environment, perform in academic subjects, interact with others or engage in physical activity. Closely related to DCD are attentional difficulties (overlap of 50%) whereby children present excessive gross motor movements (e.g. restlessness, fidgeting) or difficulty sustaining attention during fine motor tasks (Goulardins et al, 2015).

In relation to the genetics literature, similar findings have been reported for children with 22q11.2 DS, whereby psychological difficulties and a range of psychiatric symptoms have been reported throughout development (Green et al, 2009; Wang, Woodin, Kreps-Falk & Moss, 2000). These include attentional difficulties, social deficits and mood and anxiety disorders (Schneider et al, 2014). For example, Niarchou et al (2014) found more than half of their sample (86 children, 6-14 years) presented one or more psychiatric disorders (e.g. anxiety, ODD, ASD traits) in contrast to only 10% in siblings (39 controls, 6-14 years). These findings are similar to that of the present sample as each child in the sample met the criteria for difficulties on one or more questionnaire measures. Alongside this, signs of DCD (from the DCDQ) were evident in the majority (20/21). This finding can be discussed in relation to Cunningham et al (2018). In their sample of 70 children with 22q11.2, they found 80% presented signs of DCD from the DCDQ. Indicative DCD was related to an increased risk of ADHD, ASD, anxiety disorder and difficulties with sustained attention. Signs of DCD were found to link to ADHD, as children with motor coordination problems presented more inattentive symptoms. This finding is comparable to the present study as 14/21 (66.7%) presented comorbid difficulties of “suspect” DCD and signs of attentional difficulties on the Vanderbilt assessment. Alongside this, Cunningham et al (2018) found children with increased ASD symptomology had poor motor coordination. The present work also parallels this finding as 14/21 (66.7%) children had signs DCDQ and scored above the cut off on the SCQ (i.e. ASD symptoms).

### 4.3.5 Summary and discussion of the cognitive, motor and behavioural findings

At present there is evidence that CNVs increase the risk of developing an NDD. This section explored how *general* copy number variance can impact children's cognitive, motor and behavioural development. Findings from the cognitive domain suggest this sample of children are at risk of below average performance across all measures, with relative difficulties on tasks that require complex skills of abstract thinking, flexible thinking, manipulation and proficient language skills. The motor assessments present a reveal a profile of significant fine motor difficulties, with poor balance and coordination (at risk). Finally, all but one participant presented multiple behavioural difficulties, which places the sample at risk of behavioural symptoms most typical of NDDs.

Taken in combination, these findings can highlight the risks or challenges children in this sample may face. Often the findings were comparable to investigations of children with diagnosed CNV syndromes which can suggest that CNVs (in general) may contribute to phenotypical outcomes that parallel profiles of children with prevalent developmental difficulties. These findings may have implications for health professionals, educational professionals and parents, as having a rare CNV or a CNV in general may place the child at risk of poor performance in relation to children of the same age. As there is limited understanding of the phenotypical implications of rarer CNVs (i.e. variant of uncertain significance) and CNVs which are not associated with a specific syndrome, the present findings could highlight the potential difficulties some children may face accessing the relevant support (i.e. educational or social) to help meet their needs. The following will summarise the links between the cognitive, motor and behavioural data:

In relation to intellectual functioning, there was a domain specific profile identified consisting of relatively less impaired verbal IQ in contrast to non-verbal IQ which assess crystallised and fluid skills respectively. Sobin et al (2005) suggests that the poor motor functioning of children could relate to cognitive processes. The tasks that comprise the PRI measure may relate to the fine motor difficulties found to be prevalent in the present sample as the 'block design' task from WASI-2 required successful fine motor manipulation and performance under timed conditions. The behaviours that underpin successful motor movements may relate to the profile of cognitive difficulties. In line with Hulme and Snowling (2009), children develop motor schemas which are perfected throughout their interactions with the world and these schemas provide an understanding

of how movements should be executed based upon learning and practice. The acquisition and motor learning process may link to underlying cognitive factors such as WM. WM refers to the capacity to store and process information, which can underpin successful learning and knowledge acquisition (Alloway et al, 2005). For example, children with DCD have been found to have both simple and complex WM difficulties (Alloway & Archibald, 2008). These WM deficits may impact learning ability as Alloway and Temple (2007) found children with DCD performed poorly across tasks assessing simple and complex WM (1SD below mean) and they had poor attainment in numeracy and literacy.

The below average performance across cognitive tasks may also risk behavioural difficulties. Children with ASD and ADHD have been found to present executive function deficits, and poor performance on tasks assessing cognitive flexibility (Ahmadi, Mohammadi, Araghi & Zarafshan, 2014; Houghton et al, 1999; Robinson et al, 2009). These cognitive and behavioural difficulties may parallel that of children with diagnosed syndromes. For example, children with poor WM and those with ADHD have been found to show similar deficits on WM tasks, elevated signs of inattentive behaviour and difficulties with executive functions (e.g. planning, sorting) (Holmes et al, 2014). This profile may arise due to deficits in executive functions which underpin the behaviours difficulties prominent in ADHD (e.g. WM, goal directed behaviour) (Barkley, 1997). These findings are comparable to the present sample, as attentional difficulties (VADRS) and social communication difficulties (SCQ) were common alongside below average performance on WCST and complex WM measure.

These cognitive difficulties may also have implications for motor *and* behavioural outcomes. The development of motor skills allows a child to interact with the world and form knowledge of the world and this in turn contributes to their cognitive development (Adolph & Robinson, 2015; von Hofsten, 2004). Poor motor skills in this context can therefore limit exploration or interactions with others subsequently contributing to language or social communication difficulties (Leonard & Hill, 2014). For example, coordination difficulties may limit playing, engaging and interacting with others (Kennedy-Behr, Rodger & Mickan, 2011) and the development of joint attention (e.g. reaching, point or showing) (Bhat, Landa & Galloway, 2011). Children with DCD have been found to presented poor performance on cognitive (e.g. planning and memory) and motor measures (e.g. fine and gross) in contrast to children with without DCD (Asonitou, Koutsouki, Kourtessis & Charitou, 2012). Similarly, children with ADHD have been

found to have increased movement difficulties (Piek, Pitcher & Hay, 1999). Finally, children with ASD have also been reported to present sensorimotor difficulties such as poor handwriting (Fuentes, Mostofsky & Bastian, 2009) and difficulties coordinating movements (Cook, Blakemore & Press, 2013). In relation to this, the majority of the sample presented movement difficulties (on the DCDQ, MABC-2, CKAT) and there was clear below average performance across all cognitive measures, with elevated behavioural difficulties.

Similarity there may be links between the deficits in complex cognitive functions (e.g. flexible thinking and WM) and motor difficulties as presented in the sample (Goulardins et al, 2015). The prevalent motor difficulties in the sample (e.g. signs of DCD, significant manual dexterity difficulties and at risk balance performance) may risk poor psychological wellbeing due to social isolation, less engagement in play opportunities and reduced perceptions of self-worth (Cairney, Veldhuizen & Szatmari, 2010; Green, Baird & Sugden, 2006; Kirby, Williams, Thomas & Hill, 2013; Piek, Baynam & Barrett, 2006). This may parallel the present findings as emotional difficulties were prominent in the sample based on scores from the SDQ and DBC. Related to this, difficulties with motor skills may link the development of social skills and language. For example, in early development hand eye-coordination helps children to engage in tasks of joint attention with their parents (Yu & Smith, 2013, 2017) and this interaction and use of gesture links to the development of vocabulary skills (Rowe, Ozcaliskan & Goldin-Meadow, 2008).

To extend the overlap across developmental domains, there are underlying brain regions which are at play during cognitive and motor development. These cortical and subcortical systems (e.g. prefrontal cortex) work together to successfully plan and execute movements (Diamond, 2000). For example, comorbid cognitive and motor difficulties have been reported for individuals with neurodevelopmental disorders such as ADHD (Pitcher, Piek & Hay, 1999; 2003) and ASD (Leary & Hill, 1996; Liu & Breslin, 2013) which can highlight the interrelation of underlying systems (e.g. executive functions involved in generating motor plan). Similarly, these difficulties can be evidenced by the concept of 'DAMP-Deficits in Attention, Motor and Perception' whereby children can present concurrent difficulties in these domains (Gillberg, 2003). These difficulties can also extend to behavioural symptoms as severe DAMP has been found to link to problem behaviours in the classroom (Kadesjo & Gillberg, 1998). Finally, difficulties with cognitive skills (e.g. WM) which underpin learning capacity have found to manifest in

children with motor difficulties (e.g. DCD) (Alloway & Archibald, 2008; Asonitou, Koutsouki, Kourtessis & Charitou, 2012). In relation to the present data, findings across the cognitive and motor measures were in the below average range. Alongside this, the majority of the sample presented behaviours that are typical of neurodevelopmental disorders: ASD, DCDQ and ADHD which may highlight the comorbid developmental difficulties the sample may be at risk of.

In relation to the CNV literature, work has mainly focused on two developmental domains (e.g. cognitive and motor) in contrast to three as conducted in the present project. Alongside this, the profiles of children with more common CNV syndromes have been investigated in contrast to samples of children with genetic variance in general. The profiles of the present sample are similar to the findings from children with genetic syndromes, whereby comorbid cognitive, motor and behavioural difficulties are prevalent. The intellectual profile of the group did not extend as low as some genetic syndromes (e.g. WS, PWS) but some children did present comparable domain general IQ difficulties and domain specific profiles (i.e. non-verbal learning difficulties). There are also comparable findings between the present sample and the language profile of children with 22q11.2 DS (Glaser et al, 2002). Alongside this there was similar difficulties found for the present sample on tasks assessing higher cognitive function (e.g. complex WM and CF) as found in sample of children with WS and 22q11.2DS which may have implications for the behavioural findings. For example, in children with WS, Rhodes et al (2010) found executive WM impairments linked to general difficulties on the SDQ (conduct, emotional, hyperactive and peer relationship problems) and poor executive function abilities (e.g. of planning, working memory, attentional flexibility) were linked to problem behaviours. This may impact how successfully children with CNVs interact with others and regulate, understand and switch their behaviour to understand the social context as a high number of children presented “very high” total difficulties, and “major behavioural and emotional difficulties”. These behavioural difficulties may also relate to the findings presented by Cunningham et al (2018) and Niarchou et al (2014). They found the majority of children with 22q11.2 DS presented varied behavioural symptomology and more than half met the diagnostic category for more than one psychiatric or neurodevelopmental disorder with comorbid motor and cognitive difficulties.

Overall, the findings from this section suggest children with a CNV are at risk of atypical cognitive and motor development, with a risk of behavioural features typical of

neurodevelopmental disorder symptomology. On a genotype level, it is challenging to systematically quantify the impact of genetic variance, but the findings may highlight the potential implications for the resulting phenotype. Considering phenotypical outcomes, the present comorbidities (i.e. across cognitive, motor and behavioural domains) may situate within a complex system of interacting and overlapping difficulties. A deficit in one domain may active and cause a problem in other areas in a direct or indirect manner (i.e. impact of language difficulties within social contexts) (Mareva & Holmes, 2019) thus highlighting the potential implications for intervention and support for children with less common CNVs where evidence is limited.

## 4.4 Exploring the cognitive, motor and behavioural development of: children with a Copy Number Variant that situates in neurodevelopmental susceptibility loci.

### 4.4.1 Background and sample

CNVs are associated with the risk of developing a Neuro-Developmental Disorder (NDD) (Mitchell, 2015). NDDs arise early in development and impact the growth and development of the brain. CNVs are a risk factor for NDDs, but variance at specific genomic loci can increase this risk (Cooper et al, 2011; Malhotra & Sebat, 2012). These NDD-CNVs may influence phenotypical outcomes (e.g. severe physical disability and severe intellectual disability) or affect a range of developmental functions (e.g. learning, communication, motor function) (Kelleher & Corvin, 2015). NDD-CNVs are rare, pathogenetic (i.e. disease causing), can have incomplete penetrance (i.e. not all carriers will present features typical of that diagnosis), show varied symptomology (i.e. diagnostic pleiotropy) and are often inherited from an unaffected parent which may lead to subsequent challenges for genetic counselling (De Wolf, Brison, Devriendt & Peeters, 2013; Grayton et al, 2012; Rosenfeld et al, 2013).

Some of these loci are syndromic (i.e. they are associated with specific features such as obesity in PWS, or cleft palate in 22q11.2 DS) and are present in the normal population but are enriched in individuals with various NDDs (De Wolf, Brison, Devrienat & Peeters, 2013; van der Steen et al, 2016). In comparison to controls, NDD-CNVs have been identified as ‘high risk’ and have been associated with major pathogenic effects such as developmental, psychiatric, neurocognitive and behavioural disorders (Kaminsky et al,

2011). From a range of sources these include deletions and duplications to 1q21.1; 3q29; 15q13.3; 15q11.2; 16p11.2; 16p12.2 16p13.11 and 22q11.2 (De Wolf, Brison, Devriendt & Peeters, 2013; Grayton, Fernandes, Rujescu & Collier et al, 2012; Kendall et al, 2017; Rosenfeld et al, 2013; Srebniak et al, 2014; Torres, Barbosa & Maciel, 2015).

In relation to phenotypical implications associated with NDD-CNVs, Chawner et al (2019) explored the impact of CNVs that situate in an NDD susceptibility loci (NDD-CNVs) to understand the impact on child development and to identify whether these loci are associated with distinct phenotypical outcomes. In comparison to sibling controls, 80% of 258 children with an NDD-CNV were found to present symptomology of one or more psychiatric disorder (risk of ADHD, ODD, anxiety, ASD) and presented cognitive impairments on standardised measures. They found the phenotypes of NDD-CNVs were broadly similar across different loci, with only subtle qualitative and quantitative differences. The findings show that children with an NDD CNV are at risk of a range of developmental difficulties (e.g. cognitive, motor and psychopathological) and there may be shared biological processes affected by NDD-CNVs.

Based on this, the section presents the findings from an exploratory investigation of the cognitive, motor and behavioural phenotype of children with a CNV that situates in an NDD susceptibility loci (NDD-CNV loci group) in comparison to children with a CNV in a Non-NDD loci (i.e. variant which is not yet identified as being an NDD susceptibility loci in the literature the Non-NDD group) as discussed Table 4.20 and 4.21 respectively. This information is based on the Table 4.1 (section 4.3) but has been split by CNV location. It was of interest to understand whether children with an NDD CNV loci present a distinct phenotype and if they are increased risk of developmental difficulties.

The data in this section are based on the performance on the cognitive and motor assessments of those with a NDD-CNV loci (n=14) and without (n=7). The behavioural analysis is based on data from 2 additional children (Patient: 3, 17). In the NDD group, Patient 3 had learning difficulties and physical disability so was unable to partake in the cognitive and motor assessments. In the Non-NDD group, Patient 17 refused to partake in the home visits (i.e. cognitive and motor assessments) so the questionnaires were returned in the post. There was no change to the number in this group as the questionnaires were not returned due to parental English language proficiency (Patient 11).

**Table 4.20: Clinical characteristics of patients with a NDD CNV**

| Patient | Age | CNV | Type | Clinical summary from cytogenetic report |
|---|---|---|---|---|
| 1 | 10 | 16p11.2 | Dup | Social communication difficulty, learning problems, CNV within SL for microduplication syndrome. Dup linked to variable phenotype and variable penetrance – consistent with patient and likely cause of phenotype. |
| 3 | 8 | 22q11.21 | Del | Developmental delay and various health difficulties. Phenotype and genotype aligns with DiGeorge syndrome. |
| 4 | 10 | 15q13.3 | Dup | Unexplained mild learning difficulties, ?ASD, region of variable penetrance. Tentative evidence of CHRNA7 gene as risk factor for neurobehavioral disorders. |
| 8 | 7 | 16p12.2-11.2 | Dup | Developmental delay (gross motor disproportionally delayed) CNV consistent with16p11.2-16p12.2 microduplication locus associated with variable phenotype. CNV is likely cause of patient phenotype. |
| 12 | 8 | 7q11.23 | Del | Williams syndrome diagnosis |
| 16 | 7 | 16p11.2 | Del | Autistic trait, emerging learning difficulties, TIC disorder. Del lies in the 16p11.2 BP2-BP3 and region predisposes to DD and ID therefore possible contribution towards phenotype as consistent with the learning difficulties in patient. |
| 18 | 13 | 15q11.2 | Dup | Coordination difficulties, learning difficulties, speech language difficulties and SEN statement. Lies within the 15q11.2 SL which is associated with a broad phenotypic spectrum. The coordination difficulties and speech difficulties seen in patient have previously been reported in patients with a duplication to this region, therefore it is possible this duplication may be contributing to phenotype. |
| 20 | 15 | 16p12.2 | Del | Joint hypermobility and motor delay. CNV lies within 16p12.2 microdeletion risk locus for neurodevelopmental disease (broad phenotypic spectrum). CNV likely cause of patients phenotype. |
| 21 | 10 | 16p11.2 | Dup | Behaviour problems and clinical features. CNV lies within 16p11.2 microduplication SL. The behaviour problems and mild dysmorphism evident in patient align with duplications of this region, so it is possible imbalance is contributing to phenotype. |

| | | | | |
|---|---|---|---|---|
| 23 | 9 | 1q21.1-1q21.2 | Dup | Developmental delay, pathogenic, lies within the 1q21.1 microduplication SL which is associated with a broad phenotypic spectrum. The clinical features in this patient are consistent with those associated with duplication of this region so it is probable that the duplication is contributing to phenotype. |
| 24 | 12 | 22q11.21-23 | Dup | Learning difficulties, CNV presents a varied phenotype situates in a neurodevelopmental susceptibility loci. CNV likely cause of phenotype as LD key feature. |
| 25 | 7 | 15q13.3 | Dup | Undergoing ASD assessment, speech delay, repetitive hand movements at present limited literature surrounding the phenotypical outcomes associated, tentative evidence of CHRNA7 gene implicated in neuro-behavioural disorders. |
| 29 | 9 | 16p12.2 | Del | Learning difficulties and social communication difficulties. CNV lies within 16p12.2 microdeletion risk locus for neurodevelopmental disease (broad phenotypic spectrum). CNV likely cause of patient's phenotype as consistent features reported for this deletion. |
| 30 | 7 | 16p11.2 | Del | General developmental delay. 16p11.2 microdeletion syndrome. CNV likely cause of phenotype due to general developmental delay. |

**Table 4.21: Clinical characteristics of patients with a Non-NDD CNV**

| Patient | Age | CNV | Type | Clinical summary from cytogenetic report |
|---|---|---|---|---|
| 5 | 10 | 20 p12.3-p12.2 | Del | Neuro-behavioural problems. Emerging evidence of PLCB1 gene to neurobehavioral disorders, but at present not conclusive. |
| 6 | 14 | 20 p12.3-p12.2 | Del | Autistic features, behavioural problems, macrocephaly. Emerging evidence of PLCB1 gene to neurobehavioral disorders, but at present not conclusive. |
| 7 | 13 | 20p12.3-p12.2 | Del | Neuro-behavioural problems. Emerging evidence of PLCB1 gene to neurobehavioral disorders, but at present not conclusive. |
| 9 | 13 | 10p15.3-11.21 & Xq25-Xq28 | Dup / Del | Developmental delay, Microcephaly. Imbalances likely cause of phenotype and associated clinical features. |
| 11 | 11 | 12p13.32-12p13.31 | Del | Developmental delay. Although limited data on the phenotypic/genotypic association for this region the large size and high gene content of imbalance mean it is possibly contributing to patient's phenotype. |
| 15 | 10 | 17p12 | Dup | Statemented, associated health difficulties and clinical features of Hereditary Motor and Sensory Neuropathies. Charcot-Marie-Tooth hereditary (Muscle weakness, mild-moderate sensory loss, high arched feet). Features in this sample are consistent with those for duplication of this region, therefore it is likely contributing to phenotype. |
| 17 | 12 | 3q26.1-3q26.2 | Dup | Developmental Delay, auditory processing disorder, dysplastic hip. Due to size and gene content of imbalance therefore it is likely to be the cause of patients clinical features. |
| 28 | 12 | 17p12 | Dup | Duplication associated with Charcot-Marie-Tooth hereditary (Muscle weakness, mild-moderate sensory loss). Patient presents some early features consistent with Hereditary Motor and Sensory Neuropathies. |

### 4.4.2 Single case analysis – findings and discussion

The following will discuss the patient profiles of children with a CNV that situates in a neurodevelopmental susceptibility locus.

#### 4.4.2.1 1q21.1 loci

Patient 23 has a 1q21.1-1q21.2 duplication, see Figure 4.9. They present clear difficulties across the cognitive tasks. Findings from the WASI-2 show relatively intact non-verbal IQ (PR=30), in contrast to verbal IQ (PR=12). Performance fell below the 5$^{th}$ percentile across the WM (no PR for block recall as score so low for age) and language tasks which suggest severe WM difficulties and risk of language disorder respectively. Alongside this, data was not obtained for the WCST as they found this challenging to complete. Finally, significant manual dexterities are clear, with an "at risk" profile for balance functioning.

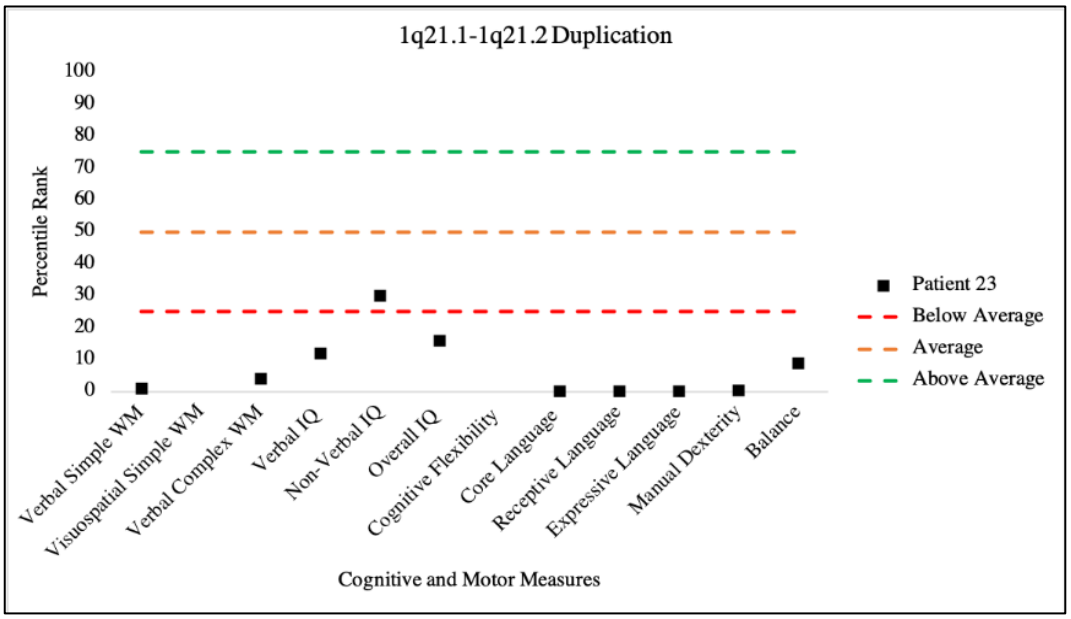


**Figure 4.9: Percentile rank performance for Patient 23 on the cognitive and motor measures**

With regard to the behavioural questionnaires, Patient 23 shows domain general behavioural difficulties as they met the criteria on all measures (8/8). This patient may face difficulties that span: social communication (signs of ASD symptomology); psychological (very high SDQ difficulties, signs of anxiety and depression, major emotional and behavioural difficulties); attention (i.e. combined profile); behavioural (i.e. conduct disorder and oppositional defiant) and movement proficiency (i.e. suspect DCD).

The cytogenetic reports of this patient detail a profile of developmental delay. In line with the current work, this was consistent across the behavioural, motor and cognitive measures. The 1q21.1 CNV has been linked to varied clinical outcomes (e.g. psychiatric, behavioural, intellectual disability, developmental delay, heart malformations) (Brunetti-Pierri et al, 2008; Mefford et al, 2008; Nevado et al, 2014; Verhagen et al, 2015). For example, Bernier et al (2016) investigated the clinical phenotype of children and adults with the deletion (n=19) and duplication (n=19). Common developmental difficulties in the duplication group were ASD, ADHD and intellectual disability with verbal and non-verbal IQ scores in the low average range and fine motor performance (more than -2SD below mean). These findings are similar to the present work.

#### 4.4.2.2 7q11.23 loci

Patient 12 has a deletion of region 7q11.23 and a diagnosis of Williams Syndrome, see Figure 4.10.


**Figure 4.10: Percentile rank performance for Patient 12 on the cognitive and motor measures**

This patient did not gain a percentile rank on the verbal and visuospatial simple WM task as their total correct score was very low for their age. They found the verbal complex WM task and the cognitive flexibility task too challenging to complete which may suggest difficulties on tasks assessing higher cognitive functions such as problem solving (set-shifting) and manipulation (verbal complex WM) as previously reported in individuals with WS (Osorio et al, 2012). The present findings suggest domain general cognitive

difficulties which include delays to language and intellectual functioning (Brock, 2007; Donnai & Karmiloff-Smith, 2000; Martens, Wilson & Reutens, 2008). Significant fine and gross movement difficulties were also found, as previously reported in individuals with WS (Carrasco et al, 2005; Tsai et al, 2008; Wuang & Tsai, 2017).

On the behavioural measures, Patient 12 presented positive signs on 5/8 measures suggesting: social communication, attentional (inattentive/hyperactive), movement (DCD-like) and high psychological difficulties. This profile spanning attentional, psychological and coordination difficulties has previously been reported for individuals with this deletion syndrome (Greer et al, 1997; Tassabehji, 2003).

#### 4.4.2.3 15q11.2 loci

Patient 18 has a duplication of 15q11.2, see Figure 4.11. They did not gain a standard score on the WM tasks (verbal simple and visuospatial simple) as their score was considerably low for their age and the complex verbal task was challenging to complete.

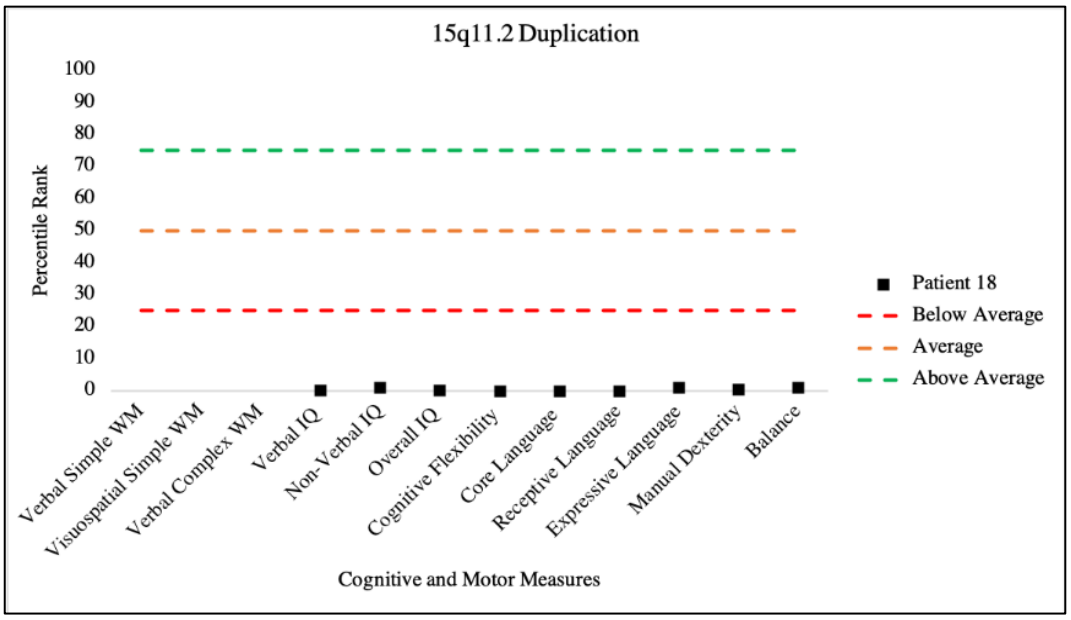


**Figure 4.11: Percentile rank performance for Patient 18 on the cognitive and motor measures**

The cytogenetic report for Patient 18 details a SEN statement alongside coordination, learning, and speech language difficulties which are consistent with the current assessment (below average performance). On the behavioural measures, Patient 18 presented signs of ASD symptomology and coordination difficulties (2/8). These

cognitive, motor and behavioural difficulties (e.g. ASD) are consistent with a broad phenotypic spectrum as described in previous reports (Unique, 2008).

#### 4.4.2.4 15q13.3 loci

Patient 4 and Patient 25 have a 15q13.3 duplication (see Figure 4.12). Patient 4 performed within the average range across the majority of cognitive assessments. They presented a domain specific profile consisting of relatively better performance on non-verbal measures (i.e. above average visuospatial simple WM and non-verbal IQ) with difficulties in receptive language. Performance on the motor assessments suggests movement difficulties on the manual dexterity task, with "at risk" balance performance. In contrast, Patient 25 presented a profile of domain general difficulties across all the cognitive assessments as these situated in the below average range (verbal complex WM too challenging). Patient 4 (4/8) presented a fewer behavioural difficulties in contrast to Patient 25 (6/8) but they both presented high psychological, coordination, emotional and behavioural, social communication difficulties.

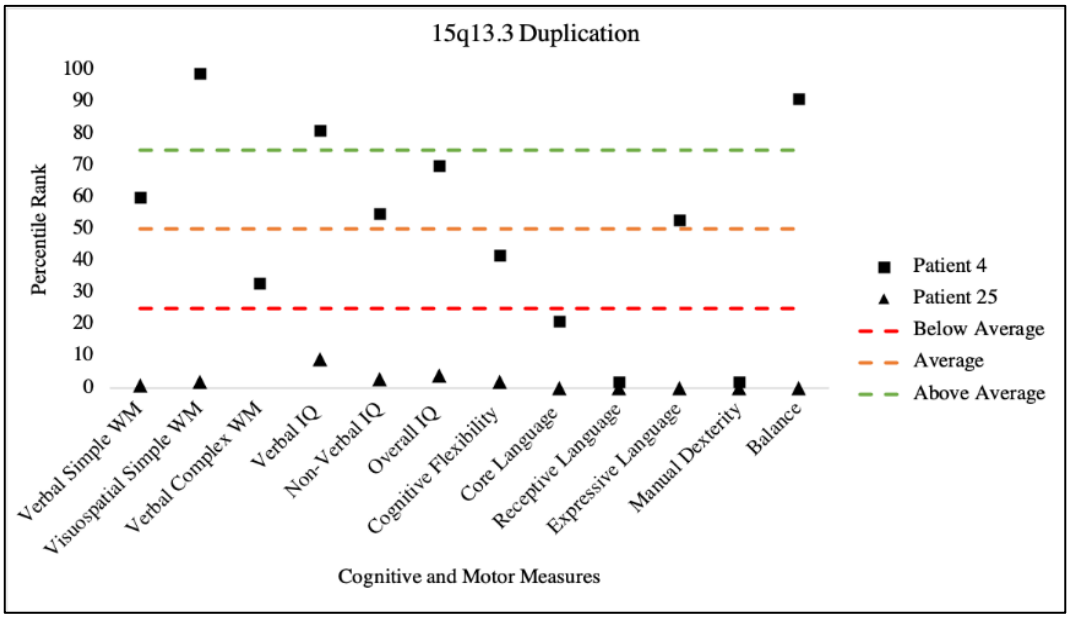


**Figure 4.12: Percentile rank performance for Patient 4 & 25 on the cognitive and motor measures**

Patient 4 presented signs on 4/8 measures: emotional and behavioural (DBC), psychological (SDQ), movement (DCDQ) and social communication (SCQ) difficulties. In comparison, Patient 25 showed a slightly higher number of difficulties (6/8) including attentional difficulties and co-morbid disruptive behavioural difficulties on the VADRS of ODD. Both patients show contrasting phenotypes, which have previously been

reported for individuals with this CNV. This consists of cognitive impairments, psychiatric disease and ADHD (Williams et al, 2012; van Bon, Mefford & de Vries, 2009) which are clear in Patient 25, while ASD traits are common to both (Miller et al, 2009).

#### 4.4.2.5 16p11.2 loci

In relation to 16p11.2, Patient 1 and 21 both had a duplication, see Figure 4.13. Patient 1 presented a domain specific profile of cognitive strengths and weaknesses. This consists of relatively intact verbal simple WM and verbal IQ with weaknesses on the remaining WM tasks (simple visual and complex verbal WM PR=2) and language measures (PR<10). The MABC-2 shows significant manual dexterity difficulties, alongside signs of psychological, major emotional and behavioural, social communication and coordination difficulties. These findings align with the cytogenic report for this patient which detail social communication difficulties and learning problems.

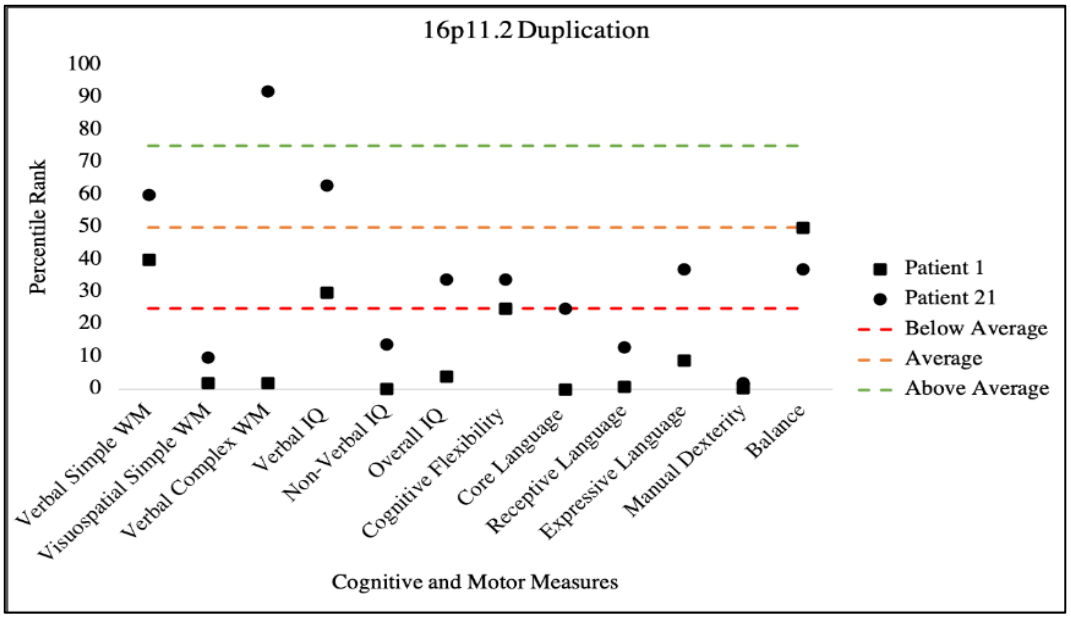


**Figure 4.13: Percentile rank performance for Patient 1 & 21 on the cognitive and motor measures**

In contrast, Patient 21 presented a mixed profile consisting of relatively intact verbal simple and complex WM in contrast to difficulties on the visuospatial based tasks (visual simple WM and non-verbal IQ). Similar to Patient 1, they presented manual dexterity difficulties but relatively intact balance performance. On the questionnaires, behavioural and emotional difficulties were prominent (e.g. signs of opposition defiant disorder,

anxiety and depression and very high psychological difficulties). These findings may align with the 'behaviour problems' described in this patient's cytogenic report.

Related to this region, Patient 8 had a duplication of 16p12.2-11.2– see Figure 4.14. The cytogenetic report details that this CNV is consistent with classical 16p11.2-16p12.2 microduplication syndrome locus, which is a relatively new syndrome (Okamoto et al, 2013) with signs of developmental delay. Domain general cognitive and motor measures were identified, with a domain-specific profile of average verbal IQ. The behavioural measures show Patient 8 had elevated levels of attentional (VADRS), coordination (DCD) and emotional and behavioural (DBC) difficulties. A diverse phenotypical spectrum consisting of developmental delay, cognitive, behavioural and emotional difficulties have previously been reported in a case study of 4 patients with this duplication syndrome (Barber et al, 2013) which may align with the present findings.

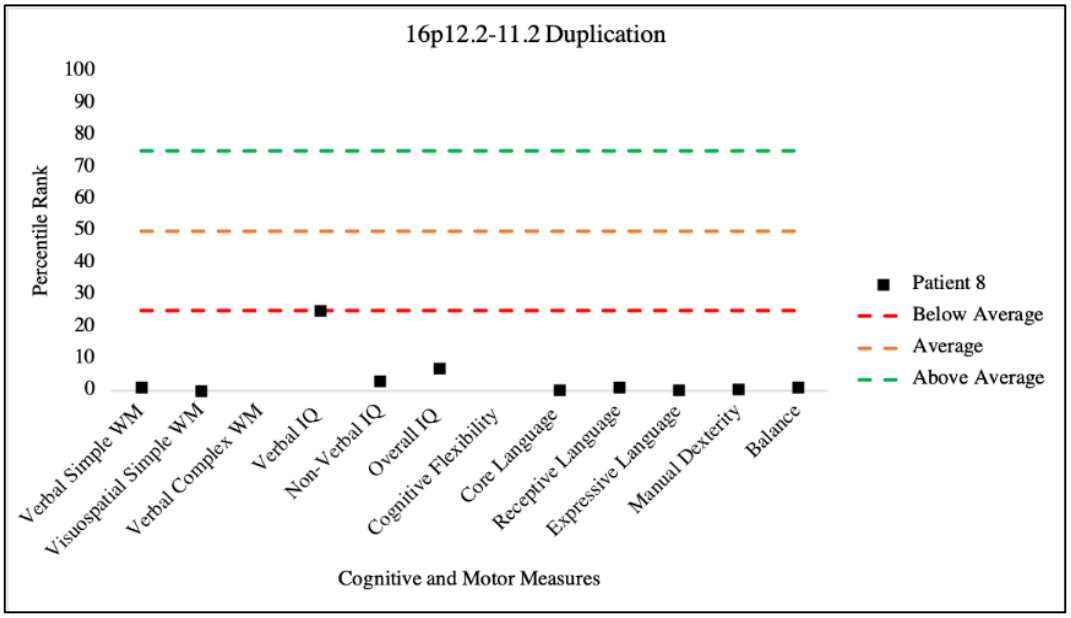


**Figure 4.14: Percentile rank performance for Patient 8 on the cognitive and motor measures**

In contrast, Patient 16 and 30 have a reciprocal deletion to this region, see Figure 4.15. Patient 16 presents a profile of below average performance on the majority of cognitive assessments (<25) with relative strengths on verbal simple WM (PR=34), verbal IQ (PR=34) and cognitive flexibility (PR=25) measures which situate in the average range. There are clear domain general movement difficulties as performance fell below the 5$^{th}$ percentile on the MABC-2. Finally, this patient screened positive on all questionnaire

outcomes (8/8) meeting all the clinical cut offs and presenting domain general behavioural difficulties. This profile aligns with the patient's cytogenetic report (16p11.2 BP2-BP3 region) which details emerging learning difficulties and autistic traits.

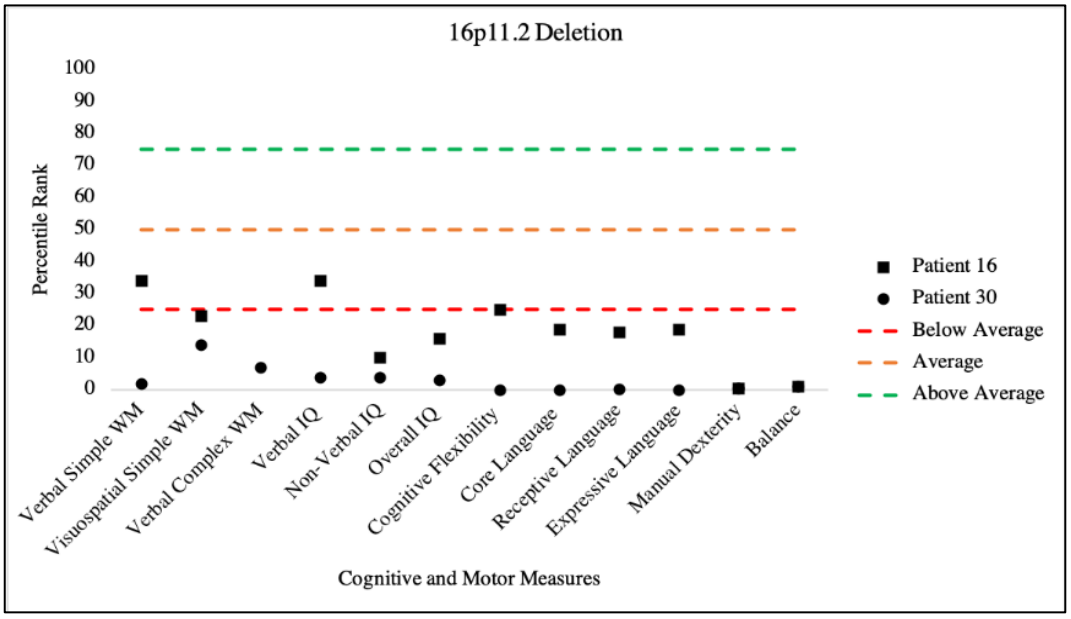


**Figure 4.15: Percentile rank performance for Patient 16 & 30 on the cognitive and motor measures**

Patient 30 has 16p11.2 microdeletion syndrome with general developmental delay (cytogenetic report). They presented below average performance across all cognitive tasks with particular difficulties on the tasks that required complex manipulation and problem-solving (i.e. complex verbal WM and cognitive flexibility tasks were too challenging to complete). On the behavioural measures, both Patient 16 (8/8) and 30 (7/8) presented clear psychological (SDQ), emotional and behavioural (DBC), social communication (SCQ), movement (DCDQ), disruptive behaviour (VADRS CD and ODD) and attentional difficulties (VADRS). Additional to this, Patient 16 screened positively on the anxiety and depression screen (VADRS). In support of the present work, Hanson et al (2015) investigated the cognitive and behavioural profiles of children and adults with the deletion in contrast to controls. The deletion group showed poorer performance on the cognitive measures (FSIQ, language) and increased behavioural difficulties. They found 93% of the CNV sample had at least one diagnosis (ASD, ASD symptomology, DCD, language disorders most common) in contrast to controls (21%).

These difficulties are found in both deletion and duplication carriers as findings report a broad phenotypical spectrum impacting cognitive, motor and behavioural domains resulting in language delays, cognitive impairments, motor delay, behavioural problems and neurodevelopmental disorder (e.g. ASD and ADHD) (Fernandez et al, 2010; Shinawi et al, 2010; Synder et al, 2016; Weiss et al, 2008). For example, D'Angelo et al (2016) found poor IQ and an increased frequency of ASD in both groups in contrast to controls.

#### 4.4.2.6 16p12.2 loci

In relation to 16p12.2, Patient 20 presented a profile of relative strengths in verbal simple WM, verbal IQ and language which situated in the average range - see Figure 4.16.

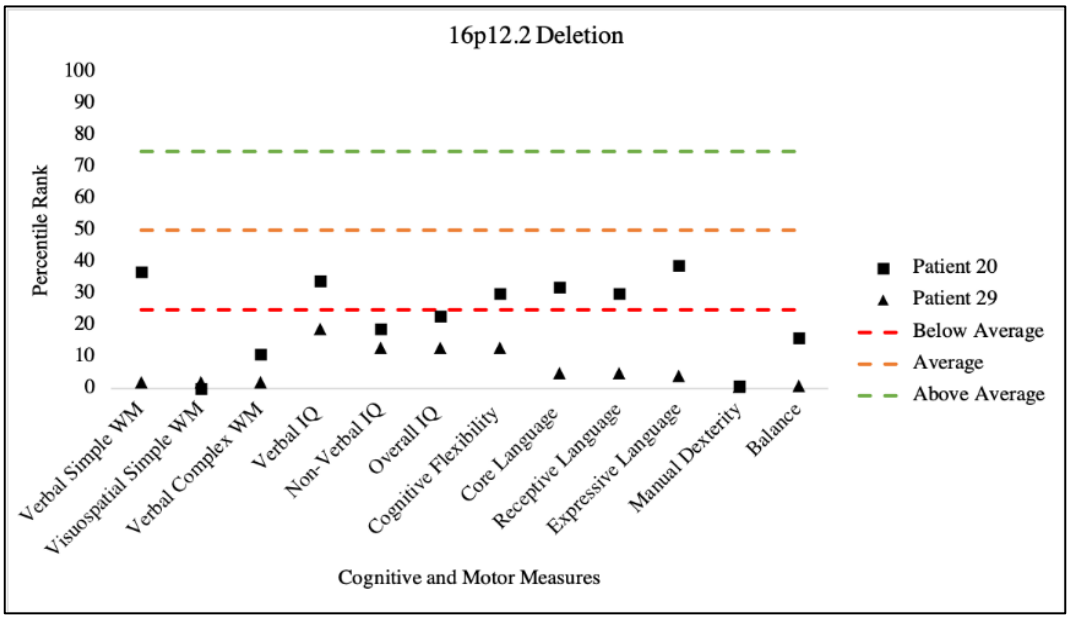


**Figure 4.16: Percentile rank performance for Patient 20 & 29 on the cognitive and motor measures**

They presented significant manual dexterity difficulties and coordination difficulties on the DCDQ and which may align with the motor delay detailed in the cytogenetic report. Alongside this, a profile of attentional difficulties was found (inattentive subtype).

This profile contrasts to that of Patient 29, who presented clear behavioural difficulties as they met the criteria on 7/8 of the questionnaire measures and domain general cognitive and motor impairments. This phenotype aligns with the learning and social communication difficulties detailed in the cytogenetic report.

Common to both patients are complex profiles, which are consistent with the broad phenotypic spectrum described in both cytogenic reports. This variability has been reported for the clinical manifestation of this CNV, which also means that some individuals with this deletion may be undiagnosed (Girirajan et al, 2010). There are around 65 cases reported in the literature, with common features of development delay, learning difficulties, speech and language delay and growth delay (Unique, 2008).

#### 4.4.2.7 22q11.2 loci

In relation to the 22q11.2 loci (see Figure 4.17), Patient 24 with the duplication presented clear difficulties across the cognitive measures with relatively intact performance on the WCST. They presented significant difficulties on the manual dexterity, with an "at risk" profile on the balance component. In relation to the behavioural measures, there are signs of difficulties across the majority of measures (6/8).

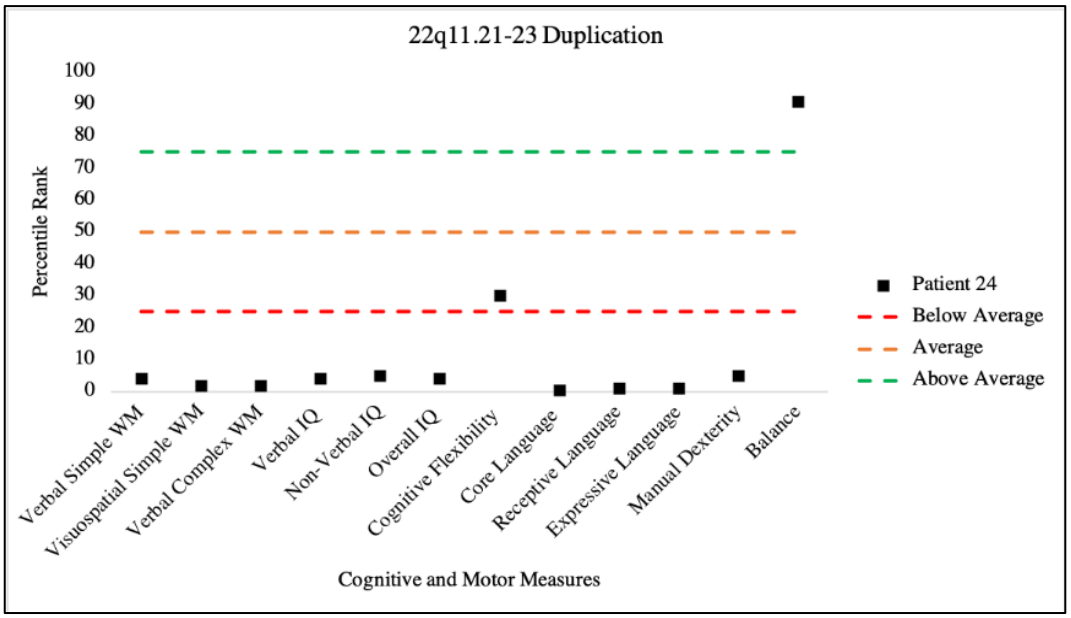


**Figure 4.17: Percentile rank performance for Patient 24 on the cognitive and motor measures**

The cytogenetic report suggests the 22q11.2 microduplication syndrome can present a wide phenotype and the learning difficulties in this patient may be consistent with this. Previous literature suggests a heterogenous phenotype, that consists of typical development, mild difficulties (e.g. learning difficulties) and severe health complications (Ensenauer et al, 2003; Yobb et al, 2005; Wentzel et al, 2008).

In relation to the reciprocal deletion, Patient 3 was unable to partake in the cognitive and motor assessments due to significant learning difficulties. Their cytogenetic report details a genotype of a 22q11.2 deletion and a phenotype that aligns with DiGeorge syndrome. This participant presented difficulties on all behavioural measures (7/7) which aligns with previous reports of individuals with this CNV (Kates, Tang, Antshel & Fremont, 2015; Ousley et al, 2007; Reichenberg, Mill & MacCabe, 2009).

In summary, in relation to the single case explorations of children with a CNV that situates in an NDD loci, it is clear that children present a complex phenotypical profile. CNVs can lead to a range of outcomes as the genetic variance may impact carriers at greater or lesser degrees which may result in children presenting domain-general difficulties, or profiles consisting of relative strengths and weaknesses. A key feature of all of the cytogenetic reports, is that the CNV is associated with a broad phenotypic phenotype which makes it challenging to define a clear distinct phenotype based on specific CNV loci, as found in the present section. The following section will explore how these profiles compare to those without a neurodevelopmental CNV.

### 4.4.3 Group analysis – findings and discussion

The sections to follow describe the cognitive, motor and behavioural data from children with a CNV at an NDD loci (NDD-CNV) in comparison to those without (Non-NDD).

#### 4.4.3.1 Intellectual functioning

In relation to Table 4.22, the group averages were similar, extending between -1 to -1.5 SDs below the mean. In line with the WASI-2 qualitative classifications, both groups situated in the "low average" classification (scores 80-89) for verbal IQ (VCI) and there were no significant differences between the performance of children with an NDD loci CNV and children without (W= 45.00, p=1.00, BF=0.410). Secondly, both groups fell into "borderline" classification for non-verbal IQ (PRI) and there were no significant differences between the NDD and Non-NDD group (W=43.50, p=.905, BF=0.423). Finally, overall intellectual functioning (FSIQ) situated in the "low average" range (similar to VCI) with no significant differences (W=42.50, p=.843, BF=0.416).

**Table 4.22: WASI-2 performance of the NDD-CNV loci & Non-NDD CNV group**

| WASI-2 Composite | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Verbal IQ (VCI) | 13 | 85.15 | 15.42 | -0.99 | 7 | 85.14 | 11.88 | -0.99 |
| Non-verbal IQ (PRI) | 13 | 77.54 | 12.37 | -1.50 | 7 | 79.57 | 17.64 | -1.36 |
| Overall IQ (FSIQ) | 13 | 79.54 | 13.16 | -1.36 | 7 | 80.86 | 15.32 | -1.28 |

The distribution of percentile ranks for the NDD (n=13) and Non-NDD group (n=7) (Figure 4.18) show the majority ranked below average. In the NDD group, only one patient was consistently average (Patient 4) with VCI in the above average range. Six children gained a score that situated in the average range, with the majority scoring relatively better on the VCI measure. Of these 6 children, 5 situated in the average on one measure (Patient: 1, 8, 16, 20, 23) with the remaining child for two measures (Patient 21). The remaining 6/12 children presented consistently low intellectual functioning (score <25). Despite the small sample size, the majority of the Non-NDD group performed below average (5/7) with only 2 children (Patient: 6, 15) in the average range.

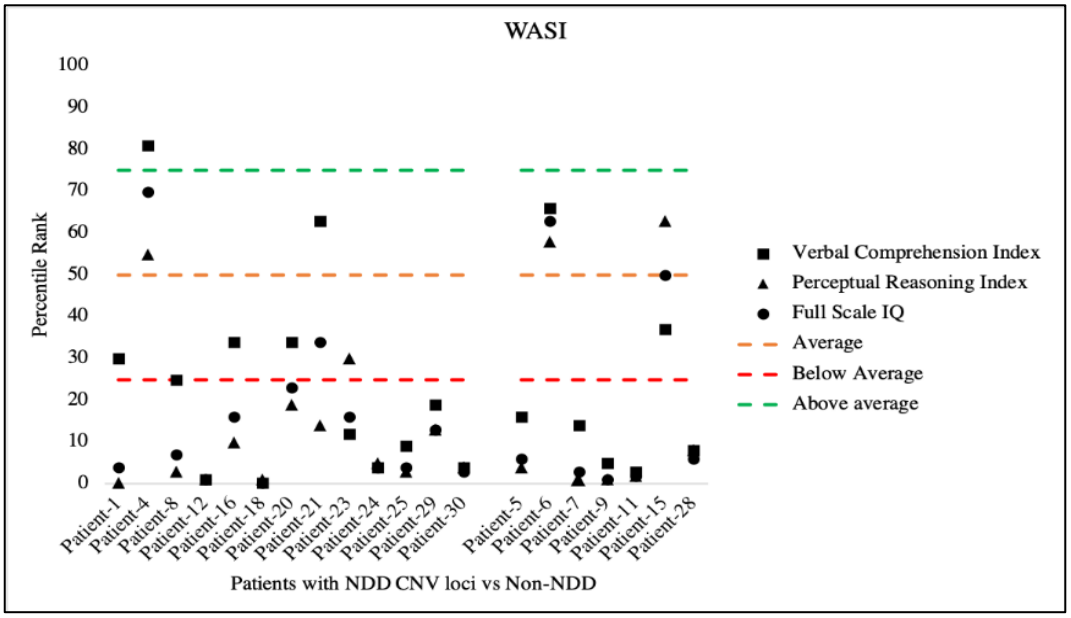


**Figure 4.18: WASI-2 percentile rank distributions of the NDD-CNV group & Non-NDD group**

### 4.4.3.2 Working Memory

The overall group mean for the WM assessments are presented below in Table 4.23. The row titled 'exclusions' excludes the participants who did not obtain a standard score on

this assessment. The missing data on the FDR and block recall were due to participants obtaining a score so low that a standard score was not available in the WMTB-C. There were 5 children who found the BDR too challenging to complete who were all from the NDD group. Table 4.24 presents the data with these participants given a score of 0, where the performance of the NDD group extends more than 2.5 SDs below the mean.

**Table 4.23: WMTB-C exclusions data of the NDD-CNV & Non-NDD CNV group**

| WMTB-C Exclusions | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Verbal Simple (FDR) | 11 | 81.91 | 16.53 | -1.21 | 7 | 93.14 | 11.65 | -0.46 |
| VS Simple (Block Recall) | 10 | 78.70 | 21.62 | -1.42 | 6 | 75.00 | 16.55 | -1.67 |
| Verbal Complex (BDR) | 8 | 82.13 | 17.62 | -1.19 | 7 | 83.71 | 14.58 | -1.09 |

**Table 4.24: WMTB-C inclusions data of the NDD-CNV & Non-NDD CNV group**

| WMTB-C Inclusions | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Verbal Simple (FDR) | 13 | 69.31 | 34.26 | -2.05 | 7 | 93.14 | 11.65 | -0.46 |
| VS Simple (Block Recall) | 13 | 60.54 | 39.26 | -2.63 | 7 | 64.29 | 32.12 | -2.38 |
| Verbal Complex (BDR) | 13 | 50.54 | 43.71 | -3.30 | 7 | 83.71 | 14.58 | -1.09 |

Scores that extend 1 SD below the mean suggest “mild” impairment, whilst scores more than 1.33 SD represent “moderate to severe” impairment (Gathercole & Alloway, 2006). Both groups fell below average across the majority of measures. Firstly, for verbal simple WM (FDR task) the NDD group presented “mild impairments”, although there were no significant differences in comparison to the non-NDD group (W=53.00, p=.203, BF=0.931). Secondly, for visuospatial simple WM performance (Block Recall) the non-NDD group presented “moderate to severe” impairments and the NDD group presented mild difficulties, however these differences were non-significant (W=23.50, p=.511, BF=0.495). Finally, both groups presented “mild” difficulties in verbal complex (BDR) and there was no difference between the performance of the NDD and non-NDD group (W=31.50, p=.728, BF=0.442 – based on exclusions). There are differences in standard scores on the FDR and BDR but given the small sample size and large standard deviation this may result in challenges finding a significant effect between groups.

The percentile rank performances of the groups are presented in Figure 4.19. The majority of the NDD group (8/13) presented domain general WM difficulties and scored below average (<25) across all 3 tasks. Three children gained a score for the FDR task which situated in the average range (Patient: 1,16, 20) and 2 children gained a score which situated in the above average range (Patient: 4, 21) in contrast to none of the children from the Non-NDD group. The majority (6/7) scored in the average range for the FDR task with 4 children gaining situating in the average range for one measure (Patient: 5, 7, 11, 28) whilst 2 children scored for two measures (Patient: 6, 15).

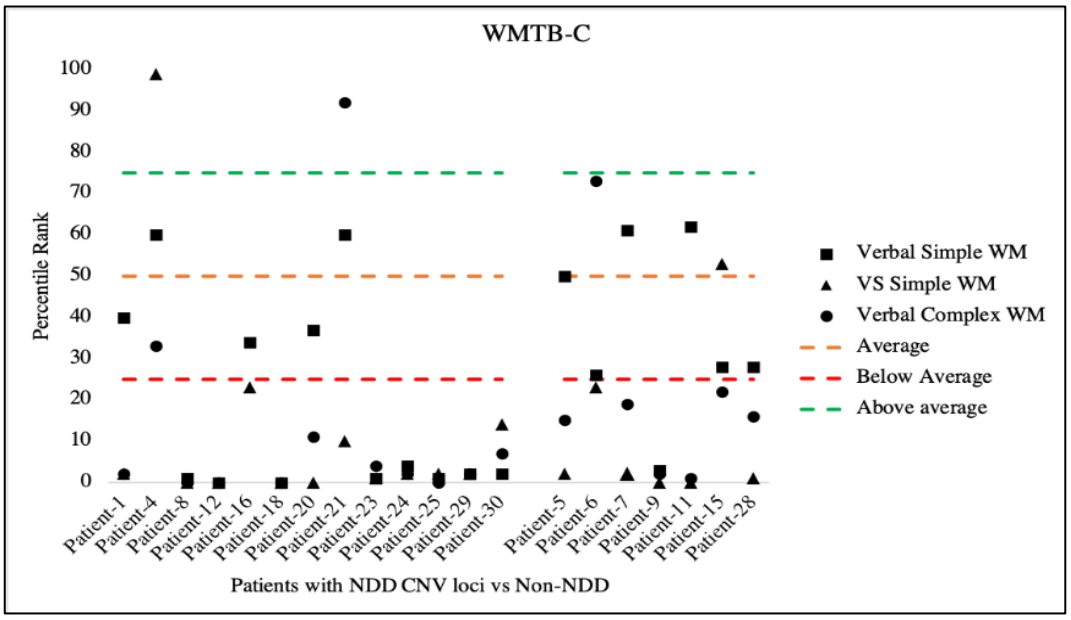


**Figure 4.19: WMTB-C percentile rank distributions of the NDD-CNV & Non-NDD group**

#### 4.4.3.3 Cognitive flexibility

In relation to the WCST, all 7 children in the Non-NDD group managed to complete the task. This contrasted to 4 children in the NDD group who found this too challenging to understand. When these participants were excluded from the descriptive analysis (Table 4.25) the average score was comparable to the Non-NDD group and there were no significant differences found in performance between the NDD and non-NDD group (W=31.00, p=1.00, BF=0.430). When assigning a score of 0 (Table 4.26) the NDD group situated considerably lower than the non-NDD group who were close to average.

**Table 4.25: WCST exclusions data of the NDD-CNV & Non-NDD CNV group**

| WCST Exclusions | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| | 9 | 85.67 | 11.57 | -0.96 | 7 | 85.86 | 14.59 | -0.94 |

**Table 4.26: WCST inclusions data of the NDD-CNV & Non-NDD CNV group**

| WCST Inclusions | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| | 13 | 59.31 | 42.22 | -2.71 | 7 | 85.86 | 14.59 | -0.94 |

Exploring the percentile rank performance in Figure 4.20, the majority of the NDD group (7/9) ranked in the average range. In contrast, the findings were mixed for the Non-NDD group as all children managed to partake, but the majority 4/7 situated below average.

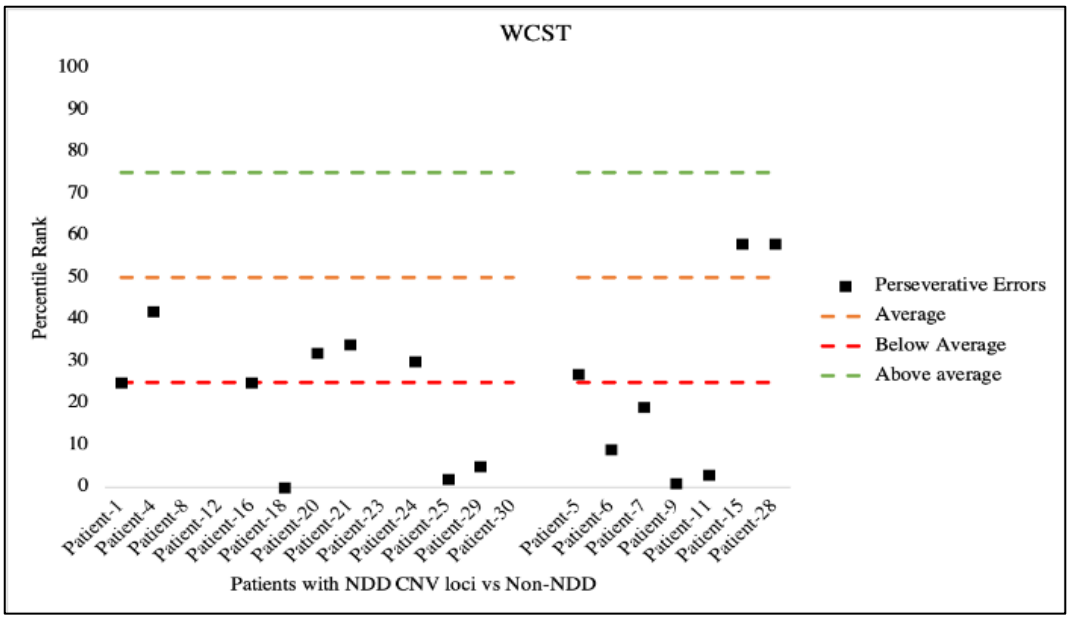


**Figure 4.20: WCST percentile rank distributions of the NDD-CNV group & Non-NDD group**

### 4.4.3.4 Language

The group averages for overall language functioning (CLS), receptive and expressive language are presented in Table 4.27. In line with the recommendations from the CELF-4, both groups show signs of language difficulties (standard score of 85 or lower). Although language functioning of the NDD group extended more than 2SD below the mean (very low range/severe classification) and the non-NDD fell 1SD below the mean

(borderline classification) there were no significant difference between the groups (W=69.50, p=.062, BF=1.651). Receptive language was lowest for both groups and would also warrant further attention (i.e. below 85). The average score for the NDD group was lower than the Non-NDD but there was no significant difference found (W=63.50, p=.165, BF=1.112). The findings are similar for the expressive language measure, as the NDD group presented poorer average scores than the non-NDD group, but these differences were also not significant (W=68.50, p=.074, BF=1.420).

**Table 4.27: CELF-4 performance of the NDD-CNV loci & Non-NDD CNV group**

| CELF-4 | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Core language (CLS) | 13 | 65.15 | 20.33 | -2.32 | 7 | 84.71 | 19.68 | -1.02 |
| Receptive Language (RLI) | 13 | 65.92 | 14.93 | -2.27 | 7 | 79.71 | 20.36 | -1.35 |
| Expressive Language (ELI) | 13 | 69.31 | 20.50 | -2.05 | 7 | 87.57 | 18.85 | -0.83 |

The percentile rank performance across all 3 measures are presented in Figure 4.21. The majority of the children in the NDD group (10/13) presented domain general language difficulties as they scored below average across all 3 measures. Three children gained a score that situated in the average range with 1 child ranking in the average range for one measure (Patient 4) and two children for 2 measures (Patient 20 and 21). None of the children scored in the above average range. This contrasted to the findings for the Non-NDD group as one child showed consistently above average language performance (Patient 6). Two children gained scores in the average range (Patient: 7 and 15) whilst 4/7 showed consistently poor performance across all measures (<25).

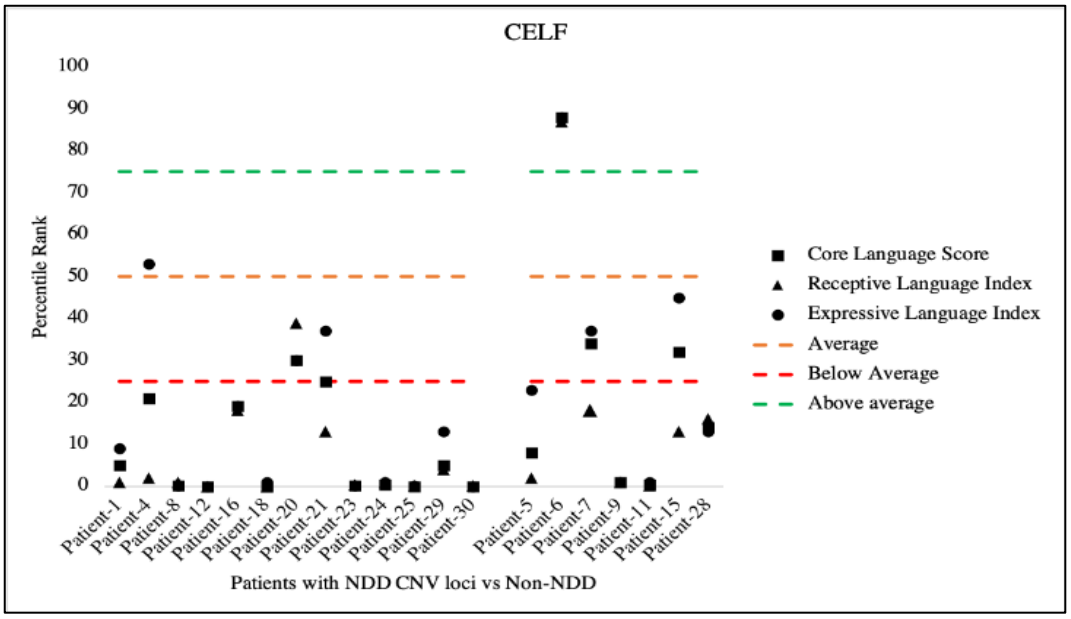


**Figure 4.21: CELF-4 percentile rank distributions of the NDD-CNV & Non-NDD group**

#### 4.4.3.5 Motor functioning

In relation to the MABC-2 (Table 4.28) across both groups, performance was worse for the Manual Dexterity (MD) component. Performance of NDD group fell more than 2SDs below the mean, suggesting "significant" difficulties (Henderson, Sugden & Barnett, 2007). The Non-NDD group average fell more than 1SD below the mean, which would indicate these children are "at risk". There was a significant difference found between the performance of the NDD and non-NDD group (W=71.00, p=.040, BF=6.215). The BF suggests there is 'moderate' evidence in favour of there being a difference between the MD ability across the groups. Findings for the balance measure extended 1SD below the mean for the NDD group suggesting they are at "at risk" in contrast to no difficulties in the non-NDD group but this was non-significant (W=62.50, p=.185, BF=0.836).

**Table 4.28: MABC-2 performance of the NDD-CNV loci & Non-NDD CNV group**

| MABC-2 | NDD loci | | | | Non-NDD loci | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Manual Dexterity | 13 | 2.54 | 1.20 | -2.49 | 7 | 5.29 | 2.93 | -1.57 |
| Balance | 13 | 5.92 | 4.55 | -1.36 | 7 | 9.00 | 4.40 | -0.33 |

The distribution of scores based on percentile rank classifications are presented in Figure 4.22. The majority (7/13) of the NDD group presented domain general motor difficulties

as they scored below the 5th percentile across both the MD and balance components. The remaining 6 children presented a domain specific profile consisting of relatively intact balance skills (>15) in comparison to MD difficulties (≥5), of this one child (Patient 23) was at risk of balance difficulties. In comparison, in the Non-NDD group only 2 children showed clear movement difficulties. This consistent of only one child presenting domain general difficulties (Patient 9) with the other being at risk of fine motor difficulties (Patient 28). Two children also presented a domain specific profile of relatively intact gross motor functioning but with fine motor difficulties (Patient: 11 and 15). Finally, 3 children presented no signs of difficulty across both measures (Patient 5, 6, 7).

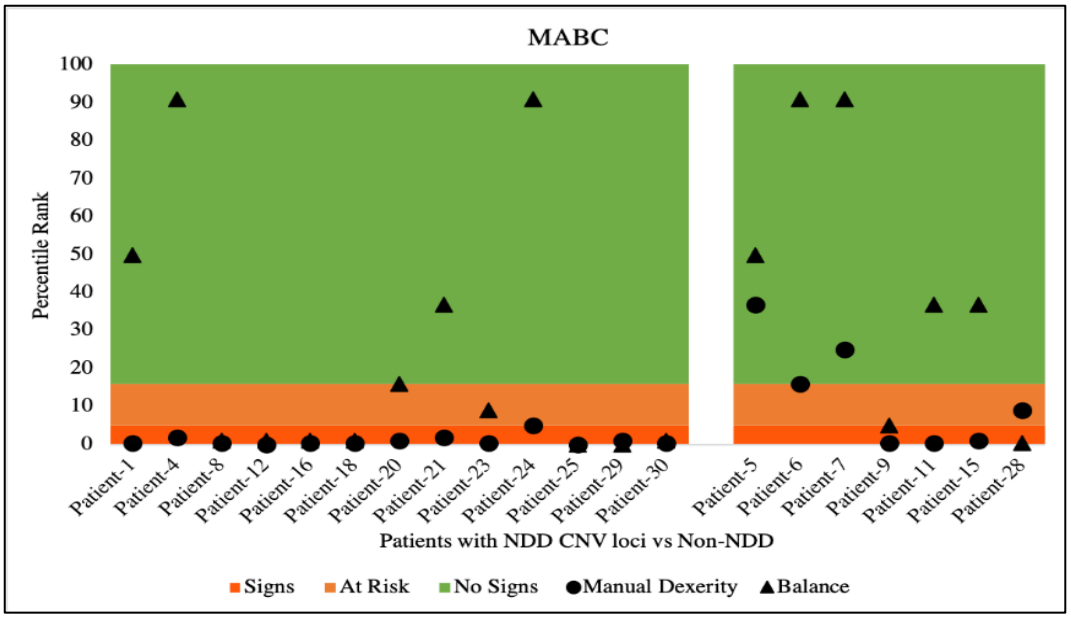


**Figure 4.22: MABC-2 percentile rank distributions of the NDD-CNV group & Non-NDD group**

### 4.4.3.6 Behavioural symptomology

The following data is based on 5 questionnaires with a total of 8 behavioural domains, see Table 4.29 which presents the mean and SD where possible.

**Table 4.29: Average & frequency of behavioural symptoms of the NDD & Non-NDD CNV group**

| Questionnaire | Patients with NDD loci CNV | | | | Patients with Non-NDD loci CNV | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | S. D | N presenting signs (%) | n | Mean | S. D | N presenting signs (%) |
| DCDQ | 14 | 33.43 | 12.01 | 13 (92.86) | 7 | 40.14 | 11.39 | 7 (100) |
| SCQ | 14 | 20.14 | 8.98 | 11 (78.57) | 7 | 14.57 | 10.61 | 4 (57.14) |
| DBC | 14 | 77 | 37.04 | 12 (85.71) | 7 | 56.43 | 12.57 | 5 (71.43) |
| SDQ | 14 | 24.00 | 7.85 | 10 (71.43) | 7 | 21.71 | 6.60 | 4 (57.14) |
| VADRS(ADHD) | 14 | | | 10 (71.43) | 7 | | | 4 (57.14) |
| VADRS (ODD) | 14 | | | 8 (57.14) | 7 | | | 5 (71.43) |
| VADRS (CD) | 14 | | | 4 (28.57) | 7 | | | 1 (14.29) |
| VADRS (A/D) | 14 | | | 5 (35.71) | 7 | | | 3 (42.86) |

The average score for the DCDQ fell over two standard deviations below the mean (M=61.79, SD=10.21) for the NDD group (-2.78) and Non-NDD group (-2.12) and the majority of patients in each group presented signs of movement difficulties. Secondly, findings from the SCQ show that the NDD group are at risk of ASD symptomology due to an average of 20 which exceeds the cut off score of 15. In contrast the Non-NDD fell below this, but more than 50% still presented signs. In relation to the DBC, the group averages both exceeded the clinical cut off (46 or greater) which could highlight that both groups are at risk of "major emotional and behavioural problems". Findings from the SDQ show the both groups averaged in the "very high" category (total difficulties score between 20-40) which can suggest this group are at risk of psychological difficulties with more than 50% of each sample presenting high or very high difficulties. Finally, based on the VADRS, attentional difficulties (ADHD symptomology) were evident in more than 50% of patients in each group. Despite the relatively small sample size, disruptive behaviours (i.e. conduct disorder) and emotional difficulties (i.e. anxiety/depression) were slightly higher in the Non-NDD group than the NDD group.

In relation to Figure 4.23, all children showed signs of one or more behavioural difficulty that was typical of a neurodevelopmental or psychological disorder. Over half of the children in the NDD group (8/14, 57%) presented behavioural difficulties on over 50% of the questionnaire measures in contrast to the Non-NDD group (3/7, 42%).

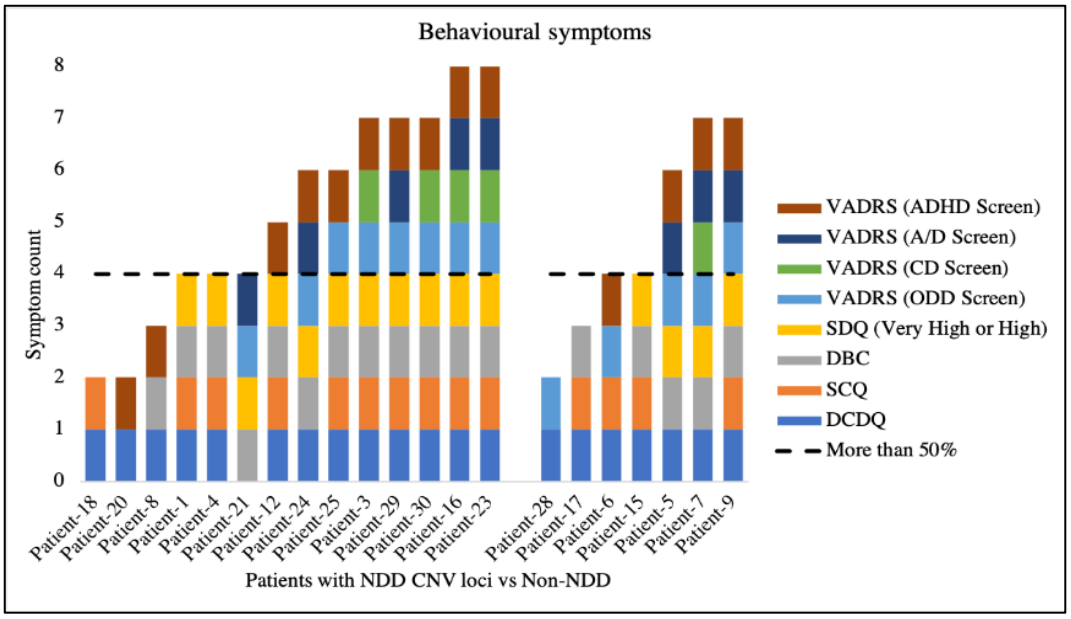


**Figure 4.23: Number of behavioural symptoms per patient in the NDD & Non-NDD group.**

### 4.4.4 General discussion of neurodevelopmental CNV loci and cognitive, motor and behavioural outcomes.

This section explored the profiles of children who have a CNV in a known NDD susceptibility loci in contrast to those without.

In relation to the single case work, it appears that children with a CNV at an NDD loci present diverse cognitive, motor and behavioural profiles. Key commonalities in the cytogenetic reports of patients (Table 4.20 and 21) is that the CNV locus is associated with a broad phenotypical spectrum, the CNV is 'likely' to be contributing to the phenotype, or there is limited evidence surrounding the CNV's clinical significance. The extent of difficulties varied based on the location, as some presented domain general difficulties whilst some presented a domain specific profile consisting of relative strengths and weaknesses. Carriers of the CNV in question are at risk of a range of difficulties that don't always meet major diagnostic criteria or the cluster of symptoms that form a syndrome which makes it challenging to understand genotype-phenotype relationship. In relation to the present work, none of the children presented consistent performance in the average and/or above average range and none of the children with a CNV at the same loci shared the same phenotypical profiles. In relation to the genetics literature, reference was made to the specific loci and a major factor was variable

expressivity and penetrance. Often the CNV literature reviewed suggests each CNV is associated with a heterogenous profile and more specific phenotyping is required to understand the shared symptomology associated with that variant.

In relation to the group comparisons, performance on the cognitive measure for both groups fell below average, with the extent of this varying by group. Despite these differences and the unequal sample sizes there were no significant differences found between both groups on all measures. For overall intellectual functioning, both groups presented similar average scores, and both situated in the "low range". Alongside this, across the majority of WM tasks, performance fell 1SD below the mean, suggesting mild impairment. The distribution of percentile rank performance was mixed, with only one child gaining consistent scores in the average range. Similar difficulties were found for cognitive flexibility as performance of both groups fell one SD below the mean. Finally, on the language assessments, the average score of the NDD group was lower than the Non-NDD group for overall language functioning, but both groups still presented a score that would risk language difficulties and require further assessment. Overall, the Bayes factors were below or close to 1 for all comparisons, which suggest anecdotal/weak evidence for any differences between groups. However, there were slight performance discrepancies on some tasks which may be detectable in larger sample sizes.

In relation to the motor assessment, both groups presented below average performance, but the groups differed by the extent of this. There was a significant difference found between groups for manual dexterity performance. The NDD group average situated in the "significant" difficulty classification, whilst the other group presented an "at risk" profile. For balance, only the NDD group was at risk. Finally, findings from the behavioural measures show each child is at risk of at least one behavioural difficulty with some children meeting the symptomology for a multiple number of behavioural difficulties across both groups. Of interest here is the different findings on the objective motor measure (MABC-2) and the subjective parental report (DCDQ) of children's motor functioning. A higher number of children presented movement difficulties as described by parents. Parental reports are a useful measure as they provide a measure of the child's day to day functioning, but these risk a responding bias. The questionnaires may serve as an opportunity to share their experiences but individuals from certain backgrounds (e.g. low SES, those with children with difficulties) may be more likely to utilise as a means for support (Hawk et al, 2013). For example, families supporting children with

intellectual disability are more likely to be socially disadvantaged and mothers are likely to experience increased social and psychological implications (Emerson, 2003). In relation to children with genetic syndromes, Hodapp, Dykens and Masino (1997) found a high level of parent stress in families of children with Prader-Willi Syndrome. Similarly, in infants, children and adolescents with 22q11.2 DS, primary caregivers were found to have increased levels of stress. These findings may highlight the potential factors implicated within the subjective and objective measures.

In summary the findings suggest that both groups are at risk of developmental difficulties but children with a CNV in a neurodevelopmental locus are at a slightly higher risk than those without. A significant difference in fine motor competence was identified, but significant differences in cognitive ability are possibly identifiable with a larger sample size. Overall all children presented atypical development and these cognitive, motor and behavioural difficulties may impact how well these children access and engage with the school curriculum, interact with others and the world. Despite the relatively small group sample sizes, these findings may also highlight the implications and impact of having a less common/rare CNV (or in general) in comparison to a CNV encompassing a commonly investigated loci/syndrome. These findings are similar to Chawner et al (2019), who identified a range of difficulties across carriers of NDD-CNV loci which were not limited to discrete phenotypes based on specific CNV loci. This complex genotype-phenotype relationship may be due to shared biological processes which subsequently manifest as a general impairments and comorbidities in individuals with variance at different genomic loci. The findings from the present single-case and group-based comparison suggest it is challenging to describe a distinctive phenotypical profile based on specific loci and having a CNV in 'general' places children at risk of developmental difficulties irrespective of the specific location or associated syndrome.

## 4.5 Exploring the cognitive, motor and behavioural development of: children with a Copy Number Variant by the type of variance (deletion and duplication)

### 4.5.1 Background and sample

Copy number variance can result in a loss (deletion) or gain (duplication) to genetic material. As a result of these reciprocal CNVs, there may be implications for development

due to gene dosage sensitivity. Genes code for proteins which are implicated in various biological processes. CNVs alter the number of genes within that region of variance which may subsequently impact gene expression, and the resulting cellular functions which are sensitive to this imbalance (Coe, Girirajan & Eichler, 2012; Harvard et al, 2011; Gamazon & Stranger, 2015; Thapar & Cooper, 2013). In the present work, single-gene analysis has not been conducted, but changes in gene dosage (i.e. loss or gain) may be of importance for investigating phenotypical outcomes. As there is only one copy of the gene, deletions may negatively affect development, while the implications of duplications are not always clear (Watson, Marques-Bonet, Sharp & Mefford, 2014). There is some evidence that suggests deletions have severe phenotypical outcomes, while duplications are milder which may go undiagnosed. Some processes rely on specific dosage sensitive processes, and any dosage imbalances may then lead to abnormal levels of expression contributing to atypical brain development with resulting cognitive disorder (Morrow, 2010). While, in line with Golzio and Katsanis (2013) deletions or duplications to the same region can have mirrored (opposite), identical, overlapping or unique effects.

It is a challenge to quantify the impact of genetic variance on phenotypical outcomes due to the complexity of this relationship. In some cases, the outcomes for deletions and duplications are clearly different. For example, Abbas, Cox, Smith and Butler (2016) report a 14-year-old girl with a 7q11.23 duplication who presented speech delay and social anxiety. The authors suggest this profile contrasts to the reciprocal CNV (deletion – Williams Syndrome) which is associated with a lack of stranger anxiety and relatively intact expressive language. In contrast, the majority of work (at specific CNV loci) highlight a complex relationship of overlapping phenotypes for deletion and duplications.

In relation to the 16p11.2 location, Hippolyte et al (2016) investigated the cognitive abilities of children and adults (4.8-59 years). For phonology, written language and vocabulary the deletion group performed worse than the duplication group, but were similar for IQ (duplication group n=44, FSIQ=75 and deletion group n=62, FSIQ=72), and both groups were lower in comparison to family controls (n=71, FSIQ=98). This profile was found to extend to psychological domains as Niarchou et al (2019) found both types of variance (to 16p11.2) was associated with an increased risk of psychiatric disorder. They a found slight variance to the frequency of ADHD, but no differences in ASD prevalence. Similarly, Shinawi et al (2010) investigated the phenotypical characteristics of individuals with a 16p11.2 deletion (n=27) and duplication (n=10). Both

groups presented similar difficulties of speech/language delay, behavioural problems, cognitive impairment and motor delay, but they differed in head size and the occurrence of psychological difficulties. The deletion group showed signs of macrencephaly (larger brain circumference) and autism, while the duplication group presented higher rates of microencephaly and ADHD. This profile of contrasting head circumferences and a broad phenotypic spectrum consisting of impaired motor functioning, developmental delay, borderline cognitive functioning and neuropsychiatric difficulties has also been reported for individuals with CNVs to 1q21.1 (Bernier et al, 2016; Brunetti-Pierri et al, 2008).

The genotype and phenotype relationship is complex as individuals may present similar domain-general difficulties, but with domain-specific features. For example, Rasmussen et al (2016) found those with a 17q12 duplication group presented a broad phenotypic spectrum, in contrast to more shared characteristics in deletion carriers. Similarly, for 16p13.11, Nagamani et al (2011) found both within and between group differences. Both groups presented cognitive impairment and behavioural abnormalities, while some individuals with the duplication had skeletal and cardiac malformations and some with the deletion had developmental delay, seizures and microcephaly.

In summary, previous work demonstrates that there is a complex relationship between the type of variance and the associated phenotypical outcomes for the same location. At present the majority of work has focused on specific CNV loci, but it was of interest to explore whether the type of genetic variance affects developmental outcomes to a greater or lesser extent. This section is based on children with a deletion (n=10) and a duplication (n=11), see Table 4.30 and 4.31 respectively. The data are based on the cognitive and motor assessments (n=9 deletion group and n=10 duplication group) and behavioural measures (n=9 deletion group and n=11 duplication group). The discrepancies in the data obtained are due to the same reasons as previously discussed (see Chapter 3). Alongside this, one patient was excluded from this analysis as they had 2 CNVs (deletion and a duplication) – see section 4.7 for exploration of this case.

**Table 4.30: Clinical characteristics of patients with a CNV deletion**

| Patient | Age | CNV | Type | Clinical summary from cytogenetic report |
|---|---|---|---|---|
| 3 | 8 | 22q11.21 | Del | Developmental delay and various health difficulties. Phenotype and genotype align with DiGeorge syndrome. |
| 5 | 10 | 20 p12.3-p12.2 | Del | Neuro-behavioural problems. Emerging evidence of PLCB1 gene to neurobehavioral disorders, but at present not conclusive. |
| 6 | 14 | 20 p12.3-p12.2 | Del | Autistic features, behavioural problems, macrocephaly. Emerging evidence of PLCB1 gene to neurobehavioral disorders, but at present not conclusive. |
| 7 | 13 | 20p12.3-p12.2 | Del | Neuro-behavioural problems. Emerging evidence of PLCB1 gene to neurobehavioral disorders, but at present not conclusive. |
| 11 | 11 | 12p13.32-12p13.31 | Del | Developmental delay. Although limited data on the phenotypic/genotypic association for this region the large size and high gene content of imbalance mean it is possibly contributing to patient's phenotype. |
| 12 | 8 | 7q11.23 | Del | Williams syndrome diagnosis |
| 16 | 7 | 16p11.2 | Del | Autistic trait, emerging learning difficulties, TIC disorder. Del lies in the 16p11.2 BP2-BP3 and region predisposes to DD and ID therefore possible contribution towards phenotype as consistent with the learning difficulties in patient. |
| 20 | 15 | 16p12.2 | Del | Joint hypermobility and motor delay. CNV lies within 16p12.2 microdeletion risk locus for neurodevelopmental disease (broad phenotypic spectrum). CNV likely cause of patient’s phenotype. |
| 29 | 9 | 16p12.2 | Del | Learning difficulties and social communication difficulties. CNV lies within 16p12.2 microdeletion risk locus for neurodevelopmental disease (broad phenotypic spectrum). CNV likely cause of patient’s phenotype as consistent features reported for this deletion. |

| | | | | |
|---|---|---|---|---|
| 30 | 7 | 16p11.2 | Del | General developmental delay. 16p11.2 microdeletion syndrome. CNV likely cause of phenotype due to general developmental delay. |

**Table 4.31: Clinical characteristics of patients with a CNV duplication**

| Patient | Age | CNV | Type | Clinical summary from cytogenetic report |
|---|---|---|---|---|
| 1 | 10 | 16p11.2 | Dup | Social communication difficulty, learning problems, CNV within SL for microduplication syndrome. Dup linked to variable phenotype and variable penetrance – consistent with patient and likely cause of phenotype. |
| 4 | 10 | 15q13.3 | Dup | Unexplained mild learning difficulties, ?ASD, region of variable penetrance. Tentative evidence of CHRNA7 gene as risk factor for neurobehavioral disorders. |
| 8 | 7 | 16p12.2-11.2 | Dup | Developmental delay (gross motor disproportionally delayed) CNV consistent with16p11.2-16p12.2 microduplication locus associated with variable phenotype. CNV is likely cause of patient phenotype. |
| 15 | 10 | 17p12 | Dup | Statemented, associated health difficulties and clinical features of Hereditary Motor and Sensory Neuropathies. Charcot-Marie-Tooth hereditary (Muscle weakness, mild-moderate sensory loss, high arched feet). Features in this sample are consistent with those for duplication of this region, therefore it is likely contributing to phenotype. |
| 17 | 12 | 3q26.1-3q26.2 | Dup | Developmental Delay, auditory processing disorder, dysplastic hip. Due to size and gene content of imbalance therefore it is likely to be the cause of patients clinical features. |
| 18 | 13 | 15q11.2 | Dup | Coordination difficulties, learning difficulties, speech language difficulties and SEN statement. Lies within the 15q11.2 SL which is associated with a broad phenotypic spectrum. The coordination difficulties and speech difficulties seen in patient have previously been reported in patients with a duplication to this region, therefore it is possible this duplication may be contributing to phenotype. |

| | | | | |
|---|---|---|---|---|
| 21 | 10 | 16p11.2 | Dup | Behaviour problems and clinical features. CNV lies within 16p11.2 microduplication SL. The behaviour problems and mild dysmorphism evident in patient align with duplications of this region, so it is possible imbalance is contributing to phenotype. |
| 23 | 9 | 1q21.1-1q21.2 | Dup | Developmental delay, pathogenic, lies within the 1q21.1 microduplication SL which is associated with a broad phenotypic spectrum. The clinical features in this patient are consistent with those associated with duplication of this region so it is probable that the duplication is contributing to phenotype. |
| 24 | 12 | 22q11.21-23 | Dup | Learning difficulties, CNV presents a varied phenotype situates in a neurodevelopmental susceptibility loci. CNV likely cause of phenotype as LD key feature. |
| 25 | 7 | 15q13.3 | Dup | Undergoing ASD assessment, speech delay, repetitive hand movements (at present limited literature surrounding the phenotypical outcomes associated, tentative evidence of CHRNA7 gene implicated in neuro-behavioural disorders. |
| 28 | 12 | 17p12 | Dup | Duplication associated with Charcot-Marie-Tooth hereditary (Muscle weakness, mild-moderate sensory loss). Patient presents some early features consistent with Hereditary Motor and Sensory Neuropathies. |

### 4.5.2 Findings and discussion

#### 4.5.2.1 Intellectual functioning

In relation to IQ, both groups performed “below average” on all but one measure (see Table 4.32). For verbal IQ (VCI) both groups fell into the “low average” classification (Wechsler, 2011) and there were no significant differences between groups ($t(17)=-0.345$, $p=.728$, BF =0.423). For non-verbal IQ, both groups scored 1SD below average, but the deletion group was slightly more impaired. The deletion group situated in the “borderline” classification while the duplication group was in the “low average” classification but this difference was non-significant ($t(17)=-0.338$, $p=.740$, BF= 0.421).

The finding were similar for overall functioning (FSIQ) as both groups situated in the "borderline" range with no significant differences (t(17)=-0.435, p=.669, BF= 0.433).

**Table 4.32: WASI-2 performance of the deletion & duplication group**

| WASI-2 | Deletion group | | | | Duplication group | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | RTM | N | Mean | SD | RTM |
| Verbal IQ (VCI) | 9 | 84.44 | 12.84 | -1.04 | 10 | 86.80 | 15.80 | -0.88 |
| Non-verbal IQ (PRI) | 9 | 77.89 | 12.27 | -1.47 | 10 | 80.10 | 15.81 | -1.33 |
| Overall IQ (FSIQ) | 9 | 79.22 | 12.82 | -1.39 | 10 | 82.00 | 14.78 | -1.20 |

In relation to the percentile rank distributions (see Figure 4.24) the majority of children in both groups performed within the below average range and none of the children consistently performed above average. In the deletion group, only one child (Patient 6) presented clear average functioning, while the majority of children situated below average (6/9). A smaller number (2/9) presented a mixed profile, ranking in the average range for verbal IQ (Patient: 16, 20). The findings were similar for the duplication group, as 2/10 scored within the average range across tasks, 4/10 below average and 4/10 presented a mixed profile. Of these 4, 3 had relatively better verbal IQ (Patient: 1, 8, 21).

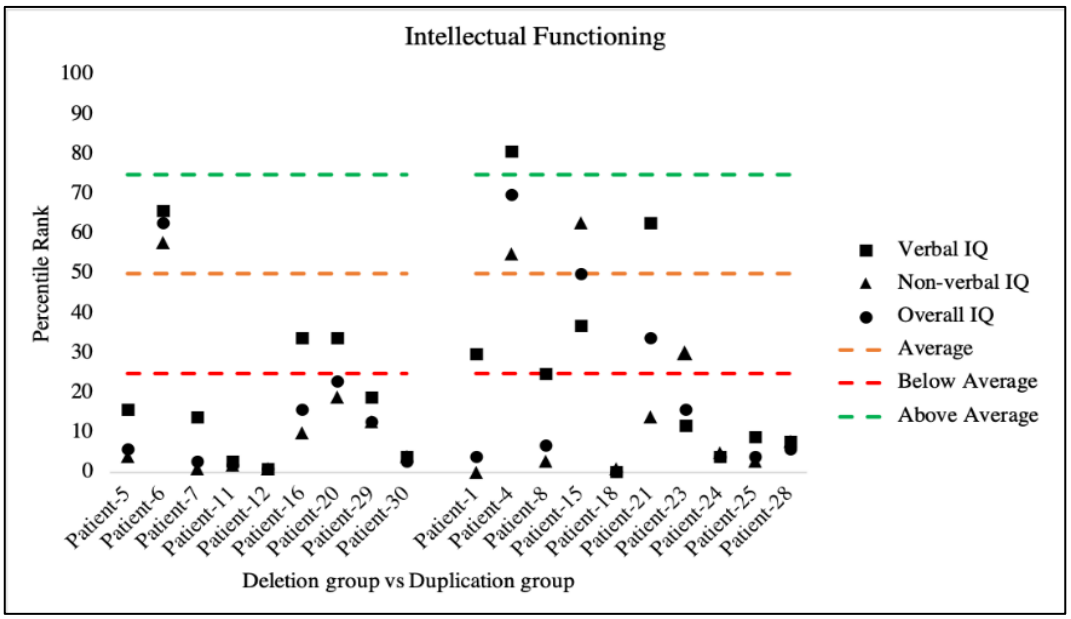


**Figure 4.24: WASI-2 Percentile rank performance of the deletion & duplication group**

#### 4.5.2.2 Working Memory

In relation to the WM tasks, the findings show relative group strengths and weaknesses which largely fall below average- see Table 4.33. On the FDR task, the deletion group performed within the average range while the duplication group fell below average (i.e. mild impairment - Gathercole & Alloway, 2006) but this difference was not significant ($t(15)=0.957$, $p=.354$, $BF=0.572$). For block recall, both groups situated below average, but they differed by severity of WM difficulties. The deletion group presented "moderate to severe" impairments while the duplication group showed "mild" impairments, but this was not significant ($W=28.50$, $p=.751$, $BF=0.539$). Finally for BDR, the deletion group presented "mild" impairment (-1SD below the mean) and the duplication group presented "average" functioning, but this was not significant ($t(12)=-0.459$, $p=.655$, $BF=0.478$).

**Table 4.33: WMTB-C exclusion data of the deletion & duplication group**

| WMTB-C Exclusions | Deletion group | | | | Duplication group | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | SD | RTM |
| Verbal Simple (FDR) | 8 | 91.00 | 13.91 | -0.60 | 9 | 83.78 | 16.82 | -1.08 |
| VS Simple (Block Recall) | 8 | 73.25 | 12.69 | -1.78 | 8 | 81.38 | 24.60 | -1.24 |
| Verbal Complex (BDR) | 7 | 81.86 | 14.44 | -1.21 | 7 | 85.86 | 18.00 | -0.94 |

When considering the inclusions data (those assigned a score of 0 as did not gain a standard score, see Table 4.34) both groups presented "moderate to severe" impairments (-1.33 SDs below mean) across all tasks.

**Table 4.34: WMTB-C inclusion data of the deletion & duplication group**

| WMTB-C Inclusions | Deletion group | | | | Duplication group | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Verbal Simple (FDR) | 9 | 80.89 | 33.01 | -1.27 | 10 | 75.40 | 30.88 | -1.64 |
| VS Simple (Block Recall) | 9 | 65.11 | 27.15 | -2.33 | 10 | 65.10 | 40.59 | -2.33 |
| Verbal Complex (BDR) | 9 | 63.67 | 38.20 | -2.42 | 10 | 60.10 | 44.00 | -2.66 |

In relation to the percentile rank distributions for WM – see Figure 4.25, none of the children performed in the above average for all tasks. One child in the duplication group (Patient 4) consistently scored in the average range across all tasks, but none of the children in the deletion group did. The majority of in the deletion group (6/9) presented

specific profiles of relative strengths and weaknesses. Of these 6 children, 5/6 showed relative strengths in simple verbal WM. In the duplication group 4/10 had a mixed profile, with 2 presenting better simple verbal WM. Finally, the number of children performing below average was similar for the deletion (3/9) and duplication group (4/10).

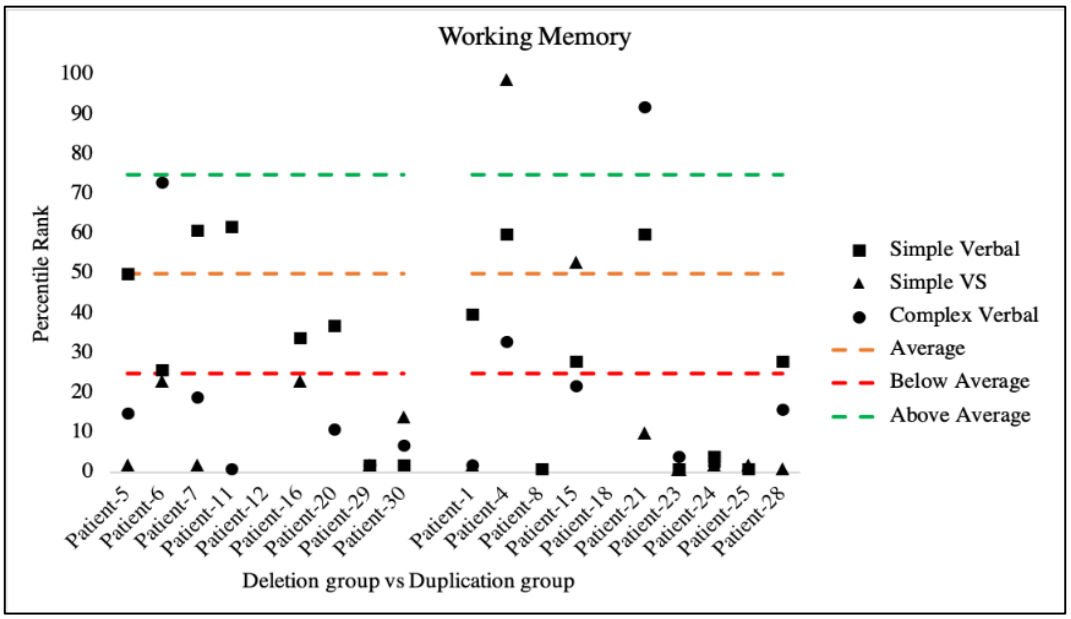


**Figure 4.25: WMTB-C percentile rank performance of the deletion & duplication group**

### 4.5.2.3 Cognitive flexibility

Some children found the WCST too challenging to complete and were excluded from the analysis (Table 4.35). In line with the WCST (Heaton et al, 1993) both groups performed below average, with no significant differences (t(13)=-0.652, p=.526, BF=0.504).

**Table 4.35: WCST exclusion data of the deletion & duplication group**

| WCST Exclusions | Deletion group | | | | Duplication group | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | N | Mean | SD | RTM | N | Mean | SD | RTM |
| | 7 | 85.00 | 7.21 | -1.00 | 8 | 89.00 | 14.72 | -0.73 |

Considering the inclusions data in Table 4.36, the deletion group performed slightly lower situating in the “moderately impaired” range, while the duplication group were “mildly to moderately impaired”.

**Table 4.36: WCST inclusion data of the deletion & duplication group**

| WCST Inclusions | Deletion group | | | | Duplication group | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | N | Mean | SD | RTM | N | Mean | SD | RTM |
| | 9 | 66.11 | 38.0 | -2.26 | 10 | 71.20 | 39.71 | -1.92 |

The distribution of percentile ranks in Figure 4.26 show none of the children placed within the above average range. The majority of the deletion group (6/9) scored below average (including the 2 children who found the task too difficult to complete). In relation to average functioning, there were fewer children in this range in the deletion group (3/9) in comparison to the duplication group (6/9). Considering the WCST classifications, only 1 child from the deletion group scored within the average range (PR=29-67) with the remaining children situating below this. In comparison, there was a higher number of children in the duplication group who had average cognitive flexibility (5/10).

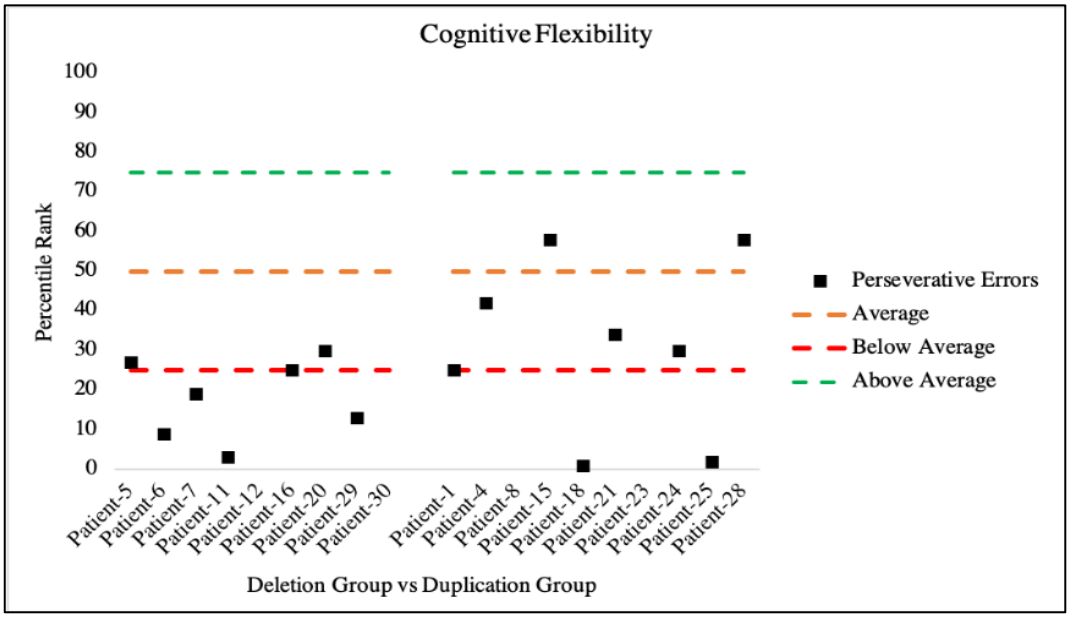


**Figure 4.26: WCST percentile rank performance of the deletion & duplication group**

### 4.5.2.4 Language

Both groups performed below average across all composites and would require monitoring (<85) (Semel & Wiig, 2006) see Table 4.37. Across all measures the deletion group performed slightly better, but these differences were non-significant. For core language, the deletion group situated in the "low range/moderate" classification of language disorder, in contrast to very "low range/severe" functioning for the deletion

group (t(17)=0.743, p=.467, BF=0.491). The classifications were the same for receptive language (t(17)=1.041, p=.312, BF=0.588). Finally, the deletion group situated in the "marginal/borderline/mild" range for expressive language in comparison to "low range/moderate" difficulties in the duplication group (t(17)=0.592, p=.562, BF= 0.457).

**Table 4.37: CELF-4 performance of the deletion & duplication group**

| Composite | Deletion group | | | | Duplication group | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | RTM | N | Mean | SD | RTM |
| Core Language (CLS) | 9 | 76.33 | 25.70 | -1.58 | 10 | 68.60 | 19.53 | -2.09 |
| Receptive Language (RLI) | 9 | 75.78 | 22.31 | -1.61 | 10 | 67.10 | 13.36 | -2.19 |
| Expressive Language (ELI) | 9 | 79.44 | 24.08 | -1.37 | 10 | 73.40 | 20.44 | -1.77 |

In relation to the percentile rank distributions – see Figure 4.27, the majority of both groups (deletion 6/9, 7/10 duplication) performed below average. In deletion group, one child presented consistently above average performance (Patient 6) with 2 children in the average range (Patient: 7, 20). In contrast, none of the children in the duplication group scored consistently in the average range, but 3/10 presented mixed profiles with relatively better expressive language performance (Patient: 4, 15, 21).

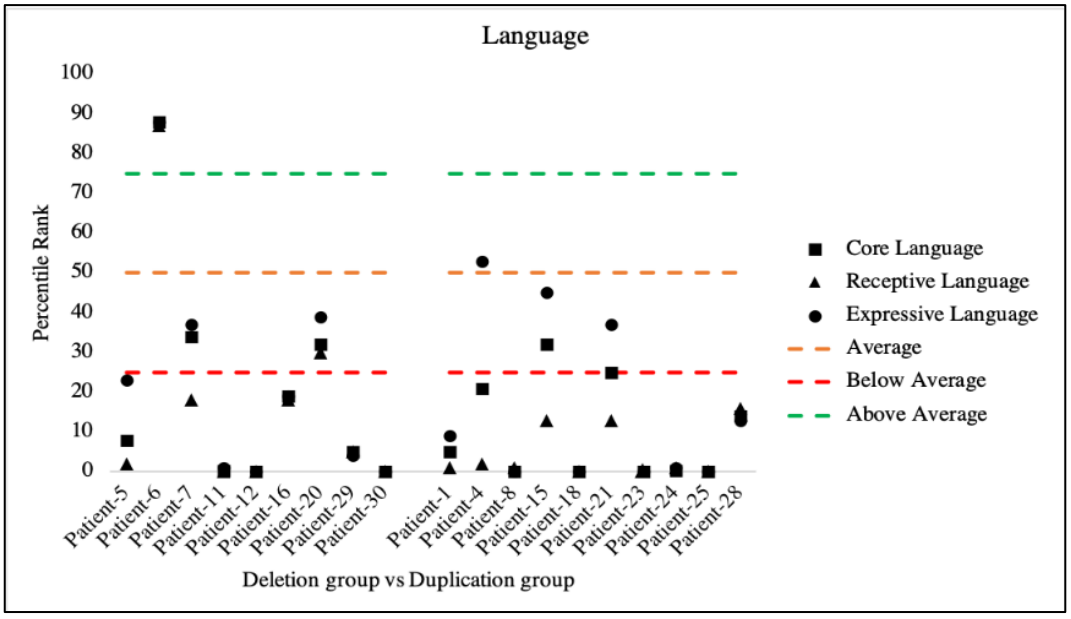


**Figure 4.27: CELF-4 percentile rank performance of the deletion & duplication group**

#### 4.5.2.5 Fine and gross motor functioning

In relation to motor functioning (see Table 4.38) for MD, the duplication group average was inferior, situating -2SDs below the mean indicating that they are in "certain need of help" (Henderson, Sugden & Barnett, 2007). In contrast, the deletion group were "at risk" (-1SD below the mean) but these group differences were not significant (W=50.50, p=.675, BF=0.545). For the balance, both groups were close to 1SD below the mean with no differences in performance (t(17)=0.005, p=.996**,** BF=0.405).

**Table 4.38: MABC-2 performance of the deletion & duplication group**

| MABC-2 Component | Deletion | | | | Duplication | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | RTM | N | Mean | SD | RTM |
| Manual Dexterity | 9 | 4.11 | 3.02 | -1.96 | 10 | 3.10 | 1.60 | -2.30 |
| Balance | 9 | 7.11 | 4.94 | -0.96 | 10 | 7.10 | 4.82 | -0.97 |

In relation to the distribution of percentile ranks (see Figure 4.28) all children in the duplication group presented deficits in fine and gross motor functioning. In contrast, 3 children in the deletion group did not (Patient: 5, 6, 7). Around half of the children in both groups presented domain general difficulties (deletion n=4, duplication n=5). In the duplication group 2/5 children presented an at-risk profile in one subcomponent (Patient: 23, 28). A higher number of children from the duplication group (5/10) presented a domain specific profile consisting of relatively intact balance functioning but with significant manual dexterity difficulties (PR<5) in comparison to the deletion group (2/9).

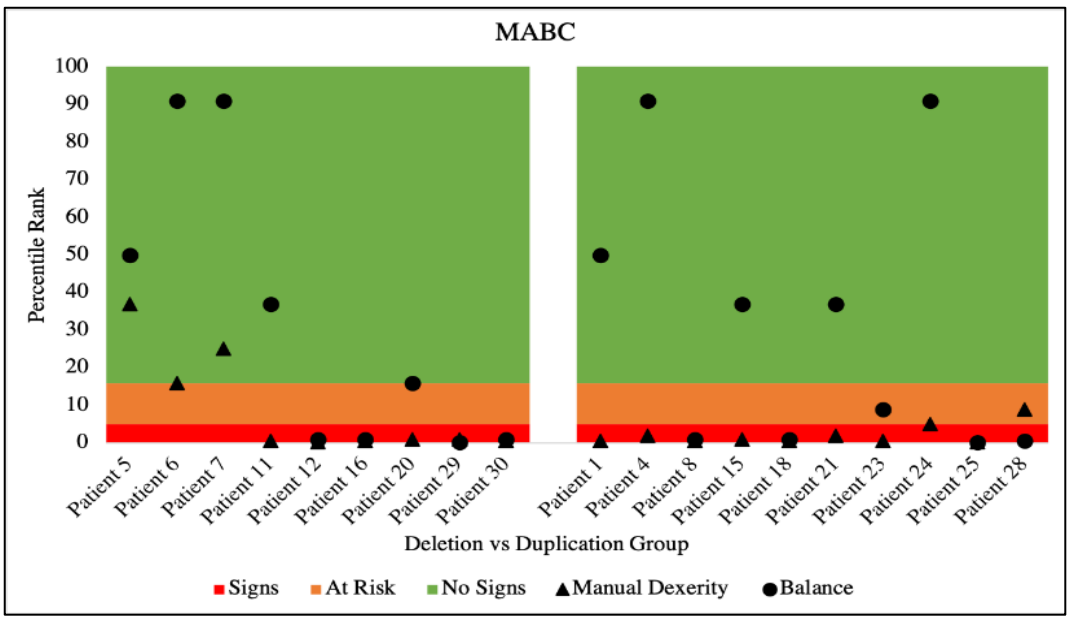


**Figure 4.28: MABC-2 percentile rank performance of the deletion & duplication group**

#### 4.5.2.6 Behavioural symptomology

On the behavioural questionnaires – see Table 4.39, the average score on the DCDQ was similar for both groups and the majority of children presented DCD like coordination difficulties. The duplication group average on the SCQ was above the cut off (score of 15) in contrast to the deletion group, but more than 50% of each group presented social communication difficulties. On the DBC, both groups averaged above the clinical cut off score and the majority presented major emotional and behavioural difficulties (i.e. above 50%). A similar profile was found on the SCQ as both groups averaged in the "very high" (20-40) difficulties range which suggests that the majority of children in both groups are at risk of developing a mental health disorder. There were clear differences in the prevalence of attentional difficulties across groups as all children in the deletion group met signs for either the inattentive, hyperactive or combined ADHD subtype on the VADRS. Finally, based on the other measures of the VADRS disruptive behaviour and emotional difficulties were more frequent those with a deletion.

**Table 4.39: Average & frequency of behavioural symptoms of the deletion & duplication group**

| Questionnaire | Deletion Group | | | | Duplication Group | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | S. D | N presenting signs (%) | n | Mean | S. D | N presenting signs (%) |
| DCDQ | 9 | 33 | 11.94 | 9 (100) | 11 | 38.73 | 12.10 | 10 (90.91) |
| SCQ | 9 | 20 | 12.31 | 6 (66.67) | 11 | 17.18 | 7.78 | 7 (63.64) |
| DBC | 9 | 81.44 | 44.24 | 7 (77.78) | 11 | 61.45 | 17.56 | 9 (81.82) |
| SDQ | 9 | 26.33 | 8.51 | 7 (77.78) | 11 | 20.64 | 5.89 | 7 (63.64) |
| VADRS(ADHD) | 9 | | | 9 (100) | 11 | | | 4 (36.36) |
| VADRS (ODD) | 9 | | | 7 (77.78) | 11 | | | 5 (45.45) |
| VADRS (CD) | 9 | | | 4 (44.44) | 11 | | | 1 (9.09) |
| VADRS (A/D) | 9 | | | 4 (44.44) | 11 | | | 3 (27.27) |

In relation to Figure 4.29, the majority of children in the deletion group (7/9) met the criteria on more than 50% of the measures in contrast to the duplication group (3/11).

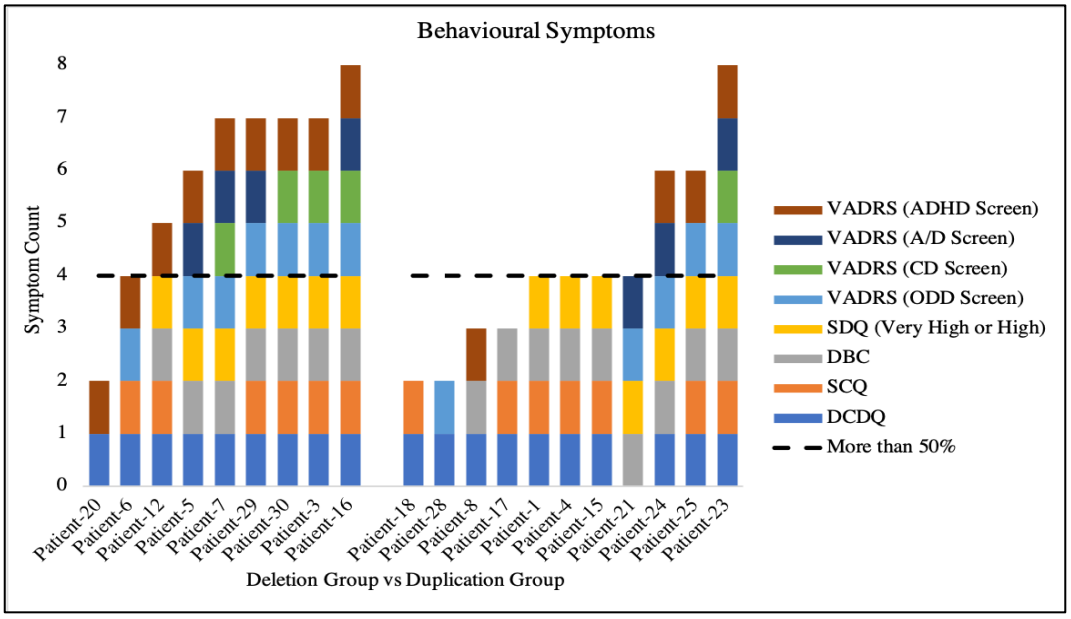


**Figure 4.29: Number of behavioural symptoms per patient in the deletion & duplication group**

In summary, both the deletion and duplication group performed similar across all measures. For IQ, they both situate below average with only small differences in the group averages (by 2-3 points). On the WM measures, the deletion group presented relative strengths in verbal simple WM but broadly the findings fell below average across

tasks. The inclusions fell considerably low, extending more than 1 SD below the mean across both groups. For cognitive flexibility, both groups performed below average. However, when considering the inclusions data, the duplication group average was slightly higher (5 points) than the deletion group but they both fell near to 2 SD's below the mean. Finally, for language functioning, the duplication group averages were slightly lower for the duplication group, but both groups presented signs of language difficulty across measures (i.e. index scores below 85).

Alongside this, the findings for both groups were also similar from the motor assessment. Although the duplication group had a slightly lower mean than the deletion group on the manual dexterity task, there were no significant differences found in performance. Finally, on the behavioural measures, the deletion group presented higher difficulties (group averages) and number (percentage) of children meeting the clinical cut off.

In relation to the percentile rank distributions, the majority of children from both groups gained scores which fell into the below average range across the cognitive measures. The duplication group performed relatively better on the cognitive flexibility task as a higher number of children performed within the average range. Alongside this, the majority of children across both groups presented significant manual dexterity difficulties and 50% of each group had domain general difficulties. Finally, on the behavioural measures all children met the criteria for one or more difficulty, but there was a higher number of children in the deletion group who met this on over 50% of the questionnaires.

Considering performance in line with the CNV literature, the severity of phenotypical outcomes was similar across groups. For example, Niarchou et al (2019) found both the 16p11.2 losses and gains were associated with an increased likelihood of psychiatric disorder with differences in the prevalence of ADHD but not ASD. These findings are similar to the present work as the deletion group presented a higher frequency of ADHD symptomology but ASD symptomology was comparable to the duplication group. Alongside this, the severity of difficulties was equivalent across groups with only slight variability within domains. For example, on the IQ, cognitive flexibility and WM tasks, the deletion group averaged slightly lower than the duplication group, but these differences were non-significant. These findings may parallel with previous research who have reported similar domain general difficulties, with only slight variation across tasks or in behaviours (Bernier et al, 2016; Brunetti-Pierri et al, 2008; Shinawi et al, 2010).

In conclusion, both the deletion and duplication group presented below average performance on the cognitive and motor measures and did not significantly differ across any tasks. Both groups also presented elevated levels of behavioural difficulties. Previous work has compared the profiles of individuals with genetic variance to a specific locus. At specific loci, often a child may meet the criteria for that syndrome, but due to factors of variable expressivity and penetrance (i.e. how many people will develop the disorder) not all children will present the same phenotypical characteristics (Grayton et al, 2012). In the introduction to this section it was discussed that the implications of duplications and deletions are not always clear, and individuals can present unique or similar features. This relationship is underpinned by the complexity surrounding gene dosages as it is not always straightforward as to how imbalances may impact biological processes and the resulting phenotype (Watson, Marques-Bonet, Sharp & Mefford, 2014). Therefore, based on this section it is fundamental to consider copy number variance in 'general' as any deviation to the normal genetic structure which results in a genetic imbalance (i.e. loss or gain) may be a significant risk factor for atypical development.

## 4.6 Exploring the cognitive, motor and behavioural development of: children in the same family affected by the same CNV

### 4.6.1 Background and sample

When exploring defined genetic 'syndromes' there are usually distinct features which are typical of that diagnosis. In the case of less common and rare CNVs, the evidence mainly shows that the CNV is associated with a broad phenotypical spectrum (Nevado et al, 2014; Watson, Marques-Bonet, Sharp & Mefford, 2014) as some individuals may have a CNV and be phenotypically 'normal' or present significant difficulties (Nagamani et al, 2011; Nowoska, 2017). This variability in clinical manifestation and expression of copy number variance is complex to understand even when categorised by type (i.e. deletion or duplication) or by location (i.e. common neurodevelopmental loci) as these can manifest similar risks for development (e.g. cognitive, motor and behavioural). These phenotypical outcomes may be due to variable expressivity (CNV may express itself differently across carriers resulting in shared or distinct features) and pleiotropy (CNV may give rise to different neurodevelopmental disorder phenotypes) (Grayton, Fernandes, Rujescu & Collier, 2012; Thapar & Cooper, 2013) which may result in challenges understanding less common variants and their associated features.

In this section, it was of interest to investigate these concepts by exploring the profiles of 3 siblings in the present sample who have the same CNV. This work was inspired by Shen et al (2010) who investigated the clinical and genomic features of 3 family members (father and two siblings) with the same deletion to 16p11.2. They were interested in understanding the phenotypical differences and similarities between carriers. In the older sibling they found a complex profile consisting of ASD, significant learning disability, significantly low intellectual functioning (IQ=46) and congenital abnormalities (physical and medical). In contrast, the younger sibling presented relatively normal developmental functioning, early signs of language delay (which developed quickly), relatively higher IQ (IQ=73) and no medical and physical issues. The father shared a similar profile to Sibling 1, as he was non-communicative, had significant learning difficulties and ASD.

Based on this, it was of interest to explore the profiles of 3 siblings from the sample group who have the same CNV inherited from their mother – see Table 4.40. The statements which are in bold, were consistent across all participants. Patient 7 had an additional CNV, but the clinical geneticist working on the project indicated that this is of uncertain significance and is not being followed up.

**Table 4.40: Clinical characteristics of 3 siblings**

| Patient | Age | CNV | Clinical summary from cytogenic report |
|---|---|---|---|
| 5 | 10 | 20p12.3-p12.2 Deletion | • Neuro-behavioural problems<br>• 20p13.3 variant of uncertain significance at this current time<br>• It may be prudent to review this patient periodically with respect to any changes in the significance for this region.<br>• Maternally inherited, but in the absence of clinical phenotype in mother the clinical significance of this imbalance is unclear but may be contributing towards the patient's phenotype<br>• **Region contains 4 genes including 2 OMIM morbid genes (PLCB1 & PLCB4).**<br>• **There is emerging evidence to link disruption of the PLCB1 gene to neurobehavioral disorders, but it is at present not conclusive. Therefore, this variant is classified as 'of uncertain significance'** |
| 6 | 14 | 20p12.3-p12.2 Deletion | • Autistic features, behavioural problems, macrocephaly<br>• Maternally inherited, but in the absence of clinical phenotype in mother the clinical significance of this imbalance is unclear although it indicates that the imbalance may be an inherited normal variant of no clinical significance |
| 7 | 13 | 20p12.3-p12.2 Deletion<br>3q25.32-3q25.32 Deletion | • Neuro-behavioural problems<br>• 3q25.32-3q25.32 loss: as there are no disease genes within this region and there is no clear pathogenic association in the literature, this balance is classified as a likely benign variant of uncertain significance. |

In relation to the 20p12.3 location, there is only emerging evidence of the associated phenotypical outcomes. The Unique-Rare Chromosomal Disorder Support Group (2008), detail that there are only 4 published reports on the 20p12 or p12.3 loci which report: developmental delay, growth delay, learning difficulty and abnormal head and facial feature growth. More recently, this deletion has been implicated in the development of an orofacial cleft (Amasdl et al, 2016; Sahoo et al, 2011).

### 4.6.2 Findings and discussion

#### 4.6.2.1 Intellectual functioning

In relation to IQ, see Figure 4.30, Patient 6 showed strengths across all composites in comparison to their siblings who presented domain general difficulties.

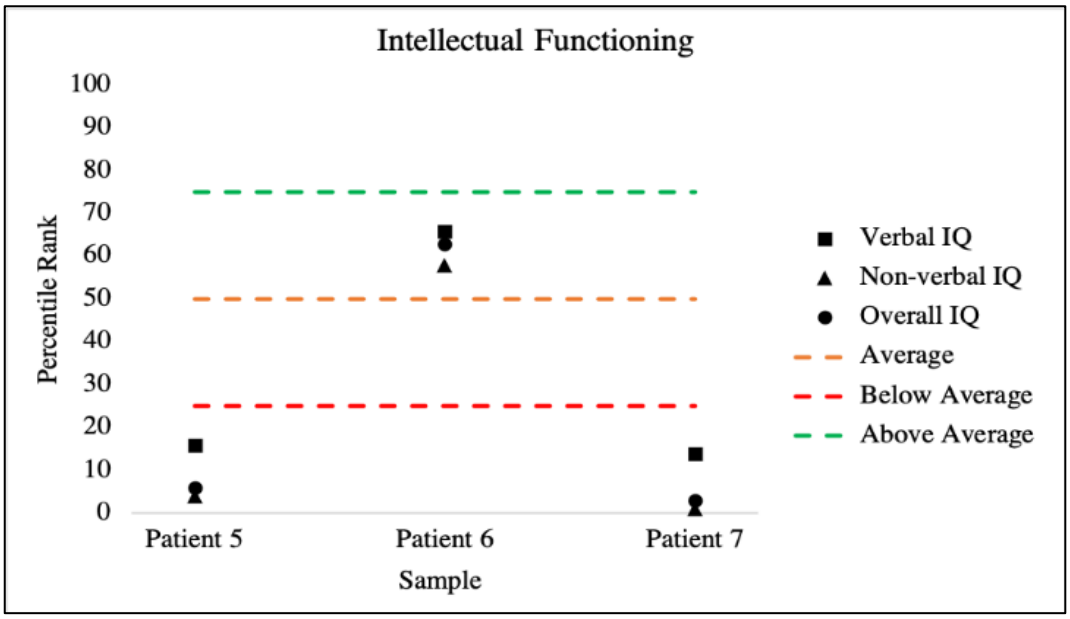


**Figure 4.30: WASI-2 performance of the 3 siblings**

#### 4.6.2.2 Working Memory

On the WTMB (see Figure 4.31), the findings were mixed. None of the children consistently performed in the average range, but they did on one task.

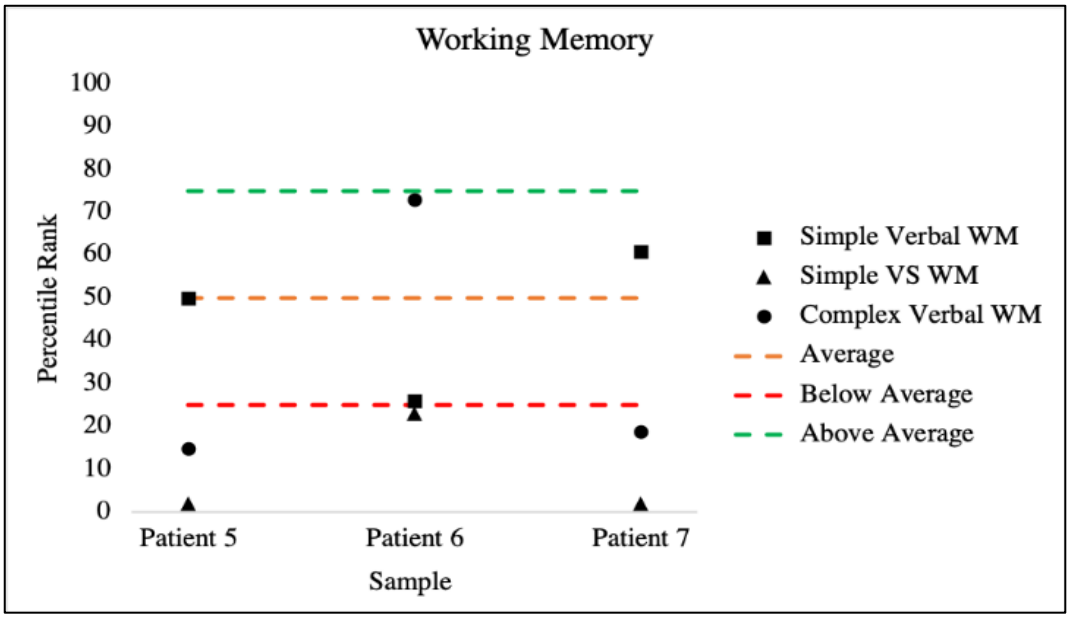


**Figure 4.31: WMTB-C performance of the 3 siblings**

Patient 5 and 7 both had average simple verbal IQ with relatively significantly impaired performance on the block recall. Patient 6 presented an alternative profile of strengths in complex verbal WM, with higher simple visuospatial WM than both siblings.

#### 4.6.2.3 Cognitive flexibility

On the WCST – see Figure 4.32, Patient 5 (PR= 27) presented better performance than Patient 6 (PR=9) and 7 (PR=19) however they all situated below average based on the WCST classification (PR=15-28).

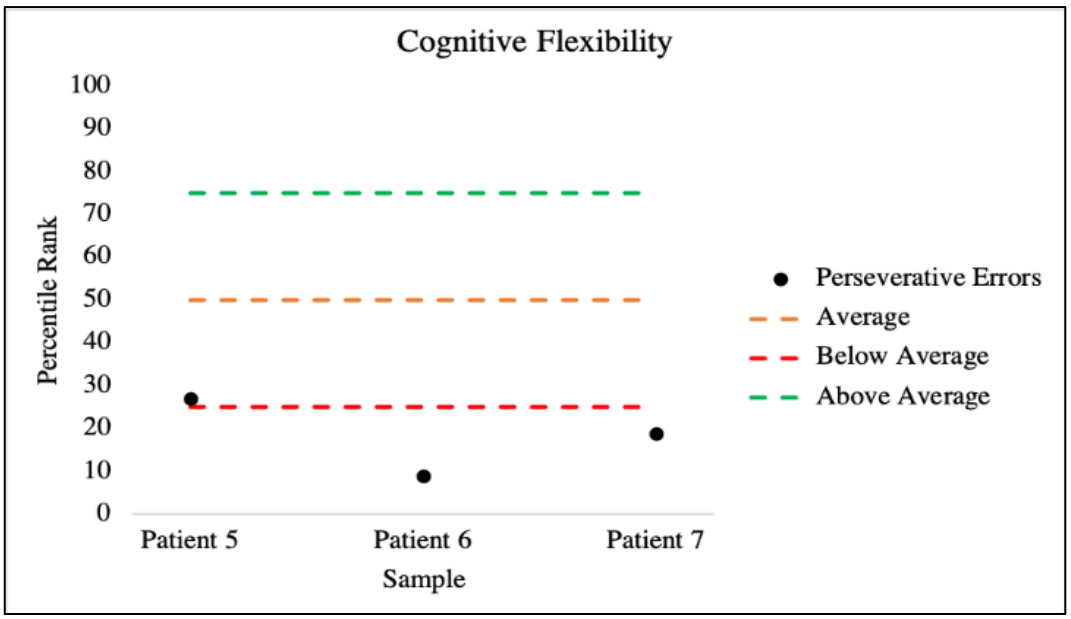


**Figure 4.32: WCST performance of the 3 siblings**

#### 4.6.2.4 Language

In relation to the CELF-4 – see Figure 4.33, there were clear differences in the language performance.

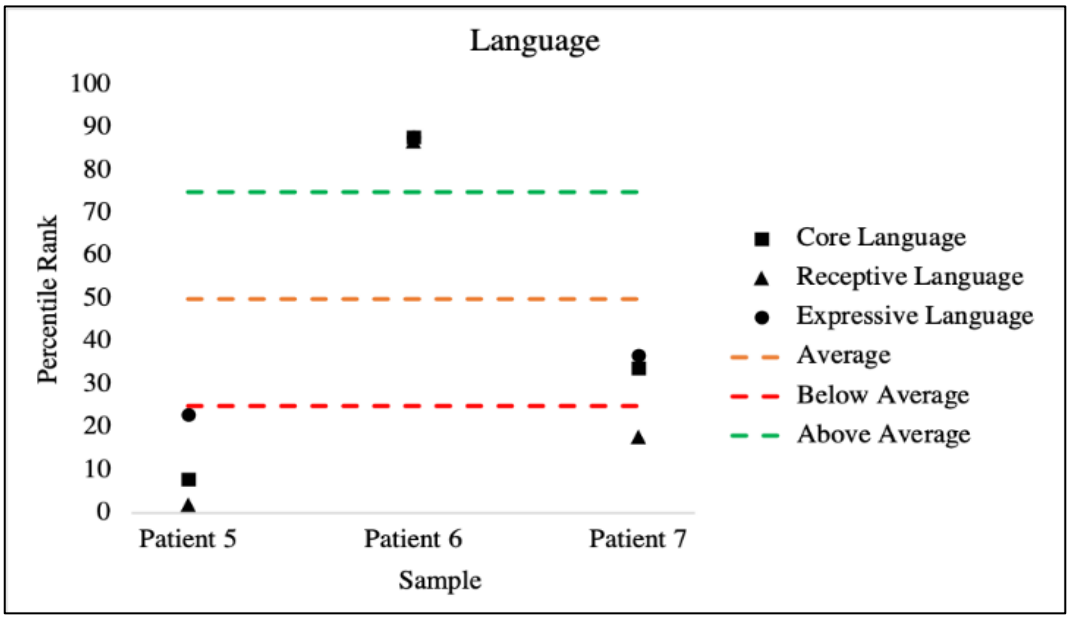


**Figure 4.33: CELF-4 performance of the 3 siblings**

Patient 6 presented above average language functioning across all composites. Patient 7 presented a domain specific profile of relative strengths in expressive language, in contrast to Patient 5 with domain general language difficulties that would warrant further attention (SS<85).

#### 4.6.2.5 Motor functioning

In relation to performance on the MABC-2 (see Figure 4.34), all 3 patients presented no signs of movement difficulties (PR>16) for both manual dexterity and balance.

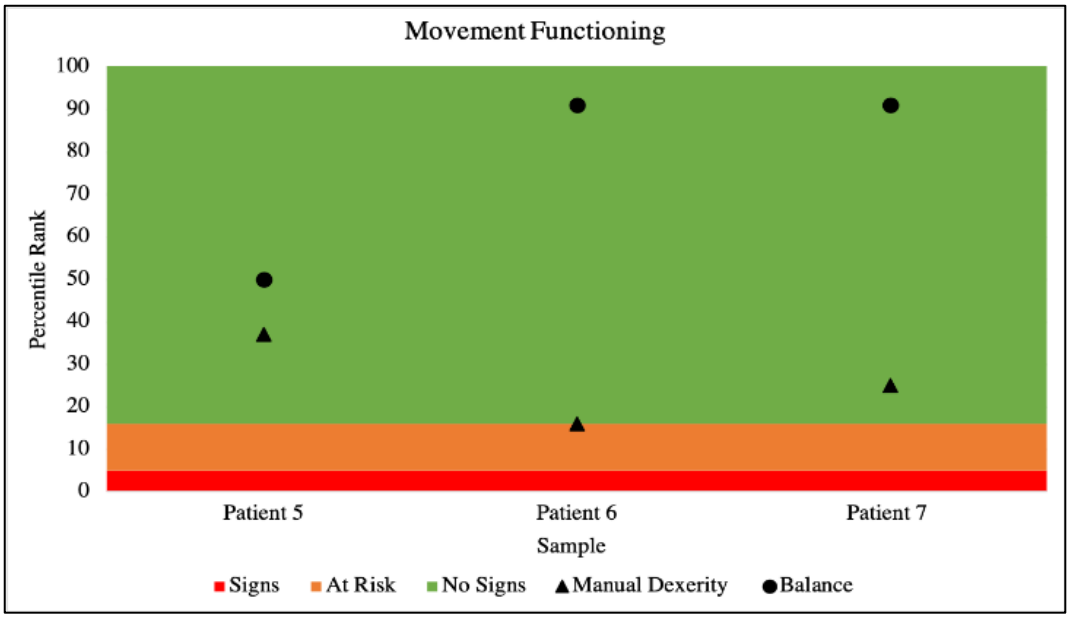


**Figure 4.34: MABC-2 performance of the 3 siblings**

### 4.6.2.6 Behavioural symptomology

On the behavioural measures, each patient presented signs of more than one difficulty – see Figure 4.35.

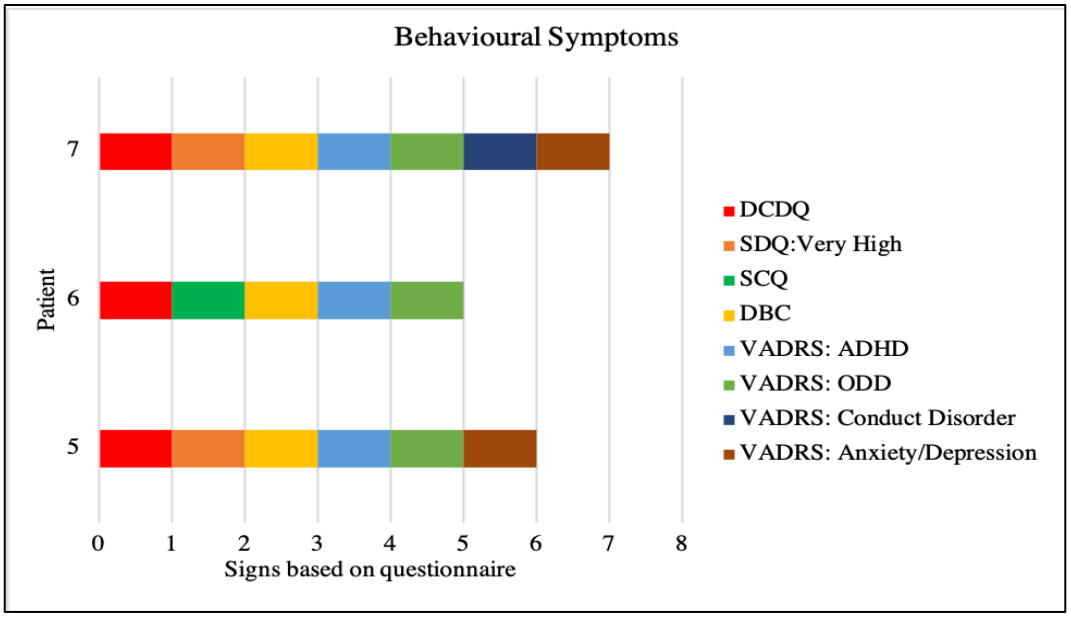


**Figure 4.35: Number of behavioural symptoms per sibling**

All 3 patients presented signs of coordination difficulty, attentional difficulties (combined and inattentive) and signs of ODD. There was a specific profile of social communication difficulties found in Patient 6, while Patient 5 and 7 presented a cluster of psychological and behavioural symptoms. This included very high difficulties (SDQ), major difficulties on the DBC and signs of ODD. Emotional difficulties were more prevalent in Patient 7 as they also met the criteria for conduct disorder and anxiety and depression (VADRS).

Overall the findings from this section suggest that the genotype and phenotype relationship is complex as each patient presented a profile consisting of strengths and weaknesses. The findings from the cognitive measures were varied across siblings while the motor and behavioural measures were more consistent. The literature common reports that there is variability in the phenotypical manifestation of CNVs at specific genomic loci and the present work aligned with this.

In relation to the work by Shen et al (2010) as discussed in the introduction, speech and language and cognitive impairments are consistent features reported for the 16p11.2 deletion (Rosenfeld et al., 2010; Shinawi et al., 2010). In contrast, the medical (spinal abnormalities) as described for one of the siblings is not consistently reported (Bijlsma et al, 2009; Fernandez et al., 2010) and was absent in the other sibling and father which may highlight issues of phenotypic variability. In relation to the present work, Patient 6 presented relatively intact IQ, language and complex verbal WM in contrast to their siblings who situated below average on the majority of the cognitive tasks. Similarly, on the behavioural measures, Patient 6 presented a unique profile consisting of more social communication difficulties in comparison to the behavioural difficulties in the siblings.

Considering the patients cytogenetic reports as discussed in Table 4.40, the CNVs were described as ‘Variants Of Uncertain Significance’. In line with Nowoska (2017) this means that there is limited evidence and understanding of the clinical significance of this variant. In relation to the outcomes for the patient, it may be a challenge for these children to gain support or access to the relevant services as there is limited evidence surrounding the clinical significance of the CNV. This may also result in challenges at genetic counselling for the family (Nagamani et al, 2011). In these specific cases, the family asked if they could have the project feedback as soon as possible to support an EHCP application, which may provide evidence for the initial value of this work.

The findings from this section may highlight the role of understanding of CNVs in 'general'. As genetic variance can impact any of the chromosomes, this may highlight the considerable number of rare variants which are relatively less well understood or identified. In the case of these 3 children, there has been limited work on the 20p region, and they are evidently at risk of atypical cognitive and behavioural difficulties. On the genetic reports there were details of the PLCB1 & PLCB4 genes as potential contributors to neurobehavioral difficulties, however these were inconclusive due to limited evidence in the literature. Alongside this, the genotype and phenotype interaction is complex, so it would be difficult to understand clinical outcomes based on single-genes (Smith, Scerif & Thomas, 2002). Finally, the variability in outcomes across the 3 siblings may sugguest that there are additional genetic, environmental or epigenetic factors that can modify or influence phenotypical outcomes (Shen et al, 2010). For example, based on the standardised measure motor assessment (MABC-2) the patients did not present movement difficulties while on the subjective parental report (DCDQ) they did.

In summary, these children are at risk of developmental difficulties which span cognitive and behavioural domains, with relative strengths in motor functioning. Often for rare CNVs, it is challenging to define a specific profile of traits or symptoms due to factors of variable expressivity and pleiotropy. As the impact of variance to 20p12.3-p12.2 is relatively less well understood, the findings from the present work may highlight the importance of considering genetic variance in general.

## 4.7 Exploring the cognitive, motor and behavioural development of: a child with multiple CNVs.

### 4.7.1 Background and sample

Both the size and number of CNVs may risk neurodevelopmental difficulties as large variants encompass more genes, however this relationship is complex and phenotypical outcomes are hard to predict (Cooper et al, 2011; Lee & Scherer, 2010; Rosenfeld, 2013; Watson, Marques-Bonet, Sharp & Mefford, 2014). To understand this, the 'simple additive model' suggests that there is a spectrum of neurodevelopmental diseases, and an increase in rare and disruptive mutations can influence phenotypic severity (Coe, Girirajan & Eichler, 2012). For example, Girirajan et al (2011) found that in contrast to the cases with Intellectual Disability (ID) alone, those with ID and multiple congenital anomalies had a significantly increase of large CNVs and individuals with dyslexia were

no different from the control group. The authors suggest that a large CNV burden is linked to severity of childhood disability. Similar findings are reported by Girirajan et al (2010) for the 16p11.2 deletion. They found the those with two mutations had more severe and distinct clinical features. They propose a 'two hit model' whereby a second hit (which can be another CNV, small base-pair mutation or a significant environmental factor) may lead to increased severity of phenotypic outcomes (Girirajan et al, 2010; Kumar, 2010).

Based on this, it was of interest to explore how a second variant may impact phenotypic outcomes. The following section reviews the profile of a patient with two CNVs. Patient 9 is 13 years old with 2 large imbalances: a duplication to 10p15.3-10p11.21 (35.4Mb) and a deletion to Xq25-Xq28 (32.62Mb). Their cytogenetic report details that genetic disruption is the likely cause of phenotype and associated clinical features of microcephaly, developmental delay and physical abnormalities (to fingers).

### 4.7.2 Findings and discussion

In relation the cognitive measures, Patient 9 presented domain general difficulties as they gained a standard score of below 85 across all tasks. In relation to percentile rank, they situated in the below average range – see Figure 4.36. They presented a similar profile to 4/19 children from the full patient sample (Patient: 12, 18, 25, 30).

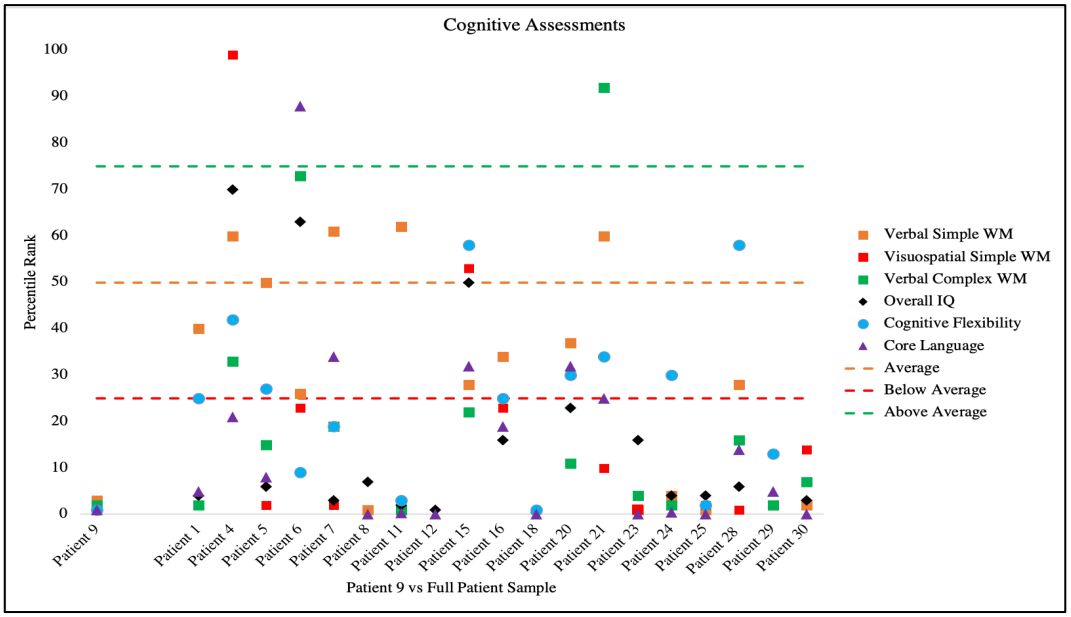


**Figure 4.36: Percentile rank performance of Patient 9 & the full sample on the cognitive assessments**

The findings were similar for motor functioning – see Figure 4.37. Patient 9 gained a percentile rank of 0.5 (SS=2) on the MD subcomponent and rank of 5 (SS=5) which suggests "significant" difficulties (<5) and they would certainly require help. Considering the full patient sample, 7/19 presented comparable domain general movement difficulties.

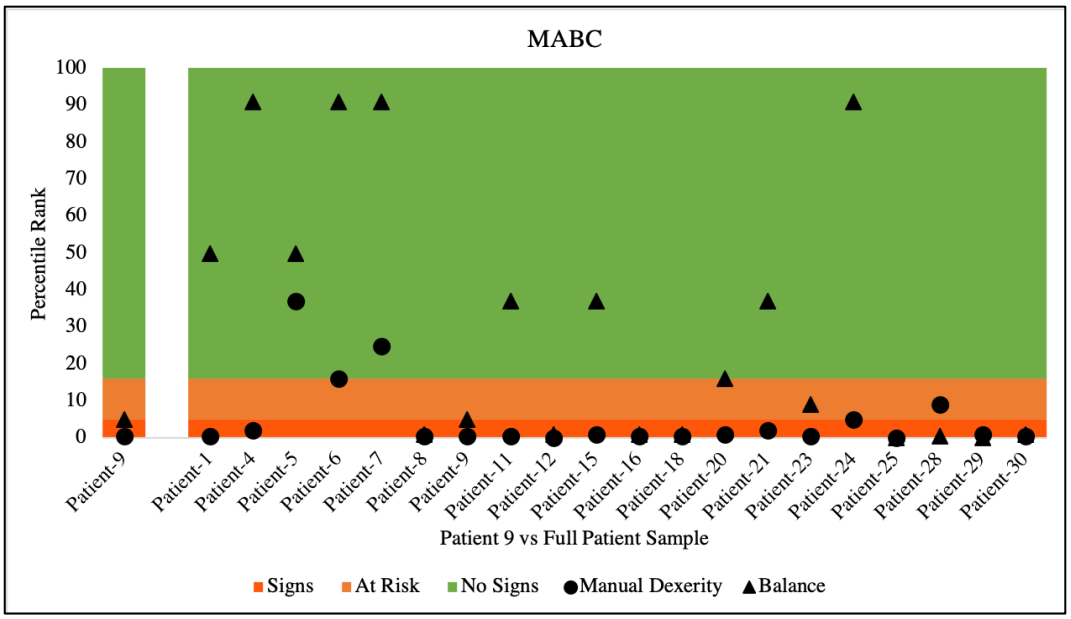


**Figure 4.37: Percentile rank performance of Patient 9 & the full sample on the motor assessments**

In relation to the behavioural measures, Patient 9 met the criterion on 7/8 measures (all but conduct disorder) – see Figure 4.38. This includes a complex profile of coordination (DCDQ); very high psychological (SDQ); social communication (SCQ); emotional and behavioural (DBC); attentional (VADRS– inattention); anxiety and depression (VADRS) and disruptive behaviour (VADRS - ODD) difficulties. A similar profile of difficulties was found for 4/20 children (Patient: 7, 29, 30, 3) from the full sample, while 2 children presented a higher number of difficulties (Patient: 16, 23).

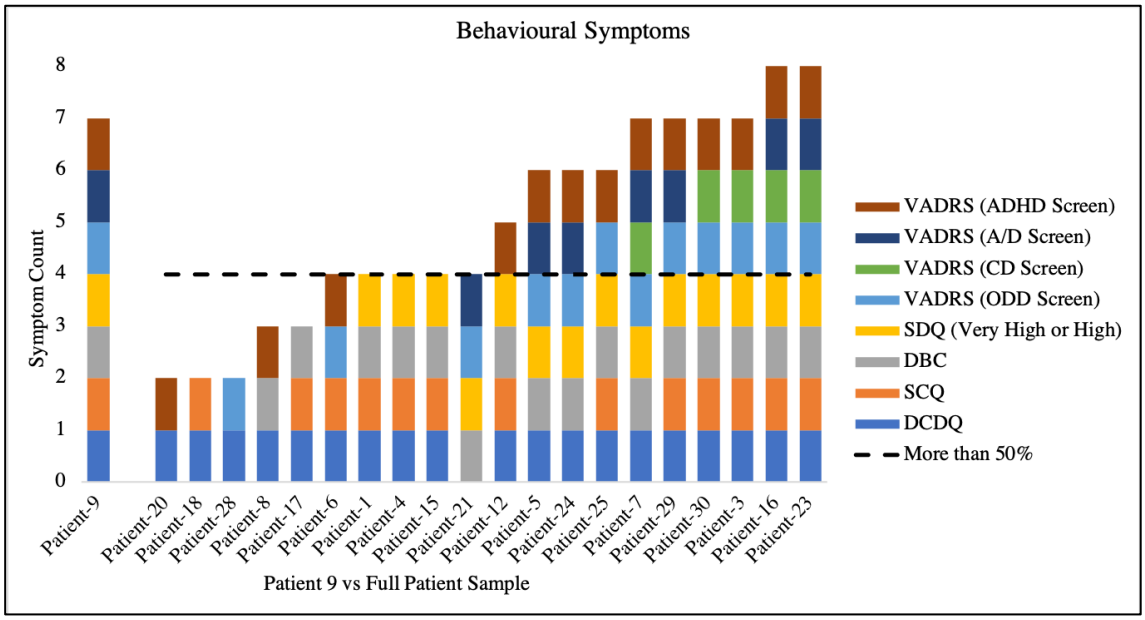


**Figure 4.38: Number of behavioural symptoms for Patient 9 & the full sample**

In line with the brief introduction, findings from the cognitive, motor and behavioural assessments show Patient 9 is at clear risk of a range of developmental difficulties. This profile may align with that of 'second hits' (Girirajan et al (2010) and the additive model (Coe, Girirajan & Eichler, 2012) whereby multiple large imbalances may interact lead to severe phenotypical outcomes. This single case analysis may provide some useful information on the role of CNVs including the potential impact of the type of variance and the quantity. It has been reported by Lee and Scherer (2010) that variances of 1Mb or greater would lead to phenotypical outcomes that would attract require medical attention. In the case of Patient 9, both variants were significantly large (>30 Mb). However, this relation is complex as both small and large variants may or may not be clinically significant (Nowakowska, 2017).

Considering the profile of Patient 9, it is clear that both large and multiple variants can have severe phenotypical outcomes. In relation to the full patient sample as discussed throughout this chapter, findings show below average cognitive and motor functioning and elevated behavioural difficulties. Related to this, some children without a second CNV were found to present profiles similar to Patient 9, which may highlight the role of understanding the developmental consequences of having a CNV in 'general'. Alongside this, there were no major group differences for children with a CNV at a specific neurodevelopmental locus (Section 4.4), or for children with a specific type of variance (Section 4.5). It is clear from these sections that CNVs and the genes implicated in those

regions interact in a complex manner and manifest phenotypically as a range of comorbid developmental difficulties. It is challenging to understand the complexity of this relationship, but the findings suggest that genetic variance may have a cascading impact on biological processes and present as atypical development in contrast to children of the same age (see section 7.2.1 for a discussion of theoretical implications).

## 4.8 Chapter summary and contributions

Evidence suggests having a CNV risks the development of a neurodevelopmental disorder. However, there is limited work on how copy number variance in general (i.e. not a specific syndrome) impacts developmental outcomes in children. Core developmental domains (cognitive and motor abilities and behavioural symptoms) were assessed. Key findings suggest:

- Children with the presence of a CNV are at risk of cognitive difficulties. These include below average general intellectual functioning (i.e. poor crystallised and fluid abilities), poor working memory (i.e. simple and complex), challenges in flexible thinking and language difficulties (i.e. overall, receptive and expressive). In comparison to children of the same age, this group of children may struggle on tasks that require successful problem solving, abstract thinking, reasoning and complex manipulation. The poor working memory skills can link to difficulties acquiring new skills and knowledge resulting in difficulties in school, classroom settings and during learning tasks. Finally, the below average language functioning may result in difficulties successfully communicating, listening, reading and writing.
- Children with a CNV are "at risk" of gross movement difficulties. While they present a profile of "significant" manual dexterity deficits (based on MABC-2). These difficulties can impact how precise, accurate and timely these children engage in hand movements which may in turn impact skills such as handwriting (i.e. as identified by the CKAT - pen skills).
- Children with copy number variance present behaviours typical of neurodevelopmental disorder symptomology. The majority presented a range of difficulties in coordination, psychological, attentional and social communication.
- CNVs have been associated with neurodevelopmental disorders but variants at specific loci can increase this risk. There was no significant difference between the performance of children with a variant at a known locus compared to those without

(besides for manual dexterity). Although this should be interpreted with caution given the small sample size, these findings may show the value of understanding CNVs in general. Some genes may work in a dosage sensitive fashion, which may result in specific biological or phenotypical outcomes being affected. However, it is a challenge to understand specific processes and how these interact as part of the complex genotype-phenotype relationship. Considering this, these findings show that any genetic imbalance (regardless of loci) is influential for development.

- In relation to CNV type, deletions can result in more severe phenotypical outcomes. On investigation of this, children with CNVs consisting of deletions and duplications presented below average cognitive and motor measures with a high number of behavioural difficulties. Similar to the previous point, it is important to consider the impact of genetic variance in general as any genetic imbalance (i.e. loss or gain) may be a significant risk factor for atypical development.
- There has been limited work on rare variants or those not associated with a syndrome. On exploration of 3 children with the same rare variant, they presented phenotypical similarities and differences. This may highlight the challenges of understanding the impact of genetic variance. Biological processes do not influence developmental outcomes in a distinct, uniform manner thus providing challenges when trying to understand or quantify the impact of the same variant across different children.
- Finally, copy number variance is important for developmental outcomes regardless of the number of variants or size. Although these factors may contribute, on investigation of a child with two large variants they presented similar domain general difficulties to some children with only one variant.

# Chapter 5 – Exploring the impact of Copy Number Variance on children's cognitive, motor and behavioural development in comparison to sibling controls

## 5.1 Introduction

Sources of individual differences in ability are based upon genetic and environmental factors (Engelhardt, Church, Harden & Tucker-Drob, 2019). The neuroconstructivist perspective provides an understanding of the multidirectional interactions between genes, environment, cognition and behaviour (Karmiloff-Smith, 2006; Scerif & Karmiloff-Smith, 2005). These factors work in a complex way, influencing a child's developmental trajectory. To gain an initial understanding of these factors, it was of interest to investigate the phenotypical profiles of children with a diagnosed CNV in comparison to their unaffected biological siblings (i.e. no CNV). Employing family controls reduces the issues associated with confounding variables. Siblings serve as a more appropriate comparison than unrelated controls due to practical considerations (i.e. cost effective), there is less selection bias (i.e. educational attainment, ethnicity confounds, birth country) (Milne et al, 2011; Weinberg & Umbach, 2000) and both groups share similar environmental exposures (Gauderman, Witte & Thomas, 1999).

Siblings share both genetic (i.e. parental inheritance) and non-genetic factors (i.e. shared home and environment) and these interact and influence phenotypical outcomes (Plomin, DeFries, McClearn & McGuffin, 2008; Jang, 2005). Firstly, siblings share approximately 50% of their genome (Mitchell, 2015) which can contribute towards phenotypical similarities, however the environment a child grows up in is also significant for their development. For example, parental attitudes towards nature and outdoor recreation have been found to associate with the amount of time children play outdoors (McFarlan, Zajicek & Waliczek, 2014). Alongside this, household chaos has been found to be predictive of children's problem behaviour and poor performance in school (Coldwell et al, 2006; Hanscombe et al, 2011). Similarly, the number of books in the home setting have been found to associate with reading skills (van Bergen et al, 2018) and cognitive competency (i.e. problem solving) in adulthood (Sikora, Evans & Kelley, 2019).

These environmental foundations may be further influenced by the impact of genetic variance. For example, a child who presents atypical development (due to a genetic disorder) may risk an altered social and physical environment due to subtle adjustments

made by parents (Massand & Karmiloff-Smith, 2015). These modifications may be present within the early dyadic interaction or emerge due to changes in parents' expectations for their children with and without a genetic disorder (Karmiloff-Smith, 2012). For example, in contrast to typically developing children, the parents of children with genetic syndromes have been found to respond differently to children's language over generalisations (John & Mervis, 2010) and the amount they permit their child to independently explore the environments around them (e.g. crawling and walking) (Karmiloff-Smith, 2012). These factors may subsequently influence the development of children with a genetic variant and those without. For example, in CNV disorders, a higher prevalence of anxiety disorders has been found in children with Williams Syndrome in contrast to their siblings (Leyfer, Woodruff-Borden & Mervis, 2009).

In relation to this gene-environment interaction, in children with 22q11.2 DS, clear differences have been reported in comparison to sibling controls. For example, Chawner et al (2017) found children with 22q11.2 DS (n=75, mean age=9.9 years, FSIQ=71.8, SD=12.9) were found to show deficits in IQ functioning in contrast to siblings (n=39, mean age=10.6, FSIQ=107.6, SD=12.8). Differences in cognitive ability were also reported by Niarchou et al (2014) in 80 children with 22q11.2 DS (mean age=10.2, FSIQ= 76.76, SD=13.0) and 39 control siblings (mean age=10.9, FSIQ=108.56, SD=15.2). Furthermore, they reported an increased risk of psychiatric difficulties in children with a CNV compared to their sibling, with 54% of the CNV group meeting the criteria for one or more disorder in contrast to only 10% of siblings. Finally, Cunningham et al (2018) reported a similar profile of neurocognitive and psychiatric difficulties in patients compared to siblings, alongside differences in movement functioning. They found only 6.3% of siblings (2/32) presented Developmental Coordination Disorder symptomology (DCDQ), which was in stark contrast to the majority of the CNV group (81.4%, 57/70).

Similar findings have been reported for individuals with the 16p11.2 deletion. Family controls have been found to perform within the average range for overall IQ, while those affected by the CNV perform below average (as much as 2 SDs below the mean), and present an increased frequency of psychiatric and developmental disorders (Hanson et al, 2015; Zufferey et al, 2012). For example, Moreno-De-Luca et al (2015) compared performance of children with this CNV to that of a control group of siblings and found siblings had significantly higher IQ (n=38, FSIQ=106, SD=10) than the patient group (n=54, FSIQ=86, SD=15). There was also a significant difference on the Social

Responsiveness Scale (a measure of social impairment symptoms associated with ASD), with increased signs and symptoms consistent with ASD in the CNV group (n=47, mean=75, SD=33) compared to siblings (n=33, mean=24, SD=25).

Overall the findings show that children with CNVs to a specific locus, or with a syndrome may be at risk of various developmental difficulties in contrast to sibling controls. This chapter explored how children with a diagnosed CNV (in general) perform in comparison to their non-affected biological siblings across standardised assessments. It was of interest to understand whether siblings present similarities or differences in phenotypical profiles.

## 5.2 Method

Siblings were recruited during the initial telephone conversation with parents (see Chapter 2). Parents were asked if any unaffected biological siblings (i.e. no CNV) would be willing to take part in the same assessments as the patient. The assessments included the same cognitive and motor measures, in the home setting, and the same parental questionnaires which were sent out prior to the home visit. In relation to the behavioural assessment, parents were asked to complete all questionnaires in the booklet, besides the Developmental Behaviour Checklist (see Appendix A and B) as this measure is used for individuals with developmental delay and/or intellectual disability (Einfeld & Tonge, 2002). The sibling consent procedure was completed at the same time as the patients.

In total 8 siblings were recruited. Full cognitive, motor and behavioural data was obtained for 5 siblings. The remaining three participants only provided questionnaire data because these children did not want to take part in the other assessments. For these 3 children the questionnaires were incomplete, so these were excluded from the present analysis. Therefore, the findings in the present chapter are based on the full data from 5 sibling controls, see Table 5.1. This table includes clinical information from the patient's cytogenetic report and information on inheritance. If the variant has been passed down from the previous generation and is present in the mother or farther then this is of maternal or paternal inheritance respectively. If the CNV has occurred for the first time then this a 'De novo' variant (State & Thapar, 2015).

**Table 5.1: Patient and control sibling characteristics**

| Patient | Age (yrs.) | Inheritance | Clinical summary | Sibling control | Age (yrs.) |
|---|---|---|---|---|---|
| 8 | 7, male | Denovo | Developmental delay (gross motor skills disproportionally delayed) | Twin sibling (dizygotic) | 7, male |
| 4 | 10, male | Paternal | Unexplained mild learning difficulties, and suspected ASD | Sibling (Twin 1, dizygotic) | 7, male |
| | | | | Sibling (Twin 2, dizygotic) | 7, female |
| 18 | 13, female | Maternal | Coordination, learning, speech and language difficulties. SEN statement | Sibling | 11, male |
| 29 | 9, female | Paternal | Learning and social communication difficulties | Sibling | 8, female |

The siblings recruited do not have a CNV. This was confirmed by parents and the Clinical Geneticist working on the project. As a general rule of thumb, genetic screening is only conducted when there is reasonable justification (Botkin et al, 2015; Bradley-Smith, Hope, Firth & Hurst, 2010; Friedman et al, 2013). Some siblings presented normal array results when tested (Patient 4: both Twin 1 and 2) and some are reported as typically developing, so genetic screening had not been justified (Sibling of Patient: 8, 18 and 29).

## 5.3 Findings and discussion

The following sections present data from the patient sample (n=4) and their sibling controls (n=5). The group comparisons are based on descriptive statistics (5.3.1) which include group averages and z-scores (Relationship To Mean, RTM). These are based on standard scores with a mean of 100, standard deviation of 15 (cognitive assessment) and

mean of 10 and standard deviation of 3 (motor assessment). Based on the small sample size, the findings from the group comparisons must be interpreted with extreme caution. Following this, percentile ranks are presented for the single case comparisons (5.4.2).

## 5.3.1 Group comparison

### 5.3.1.1 Intellectual functioning

In relation to IQ (see Table 5.2) the patient group were consistently in the "low average" classification (Wechsler, 2011). The sibling group presented "low average" verbal IQ (VCI) performance in comparison to "average" non-verbal IQ functioning (PRI).

**Table 5.2: WASI-2 performance of the patient and sibling group**

| WASI-2 Composite | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | S. D | RTM | N | Mean | S. D | RTM |
| Verbal IQ (VCI) | 4 | 87.00 | 22.55 | -0.87 | 5 | 88.60 | 13.85 | -0.76 |
| Non Verbal IQ (PRI) | 4 | 80.25 | 16.32 | -1.32 | 5 | 101.40 | 10.69 | -0.09 |
| Overall IQ (FSIQ) | 4 | 82.00 | 20.18 | -1.20 | 5 | 94.00 | 11.60 | -0.40 |

### 5.3.1.2 Working Memory

The WM data is presented in two ways. Firstly, those who managed to complete the task (exclusions). Secondly, those who have been assigned a score of 0 (inclusions) as they found the task it too challenging or did not obtain a standard score.

There are differences in the WM performance of siblings and patients – see Table 5.3. This table excludes the children who did not complete the task as it was too challenging (on BDR) and did not obtain a standard score as the total number of correct responses were extremely low, given their age (on the FDR and BR). The sibling group performed with the "average" range across all 3 tasks, while the patient group only performed in the "average" range for the block recall task. The sibling group presented relative strengths in simple and complex verbal WM in comparison to lower simple visuospatial WM.

**Table 5.3: WMTB-C exclusions data of the patient and sibling group**

| WMTB-C - Exclusions | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | S. D | RTM | n | Mean | S. D | RTM |
| Verbal Simple (FDR) | 3 | 79.67 | 21.22 | -1.35 | 5 | 106.6 | 20.55 | 0.47 |
| VS Simple (Block Recall) | 2 | 102 | 45.25 | 0.13 | 4 | 86 | 24.90 | -0.93 |
| Verbal Complex (BDR) | 2 | 81.5 | 16.26 | -1.23 | 5 | 94 | 10.44 | -0.4 |

Table 5.4 includes the data from cases who were assigned a score of 0 as they failed to complete the tasks or gain a standard score. In relation to this, the patient group averages extended more than 2.5 SDs below the mean in contrast to the findings from Table 5.3 presenting "moderate to severe impairments" (more than 1.33 SD below the mean, Gathercole & Alloway, 2006) across all tasks. The siblings situated in this range for the block recall task but presented relatively better simple and complex verbal WM.

**Table 5.4: WMTB-C inclusions data of the patient and sibling group**

| WMTB-C - Inclusions | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | S. D | RTM | n | Mean | S. D | RTM |
| Verbal Simple (FDR) | 4 | 59.75 | 43.44 | -2.68 | 5 | 106.6 | 20.55 | 0.44 |
| VS Simple (Block Recall) | 4 | 51.00 | 64.43 | -3.27 | 5 | 68.8 | 44.09 | -2.08 |
| Verbal Complex (BDR) | 4 | 40.75 | 47.98 | -3.95 | 5 | 94 | 10.44 | -0.4 |

#### 5.3.1.3 Cognitive flexibility

Two children (one from each group) found the WCST too difficult to complete and were excluded from the analysis (see Table 5.5). The patient group performed within the "mildly impaired" range, while siblings presented relatively better performance in the "average" range (Heaton et al, 1993).

**Table 5.5: WCST exclusions data of the patient and sibling group**

| WCST Exclusions | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | n | Mean | S. D | RTM | n | Mean | S. D | RTM |
| | 3 | 81.33 | 16.56 | -1.24 | 4 | 102.25 | 1.63 | 0.15 |

The children who found the task too challenging were assigned a score of 0 – see Table 5.6. Based on this, both groups were "below average", but the patient group situated in the "moderately-to-severely" impaired while siblings were "mildly impaired".

**Table 5.6: WCST inclusions data of the patient and sibling group**

| WCST Inclusions | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | n | Mean | S. D | RTM | n | Mean | S. D | RTM |
| | 4 | 61.00 | 42.86 | -2.60 | 5 | 81.80 | 47.90 | -1.21 |

### 5.3.1.4 Language

In relation to the language assessment in Table 5.7, the patient group presented clear language difficulties in comparison to siblings (-2SD below the mean). Across all measures they situated in the "very low/severe" range for core, receptive and expressive language functioning and would require further assessment due to standard scores below 85 (Semel & Wiig, 2006). In contrast, the siblings presented relatively intact functioning as they situated in the "average" range across all composites.

**Table 5.7: CELF-4 performance of the patient and sibling group**

| CELF-4 Composite | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | S. D | RTM | n | Mean | S. D | RTM |
| Core language (CLI) | 4 | 64.5 | 21.56 | -2.34 | 5 | 97.60 | 16.07 | -0.16 |
| Receptive Language (RLI) | 4 | 64 | 12.52 | -2.40 | 5 | 99.80 | 20.96 | -0.01 |
| Expressive Language (ELI) | 4 | 69 | 24.22 | -2.07 | 5 | 98.60 | 18.98 | -0.09 |

### 5.3.1.5 Motor functioning

In relation to the MABC-2 (see Table 5.8) both groups presented signs of movement difficulties but differed by severity. In relation to manual dexterity, the patients averaged more than 2SDs below the mean, which indicates "certain need of help" (Henderson, Sugden & Barnett, 2007). In contrast, the siblings were "at risk of difficulties" (as 1SD below the mean) and guidance recommend further monitoring. On the balance subdomain the patients were "at risk" of difficulties, while the siblings were close to "average".

**Table 5.8: MABC-2 performance of the patient and sibling group**

| MABC-2 | Patient | | | | Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | S. D | RTM | n | Mean | S. D | RTM |
| Manual Dexterity | 4 | 2.75 | 0.96 | -2.42 | 5 | 6.20 | 1.10 | -1.27 |
| Balance | 4 | 5.25 | 5.91 | -1.58 | 5 | 9.40 | 3.58 | -0.2 |

### 5.3.1.6 Behavioural symptomology

The findings from the questionnaires are presented in Figure 5.1. Despite the small size, 4/5 patient cases presented a higher number of behavioural difficulties than the sibling group, with the remaining child presenting more. Across the patient group, coordination (DCD-like symptomology) was present in all cases, whilst social communication difficulties (ASD-like symptomology) were evident in four out of five cases.

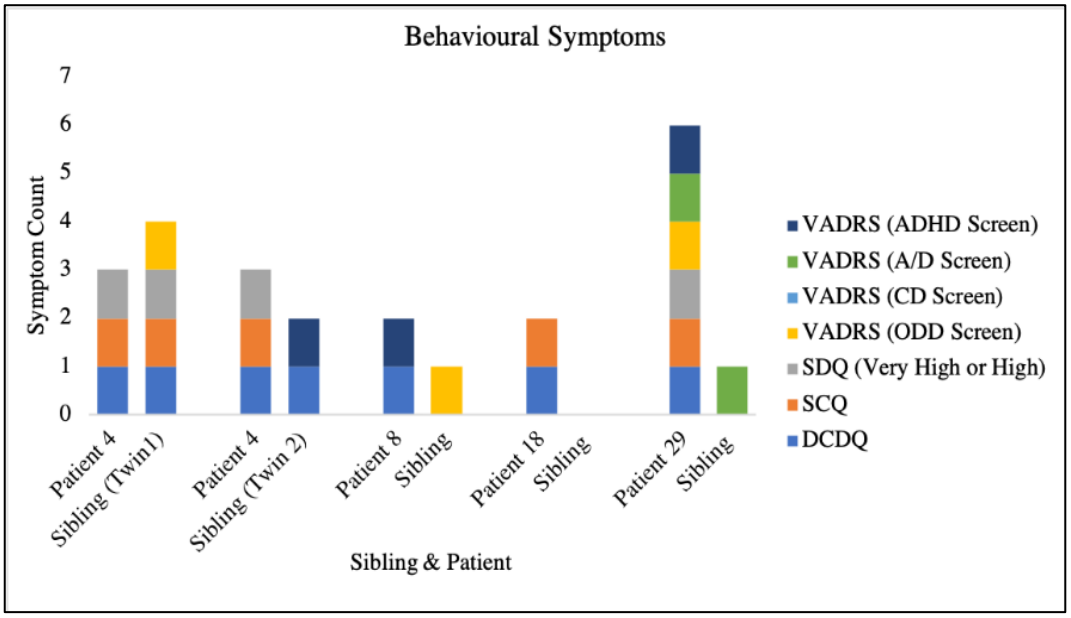


**Figure 5.1: Number of behavioural symptoms per patient & sibling**

In conclusion, findings from the cognitive measures show the patient averages frequently fell more than 1-2 SD below the mean, while the sibling group generally did not perform as poorly as this. The patient group also presented poorer motor functioning than siblings and a more consistent profile of behavioural difficulties in at least one area, typical of children with neurodevelopmental disorders.

### 5.3.2 Single case comparison

#### 5.3.2.1 Patient 8 and Sibling Twin

In relation to the cognitive measures (see Figure 5.2) Patient 8 and their twin (dizygotic) both performed below average on the majority of tasks, but they differed by the severity of impairment. On the WM tasks, the sibling performed slightly better than the patient on the FDR task. They both performed poorly on the block recall task (so low a percentile rank was not obtained) and the sibling showed relative strengths on the BDR task (PR=46) while the patient found this too challenging to complete. For IQ they both presented below average performance with the patient showing relatively better verbal IQ functioning with a contrasting profile in the sibling. Both children scored below average for language, but there were clear differences as the patient (PR=1,1,1) performed worse than their sibling (PR=19, 2, 23) for core, receptive and expressive language respectively. In relation to pragmatics, the sibling met the age criterion (i.e. "adequate communication abilities in context") while the patient did not.

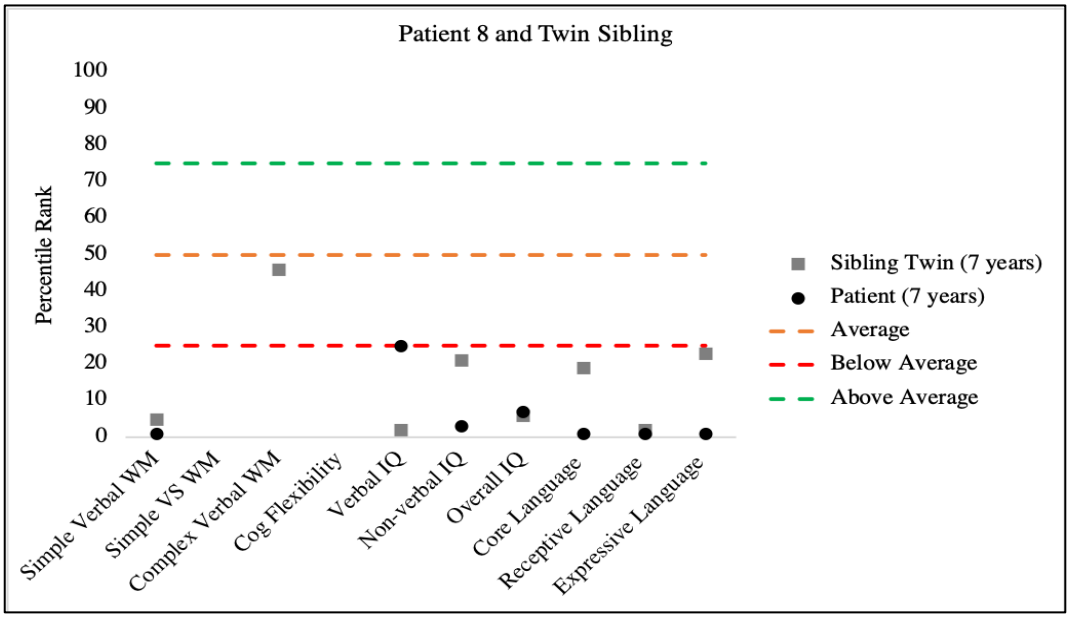


**Figure 5.2: Percentile rank performance of Patient 8 & Twin Sibling on the cognitive measures**

For motor functioning, the patient presented clear Manual Dexterity (MD) (Percentile Rank, PR=1) and Balance (PR=1) difficulties but the sibling presented an only 'at risk' profile for balance (PR=9) and relatively intact MD (PR=16). On the behavioural measures, there was a complex profile found across both children. The patient had a

higher number of difficulties than their sibling. The patient's behaviour was consistent with a "combined" ADHD profile (i.e. both inattentive and hyperactivity/impulsivity symptoms), showed signs of DCD but their psychological strengths and difficulties score was 'close to average'. In contrast, their sibling had only a 'slightly raised' profile, with elevated disruptive behavioural difficulties due to positive signs of ODD.

In conclusion, these children present a complex profile which spans cognitive, motor and behavioural domains. Both children present domain specific strengths and weaknesses which broadly situated below average. Overall, the sibling showed slightly better performance in contrast to the patient, but this was not consistent across every measure.

#### 5.3.2.2 Patient 4 and Sibling (Twin 1)

In relation to the cognitive functioning of Patient 4 and their sibling (see Figure 5.3), they both presented a complex profile consisting of strengths and weaknesses, which mostly situated in the "average" range.

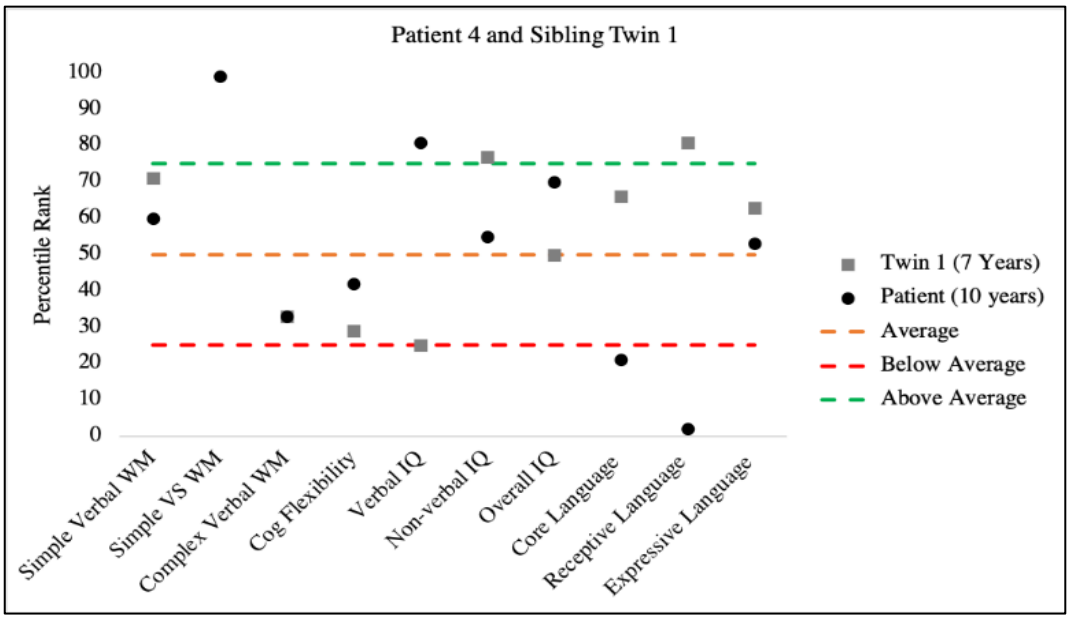


**Figure 5.3: Percentile rank performance of Patient 4 & Twin 1 on the cognitive measures**

For WM, they both scored within the average range for 2/3 subtasks but on the block recall task, there was a unique profile of above average performance by the patient (PR= 99) but significantly poorer performance by the sibling as they did not obtain a percentile rank. Alongside this, they both scored within the "average" range for cognitive flexibility and IQ. On the language assessment there was a domain-specific profile for the patient,

who had relatively better expressive language performance (PR=53) than receptive language (PR=2). Meanwhile, the sibling presented a consistent profile of average language functioning. For pragmatics, they both presented "inadequate" abilities for their age (on criterion score). There were clear differences in motor functioning. The patient showed MD difficulties (PR=2) but relative strengths in balance (PR=91). The sibling presented relatively intact functioning across both subdomains (MD PR=16, Balance PR=75). Finally, for behavioural symptoms they both presented signs of psychological difficulties (above the "very high" threshold on SDQ); social communication and coordination difficulties. Alongside this, the sibling presented signs of Oppositional Defiant Disorder (ODD) on the VADRS (Parent), in contrast to the patient who did not show any difficulties on this parental report questionnaire.

In summary, it is hard to draw any clear conclusions. The patient presents a domain specific language profile and behavioural symptoms similar to their sibling. Due to phenotypical concerns, this sibling was genetically tested and presented normal results.

#### 5.3.2.3 4p and Sibling (Twin 2)

Similar to Twin 1, Twin 2 performed within the average range on the majority of measures, see Figure 5.4. On the WM tasks, they both scored within the average range on the majority of measures, but the sibling presented relative difficulties on the complex WM task (PR=12) in contrast to the patient (PR=33). They both scored within the average range for cognitive flexibility, but Patient 4 also presented consistent average IQ functioning. Finally, for language the sibling showed better performance across all domains including pragmatics (met criterion).

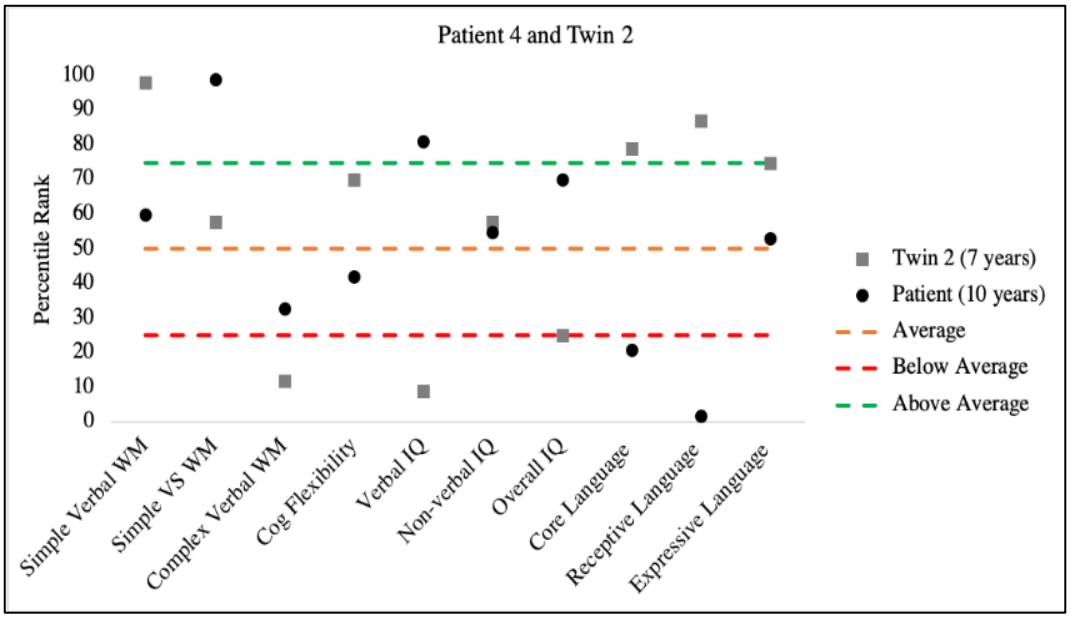


**Figure 5.4: Percentile rank performance of Patient 4 & Twin 2 on the cognitive measures**

For motor functioning both children showed the same profile of relatively intact balance skills (PR=91) in contrast to significant MD difficulties (Sibling PR=5, Patient PR=2). Finally, for behavioural symptoms, they both showed signs of DCD. The sibling showed signs of elevated inattentive symptoms and slightly raised psychological difficulties, whilst the patient had "very high" psychological and social communication difficulties.

In summary, similar to Twin 1 it is difficult to draw any general conclusions as both children performed within in the average range on the majority of measures. Patient 4 showed a slight increased risk (3/7) of behavioural difficulties than their sibling (2/7) with considerably worse language performance. Due to phenotypical concerns this sibling was also tested and showed normal array results.

#### 5.3.2.4 Patient 18 and Sibling

There was a clear discrepancy in the performance between Patient 18 and their sibling (see Figure 5.5) across all cognitive and motor measures (PR=1). For WM, Patient 18 scored much lower for their age and did not obtain a percentile rank (on FDR and Block recall). They also found the BDR too difficult to complete. Both children met the criterion score for pragmatics showing adequate skills in context. On the behavioural measures, they both showed close to average psychological strengths and difficulties, but the Patient also presented social difficulties and coordination difficulties. Overall, this child and their

sibling presented clear differences in cognitive and motor functioning but had similar parent-reported psychological profiles.

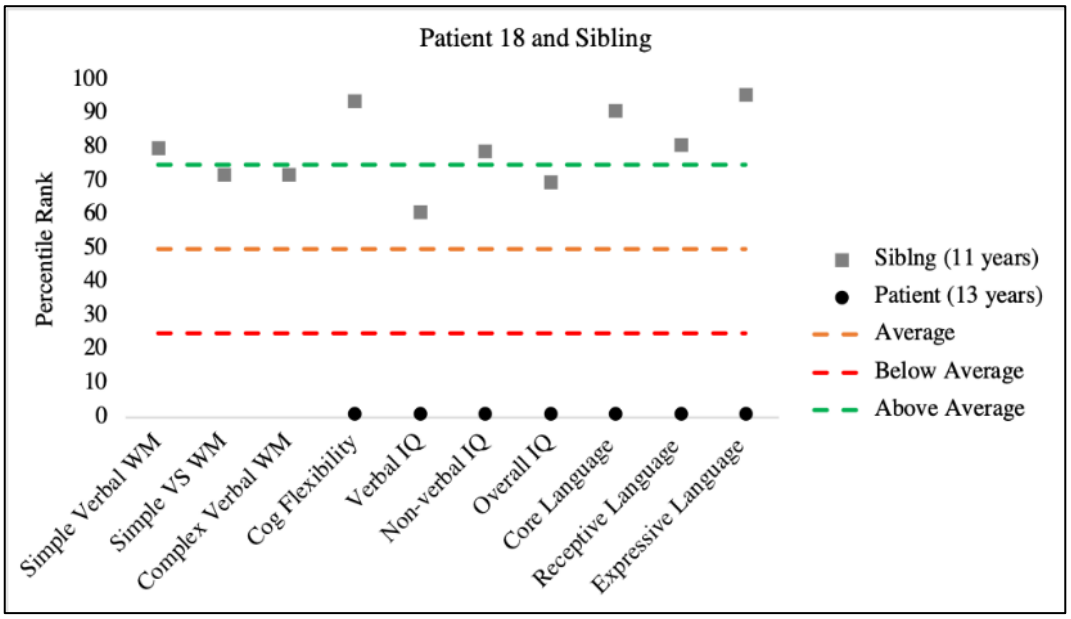


**Figure 5.5: Percentile rank performance of Patient 18 & Sibling on the cognitive measures**

### 5.3.2.5 Patient 29 and Sibling

Findings from the cognitive measures are presented in Figure 5.6.

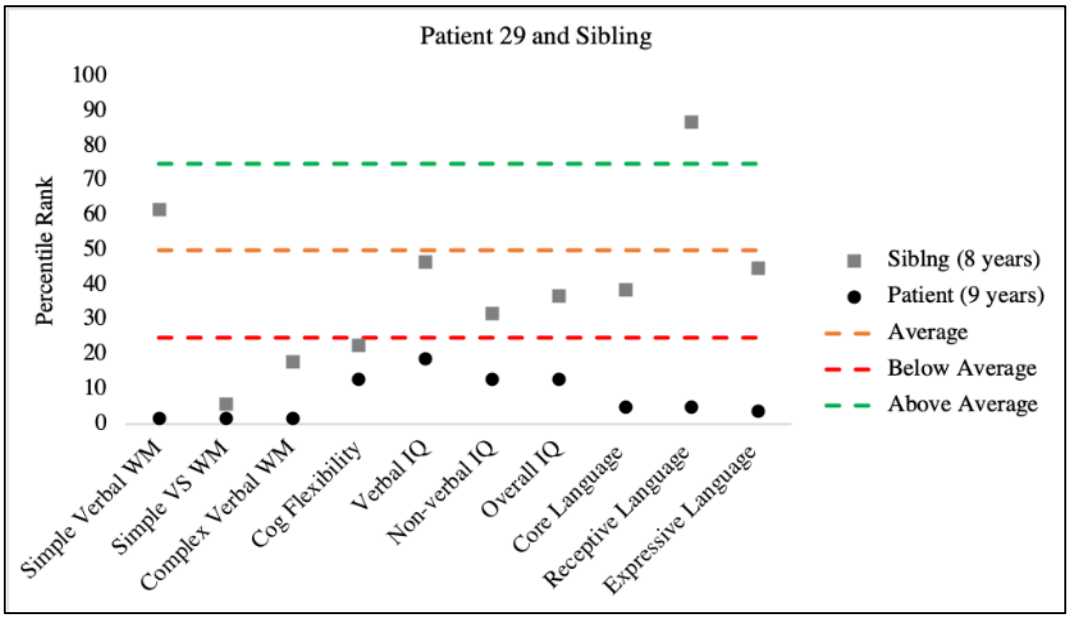


**Figure 5.6: Percentile rank performance of Patient 29 & Sibling on the cognitive measures**

For WM, the sibling and patient both situated below average for the majority of tasks, but the sibling showed relative strengths in simple verbal WM (PR=62). For cognitive

flexibility they both scored below average, but the sibling (PR=23) again performed marginally better than the Patient (PR=13). The sibling presented a consistent profile of average functioning across the IQ and language subtasks (and pragmatics) in contrast to an alternative profile in the Patient. For motor functioning they both presented significant Manual Dexterity (MD) difficulties. However, whilst the patient presented 'domain general' difficulties' (MD PR=1, Balance PR=0.1) the sibling was only 'at risk' on for balance (MD PR=5, Balance PR=9). On the behaviour measures, the patient presented a higher number of difficulties (7/7) that included being above the threshold for a "very high" risk of psychological difficulties; a combined ADHD profile; signs of ODD; signs of anxiety and depression and coordination difficulties. In contrast, their sibling only met the criteria for concern on the anxiety and depression screen. Overall, in this case comparison, the Patient was significantly impaired across all measures in comparison to their sibling. However, there is a complexity here, as this sibling has not been genetically screened, whilst the CNV is inherited rather than De novo.

## 5.4 General discussion

In summary, the findings broadly show that children with a CNV are more at risk of cognitive, motor and behavioural difficulties in contrast to sibling controls. The siblings present a complex profile consisting of relative strengths and weaknesses but the severity of these seldom extend as low as their siblings with a genetic variant. On a group level a descriptive but not inferential analysis was conducted on a small number of children. Therefore, the data should be interpreted with extreme caution because it is difficult to draw firm conclusions from trends in such data. Similarly, in relation to the single case work, it is challenging to systematically untangle the genetic and non-genetic interactive factors that likely have impacted each of these children's developmental trajectories (Plomin, DeFries, McClearn & McGuffin, 2008).

### 5.4.1 Group based comparison

In relation to the group-based comparisons, it is difficult to draw clear conclusions based upon the small sample size. Broadly though, the sibling group performed slightly better than the patient group for non-verbal IQ, situating them in the average range for overall intellectual functioning. In relation to Working Memory, the sibling group also presented relatively better performance, situating them in the average range. Considering the children who did not obtain a standard score because they found the task too challenging

to be scored on the standardised scale, with this data included it shows the patient group fell consistently within the "moderately to severely impaired" range across all tasks, highlighting the severity of impairment. Similarly, the siblings presented "average" cognitive flexibility while the patients presented "mild" impairments. Finally, for language the patient group presented clear domain general difficulties (-2SDs) in comparison to their siblings who were in the "average" range.

Similar to the findings from the cognitive measures, the sibling group performed relatively better than the patient group on the motor measures. The sibling group were found to be "at risk" of manual dexterity difficulties (-1SD) but not to the same extent as the CNV group, who were defined as "in certain need of help" (-2SDs). These groups showed a similar discrepancy on the balance component. On the behavioural measures, the majority of the patient group also exhibited a higher number of difficulties, with an increased prevalence of DCD and ASD like symptomology. Of interest was the number of siblings who presented higher signs of psychological difficulties and disruptive behaviours (Sibling 4 – Twin 1, Sibling 8, Sibling 29). Although the present sample size is relatively small and diagnoses are not being made, previous work suggests the siblings of children with developmental disabilities and autism may be at risk of social and behavioural adjustment problems (Orsmond & Seltzer, 2007; Ross & Cuskelly, 2006). These results may provide an initial understanding of the psychological functioning of siblings of children with a genetic variant. Previous work in siblings of children with chronic illness and developmental difficulties suggest the unaffected sibling may be at greater risk of negative psychological effects due to feeling forgotten about or receiving less attention (Lamsal & Ungar, 2019; Sharpe & Rossiter, 2002).

### 5.4.2 Single case comparison

In relation to the case comparisons, clear conclusions are difficult to draw. In some cases, patients and their siblings presented similarities (Patient 8); contrasting profiles of relative strengths and weaknesses (Patient 4) or clear differences in cognitive, motor and behavioural functioning (Patient 18 and 29). There are various factors which may contribute towards these outcomes.

Firstly, Patient 8 was compared against their non-identical sibling. There were no clear performance differences between both children as they performed below average on the majority of measures. The only distinction was on the behavioural measures. The sibling

presented higher psychological difficulties (slightly raised) in comparison to the patient (close to average) and presented signs of disruptive behaviour (ODD). These difficulties may link to the factors previously discussed, relating to the additional challenges associated with having a sibling with neurodevelopmental difficulties.

A potential explanation for the similarities in performance may be due to 'germline mosaicism'. This occurs when there is a mutation present in the parent's germline, but it is not detectable in the parental blood sample (Cassidy & Allanson, 2005). If a mutation occurs in the parental germline (sperm or an egg cell) prior to conception and then this is fertilised, this would lead to a denovo variant in the offspring (as present in Patient 8). This variant would be present in every child thereafter but would not be detectable in the parent, which may be a potential explanation for the current findings. This also proves challenging for phenotypical outcomes as its difficult to distinguish whether differences are attributed to shared environments or shared environmental risk factors.

In relation to Patient 4 and their siblings (who were twins), the 3 children presented a complex profile consisting of relative strengths and weaknesses. Each child presented a domain specific profile whereby they situated both "below" and "above" average on different measures. Twin 1 presented relatively better language and motor skills than the patient but had a profile of elevated disruptive behaviours. Similarly, Twin 2 had similar motor skills to the patient, presented relatively better language functioning but had signs of attentional difficulties. Based upon phenotypical concern and potential familial risk (paternal variant) both siblings were genetically screened, and the findings were negative. Therefore, in the absence of any shared genetic markers, the similarities in phenotypical profiles may be due to non-shared environments (e.g. interaction with peers or experiences at school) or shared environmental factors (e.g. parental influences).

Naturally, parents create and influence the environment the child develops in from an early age. This can influence a child's cognitive development (i.e. number of books in the home, van Bergen et al, 2018) or psychological development (i.e. amount of household chaos, Coldwell et al, 2006; Hanscombe et al, 2011; Sikora, 2019). A major factor is how they interact with their child (i.e. parenting style) and this can have either a positive or negative impact on development. For example, Karmiloff-smith (2010) found controlling mothers were less responsive to their infants' vocalisations and less sensitive mothers were found to interrupt their infant's exploration, and the child was receptive to this. In contrast sensitive mothers would allow their child to explore their environment which in

turn promotes their cognitive and skill development. These early interactions and experiences are influential for future development as they influence a child's understanding of the world and provide the foundation for learning. Related to parenting style, the parental phenotype itself may also influence the child's phenotype due to shared genotypes and environmental factors. For example, parental educational background has been found to associate with children's intellectual functioning (Klaassen, 2016) and the mother's prenatal anxiety can link to children's emotional and behavioural development (Meaney & O'Donnell, 2015). This may highlight the role of parental factors (which were a consistent feature across this family) in the absence of shared genetic risks.

Patient 18 and their sibling presented clear differences in performance across tasks. A potential explanation for this may be due to an interaction between (initial) genetic and (subsequent) environmental factors. Throughout early development, a child gradually becomes more specialised and efficient at tasks due to neuronal factors (e.g. synaptic pruning). If there is a genetic mutation, then a child may risk a modified environment, which in turn impacts development outcomes. As discussed in the introduction, parental expectations may change once parents are informed they have a child with a genetic variant (Massand & Karmiloff-Smith, 2015). This can then have a reciprocal influence on developmental outcomes as this has subtle modifications for the environment's parents create. Over time this can widen the gap between peers or in relation to children who are typically developing contributing towards an atypical developmental trajectory which persists due to early exposures. For example, parents are more likely to create different environments for their child if they have a Neurodevelopmental Disorder than if they are typically developing, which may subsequently impact cognitive milestones and further opportunities for development (Karmiloff-Smith, 2012). In relation to behaviour, the Patient presented social and coordination difficulties, which may link to the neurodevelopmental difficulties which are associated with CNVs (Mitchell, 2015). However, both children did not present signs of psychological or emotional difficulties. Research suggests having a sibling with a neurodevelopmental disorder can in some cases have a positive impact on siblings. This includes increased emotional development, psychological wellbeing and competence (Lamsal & Ungar, 2019). For example, parents of children with Williams Syndrome reported that their unaffected child was more caring, mature and understanding (Scallan, Senior & Reilly, 2011). This may highlight the impact of environmental modifications and shared parental influences which may result in both

similarities and differences in phenotypes. Although this contradicts the previous point that having a sibling with a CNV could lead to increased risk for behaviour problems, this may highlight the complexity of making clear predictions about how all these factors interact and impact phenotypical outcomes.

Finally, in relation to Patient 29 and their sibling there is a complexity of both genetic and environmental factors. Firstly, the variant in the patient was paternally inherited and the sibling had not been genetically screened, so we cannot be certain that the sibling is not at genetic risk. Secondly, in relation to environmental factors, both children presented below average performance in some measures, but the Patient went beyond this in presenting consistent difficulties. The sibling presented an increased risk of anxiety and depression which may be attributed to shared environments. Having a sibling with a social, cognitive, physical or communication difficulties may lead the healthy sibling to experiencing negative feelings (i.e. feeling forgotten about, neglected or disregard) which may impact their own health and wellbeing (Lamsal & Ungar, 2019; Sharpe & Rossiter, 2002). The unaffected sibling may also receive less attention from parents or family members which may contribute towards psychological difficulties (Lamsal & Ungar, 2019) and the age of the children may be a factor of consideration (i.e. older children may have caring responsibilities). In this case, these children were of very similar age which may be a challenging for the unaffected sibling due to subtle environment differences. Siblings of the same family may experience differences in peer interactions and parental treatment which may contribute towards phenotypical differentiation (Plomin & Daniels, 2011). Parental differentiation can offer in the presence of health problems where one child may be favoured, and an unfavoured child may experience lower levels of self-esteem, higher levels of depression and externalising problems (Suitor et al, 2008). However, as mentioned above, it is challenging to control the interaction between genetic and non-genetic factors and how these influence the developmental trajectory.

In summary, children with genetic variance are broadly at risk of developmental difficulties in contrast to non-affected siblings. This chapter explored the profiles of a small number of children; therefore, it is difficult to draw any specific conclusions. There was a complex pattern of both similarities and differences in performance of case comparisons. Firstly, it is difficult to control for non-genetic factors such as environmental modifications. Related to this, it is challenging to predict the outcome of genetic processes biological processes operate in a complex manner even those who share

100% of their genome (monozygotic twins) are subject to differences in gene expression due to interaction with environmental confounds (Mitchell, 2015; Thapar & Rutter, 2015). Alongside this, it is challenging to understand the genotype and phenotype relationship as some genetic variants may only have influential outcomes dependant on the presence of specific environmental triggers. The present discussion may provide some insight into this complex relationship, similarities may be attributed to shared genetic risk factors while phenotypical differences could be situated in environmental factors.

# Chapter 6 – Exploring the cognitive and motor development of children with a Copy Number Variant in comparison to controls from a Special Educational Needs school.

## 6.1 Introduction

As previously discussed throughout this thesis, research has shown that CNV's are associated with neurodevelopmental disorder risk (Mitchell, 2015), but there is limited understanding of how CNVs in general (in contrast to more specific loci and syndromes) impact phenotypical outcomes. As shown by the results in Chapter 4, children with a CNV were found to have below average cognitive and motor functioning and a range of behavioural symptoms typical of neurodevelopmental disorders. These findings may have implications for learning potential and educational achievement for both short-term (e.g. key stage transitions) and long-term outcomes (e.g. qualifications, higher education, employment). Based on this, it was of interest to investigate the cognitive and motor abilities of children with a CNV in comparison to children with a recognised statement of Special Educational Needs and Disability (SEND).

Children with SEND can have difficulties across 4 broad areas: (1) communication and interaction, (2) cognition and learning, (3) social, emotional and mental health (4) physical/and or sensory needs (Department of Education, 2015). There are two main groups of children with SEND. Firstly, those with a document of legal provision via an Educational Health Care Plan (EHCP) which describes the health, social and educational support required to help reduce the barriers to learning, and secondly those without any formal provision (Department for Education-National Audit Office, 2019). Recent statistics show that 1.3 million students are recorded as having SEND (14.9% of all pupils) and 20.6% of these children with SEND have an EHCP in place, which is indicative of them having particularly substantive additional support needs. The majority of children with a statement of SEND (76.4%) do not have a plan in place but are identified as requiring some additional support, and are mainly schooled in mainstream settings (91.6% - number of SEND children in mainstream school) (Department for Education-National Audit Office, 2019). This highlights the large number of children within mainstream classroom settings with no formal documentation of educational difficulties, which may contribute towards limited academic progress.

Overall, we have an understanding of common genetic syndromes, however there is limited knowledge of how rare/less investigated CNVs may influence developmental outcomes. Although educational or attainment-based measures were not obtained in the present work, the assessment measures (standardised cognitive and motor tasks) implemented broadly align with the 4 areas of need previously discussed (Department of Education, 2015). Alongside this, the motor and cognitive measures have been used in clinical groups or have been predictive of poor performance in education (Abu-Hilal, Al-Baili, Sartawi, Abdel-Fattah & Al-Qaryouti, 2011; Akbar, Loomis & Paul, 2013; Canivez, Konold, Collins & Wilson, 2009; Cordier, Munro, Wilkes-Gillan & Docking, 2013; Gathercole & Alloway, 2008; Hagaman, Trout, DeSalvo, Gehringer & Epstein, 2010; Harrowell, Hollen, Lingam & Emond, 2018; McKean et al, 2017; Ozonoff, 1995; Snow, 1998; Webster et al, 2006; Wuang, Su & Su, 2011). Based on this, it was of interest to investigate whether the profiles of children with a diagnosed CNV are similar or different to children with specialist educational provision.

## 6.2 Method

Children from a SEND high school provision were recruited via our collaboration with the Special Educational Needs & Disabilities Co-ordinator (SENDCo). These children had SEND which were not genetic in origin. The SENDCo was provided a list of ages from the patient sample and approached children who they felt would be academically able to partake in the tasks and who were of similar age. Although efforts were made to match the two samples exactly, the school could not provide us with students who matched exactly. Based on this, 5 patients who were of closest age were investigated for the group investigation (see Table 6.1). For the single case analysis, participants from both samples were matched as close as possible (given the constrains of the study) by age and gender - see Table 6.2.

**Table 6.1: Patient and SEND sample matched by closest age**

| SEND Case | Age (years: months) | Patient Case | Age (years: months) |
|---|---|---|---|
| 1 | 16:8 | | No control available |
| 2 | 15:8 | 20 | 15:6 |
| 3 | 15:2 | 20 | 15:6 |
| 4 | 13:10 | 7, 9, 18 | 13:2, 13:0, 13:8 |
| 5 | 14:8 | 6 | 14:2 |

**Table 6.2: Patient & SEND sample matched by age and gender**

| SEND Case | Age (year: months)/gender | Patient | Age and Gender matched |
|---|---|---|---|
| 1 | 16:8 male | No control available | |
| 2 | 15:8 female | No control available | |
| 3 | 15:2 female | No control available | |
| 4 | 13:10 male | Patient 7 | 13:2 male |
| 5 | 14:8 male | Patient 6 | 14:2 male |

Information letters and consent forms were sent to parents via the SENDCo. Once signed consent was received participants completed the cognitive and motor measures in the school setting (see Chapter 2 for details). The cognitive tasks were administered in the SENDCo's office (a quiet space) and balance tasks took place in the dining area (open space). Behavioural measures were not included in this investigation as the SENDCo said these would be too time consuming for teachers to complete. We gained permission to use the Strengths and Difficulties Questionnaire to gain an understand of psychological functioning, but none of these were completed by teachers due to their workload.

## 6.3 Results

The following sections present the data as group and single-case comparisons. Firstly, descriptive statistics are used to explore the performance of the SEND group (n=5) with the 5 closest aged patients. The mean, standard deviation and corresponding Z-score are reported (Relationship To Mean, RTM). However, given the small sample size, the findings from this must be interpreted with caution. Secondly, percentile rank distributions are used to explore performance of the SEND sample (n=5) in comparison

to the full patient sample (n=20). Finally, percentile rank distributions are used for the single case comparisons (n=2).

### 6.3.1 Group comparison

#### 6.3.1.1 Intellectual functioning

Findings from the WASI-2 are presented in Table 6.3. The SEND group averaged more than 2SDs below the mean across all IQ composites. They had relatively better verbal IQ (borderline classification) in comparison to "extremely low" non-verbal and overall IQ. In comparison, the patient group did not perform as low as this, but still situated 1SD below the mean in the "low average" classification across all measures.

**Table 6.3: WASI-2 performance of the patient and SEND sample.**

| WASI-2 Composite | SEND Group | | | | Patient Group | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | RTM | n | Mean | SD | RTM |
| Verbal IQ (VCI) | 5 | 72.2 | 14.18 | -1.85 | 5 | 85.4 | 18.92 | -0.97 |
| Non-verbal IQ (PRI) | 5 | 60.2 | 10.11 | -2.65 | 5 | 81 | 16.85 | -1.27 |
| Overall IQ (FSIQ) | 5 | 63.8 | 11.80 | -2.41 | 5 | 81.8 | 18.58 | -1.21 |

The distribution of the percentile rank scores are presented in Figure 6.1.

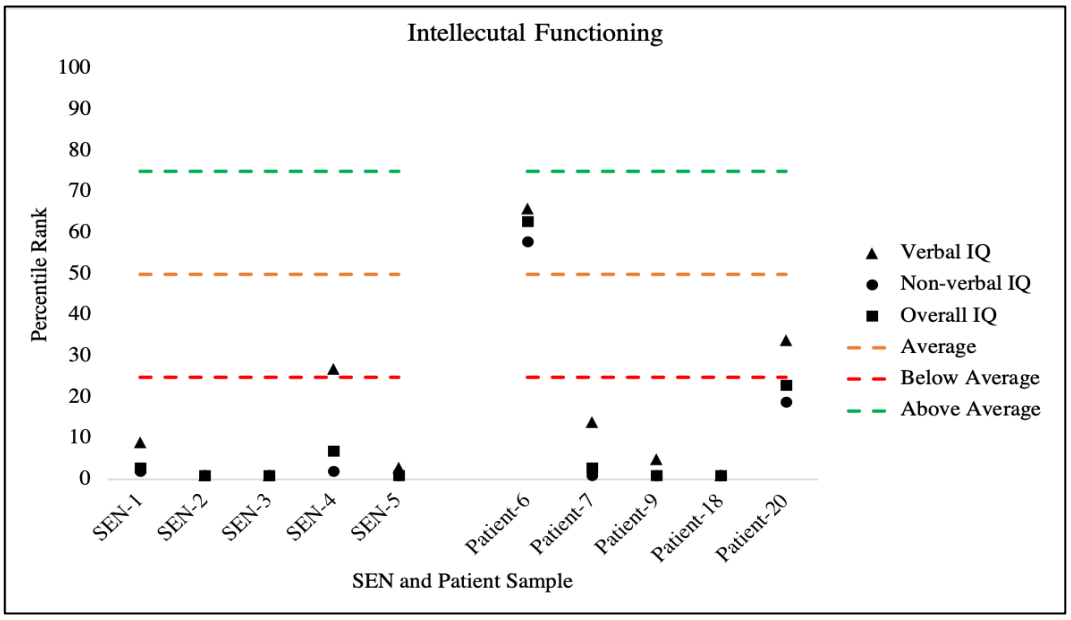


**Figure 6.1: WASI-2 percentile rank performance of the patient & matched SEND sample**

All children in the SEND group performed below average for FSIQ. Case 4 presented relative strengths in verbal IQ, but with poorer non-verbal IQ which reduced their overall functioning. The findings are mixed for the patient sample, as 3/5 patients presented clear below average performance across all IQ domains, one presented relative strengths in verbal IQ and one patient situated in the average range across all domains.

In relation to the full patient sample (see Figure 6.2) the majority (16/20, 80%) presented below average overall IQ which paralleled that of the SEND sample. A smaller number of children situated in the average range (4/20, 20%) (Patient: 4, 6, 15, 21).

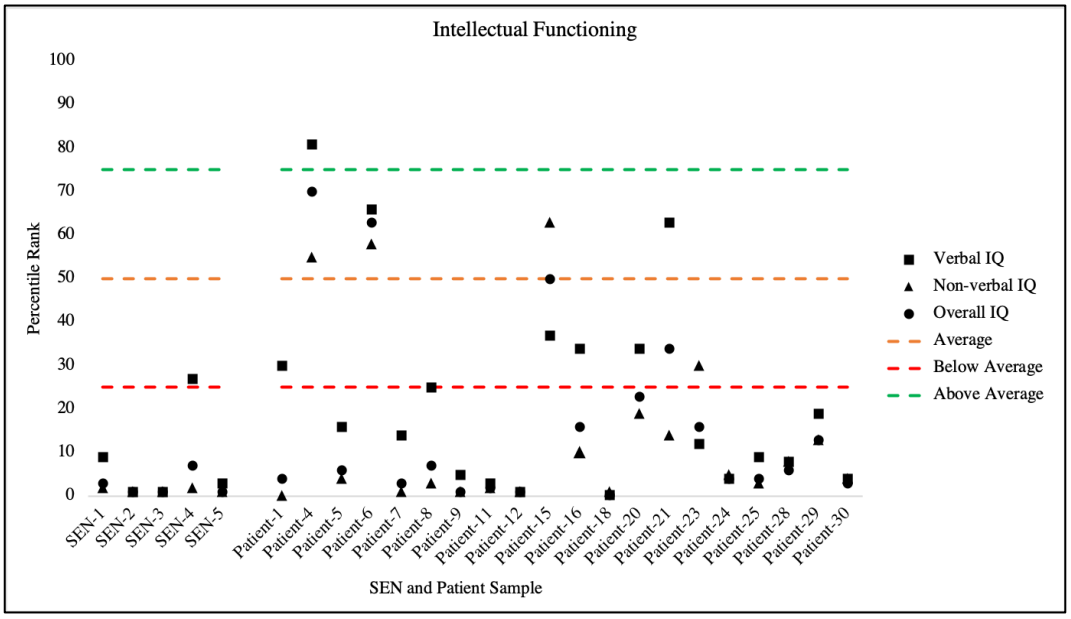


**Figure 6.2: WASI-2 percentile rank performance of the full patient & SEND sample.**

Overall, the SEND group presented significantly below average intellectual functioning for their age (-2SD). Based on the percentile rank distributions, around 50% of the patient sample presented similar profiles to this.

#### 6.3.1.2 Working Memory

Findings from the WMTB-C are presented in Table 6.4 (exclusions). This table excludes the children who did not gain a standard score due to low scores on the FDR or block recall (verbal and visuospatial simple WM respectively) or found the BDR task too difficult to complete (complex verbal WM). The SEND group performed poorly across all tasks presenting "moderate to severe" WM impairments due to average scores which exceeded 1.33 SD below the mean (Gathercole & Alloway, 2006). The patient group

scored within this range on the block recall task, with relatively better performance on the FDR and BDR tasks but these were still below average (within 1SD below the mean). When considering the inclusion data (assigning a score of 0) both groups presented "moderate to severely impaired" WM – see Table 6.5.

**Table 6.4: WMTB-C exclusion data of the patient & SEND sample**

| WMTB-C Exclusions | SEND Group | | | | Patient Group | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | RTM | n | Mean | SD | RTM |
| Simple Verbal (FDR) | 5 | 77 | 8.60 | -1.53 | 4 | 87.75 | 11.41 | -0.82 |
| Simple VS (Block Recall) | 4 | 66.75 | 7.50 | -2.22 | 3 | 77 | 15.87 | -1.53 |
| Complex Verbal (BDR) | 5 | 72 | 7.84 | -1.87 | 4 | 85.5 | 16.82 | -0.97 |

**Table 6.5: WMTB-C inclusion data of the patient and SEND sample**

| WMTB-C Inclusions | SEND Group | | | | Patient Group | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | RTM | n | Mean | SD | RTM |
| Simple Verbal (FDR) | 5 | 77 | 8.60 | -1.53 | 5 | 70.2 | 40.47 | -1.99 |
| Simple VS (Block Recall) | 5 | 53.40 | 30.55 | -2.22 | 5 | 51 | 46.62 | -3.27 |
| Complex Verbal (BDR) | 5 | 72 | 7.84 | -1.87 | 5 | 68.4 | 40.92 | -2.11 |

Investigating the percentile rank position of the groups in Figure 6.3, the findings show the SEND group presented clear WM impairments. One child (Case 1) presented relative strengths in simple verbal WM. This profile was similar in the patient sample as two children had poor simple visuospatial and verbal complex WM (Patient 7 and 20).

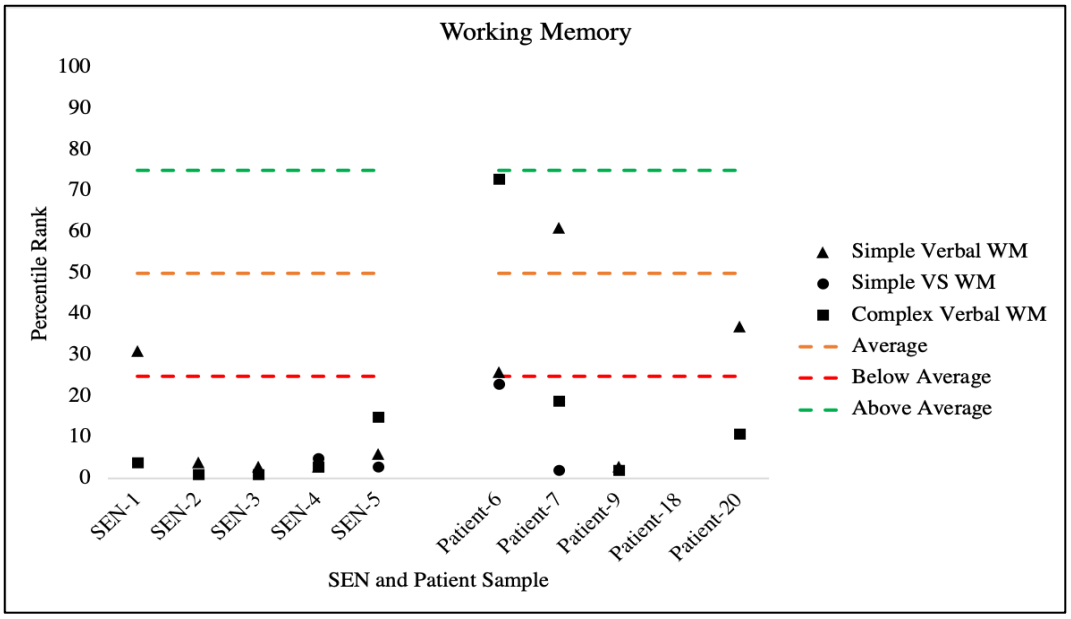


**Figure 6.3: WMTB-C percentile rank performance of the patient & matched SEND sample.**

In comparison to the full patient sample in Figure 6.4, only one child performed above average across all tasks.

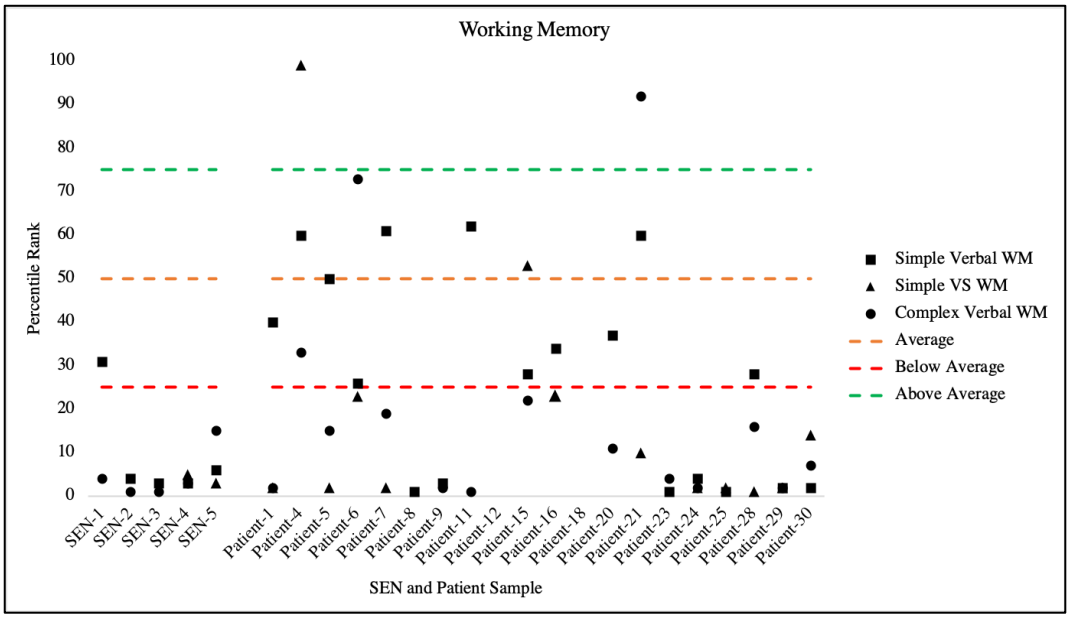


**Figure 6.4: WMTB-C percentile rank performance of the full patient & SEND sample.**

The majority of the sample (10/20) showed a mixed profile, with 7 children (Patient: 1, 5, 7, 11, 16, 20, 28) presenting relatively preserved simple verbal WM in the average range with complex verbal WM in the below average range (no score available for one child as task was too difficult). Finally, 9 children performed in the below average range (>25) across all 3 tasks. Of these, two children (Patient: 12, 18) did not gain a percentile

rank on any of the measures as they scored significantly low for their age (on FDR, Block recall) and found the task too challenging (BDR).

Overall the SEND group presented more Working Memory impairments in comparison to the patient group across the 3 tasks. The patient group did present difficulties, but these did not extend as low as the SEND group. In relation to the percentile rank distributions, the SEND group presented clear domain general difficulties for their age in the majority of cases, with a similar profile in almost 50% of the patient sample.

#### 6.3.1.3 Cognitive Flexibility

In relation to the WCST, 3 children from the SEND group obtained the lowest standard score available (of <55). These children were then assigned a score of 55, see Table 6.6. The SEND group averaged in the "moderately to severely impaired" classification range which was lower than the patient group who were "mildly impaired".

**Table 6.6: WCST performance of the patient and SEND sample**

| WCST | SEND Group | | | | Patient Group | | | |
|---|---|---|---|---|---|---|---|---|
| Perseverative errors | n | Mean | SD | RTM | n | Mean | SD | RTM |
| | 5 | 59.2 | 7.82 | -2.72 | 5 | 78.6 | 13.78 | -1.43 |

The percentile rank performance of the SEND group in Figure 6.5 show 4/5 children situated in the "moderately-to-severely impaired" range, with Case 4 situating in the "mildly-to-moderately impaired" range. The patient group profiles were mixed with scores in the "average" (Patient 20); "below average" (Patient 7); "mildly impaired" (Patient 6) and "moderately to severely impaired range" (Patient 9 and 18).

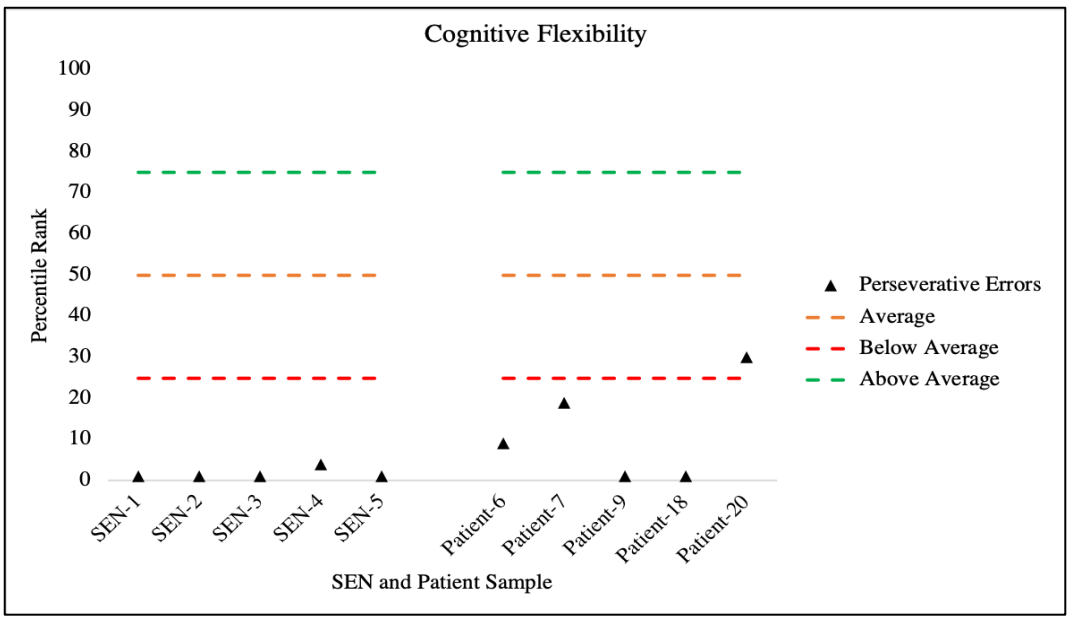


**Figure 6.5: WCST percentile rank performance of the patient & matched SEND sample.**

In comparison to the full patient sample in Figure 6.6, 4 children found this task too challenging to complete. Excluding these, around half of the sample (9/16) presented below average performance (<25). Comparatively, in line with the WCST manual classification range (average PR=29-67) the majority of the sample (10/16) presented below average (and further impaired) cognitive flexibility (Heaton et al, 1993).

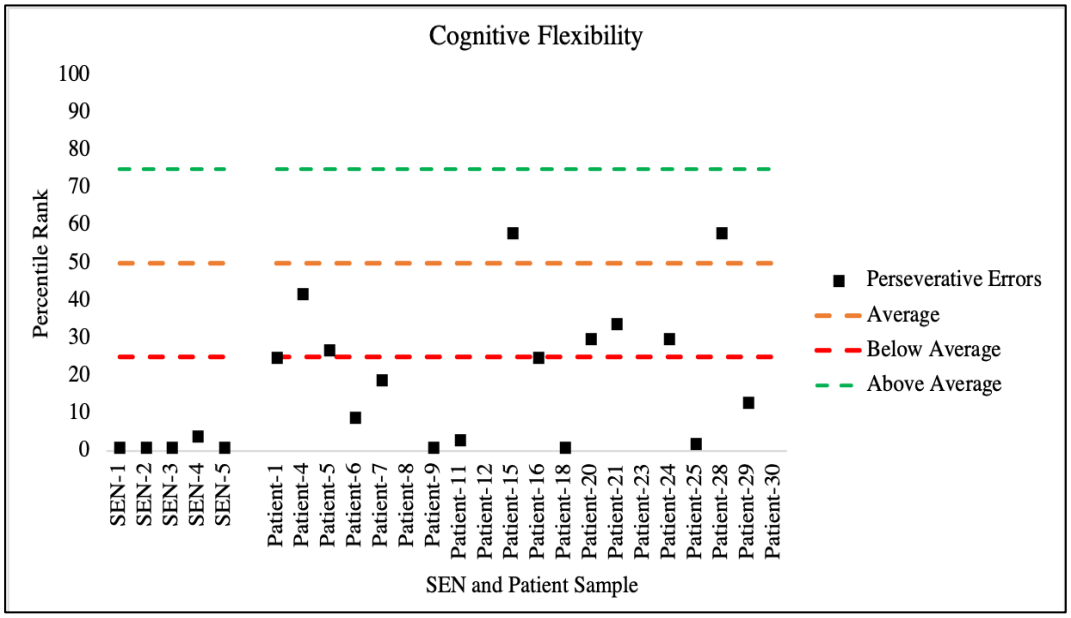


**Figure 6.6: WCST percentile rank performance of the full patient & SEND sample.**

Overall the SEND sample presented clear cognitive flexibility difficulties. Similar performance was clear in more than 50% of the patient sample.

#### 6.3.1.4 Language

For both groups, performance on the CELF fell below the criterion score of difficulty (i.e. standard score of 85) which would suggest signs of language difficulty and further testing would be required (Semel & Wiig, 2006), see Table 6.7. The performance of the SEND group exceeded more than 2.5 SDs below the mean situating in the "very low/severe" severity range of language disorder across all measures. In comparison, the patient group average situated below average in the "marginal/borderline/mild" classification.

**Table 6.7: CELF-4 performance of the patient and SEND sample.**

| CELF-4 Composite | SEND Group | | | | Patient Group | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | RTM | n | Mean | SD | RTM |
| Core Language (CLS) | 5 | 55.4 | 16.24 | -2.97 | 5 | 82.2 | 29.69 | -1.19 |
| Receptive Language (RLI) | 5 | 62.4 | 16.04 | -2.51 | 5 | 82 | 27.61 | -1.20 |
| Expressive Language (ELI) | 5 | 60.4 | 15.96 | -2.64 | 5 | 84 | 28.84 | -1.07 |

Based on the percentile ranks in Figure 6.7, the SEND sample presented clear below average language functioning for their age (<25). The findings are mixed for the patient sample, ranging from above average (Patient 6); average (Patient 20 and 7) to clear below average performance (Patient 9 and 18).

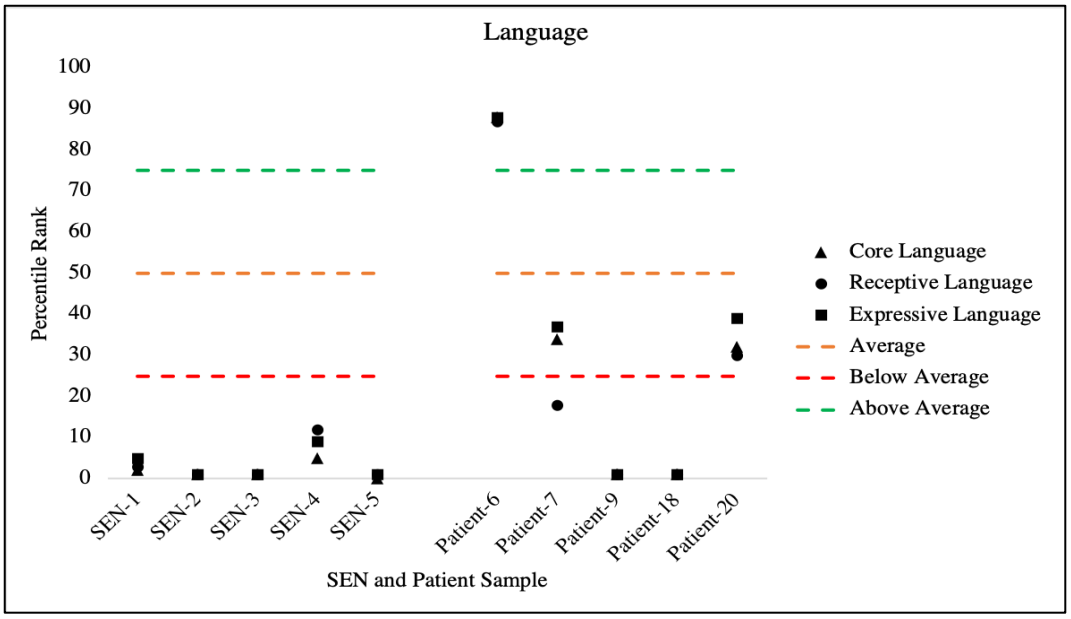


**Figure 6.7: CELF-4 percentile rank performance of the patient & matched SEND sample.**

In relation to the full patient sample (see Figure 6.8) the majority presented a language profile similar to that of the SEND group. This consisted of 14/20 (70%) situating below average across all language domains. The remaining 6 children presented unique profiles consisting of "above average" (Patient 6), "average" (Patient 20) and domain-specific profile of relatively better expressive language in the average range (Patient: 4, 7, 15, 21).

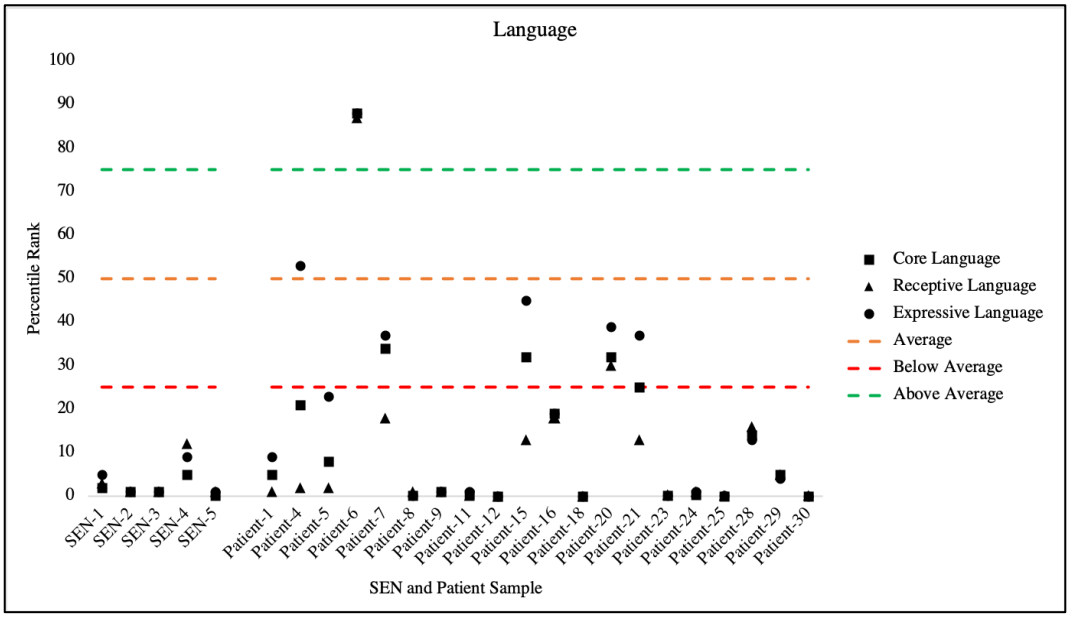


**Figure 6.8: CELF-4 percentile rank performance of the full patient & SEND sample.**

Overall on a group level both patients and the SEND sample presented clear difficulties, but the SEND group were more severe. However, considering the percentile ranks, the SEND group presented clear domain general difficulties with a comparable profile of core language functioning in the majority of the patient group (16/20).

#### 6.3.1.5 Motor assessment

On the MABC-2 (see Table 6.8) the SEND group presented poorer overall motor functioning. Findings from the Manual Dexterity (MD) and balance components show clear difficulties which may warrant further support as these fell 2SDs below the mean (Henderson, Sugden & Barnett, 2007). In comparison, the patient group were "at risk" of MD difficulties (-1SD below the mean), with relatively intact balance functioning.

**Table 6.8: MABC-2 performance of the patient and SEND sample.**

| MABC-2 Composite | SEND Group | | | | Patient Group | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | RTM | N | Mean | SD | RTM |
| Manual Dexterity | 5 | 3.2 | 2.68 | -2.27 | 5 | 4.4 | 2.88 | -1.87 |
| Balance | 5 | 3.6 | 3.71 | -2.13 | 5 | 8.6 | 5.13 | -0.47 |

Based on the percentile rank distributions in Figure 6.9 a mixed profile of motor functioning was found in both groups.

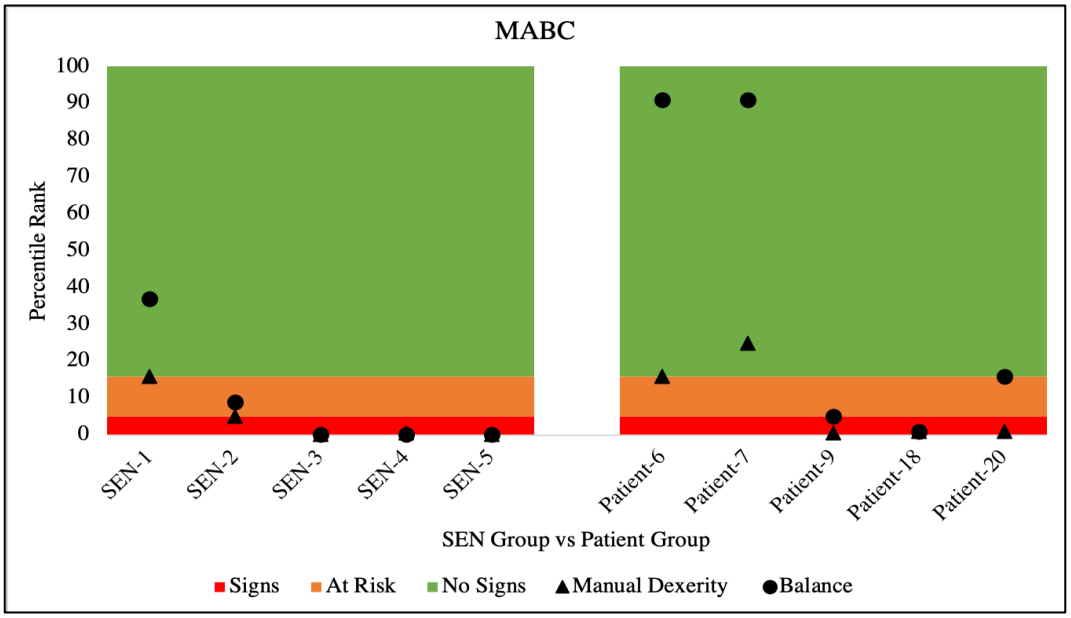


**Figure 6.9: MABC-2 percentile rank performance of the patient & matched SEND sample.**

In the SEND group, 3/5 presented domain general difficulties (Case 3, 4 and 5), one child presented significant MD difficulties with at risk balance profile (Case 2) and one had relatively spared motor functioning (Case 1, PR >15). A similar profile was found in the patient group, domain general difficulties were found in 2/5 (Patient 9 and 18), significant MD impairment was found in 1/5 (Patient 20) and 2/5 showed no signs (Patient 6 and 7).

Considering performance of the full patient sample (see Figure 6.10) only 3 children had relatively intact motor functioning across both components (Patient: 5, 6, 7). However, a higher number (8/20, 40%) had significant domain-general difficulties, with a similar number of children (9/20, 45%) presenting a domain-specific profile (i.e. significant MD or balance). Despite the small sample size, the majority of the SEND group presented domain general movement difficulties, which were comparable to the Patient group.

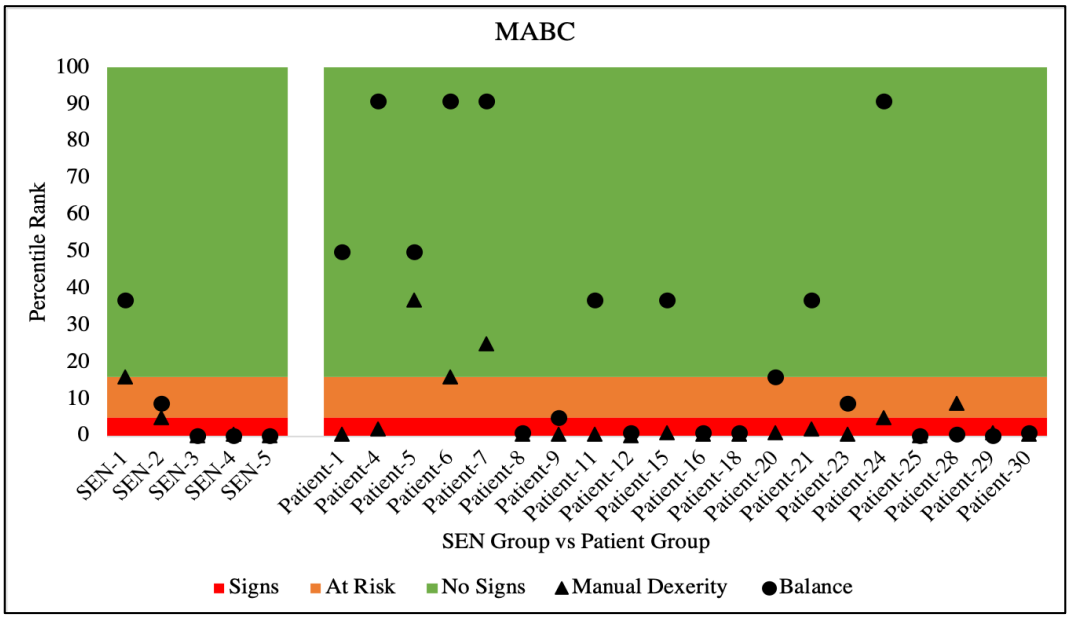


**Figure 6.10: MABC-2 percentile rank performance of the full patient & SEND sample.**

In summary, findings from the cognitive and motor group averages show that the SEND group were more impaired compared to the patient sample. Performance of the SEND group frequently fell more than 2SDs below the mean, while the patient sample extended near to 1SD below the mean. In relation to the CNV group, performance situated below average and was generally more heterogeneous but strongly skewed towards high levels of impairment. Considering this and the percentile rank distributions, almost 50% of the patient group presented comparable profiles to the SEND cases.

### 6.3.2 Single case comparison

#### 6.3.2.1 Patient 7 and Case 4

In relation to SEND Case 4 and Patient 7 (see Figure 6.11) neither of the children presented scores that consistently situated in the average range. The SEND case scored below the 15th percentile across the majority of measures, with relatively better verbal IQ performance (PR=27). Patient 7 showed a mixed profile ranging from the 1st to 61st percentile, with relative strengths in simple verbal WM (PR=61) with weaknesses in non-verbal ability (non-verbal IQ PR=1 and simple visuospatial WM PR=2). Patient 7 presented preserved motor abilities in MD and balance performance (PR>15) while the SEND case presented significant domain general movement difficulties (PR<5).

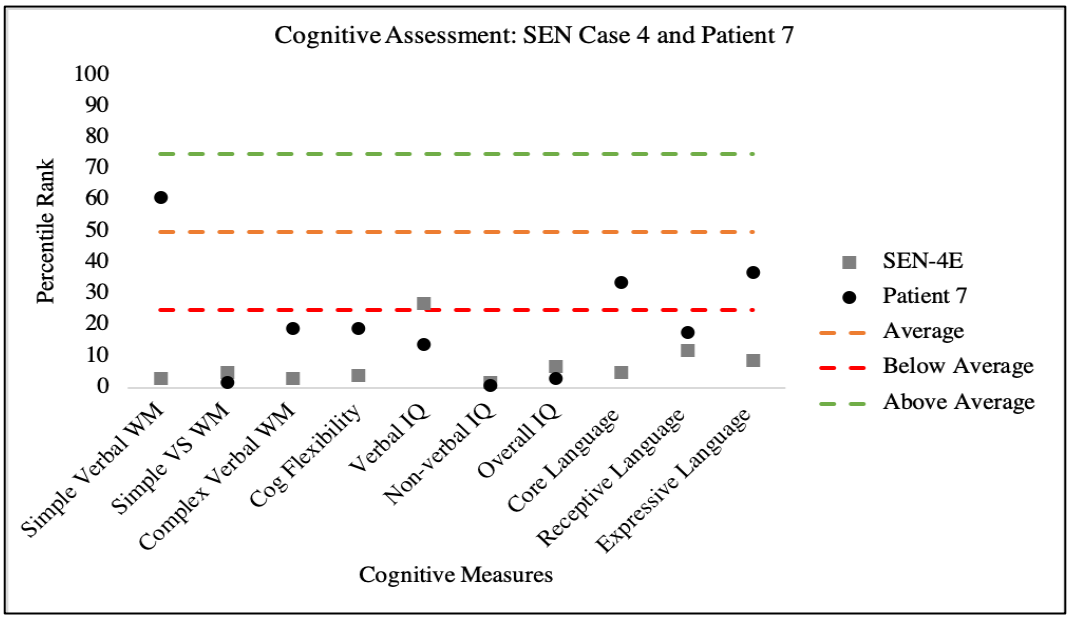


**Figure 6.11: Case 4 & Patient 7 percentile rank distributions from the cognitive assessments**

#### 6.3.2.2 Patient 6 and Case 5

In relation to Case 5 (see Figure 6.12) there were clear performance discrepancies in comparison to Patient 6. The SEND case presented consistently below average cognitive functioning across all measures while Patient 6 presented profile of below average (cognitive flexibility, simple VS WM); average (simple verbal WM, complex verbal WM, IQ) and above average (language) performance. There was also a clear distinction on the motor functioning of both children, as the SEND case present clear difficulties on both components (PR=0.1) while Patient 6 showed no signs of difficulty (PR>15).

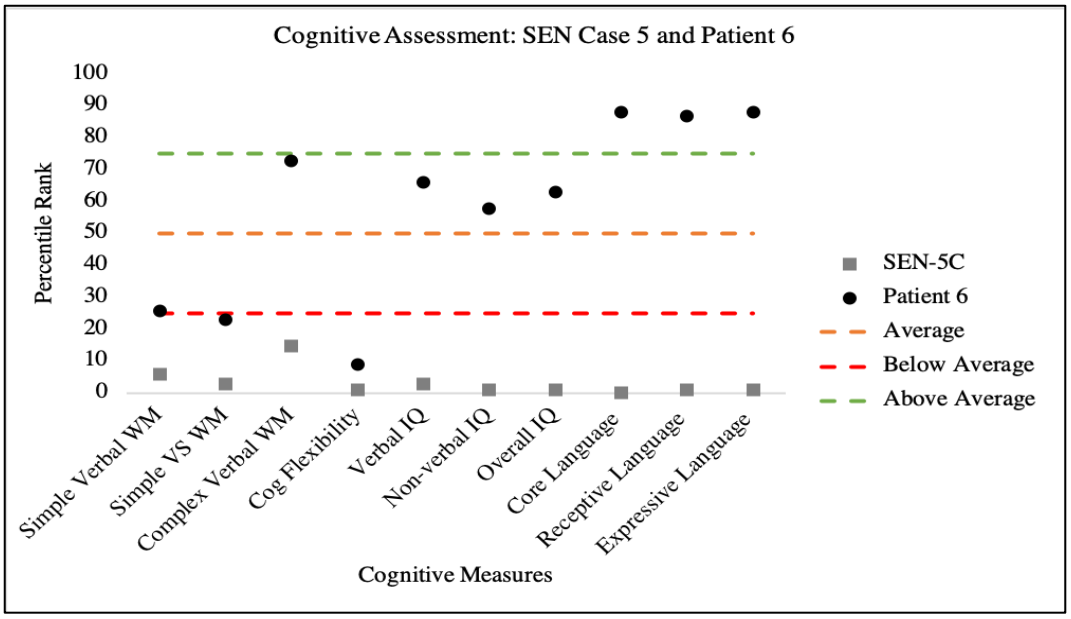


**Figure 6.12: Case 5 & Patient 6 percentile rank distributions from the cognitive assessments**

## 6.4 Discussion

This chapter explored a sample of children with SEND and explored how representing their cognitive and motor profiles were to children with a diagnosed CNV. On a group level the descriptive analysis was conducted on a small number of children, therefore the data should be interpreted with caution and it is difficult to draw any specific conclusions. On average both groups of children presented below average performance across the cognitive and motor assessments, but they differed by the severity of impairment. The SEND sample presented clear difficulties which fell close to 2SD below the mean, while the patient group situated 1SD below the mean with a more variable profile. However, considering the percentile rank distributions, a large number of CNV (more than 50%) cases presented comparable cognitive and motor profiles to the SEND group. For the remaining minority of cases, these children appear comparatively closer to the normal range but are clearly rarely performing close or above a level expected for their age which may result in difficulties accessing the appropriate education support or intervention.

In relation to the cognitive assessments, the majority of the patient sample presented below average intellectual functioning which was similar to the SEND group. This may result in challenges keeping up with the demands of learning and academic contexts (Karande, Kanchan & Kulkarni, 2008) due to limited factual knowledge and difficulties with abstract and fluid reasoning (Wechsler, 2011). In relation to Working Memory, both

groups were particularly impaired on the complex verbal WM task which may indicate difficulties in learning and manipulating new content (Alloway, Gathercole, Adams & Willis, 2005). Related to this higher cognitive function, is how well children can problem solve or think flexibly, and the majority of both groups presented deficits in this ability. This may impact how efficiently children can think creatively, take new perspectives, adapt to circumstances and approach learning tasks (i.e. school readiness) (Diamond, 2014; Vitiello, Greenfield, Munis & George, 2011). Finally, in relation to language, both groups fell below the threshold and would require further assessment. The SEND group average was lower than that of the patient group, but when considering the percentile rank distributions, around 50% of patients presented domain general difficulties. Such language difficulties may impact how well children can understand others and express their needs effectively but also increase the risk of poor academic progress, mental health problems and criminal behaviour (Law, Charlton & Asmussen 2017).

Related to these cognitive difficulties is the poor motor functioning found in both groups. Although the severity of movement performance was worse in the SEND cases, the majority of patients presented significant difficulties in at least one component. These fine and gross motor impairments may affect how well children can access learning resources (e.g. explorative play), progress academically (e.g. handwriting) and interact with others (e.g. playing). They may also influence children's engagement in tasks that require precision and accuracy (e.g. daily living tasks) and successful adaption and control of their body (e.g. sitting or dealing with environmental demands) (Adolph, 2008; Bart, Hajami & Bar-Haim, 2007; Marr, Cermak, Cohn & Henderson, 2003).

In relation to the matched control comparisons, the children in the SEND group consistently situated below average suggesting significant impairments. In comparison, the patient controls exhibited a more heterogeneous phenotype, ranging from domain general difficulties to more specific profiles consisting of relative strengths and weaknesses. Copy number variance has been associated with the risk of developing neurodevelopmental difficulties (e.g. ASD, developmental delay) (Kelleher & Corvin, 2015). There is emerging evidence of the educational needs of children with more common CNV syndromes which have been associated with a distinct 'behavioural phenotype' consisting of relative strengths and weaknesses (Fidler, Hodapp & Dykens, 2002; Reilly, 2012; Reilly, Senior & Murtagh, 2015). For example considering more common and well-studied CNV syndromes such as Williams syndrome, mild Intellectual

Disability; relatively better verbal IQ; expressive language and facial recognition skills in contrast to poorer non-verbal IQ and spatial ability are common phenotypical traits (Martens, Wilson & Reutens, 2008; Mervis & Klein-Tasman, 2000). Alongside this, Prader-Willi Syndrome (PWS) has been associated with excessive interest in food, obesity, mild ID, poor social communication and special school provision (Cassidy, 1997; Whittington et al, 2004). Finally, 22q11.2 DS (Velo-Cardio-Facial Syndrome, VCFS) has also been characterised by a profile of 'non-verbal learning difficulty' consisting of difficulties in maths arithmetic and non-verbal IQ with relative strengths in verbal ability (memory and IQ) (Moss et al, 1999; Woodin et al, 2001). In relation to these more common syndromes, Reilly, Senior and Murtagh (2015) explored the perspectives of teachers (n=204). In relation to teachers views on how knowledgeable they felt about the syndrome, 72% of teachers from mainstream schools said they had limited/no knowledge of WS with 54% of teachers from specialised settings. The findings were similar for VCFS as 60% of mainstream teachers had limited/no knowledge with 82% from specialised settings. The majority of teachers also felt that the needs of children with CNV genetic syndromes, PWS (76%), WS (58%) and VCFS (70%) are similar to those with intellectual disability and that children will struggle to reach their full potential in a mainstream education as they require specialist support and present a range of complex needs (PWS=79%, WS=67%, VCFS=67%). Only 11% of teachers had training on the child's genetic syndrome and 60% of teachers of children with 22q11.2 said they would like further training. Overall, these findings may highlight the limited knowledge of more CNV syndromes (less common CNVs) in educational settings, which may impact how successful children can access the curriculum and learning opportunities.

In relation to education and employment trajectories, Mosheva et al (2019) explored the profile of individuals with 22q11.2DS from childhood to adulthood. They found cognitive abilities predicted the type of education system placement (i.e. mainstream or special educational setting) and those in mainstream schooling had significantly higher IQ. Given the phenotypical similarities of children with CNVs (in general) to those with variance to a specific locus or that associated with a syndrome, these findings may provide an insight into the potential implications for children. They may be at risk of difficulties with learning, accessing the curriculum effectively and understanding how to successfully build on their knowledge. As previously discussed in Chapter 3 an initial attempt was made to understand the potential impact of the project for families. It was identified from

the evaluation data that parents found the performance summary report useful and utilised this to support applications for additional provisions for their child.

Across the cognitive and motor measures around 50% or more of the patient group presented difficulties comparable to children with a statement of educational provision. The present work in ages 7-16 years may support a case in raising awareness of copy number variance in general and the implications for the developmental trajectory. From an early age language, physical, personal, social and emotional development are key areas which form the basis for learning (Department for Education, 2017) and these skills are strengthened throughout the national curriculum (e.g. literacy, mathematics and creative thinking). If children struggle in these domains early in development, this may risk challenges for them at school and throughout their development. Therefore, to support children with CNVs and who are at risk of underachievement, it may be useful to apply for additional provisions (e.g. my support plan, placed on SEND register or EHCP for complex needs) to enable the child to meet their needs and aspirations with consideration of their developmental functioning level in contrast to their peers. Children with SEND are usually taught in smaller class sizes or work away from the classroom which may enable children to gain tailored support their learning (Webster & Blatchford, 2017). Based on this, it may be useful for schools to engage in differentiated teaching approaches for these children (e.g. classroom support, visual aids) to support the learning process where possible (Code of Practice, 2015). Alongside this, it would be beneficial for schools to understand and identify the potential developmental risk factors associated with genetic variance early in formal education to promote timely intervention (i.e. early years).

## 6.5 Chapter contributions

- A high proportion of children with a CNV are at risk of performing similar to children with special educational needs on assessments of cognitive and motor functioning.
- These assessments explore the fundamental skills which underpin and support learning processes and skill development which may result in these children facing challenges in comparison to peers of the same age.
- At present there is relatively more understanding of the developmental profiles of more common genetic syndromes. Findings from the present chapter show around 50% of children with a CNV present profiles similar to children with a recognised statement of educational provision (i.e. EHCP).

- This may raise awareness that the phenotypical implications of genetic variance should be considered or monitored within educational settings.

# Chapter 7 – Discussion and Conclusions

## 7.1 Overview

At present there is a relatively well-developed understanding of the outcomes associated with more common CNV syndromes and loci. Alongside this we know CNVs are influential in neurodevelopmental disorders, and factors concerning gene content, CNV type and inheritance may contribute towards atypical phenotypical outcomes (Kaminsky et al, 2011). This project was interested in understanding the genotype-phenotype relationship, focusing on how genetic variance 'in general' may influence cognitive, motor and behavioural development. This was achieved using a battery of standardised assessments, which provided an understanding of performance in contrast to children of the same age. The cognitive abilities investigated underpin a range of skills which are central to children's learning. Alongside this, the movement assessment explored fine and gross motor proficiency, which enable children to successfully navigate the world and manipulate objects. Finally, a range of questionnaires were used to investigate behaviours symptomatic of neurodevelopmental disorders. Overall, these children were at risk of atypical cognitive and motor development with elevated behavioural difficulties. Some children presented clear domain general difficulties, while some presented domain specific profiles of relative strengths and weaknesses. This neurodiversity and variable expression highlights the complexity of the genotype and phenotype relationship, but also provides insight into the role of genetic variance for a developing child system.

## 7.2 Project implications

### 7.2.1 Research and theoretical implications

In Chapter 4, an exploratory investigation of the full patient sample was conducted. The findings showed that performance situated below average range across the cognitive tasks. The group presented relative strengths on tasks that relied on simple storage and retrieval processes (e.g. verbal IQ and simple verbal WM) with particular difficulties on tasks assessing higher executive function such as problem solving or manipulation of information (i.e. cognitive flexibility, complex verbal WM, non-verbal IQ). Alongside this, the sample presented clear language difficulties that would require further assessment. In relation to the genetics literature, this cognitive profile was similar to children with more common CNV syndromes such as 22q11.2 DS and Williams

Syndrome (WS). In these cases, children have been found to have difficulties with general cognitive ability, higher cognitive functions and language functioning, with a similar domain-specific profile of relatively better verbal IQ than non-verbal IQ (see section 4.3.2.5). In relation to movement functioning, there were two main groups. One group presented clear domain general difficulties spanning both manual dexterity and balance, while the other presented significant manual dexterity difficulties with risks to balance development. Similar to the cognitive domain, the patient group presented profiles which are comparable to children with diagnosed CNV syndromes (e.g. WS, 22q11.2 DS). In these children, motor delays which impact both fine and gross motor skills have been reported, which may limit daily activities, learning and effective interaction with the world (see section 4.3.3.3). Finally, based on the behavioural questionnaires, each patient presented symptoms that met the criteria on more than one measure. Across 5 questionnaires, with 8 potential behavioural outcome measures, the average symptom count was 5.05, with movement, psychological, social communication, emotional and behavioural difficulties most frequent. Similar psychological and coordination difficulties have been reported in children with 22q11.2 DS (see section 4.3.4.6 for discussion).

The Pennington (2006) Multiple Deficit Model may provide a useful perspective on the findings. This model highlights the cascading impact of genetic factors on phenotypical development. Development is based on a complex interaction of various cell types, genes, fibre pathways and brain regions (Mitchell, 2015). To situate this work, children in the sample presented difficulties across all measures. This could suggest that CNVs may serve as a risk factor or are influential for developmental processes. Deletions or duplications to genetic material may subsequently impact critical biological functions implicated in neural and brain development systems due to genetic dosage imbalances. These discrepancies may contribute towards atypical development and impact a range of functions spanning developmental domains (i.e. comorbidity) (Pescosolido, Yang, Sabbagh & Morrow, 2012; Reichenberg, Mill & MacCabe, 2009). The sample presented comorbid cognitive, motor and behavioural difficulties, which may be attributed to shared biological and genetic processes (i.e. pleiotropy). To further this, phenotypical heterogeneity and atypical development was clear irrespective of factors concerning the number, type, location or inheritance of the CNV.

In relation to location, it was of interest to explore the phenotypes of children with variance to a specific locus associated with an increased risk of neurodevelopmental

disorder (NDD-CNV). This group was compared to children with rare, less commonly investigated CNVs (Non-NDD CNV). Based on the single case analysis, children with an NDD-CNV at similar genetic loci did not present a typical phenotypical profile or cluster of symptoms. Some presented clear domain general difficulties, while some had specific strengths and weaknesses. None of the children consistently performed in the average range, but the majority situated below average across tasks. As children with the same CNV presented varied profiles, this may highlight the issue of variable expressivity and how genetic variance has a cascading impact on different developmental domains in a complex manner. On a group level, both groups presented below average performance across the cognitive tasks. The NDD-CNV group performed relatively worse (-2SD below the mean) than the Non-NDD group (-1SD) across some tasks. However, these differences were non-significant, which may be due to the relatively small sample size resulting in difficulties detecting an effect. In relation to the motor assessment, there was a significant difference in the manual dexterity performance of the NDD-CNV group (-2SD below mean, significant) in contrast to the Non-NDD group (-1SD, at risk). These profiles were similar for balance functioning as the NDD group were at risk of difficulties, while the Non-NDD group presented relatively intact functioning (non-significant). In relation to behavioural difficulties, it is hard to draw general conclusions due to unequal sample sizes. However, across the 8 behavioural outcomes, both groups presented a similar average number of symptoms (NDD=5.21, range 2-8; Non-NDD=4.71, range 2-7). While children with an NDD-CNV are at increased risk of difficulties (as discussed in the literature), the below average performance of the non-NDD group may also indicate that a variant to any genetic loci may risk atypical development in comparison to children of the same age (i.e. below average functioning).

Related to this, the findings were similar for the exploration of the type of variance (i.e., deletion or duplication). There was a slight difference in the extent of cognitive difficulties (although non-significant) between those with a deletion and duplication. However, both groups presented below average cognitive functioning (-1SD) with the findings extending to more than -2SD below the mean for across some tasks (WM, language) with no specific pattern. In relation to motor functioning, both groups presented relatively intact balance functioning. However, for manual dexterity, they both presented difficulties, but the duplication group was slightly more impaired (-2SD) than the deletion group (-1SD) (non-significant). Finally, on the behavioural measures, a higher number of

children in the deletion group (average behavioural symptoms=5.89) met the criteria on over 50% of the questionnaires than the duplication group (average behavioural symptoms=4.18). Given the comparable performance across groups, this could highlight that any deviation to the normal genetic structure which results in a genetic imbalance (i.e. loss or gain) may be a significant risk factor for atypical development.

In relation to inheritance, it was of interest to explore the cognitive, motor and behavioural functioning of children from the same family with the same CNV. These 3 children presented clear strengths in motor functioning, but each presented a domain specific cognitive and behavioural profile which broadly situated below average. The findings from this exploration may highlight issues of variable expressivity and how genetic variance operates in a complex manner influencing phenotypic outcomes to varying extents. Finally, it was of interest to explore if the number CNVs influenced phenotypical outcomes. This was achieved by comparing the performance of a patient with 2 CNVs against the full sample. Although this patient presented significantly low cognitive and motor functioning (percentile rank <5) and elevated behavioural difficulties (7/8 measures) a similar profile was found in some children with only 1 CNV. This may support the idea that any genetic deviation is critical for development.

Overall in relation to Pennington (2006) and the findings from Chapter 4, the genotype and phenotype relationship is complex and probabilistic, and CNVs may be a risk factor for atypical development. Due to factors of variable expressivity, it is hard to systematically quantify phenotypical outcomes, but we know that children with CNVs are at risk of below average cognitive and motor functioning and risk behaviours typical of neurodevelopmental disorders. In relation to this, it was of interest to understand the extent of these difficulties. Based on this, Chapter 6 explored the profile of children with a diagnosed CNV against children with special educational needs (which were not genetic in origin) within a specialist provision. On a group level, children with a CNV performed around 1SD below the mean, while the SEND group situated more than 2SDs below. However, when the percentile rank distributions of the SEND group and the full patient sample were compared, there were clear similarities. On the cognitive measures, the majority of patients (16/20) presented equivalent core language and overall intellectual functioning profiles. Alongside this, around 50% of the patient sample presented similar working memory, cognitive flexibility and motor functioning. These findings showed that children with a CNV present comparable cognitive and motor functioning to children

with a recognised statement of special educational provision. This may highlight the potential extent of developmental difficulties associated with CNVs in 'general'.

The genotype and phenotype relationship is complex and is influenced by environmental factors. These factors work in an inter-dependant way and it is difficult to systematically detangle and understand their relationship. For example, genetic and environmental factors may have a combined impact on phenotypical outcomes, alternatively the environment may regulate the expression genetic factors or genetic factors may impact how the environment influences phenotypical outcomes (van Loo & Martens, 2007). It was of interest to initially explore these concepts by comparing the performance of patients to their unaffected siblings (see Chapter 5). On a group level, siblings presented relatively better cognitive and motor functioning (situating in the average range) and a lower number of behavioural difficulties. However, given the small sample size it was challenging to draw any specific conclusions.

In relation to the matched case investigations, some patients and their siblings had clear performance differences, contrasting strengths and weaknesses and similar profiles. In the cases of phenotypical similarities, factors of unidentified genetic variance and germline mosaicism was discussed for some children. Genetic mosaicism occurs when there is a mutation present in the parent's germline, but it is not detectable in the parental blood sample but leads to a denovo variant in the offspring (Cassidy & Allanson, 2005). Alongside this, in the absence of any shared genetic markers, similarities in phenotypical profiles may be due to non-shared environments (e.g. interaction with peers or experiences at school) or shared environmental factors (i.e. parental influences). The Intergenerational Multiple Deficit Model (van Bergen et al, 2014) (extension of Pennington model) may provide a useful perspective on the findings. This model discusses the gene and environment interaction considering the role of parents. Parents pass on their genes via genetic pathways, and behaviours via environmental pathways (cultural transmission). Parents may therefore influence developmental outcomes, either through the environments they create for children or via parenting styles. For example, a child's cognitive development may be influenced by the availability of resources in the home (e.g. number of books in the home, van Bergen et al, 2018). Alternatively, their psychological development may be influenced by home factors (e.g. household chaos) (Coldwell et al, 2006; Hanscombe et al, 2011; Sikora, 2019). Alongside this, parental behaviours and their own phenotypes may also impact children's cognitive development

(Klaassen, 2016; Landry et al, 2008; Meaney & O'Donnell, 2015). For example, parenting styles can have a positive or negative impact on development, as more sensitive mothers were found to support their child's exploration of the environment while less respondent mothers would interrupt their infant's exploration (Karmiloff-Smith, 2010). Related to this, it was discussed that the parental phenotype itself may also impact the child's phenotype. For example, parental educational background can influence children's intellectual functioning (Klaassen, 2016) or the mother's prenatal anxiety may be critical for the child's emotional and behavioural development (Meaney & O'Donnell, 2015). Contrastingly, phenotypical differences may also be facilitated by parental factors. Genetic factors may influence parental expectations of their child and the opportunities they create for them early in development, which may in turn contribute towards atypical development (Massand & Karmiloff-Smith, 2015; Karmiloff-Smith, 2012). Overall these findings may highlight the complex gene-environment interaction– see section 5.4.

Overall CNVs impact the number of genes in the affected region. This causes a genetic imbalance which then has a feedforward impact on other biological processes which are likely to have widespread implications on development, leading to heterogenous outcomes. Some processes are time dependant, so a genetic disruption may have consequences or impact developmental outcomes such as essential cellular and neuronal functions (Johnson, 2015). In some cases, phenotypical similarities may arise due to shared molecular mechanisms, and factors of pleiotropy (one gene may have multiple outcomes) but these factors in conjunction with the environment may affect a child's developmental trajectory to varied extents. These findings may situate well within a Neuroconstructivist perspective (Karmilloff-Smith, 2009) which considers the complex interplay between genes, brain development and phenotypical outcomes. These factors then work in a probabilistic fashion combined with both intrinsic (i.e. other biological or developmental process) and extrinsic (i.e. environmental) factors which may impact a child's developmental trajectory. As a consequence, children may present various difficulties which span developmental domains or meet the diagnostic criteria for more than one neurodevelopmental disorder (Pennington, Willcutt & Rhee, 2005) or lead to a profile of domain general or specific strengths and weakness. This was clear in the single case work as all children presented a complex profile even when they had a CNV to the same genetic region, suggesting that children can be affected by genetic variance to greater or lesser extents and the phenotypic implications are not uniform. Over the course

of development, a child will become more efficient at tasks and this will support a gradual specialisation of brain processes. However, if a child has a genetic variant, they may be at increased risk of atypical brain development from the outset due to abnormal levels of gene expression (Morrow, 2010). This combined with environmental influences may contribute towards developmental difficulties which span different domains.

In summary children with a CNV presented a range of difficulties which spanned cognitive, motor and behavioural domains. This may highlight that these children are at risk of difficulties in areas that support the basis of skill development and learning. These findings were comparable to the phenotypes described in the literature for children with more common CNV syndromes in which developmental difficulties are prevalent. In the case of syndromes, often children have a specific profile of common features which meet a diagnostic criterion. However, in the present work some children had rare variants (with limited evidence of clinical significance), often these were not associated with a genetic syndrome and it was only speculative that the CNV was contributing to the phenotype. Based on this, the present findings may highlight the potential difficulties some children may face in accessing support to help meet their needs. The links between cognitive, motor and behavioural development are discussed in section 4.3.5.

### 7.2.2 Implications for practice

At present there is relatively better understanding of the profiles of more common CNV syndromes or variants to specific loci. In relation to CNVs 'in general', we know these contribute towards neurodevelopmental disorder risk, and may lead to a range of phenotypes due to variable expressivity (Nevado et al, 2014). The present work extends this by highlighting that genetic variance may risk atypical cognitive, motor and behavioural development and that any CNV should be monitored closely, irrespective of type, location, or number.

Within the education system, teachers and parents have been found to have limited understanding of the symptomology associated with genetic syndromes (e.g. WS and 22q11.2 DS) (Reilly, Senior & Murtagh, 2015) and education services themselves may not be fully adjusted to these specific profiles (Fidler et al, 2002). Although this project is not investigating specific CNV syndromes, this may provide an insight into the current understanding of the aetiology of developmental difficulties. As these syndromes are relatively better understood, this may raise concern as to the understanding surrounding

of less common CNVs, CNVs in general, or those CNVs not associated with a distinct phenotype thus resulting in challenges for some children gaining relevant support. This may link to the findings from Chapter 3 and highlight the preliminary benefit of this project for families. Questionnaire evaluations were sent to family on completion of the assessments and once they had received a feedback booklet. The majority of parents found the project useful for their understanding of their child's cognitive, motor, behavioural and overall development. Alongside this, the majority utilised the feedback report to assist application for additional support (disability living allowance and EHCP).

In relation to supporting families, it should be highlighted that CNVs are influential for development regardless of the loci, type, number or inheritance. Although there are specific genes that influence critical biological processes that implicated in the mutation, it is hard to specifically quantify or standardise the resulting phenotypical outcomes due to this complexity. Factors of phenotypic severity, inheritance and gender have been reported for more common CNVs and present issues for genetic counselling (De Wolf, Brison, Devriendt & Peeters, 2013). Alongside this, in the patient cytogenetic reports it was detailed that it is difficult to understand whether the CNV is contributing towards the child's phenotype due to limited evidence and or the child did not meet the symptomology for a diagnosed syndrome. This is further complicated by issues of variable expressivity, as it is difficult to define a specific phenotype as children may present a range of outcomes which vary by severity. In these cases, it may be challenging for families to access support or relevant information due to the complex nature of CNVs. However, if education systems are informed as to the significance of CNVs, this may raise awareness and understanding to ultimately support children's learning and development.

Therefore, the present work may have implications for practice, as having a CNV may serve as a risk marker for careful monitoring within preschool or educational settings. Although CNVs are pleiotropic and probabilistic in their phenotypical manifestation, they may have a critical function for a child's developmental trajectory due to their biological significance. This may highlight the role of effective communication between health and education services. In line with this, some children with a CNV may not present the specific symptoms which meet a syndrome diagnosis, or in the case of rare variants there may be limited evidence of their clinical significance. Children with a CNV are at risk of difficulties within mainstream classes due to below average cognitive and motor functioning and elevated behavioural difficulties. These findings highlight that these

children are likely to require adjustments in the classroom, to learning tasks and additional resources to help them work in line with age related expectations. The abilities investigated underpin successful learning and knowledge acquisition, which structured learning settings rely heavily on and form the foundations for successful social, emotional and mental health development. This may highlight the importance of effective communication and early intervention, to ensure children receive the support required to access the curriculum for their age.

## 7.3 Limitations and future directions

The issues faced throughout this project were discussed in Chapter 3 and the following section discusses these with scope for future work.

Chapter 3 explored issues concerning the feasibility of setting up a clinical project, recruiting a paediatric sample and implementing standardised assessments within the home setting. When recruiting a patient sample the clinician's involvement and specific factors concerning patients are influential. Although convenient for families, implementing assessments within the home setting may be a challenge given space considerations and it is difficult to control extraneous environmental variables. It was suggested that projects requiring NHS ethics should be planned with a clear understanding of the required approvals, timelines and documentation. Alongside this, there should be an understanding of any patient-specific and home-specific factors which may affect recruitment, efficiency and safety of the data collection methods.

In relation to the findings, single case and group-based comparisons were reported, however the latter are to be interpreted with caution. As the findings are based upon on a relatively small sample size it is difficult to draw any general conclusion, find any specific patterns in the data or detect a statistically significant effect on a group level. We faced unforeseen difficulties with the recruitment as at the start of the project as the clinic thought a large number of families would be keen to take part. Alongside this, we faced issues with recruitment as we only had one clinician working with the project, which limited the opportunity of reaching and recruiting a large number of families. However, the single case explorations are of initial benefit.

Alongside this, it may be difficult to capture the profiles of a wide range of children with CNVs. The families that chose to take part may feel that their child required support resulting in an ascertainment bias. Despite these factors, this project aimed to provide an

initial investigation of the impact of CNVs on development, so there is scope to collaborate with charities, more hospitals, more clinicians or similar projects to help reach more families. For example, similar projects such as ECHO (Niarchou et al, 2014) explore the experiences of Children with 22q11.2 deletion and duplication syndromes. Similarly, the IMAGINE ID study (Chawner et al, 2019) explored the genetic contribution to long-term mental health outcomes in children with Intellectual Disability. These projects recruited via regional genetics centres, genetic databases and chromosomal support groups. Alongside this, they supplied incentives and the opportunity conduct the assessments within a laboratory setting which may be of interest for future projects.

Although a comprehensive assessment battery was employed, the assessments were conducted at one time point and within the home. This may result in difficulties understanding children's development over time and across settings (e.g. school). To understand the impact of CNVs in more detail, future work could follow up performance at a later date, which would provide understanding of whether CNVs impact children's developmental trajectories over time (Thomas, Ansari, Jarrold, & Karmiloff-Smith, 2009). Related to this, previous work has been conducted longitudinally in children with 22q11.2 DS (Chawner et al, 2017) and found cognitive abilities linked to the type of education placement and employment type in adulthood (Mosheva et al, 2019). This may be of relevance to the present project, investigating the longer-term development of children with genetic variance. Similarly, in relation to educational outcomes, it would be beneficial to explore the teachers and SENDCo's understanding of CNVs and knowledge of how CNVs may be influential for developmental and educational outcomes. Alongside this, as discussed in the previous section, teachers and parents had limited understanding of the phenotypes of more common CNV syndromes. Therefore, exploring teachers understanding of CNVs, may support children in accesses relevant support. This may enhance the communication between health and education settings as at present this dialogue varies widely (Mukherjee, Lightfoot & Sloper, 2000; 2002).

Related to this, the participants in the current project were aged between 7-16 years. It would be of benefit to understand how CNVs manifest and impact development in children from a younger age. This could support prompt intervention and an understanding of strengths and difficulties early in development. As early learning and schooling experiences provide the foundations for skill and knowledge development, children may risk falling behind their peers if their difficulties have not been identified.

As children progress through education, they work in more structured learning environments so children with cognitive difficulties may find these situations challenging or find the content difficult to understand as they have not met the developmental milestones for their age (on standardised assessments). In these cases, it may be challenging for children to catch up or perform in line with their peers (Alloway, Gathercole, Kirkwood & Elliot, 2009). Therefore, investigating the profiles of children in a pre-school or early years setting may be beneficial for the longer term and for potential intervention. Genetic variance in 'general', should serve as a risk marker for close monitoring to enable children to access enhanced support in the classroom (i.e. SEN support) or formal provision (i.e. Educational Health and Care plan).

Largely the present work shows that the relationship between genotype and phenotype is complex. A CNV itself may increase the risk of experiencing adverse experiences in childhood but also increase a child's exposure risk. In line with work surrounding 'Adverse Childhood Experiences' (Dube, 2001) multiple adversities may cluster leading to detrimental outcomes in adulthood. These adverse experiences may include societal, cultural and familial factors which have been difficult to control for in the present work.

In relation to societal factors, it is challenging to control for Socio-Economic Status (SES) and early developmental history. Factors concerning SES are influential for children's cognitive development from the early years (Dickerson & Popli, 2016) and can impact language ability (Law, Charlton & Asmussen, 2017) and executive function (Hackman, Gallop, Evans & Farah, 2015). For example, Shashi et al (2010) found children with 22q11.2 DS from lower SES families presented higher rates of behavioural difficulties than those from higher SES backgrounds. In relation to the present sample, the majority were recruited from a specific region due to the clinician's involvement. According to the English Indices of Deprivation (Ministry of Housing, Communities and Local Government, 2019) this region ranked within the top 10 local authorities for the highest proportion of neighbourhoods in the most deprived 10% of neighbourhoods (nationally); for income deprivation; employment deprivation and for income deprivation affecting children. Based on this, future work could explore parental education (i.e. highest qualification) and family income to understand whether these factors mediate developmental outcomes. Alongside this, exploring the presence of Adverse Childhood Experiences (e.g. maternal health, risky behaviours, opportunities) would be beneficial for understanding significant life events and investigating whether these have an impact

on developmental and educational outcomes (Dube, 2001; Smith, 2018). Family based factors may also be influential as parenting behaviours or attachment styles may contribute towards psychological development (Fearon, 2010). Similarly, child development may also be influenced by birth factors such as prenatal infection (Atladottir, 2010; 2012); prenatal nutrition (Roth et al, 2011; Suren, 2013) or obstetric complications (Gardener, 2009). An insight into these could be captured by an understanding early developmental factors via questionnaires or parental interview.

In summary, it is challenging to control for environmental and genetic factors that influence a child's development. In line with Brofenbrenner (1995) there may be distal factors in the macrosystem a child situates in (i.e. community) alongside more proximal risks from their immediate microsystems (i.e. experiences in family, school, peers). These non-shared environments (i.e. school experiences), shared environmental (i.e. parental factors) and individual factors are influential for a child's developmental trajectory. However, the present project provides insight into how genetic variance may mediate these relationships, leading to atypical cognitive, motor and behavioural development.

## 7.4 Conclusion

This collaborative project provided an initial understanding the impact of genetic variance on specific developmental abilities. In contrast to well-defined CNV syndromes (e.g. Williams Syndrome, 22q11.2 DS) there is limited evidence of the clinical significance of less common CNVs in the literature and within clinical settings (i.e. variants of uncertain significance). The relationship between genotype and phenotype is complex as some children presented domain general difficulties while some presented relative strengths and weaknesses, ultimately providing challenges when defining a specific cluster of symptoms associated with a CNV due to variable expression. This work found that any genetic imbalance irrespective of location, dosage imbalance, or size places children at risk of atypical cognitive and motor development with elevated number of symptoms typical of neurodevelopmental disorders. This may raise awareness and an understanding of how structural variants may influence child development which may be of benefit to support educational settings, children and their families.

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# Appendix A: Parent Questionnaire Booklet

## Parent Questionnaire: Patient

This questionnaire should be completed by a parent and given to the researcher when they come to visit.

The questionnaire pack should take approximately an hour to complete. We kindly ask that you respond to the best of your knowledge: there are no right or wrong responses.

**Child's name** _____

**Date of birth** __ __ / __ __ / __ __ __ __

**Date completed** __ __ / __ __ / __ __ __ __

**Questionnaire checklist**

1. Strengths and Difficulties Questionnaire ☐
2. Social Communication Questionnaire ☐
3. Vanderbilt ADHD Diagnostic Assessment Rating Scale ☐
4. Developmental Behaviour Checklist ☐
5. Developmental Coordination Disorder Questionnaire ☐
6. Observational Rating Scale ☐
7. Pragmatics Profile ☐

Thank you very much for your help. Your participation in this research project is greatly appreciated.

If you have any queries, please contact:

*Joyti Panesar (Primary Researcher)*

ps12jp@leeds.ac.uk

**1. Strengths and Difficulties Questionnaire**

• Please give your answers based on your child's behaviour over the last six months

• For each item please mark the box for 'Not True', 'Somewhat True' or 'Certainly True'

| | | Not true | Somewhat true | Certainly true |
|---|---|---|---|---|
| 1. | Considerate of other people's feelings | □1 | □2 | □3 |
| 2. | Restless, overactive, cannot stay still for long | □1 | □2 | □3 |
| 3. | Often complains of headaches, stomach-aches or sickness | □1 | □2 | □3 |
| 4. | Shares readily with other children (treats, toys, pencils etc.) | □1 | □2 | □3 |
| 5. | Often has temper tantrums or hot tampers | □1 | □2 | □3 |
| 6. | Rather solitary, tends to play alone | □1 | □2 | □3 |
| 7. | Generally obedient, usually does what adults request | □1 | □2 | □3 |
| 8. | Many worries, often seems worried | □1 | □2 | □3 |
| 9. | Helpful if someone is hurt, upset or feeling ill | □1 | □2 | □3 |
| 10. | Constantly fidgeting or squirming | □1 | □2 | □3 |
| 11. | Has at least one good friend | □1 | □2 | □3 |
| 12. | Often fights with other children or bullies them | □1 | □2 | □3 |
| 13. | Often unhappy, down-hearted or tearful | □1 | □2 | □3 |
| 14. | Generally liked by other children | □1 | □2 | □3 |
| 15. | Easily distracted, concentration wanders | □1 | □2 | □3 |
| 16. | Nervous or clingy in new situations, easily loses confidence | □1 | □2 | □3 |
| 17. | Kind to younger children | □1 | □2 | □3 |
| 18. | Often tells lies or cheats | □1 | □2 | □3 |
| 19. | Picked on or bullied by other children | □1 | □2 | □3 |
| 20. | Often volunteers to help others (parents, teachers, other children) | □1 | □2 | □3 |
| 21. | Thinks things out before acting | □1 | □2 | □3 |
| 22. | Steals from home, school or elsewhere | □1 | □2 | □3 |
| 23. | Gets on better with adults than with other children | □1 | □2 | □3 |
| 24. | Many fears, easily scared | □1 | □2 | □3 |
| 25. | Sees tasks through to the end, good attention span | □1 | □2 | □3 |

Do you have any other comments or concerns?

**2. Social Communication Questionnaire**

• Please place a cross in each box ('Yes' or 'No') that best describes your child

| | | | |
|---|---|---|---|
| 1. | Is she/he now able to talk using short phrases or sentences? | Yes | No |
| **If No, please proceed to question 8** | | | |
| 2. | Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you said? | Yes | No |
| 3. | Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way? That is, (either phrases she/he has heard other people use or ones she/he has made up). | Yes | No |
| 4. | Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times? | Yes | No |
| 5. | Does she/he ever get her/his pronouns mixed up (e.g., saying 'you' or 'she/he' for I)? | Yes | No |
| 6. | Has she/he ever used words that she/he seems to have invented or made up her/himself; put things in odd, indirect ways; or metaphorical ways of saying things? (e.g., saying hot rain for steam)? | Yes | No |
| 7. | Has she/he ever said the same thing over and over in exactly the same way, or insisted that you say the same things over and over again? | Yes | No |
| 8. | Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he has to have you go through? | Yes | No |
| 9. | Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell? | Yes | No |
| 10. | Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g. pointing with your finger, putting your hand on a doorknob to get you to open the door)? | Yes | No |
| 11. | Has she/he ever had any interests that pre-occupy her/him and might seem odd to other people (e.g. traffic lights, drain pipes or timetables)? | Yes | No |
| 12. | Has she/he ever seemed to be more interested in a certain part of a toy (e.g. spinning the wheels of a car) or an object rather than using the object as it was intended? | Yes | No |
| 13. | Has she/he ever had any special interests that were *unusual* in their intensity but otherwise appropriate for her/him age and peer group (e.g. trains, dinosaurs)? | Yes | No |
| 14. | Has she/he ever seemed to be *unusually* interested in the sight, sound, taste or smell of things or people? | Yes | No |
| 15. | Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping, or moving her/his fingers in front of her/his eyes? | Yes | No |
| 16. | Has she/he ever had any complicated movement of her/his whole body, such as spinning or repeatedly bouncing up and down? | Yes | No |
| 17. | Does she/he ever injure her/himself deliberately, such as hitting her/himself, biting her/him arm or banging her/his head? | Yes | No |

| | | | |
|---|---|---|---|
| 18. | Does she/he have any objects (*other* than a soft toy or comfort blanket) that she/he had to carry around? | Yes | No |
| 19. | Does she/he have any particular friends or a best friend? | Yes | No |
| **For the following behaviours, please focus on the time period between your child's 4th birthday and 5th birthday.** | | | |
| **You may find it easier to remember how things were at that time by focusing on key events such as starting school, moving house, Christmas time, or any other events that are particularly memorable for you as a family.** | | | |
| 20. | When she/he was 4 to 5 did she/he ever talk with you just to be friendly (rather than to get something)? | Yes | No |
| 21. | When she/he was 4 to 5 did she/he ever *spontaneously* copy you (or other people), or what you were doing (such as hoovering, gardening, mending things)? | Yes | No |
| 22. | When she/he was 4 to 5 did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)? | Yes | No |
| 23. | When she/he was 4 to 5 did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted? | Yes | No |
| 24. | When she/he was 4 to 5 did she/he nod her/his head to mean "yes"? | Yes | No |
| 25. | When she/he was 4 to 5 did she/he shake her/his head to mean "no"? | Yes | No |
| 26. | When she/he was 4 to 5 did she/he usually look you directly in the face when doing things with you or talking with you? | Yes | No |
| 27. | When she/he was 4 to 5 did she/he smile back if someone smiled at her/him? | Yes | No |
| 28. | When she/he was 4 to 5 did she/he ever show you things that interested her/him to engage your attention? | Yes | No |
| 29. | When she/he was 4 to 5 did she/he ever offer to share things other than food with you? | Yes | No |
| 30. | When she/he was 4 to 5 did she/he ever seem to want you to join in her/his enjoyment of something? | Yes | No |
| 31. | When she/he was 4 to 5 did she/he ever try to comfort you if you were sad or hurt? | Yes | No |
| 32. | Between the ages of 4 to 5 when she/he wanted something or wanted help, did she/he used to look at you and use gestures with sounds or words to get your attention? | Yes | No |
| 33. | Between the ages of 4 to 5 did she/he show a normal range of facial expression? | Yes | No |
| 34. | When she/he was 4 to 5 did she/he ever spontaneously join in and try to copy actions in social games – such as The Mulberry Bush or The Farmer's in his Den? | Yes | No |
| 35. | When she/he was 4 to 5 did she/he play any pretend or make believe games? | Yes | No |
| 36. | When she/he was 4 to 5 did she/he seem interested in other children of approximately the same age whom she/he did not know? | Yes | No |
| 37. | When she/he was 4 to 5 did she/he respond positively when another child approached her/him? | Yes | No |
| 38. | When she/he was 4 to 5 if you came into a room and started talking to her/him without calling her/his name, did she/he usually look up and pay attention to you? | Yes | No |
| 39. | When she/he was 4 to 5 did she/he ever play imaginative games with another child in such a way that you could tell they understood what each other was pretending? | Yes | No |
| 40. | When she/he was 4 to 5 did she/he play co-operatively in games that need some form of joining in with a group of other children, such as hide and seek or ball games? | Yes | No |

**3. Vanderbilt ADHD Diagnostic Assessment Rating Scale**

• Please give your answers based on your child's behaviour over the last six months

• Some of the behaviours may not apply to your child, if this is the case just leave it blank

• For any of the items that do, please circle the number corresponding to (0) Never, (1) Occasionally, (2) Often or (3) Very often

| | | Never | Occasionally | Often | Very often |
|---|---|---|---|---|---|
| 1. | Does not pay attention to details or makes careless mistakes with, for example, homework | 0 | 1 | 2 | 3 |
| 2. | Has difficulty keeping attention to what needs to be done | 0 | 1 | 2 | 3 |
| 3. | Does not seem to listen when spoken to directly | 0 | 1 | 2 | 3 |
| 4. | Does not follow through when given directions and fails to finish activities | 0 | 1 | 2 | 3 |
| 5. | Has difficulty organising tasks and activities | 0 | 1 | 2 | 3 |
| 6. | Avoids, dislikes, or does not want to start tasks that require ongoing mental effort | 0 | 1 | 2 | 3 |
| 7. | Loses things necessary for tasks or activities (toys, assignments, pencils, or books) | 0 | 1 | 2 | 3 |
| 8. | Is easily distracted by noises or other stimuli | 0 | 1 | 2 | 3 |
| 9. | Is forgetful in daily activities | 0 | 1 | 2 | 3 |
| 10. | Fidgets with hands or feet or squirms in seat | 0 | 1 | 2 | 3 |
| 11. | Leaves seat when remaining seated is expected | 0 | 1 | 2 | 3 |
| 12. | Runs about or climbs too much when remaining seated is expected | 0 | 1 | 2 | 3 |
| 13. | Has difficulty playing or beginning quiet play activities | 0 | 1 | 2 | 3 |
| 14. | Is "on the go" or often acts as if "driven by a motor" | 0 | 1 | 2 | 3 |
| 15. | Talks too much | 0 | 1 | 2 | 3 |
| 16. | Blurts out answers before questions have been completed | 0 | 1 | 2 | 3 |
| 17. | Has difficulty waiting his or her turn | 0 | 1 | 2 | 3 |
| 18. | Interrupts or intrudes in on other's conversations and/or activities | 0 | 1 | 2 | 3 |
| 19. | Argues with adults | 0 | 1 | 2 | 3 |
| 20. | Loses temper | 0 | 1 | 2 | 3 |
| 21. | Actively defies or refuses to go along with adults' requests or rules | 0 | 1 | 2 | 3 |
| 22. | Deliberately annoys people | 0 | 1 | 2 | 3 |
| 23. | Blames others for his or her mistakes or misbehaviors | 0 | 1 | 2 | 3 |
| 24. | Is touchy or easily annoyed by others | 0 | 1 | 2 | 3 |
| 25. | Is angry or resentful | 0 | 1 | 2 | 3 |
| 26. | Is spiteful and wants to get even | 0 | 1 | 2 | 3 |
| 27. | Bullies, threatens, or intimidates others | 0 | 1 | 2 | 3 |
| 28. | Starts physical fights | 0 | 1 | 2 | 3 |
| 29. | Lies to get out of trouble or to avoid obligations (i.e., "cons" others) | 0 | 1 | 2 | 3 |
| 30. | Is truant from school (skips school) without permission | 0 | 1 | 2 | 3 |
| 31. | Is physically cruel to people | 0 | 1 | 2 | 3 |
| 32. | Has stolen things that have value | 0 | 1 | 2 | 3 |
| 33. | Deliberately destroys other's property | 0 | 1 | 2 | 3 |
| 34. | Has used a weapon that can cause serious harm (bat, knife, brick, gun | 0 | 1 | 2 | 3 |
| 35. | Is physically cruel to animals | 0 | 1 | 2 | 3 |
| 36. | Has deliberately set fires to cause damage | 0 | 1 | 2 | 3 |
| 37. | Has broken into someone else's home, business, or car | 0 | 1 | 2 | 3 |
| 38. | Has stayed out at night without permission | 0 | 1 | 2 | 3 |
| 39. | Has run away from home overnight | 0 | 1 | 2 | 3 |
| 40. | Has forced someone into sexual activity | 0 | 1 | 2 | 3 |
| 41. | Is fearful, anxious, or worried | 0 | 1 | 2 | 3 |
| 42. | Is afraid to try new things for fear of making mistakes | 0 | 1 | 2 | 3 |
| 43. | Feels worthless or inferior | 0 | 1 | 2 | 3 |
| 44. | Blames self for problems, feels guilty | 0 | 1 | 2 | 3 |
| 45. | Feels lonely, unwanted, or unloved; complains that "no one loves him or her" | 0 | 1 | 2 | 3 |
| 46. | Is sad, unhappy, or depressed | 0 | 1 | 2 | 3 |
| 47. | Is self-conscious or easily embarrassed | 0 | 1 | 2 | 3 |

| **Performance** | | Excellent | Above Average | Average | Somewhat of a problem | Problematic |
|---|---|---|---|---|---|---|
| 48. | Overall school performance | 1 | 2 | 3 | 4 | 5 |
| 49. | Reading | 1 | 2 | 3 | 4 | 5 |
| 50. | Writing | 1 | 2 | 3 | 4 | 5 |
| 51. | Mathematics | 1 | 2 | 3 | 4 | 5 |
| 52. | Relationship with parents | 1 | 2 | 3 | 4 | 5 |
| 53. | Relationship with siblings | 1 | 2 | 3 | 4 | 5 |
| 54. | Relationship with peers | 1 | 2 | 3 | 4 | 5 |
| 55. | Participation in organised activities (e.g. Teams) | 1 | 2 | 3 | 4 | 5 |

**4. Developmental Behaviour Checklist**

• Please give your answers based on your child's behaviour over the last six months

• Mark the box indicating 'Not True' (0), 'Somewhat True' (1), and 'Certainly True' (0)

• If your child cannot perform an item, please mark in the box 'Not True' (0)

| | |
|---|---|
| **Is the child:**<br>(please circle) | Unable to see<br>Unable to hear<br>Unable to speak/ speaks very little<br>Subject to other serious medical condition |
| **Please describe:** | |
| What does he/she do best? | |
| What do other people like about him/her? | |
| What are his/her favourite activities? | |
| Is there anything you feel he/she does as well as or better than others? | |
| Have you sought help for any behaviour or emotional problems, apart from slow development, of the child or teenager in your care? | Yes/No<br>If so, from whom? |

| | | **Not true** | **Somewhat true** | **Certainly true** |
|---|---|---|---|---|
| 1. | Appears depressed, downcast or unhappy. | 0 | 1 | 2 |
| 2. | Avoids eye contact. Won't look you straight in the eye. | 0 | 1 | 2 |
| 3. | Aloof, in her/his own world. | 0 | 1 | 2 |
| 4. | Abusive. Swears at others. | 0 | 1 | 2 |
| 5. | Arranges objects or routine in a strict order.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 6. | Bangs head. | 0 | 1 | 2 |
| 7. | Becomes over-excited. | 0 | 1 | 2 |
| 8. | Bites others. | 0 | 1 | 2 |
| 9. | Cannot attend to one activity for any length of time, poor attention span. | 0 | 1 | 2 |
| 10. | Chews or mouths objects, or body parts. | 0 | 1 | 2 |
| 11. | Cries easily for no reason, or over small upsets. | 0 | 1 | 2 |
| 12. | Covers ears or is distressed when hears particular sounds.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 13. | Confuses the use of pronouns e.g. uses "you" instead of "I". | 0 | 1 | 2 |
| 14. | Deliberately runs away. | 0 | 1 | 2 |
| 15. | Delusions: has a firmly held belief or idea that can't possibly be true.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 16. | Distressed about being alone. | 0 | 1 | 2 |
| 17. | Doesn't show affection. | 0 | 1 | 2 |
| 18. | Doesn't respond to other's feelings, e.g. shows no response if a family member is crying. | 0 | 1 | 2 |
| 19. | Easily distracted from her/his task, e.g. by noises. | 0 | 1 | 2 |
| 20. | Easily led by others | 0 | 1 | 2 |
| 21 | Eats non-food items, e.g. dirt, grass, soap. | 0 | 1 | 2 |
| 22. | Excessively distressed if separated from familiar person. | 0 | 1 | 2 |
| 23. | Fears particular things or situations, e.g. the dark or insects.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 24. | Facial twitches or grimaces. | 0 | 1 | 2 |
| 25. | Flicks, taps, twirls objects repeatedly. | 0 | 1 | 2 |
| 26. | Fussy eater or has food fads. | 0 | 1 | 2 |
| 27. | Gorges food. Will do anything to get food, e.g. takes food out of garbage bins or steals food. | 0 | 1 | 2 |
| 28. | Gets obsessed with an idea or activity. | 0 | 1 | 2 |

| | | | | |
|---|---|---|---|---|
| | If yes, please describe:<br>……<br>……<br>…… | | | |
| 29. | Grinds teeth. | 0 | 1 | 2 |
| 30. | Has nightmares, night terrors or walks in sleep. | 0 | 1 | 2 |
| 31. | Has temper tantrums, e.g. stamps feet, slams doors. | 0 | 1 | 2 |
| 32. | Hides things. | 0 | 1 | 2 |
| 33. | Hits self or bites self | 0 | 1 | 2 |
| 34. | Hums, whines, grunts, squeals or makes other non-speech noises | 0 | 1 | 2 |
| 35. | Impatient | 0 | 1 | 2 |
| 36. | Inappropriate sexual activity with another | 0 | 1 | 2 |
| 37. | Impulsive, acts before thinking | 0 | 1 | 2 |
| 38. | Irritable | 0 | 1 | 2 |
| 39. | Jealous | 0 | 1 | 2 |
| 40. | Kicks, hits others | 0 | 1 | 2 |
| 41. | Lacks self-confidence, poor self-esteem | 0 | 1 | 2 |
| 42. | Laughs or giggles for no obvious reason | 0 | 1 | 2 |
| 43. | Lights fires | 0 | 1 | 2 |
| 44. | Likes to hold or play with an unusual object, e.g. string, twigs; overly fascinated with something, e.g. water.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 45. | Loss of appetite | 0 | 1 | 2 |
| 46. | Masturbates or exposes self in public | 0 | 1 | 2 |
| 47. | Mood changes rapidly for no apparent reason. | 0 | 1 | 2 |
| 48. | Moves slowly, underactive, does little, e.g. only sits and watches others. | 0 | 1 | 2 |
| 49. | Noisy or boisterous. | 0 | 1 | 2 |
| 50. | Overactive, restless, unable to sit still | 0 | 1 | 2 |
| 51. | Over affectionate. | | | |
| 52. | Over breathes, vomits, has headaches or complains of being sick for no physical reason. | | | |
| 53. | Overly attention seeking | | | |
| 54. | Overly interested in looking at, listening to or dismantling mechanical things e.g. lawnmower, vacuum cleaner | | | |
| 55. | Poor sense of danger | | | |
| 56. | Prefers the company of adults or younger children. Doesn't mix with her/his own age group. | 0 | 1 | 2 |
| 57. | Prefers to do things on her/his own. Tends to be a loner. | 0 | 1 | 2 |
| 58. | Preoccupied with only one or two particular interests.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 59. | Refuses to go to school or activity Centre. | 0 | 1 | 2 |
| 60. | Repeated movements of hands, body, head or face, e.g. hand flapping or rocking. | 0 | 1 | 2 |
| 61. | Resists being cuddled, touched or held. | 0 | 1 | 2 |
| 62. | Repeats back what others say like an echo. | 0 | 1 | 2 |
| 63. | Repeats the same word or phrase over and over. | 0 | 1 | 2 |
| 64. | Smells, tastes, or licks objects. | 0 | 1 | 2 |
| 65. | Scratches or picks her/his skin. | 0 | 1 | 2 |
| 66. | Screams a lot. | 0 | 1 | 2 |
| 67. | Sleeps too little. Disrupted sleep. | 0 | 1 | 2 |
| 68. | Stares at lights or spinning objects. | 0 | 1 | 2 |
| 69. | Sleeps too much. | 0 | 1 | 2 |
| 70. | Soils outside toilet though toilet trained. Smears or plays with faeces. | 0 | 1 | 2 |
| 71. | Speaks in whispers, high pitched voice, or other unusual tone or rhythm. | 0 | 1 | 2 |
| 72. | Switches lights on and off, pours water over and over; or similar repetitive activity.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 73. | Steals | 0 | 1 | 2 |
| 74. | Stubborn, disobedient or uncooperative. | | | |

| | | | | |
|---|---|---|---|---|
| 75. | Shy. | 0 | 1 | 2 |
| 76. | Strips off clothes or throws away clothes. | 0 | 1 | 2 |
| 77. | Says she/he can do things that she/he is not capable of. | 0 | 1 | 2 |
| 78. | Stands too close to others | 0 | 1 | 2 |
| 79. | Sees, hears, something which isn't there. Hallucinations.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 80. | Talks about suicide. | 0 | 1 | 2 |
| 81. | Talks too much or too fast. | 0 | 1 | 2 |
| 82. | Talks to self or imaginary people or objects. | 0 | 1 | 2 |
| 83. | Tells lies. | 0 | 1 | 2 |
| 84. | Thoughts are unconnected. Different ideas are jumbled together with meaning difficult to follow. | 0 | 1 | 2 |
| 85. | Tense, anxious, worried. | 0 | 1 | 2 |
| 86. | Throws or breaks objects | 0 | 1 | 2 |
| 87. | Tries to manipulate or provoke others. | 0 | 1 | 2 |
| 88. | Under reacts to pain. | 0 | 1 | 2 |
| 89. | Unrealistically happy or elated. | 0 | 1 | 2 |
| 90. | Unusual body movements, posture, or way of walking.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 91. | Upset and distressed over small changes in routine or environment.<br>If yes, please describe:<br>……<br>……<br>…… | 0 | 1 | 2 |
| 92. | Urinates outside toilet, although toilet trained. | 0 | 1 | 2 |
| 93. | Very bossy. | 0 | 1 | 2 |
| 94. | Wanders aimlessly. | 0 | 1 | 2 |
| 95. | Whines or complains a lot. | 0 | 1 | 2 |

| | | | | |
|---|---|---|---|---|
| | Please write in any problems your child has that were not listed above.<br>……<br>……<br>……<br>……<br>…… | | | |
| | | **Not true** | **Somewhat true** | **Certainly true** |
| 96. | Overall, do you feel your child has problems with feelings or behaviour, in addition to problems with development?<br>If not, please cross the box for **'not true' (0).** If so, but they are minor, cross the box for **'somewhat true' (1).** If they're major problems, cross the box for **'certainly true' (2).** | 0 | 1 | 2 |

Are there any other comments you would like to make?

**5. Developmental Coordination Disorder Questionnaire**

• Please compare the degree of coordination your child has with other children of the same age when answering the questions.

• Circle the one number that best describes your child.

• If you change your answer and want to circle another number, please circle the correct response twice.

| | Like your child: | Not at all | A bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 1. | Your child *throws* a ball in a controlled and accurate fashion | 1 | 2 | 3 | 4 | 5 |
| 2. | Your child *catches* a small ball (e.g. tennis ball size) thrown from a distance of 6-8 feet (1.8-2.4 metres) | 1 | 2 | 3 | 4 | 5 |
| 3. | Your child *hits* an approaching ball with a bat or racquet accurately | 1 | 2 | 3 | 4 | 5 |
| 4. | Your child *jumps* easily over obstacles found in a garden or play environment | 1 | 2 | 3 | 4 | 5 |
| 5. | Your child *runs* as fast and in a similar way to other children of the same age and gender | 1 | 2 | 3 | 4 | 5 |
| 6. | If your child has a *plan* to do a motor activity, she/he can organise her/his body to follow the plan and effectively complete the task (e.g., building a cardboard or cushion 'fort', moving on playground equipment, building a house or a structure with blocks, or using craft materials) | 1 | 2 | 3 | 4 | 5 |
| 7. | Your child's printing or writing or drawing in class is fast enough to keep up with the rest of the children in her/his class | 1 | 2 | 3 | 4 | 5 |
| 8. | Your child's printing or *writing* letters, numbers and words is legible, precise, and accurate or, if your child is not yet printing, she/he colours and draws in a coordinated way and makes pictures you recognise | 1 | 2 | 3 | 4 | 5 |
| 9. | Your child uses appropriate *effort* or tension when printing or writing or drawing (no excessive pressure or tightness of grasp on the pencil, writing is not too heavy or dark, or too light. | 1 | 2 | 3 | 4 | 5 |
| 10. | Your child *cuts* pictures and shapes accurately | 1 | 2 | 3 | 4 | 5 |
| 11. | Your child is interested in, and *likes* participating in sports or active games requiring good motor skills | 1 | 2 | 3 | 4 | 5 |
| 12. | Your child learns *new motor tasks* (e.g., swimming, rollerblading) easily and does not require more practice or time than other children to achieve the same level of skill. | 1 | 2 | 3 | 4 | 5 |
| 13. | Your child is *quick and competent* in tidying up, putting on shoes, tying shoes, dressing etc. | 1 | 2 | 3 | 4 | 5 |
| 14. | Your child would *never* be described as a *'bull in a china shop'* (that is, appears so clumsy that they might break fragile things in a small room) | 1 | 2 | 3 | 4 | 5 |
| 15. | Your child does *not fatigue easily* or appear to slouch and 'fall out' of her/his chair if she/he's required to sit for long periods | 1 | 2 | 3 | 4 | 5 |

**6. Observational Rating Scale**

• Please tick below the appropriate heading to indicate when this behaviour occurs: 'Never', 'Sometimes', 'Often' or 'Always'

| Listening | This Happens: | Never | Sometimes | Often | Always |
|---|---|---|---|---|---|
| 1. | Has trouble paying attention | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 2. | Has trouble following spoken directions | | | | |
| 3. | Has trouble remembering things people say | | | | |
| 4. | Has trouble understanding what people are saying | | | | |
| 5. | Has to ask people to repeat what they have said | | | | |
| 6. | Has trouble understanding the meaning of words | | | | |
| 7. | Has trouble understanding new ideas | | | | |
| 8. | Has trouble looking at people when talking or listening | | | | |
| 9. | Has trouble understanding facial expressions, gestures or body language | | | | |

| **Speaking** | **This Happens:** | **Never** | **Sometimes** | **Often** | **Always** |
|---|---|---|---|---|---|
| 10. | Has trouble answering questions people ask | | | | |
| 11. | Has trouble answering questions as quickly as other students | | | | |
| 12. | Has trouble asking for help when needed | | | | |
| 13. | Has trouble asking questions | | | | |
| 14. | Has trouble using a variety of vocabulary words when talking | | | | |
| 15. | Has trouble thinking of (finding) the right word to say | | | | |
| 16. | Has trouble expressing thoughts | | | | |
| 17. | Has trouble describing things to people | | | | |
| 18. | Has trouble staying on the subject when talking | | | | |
| 19. | Has trouble getting to the point when talking | | | | |
| 20. | Has trouble putting events in the right order when telling stories or talking about things that happened | | | | |
| 21. | Uses poor grammar when talking | | | | |
| 22. | Has trouble using complete sentences when talking | | | | |
| 23. | Talks in short, choppy sentences | | | | |
| 24. | Has trouble expanding an answer or providing details when talking | | | | |
| 25. | Has trouble having a conversation with someone | | | | |
| 26. | Has trouble talking with a group of people | | | | |
| 27. | Has trouble saying something another way when someone doesn't understand | | | | |
| 28. | Gets upset when people don't understand | | | | |

| **Reading** | **This Happens:** | **Never** | **Sometimes** | **Often** | **Always** |
|---|---|---|---|---|---|
| 29. | Has trouble sounding out words when reading | | | | |
| 30. | Has trouble understanding what was read | | | | |
| 31. | Has trouble explaining what was read | | | | |
| 32. | Has trouble identifying the main idea | | | | |
| 33. | Has trouble remembering details | | | | |
| 34. | Has trouble following written directions | | | | |

| **Writing** | **This Happens:** | **Never** | **Sometimes** | **Often** | **Always** |
|---|---|---|---|---|---|
| 35. | Has trouble writing down thoughts | | | | |
| 36. | Uses poor grammar when writing | | | | |
| 37. | Has trouble writing complete sentences | | | | |
| 38. | Writes short, choppy sentences | | | | |
| 39. | Has trouble expanding an answer or providing details when writing | | | | |
| 40. | Has trouble putting words in the right order when writing sentences | | | | |

**Now choose the problems that concern you the most by circling the numbers preceding the sentence.**

Please list any other problems that you have observed or concerns that you have about the students' listening, speaking, reading and writing skills and rate them (Never, Sometimes, Often or Always).

| | **Never** | **Sometimes** | **Often** | **Always** |
|---|---|---|---|---|
| | **Never** | **Sometimes** | **Often** | **Always** |
| | **Never** | **Sometimes** | **Often** | **Always** |
| | **Never** | **Sometimes** | **Often** | **Always** |
| | **Never** | **Sometimes** | **Often** | **Always** |
| | **Never** | **Sometimes** | **Often** | **Always** |

**7. Pragmatics Profile**

• Please indicate your child's skill level by circling the appropriate box: 'Never', 'Sometimes', 'Often', 'Always', 'Not Observed' or 'Not Appropriate'

| **Rituals and conversational skills**<br>**The child:** | | **Never** | **Some times** | **Often** | **Always** | **NO** | **NA** |
|---|---|---|---|---|---|---|---|
| 1. | Makes/responds to greetings to/from others | 1 | 2 | 3 | 4 | NO | NA |
| 2. | Makes/responds to farewells to/from others | 1 | 2 | 3 | 4 | NO | NA |
| 3. | Begins/ends conversations (face-to-face, phone etc.,) appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 4. | Observes turn-taking rules in the classroom or social interactions | 1 | 2 | 3 | 4 | NO | NA |
| 5. | Maintains eye contact, appropriate body position during conversations | 1 | 2 | 3 | 4 | NO | NA |
| 6. | Introduces appropriate topics of conversation | 1 | 2 | 3 | 4 | NO | NA |
| 7. | Maintains topics using appropriate strategies (e.g., nods, responds with "hmmm…") | 1 | 2 | 3 | 4 | NO | NA |
| 8. | Makes relevant contributions to a topic during conversations/discussion | 1 | 2 | 3 | 4 | NO | NA |
| 9. | Asks appropriate questions during conversations and discussion | 1 | 2 | 3 | 4 | NO | NA |
| 10. | Avoids use of repetitive/redundant information | 1 | 2 | 3 | 4 | NO | NA |
| 11. | Asks for/responds to requests for clarification during conversation/discussion | 1 | 2 | 3 | 4 | NO | NA |
| 12. | Adjusts/modifies language based on the communication situation (communication partner [s], topic, place) | 1 | 2 | 3 | 4 | NO | NA |
| 13. | Uses the language (jargon/lingo) of his/her peer group appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 14. | Tells/understands jokes/stories that are appropriate to the situation | 1 | 2 | 3 | 4 | NO | NA |
| 15. | Shows appropriate sense of humor during communication situations | 1 | 2 | 3 | 4 | NO | NA |
| 16. | Joins or leaves an ongoing communication interaction appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 17. | Participates/interacts appropriately in structured group activities | 1 | 2 | 3 | 4 | NO | NA |
| 18. | Participates/interacts appropriately in unstructured group activities | 1 | 2 | 3 | 4 | NO | NA |
| 19. | Uses other media (email, phone, answering machine) appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 20. | Responds to introductions and introduces others | 1 | 2 | 3 | 4 | NO | NA |
| 21. | Uses appropriate strategies for getting attention | 1 | 2 | 3 | 4 | NO | NA |
| 22. | Uses appropriate strategies for responding to interruptions and interrupting others | 1 | 2 | 3 | 4 | NO | NA |

| **Asking For, Giving and Responding to information**<br>**The child:** | | **Never** | **Some times** | **Often** | **Always** | **NO** | **NA** |
|---|---|---|---|---|---|---|---|
| 23. | Gives/asks for directions using appropriate language | 1 | 2 | 3 | 4 | NO | NA |
| 24. | Gives/asks for the time of events | 1 | 2 | 3 | 4 | NO | NA |
| 25. | Gives/asks for reasons and cases for actions/conditions/choices | 1 | 2 | 3 | 4 | NO | NA |
| 26. | Asks for help from others appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 27. | Offers to help others appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 28. | Gives/responds to advice or suggestions appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 29. | Asks others for permission when required | 1 | 2 | 3 | 4 | NO | NA |
| 30. | Agrees and disagrees using appropriate language | 1 | 2 | 3 | 4 | NO | NA |
| 31. | Asks for clarification if he/she is confused or if the situation is unclear | 1 | 2 | 3 | 4 | NO | NA |
| 32. | Accepts/rejects invitations appropriately, using appropriate language | 1 | 2 | 3 | 4 | NO | NA |
| 33. | Starts/responds to verbal and nonverbal negotiations appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 34. | Reminds others/ responds to reminders appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 35. | Asks others to change their actions/states appropriately (please move, stop tapping) | 1 | 2 | 3 | 4 | NO | NA |
| 36. | Apologies. Accepts apologies appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 37. | Responds appropriately when asked to change his/her actions (by accepting/rejecting) | 1 | 2 | 3 | 4 | NO | NA |
| 38. | Responds to testing, anger, failure, disappointment appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 39. | Offers/ responds to expressions of affection, appreciation appropriately | 1 | 2 | 3 | 4 | NO | NA |

| **Nonverbal Communication Skills** | | **Never** | **Some times** | **Often** | **Always** | **NO** | **NA** |
|---|---|---|---|---|---|---|---|
| Note: examples of nonverbal skills might include waving to greet someone, gesturing to give someone a reminder, or adding to show one's agreement. | | | | | | | |
| **The child reads and interprets the following nonverbal messages accurately:** | | | | | | | |
| 40. | Facial cues | 1 | 2 | 3 | 4 | NO | NA |
| 41. | Body language | 1 | 2 | 3 | 4 | NO | NA |
| 42. | Tone of voice | 1 | 2 | 3 | 4 | NO | NA |

| The child demonstrates appropriate use of the following nonverbal support: | | | | | | | |
|---|---|---|---|---|---|---|---|
| 43. | Facial cues | 1 | 2 | 3 | 4 | NO | NA |
| 44. | Body language | 1 | 2 | 3 | 4 | NO | NA |
| 45. | Voice intonation | 1 | 2 | 3 | 4 | NO | NA |
| 46. | Appropriately expresses messages nonverbally | 1 | 2 | 3 | 4 | NO | NA |
| 47. | Uses nonverbal cues appropriate to the situation | 1 | 2 | 3 | 4 | NO | NA |
| 48. | Adjusts body distance (sit/stand) appropriate to the situation | 1 | 2 | 3 | 4 | NO | NA |
| 49. | Presents matching nonverbal and verbal messages | 1 | 2 | 3 | 4 | NO | NA |
| 50. | Knows how someone is feeling based on nonverbal cues | 1 | 2 | 3 | 4 | NO | NA |
| 51. | Reads the social situation (script) correctly and behaves/responds appropriately | 1 | 2 | 3 | 4 | NO | NA |
| 52. | Understands posted and implied group/school rules | 1 | 2 | 3 | 4 | NO | NA |

**Thank you very much for completing this questionnaire.**

**If you have found any aspects of this questionnaire difficult to answer and feel the need for support, please refer to the contact details given at the start of this document or on the information sheet.**

# Appendix B: Sibling Questionnaire Booklet

## Parent Questionnaire: Sibling

This questionnaire should be completed by a parent and given to the researcher when they come to visit.

The questionnaire pack should take approximately an hour to complete. We kindly ask that you respond to the best of your knowledge: there are no right or wrong responses.

**Child's name** _____

**Date of birth** __ __ / __ __ / __ __ __ __

**Date completed** __ __ / __ __ / __ __ __ __

**Questionnaire checklist**

1. Strengths and Difficulties Questionnaire ☐
2. Social Communication Questionnaire ☐
3. Vanderbilt ADHD Diagnostic Assessment Rating Scale ☐
4. Developmental Coordination Disorder Questionnaire ☐
5. Observational Rating Scale ☐
6. Pragmatics Profile ☐

Thank you very much for your help. Your participation in this research project is greatly appreciated.

If you have any queries, please contact:

*Joyti Panesar (Primary Researcher)*

# Appendix C: Example Performance Feedback Report

## PERFORMANCE FEEDBACK BOOKLET

NAME

DATE

AGE

This booklet will provide you with some information about the cognitive and motor tasks that your child completed, and the questionnaires that you filled in. The booklet will provide a summary of your child's performance on each task, which may help to identify where your child's strengths and weaknesses lie. However, please note that this is not a clinical assessment, and represents how your child performed on one particular occasion. Performance can also be affected by other factors, such as tiredness, or interest in the tasks. Any issues raised by this report would need to be followed up in consultation with the child's geneticist, clinical psychologist, educational psychologist, and/or GP.

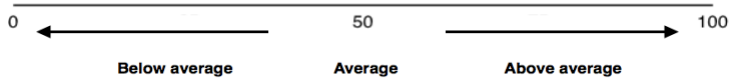
**Part 1: Cognitive and Motor Tasks**

**Scoring**

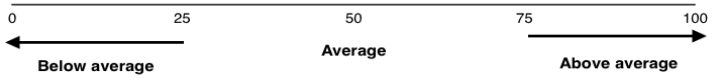
Children's performance on these tasks are reported as 'percentile scores'. A percentile shows how well your child did in comparison to other children of the same age. The percentiles are given on a scale from 0 – 100. These numbers do **not** show the total score that your child got on a task (i.e. percentage of answers correct), instead they show where your child lies in terms of 'average', 'below average', and 'above average' performance on a task given their age.

Some examples might help to illustrate how percentiles work.

A percentile of **50** would mean that your child is performing at the 'average' for that particular task. Anything below 50 means performance that is below average, and anything above 50 means performance that is above average.




A percentile of **25** or less would mean that your child is performing below average, and is in the bottom quarter.




A percentile of **75** or more would mean that your child is performing above average, and is in the top quarter.

## Cognitive skills

Your child took part in tasks that assessed their cognitive abilities. These abilities relate to the skills that help us to remember, process information, and communicate.

### (1) General intellectual functioning

What is this?

This task provides an overall picture of a child's general cognitive skills, sometimes referred to as IQ. We assessed this using the Wechsler Abbreviated Scale of Intelligence. The task is divided into two different sections - Verbal Ability and Non-Verbal Ability. These two sections are then combined to give an overall score.

*Verbal ability*

The **verbal tasks** assess areas such as word knowledge, language learning ability, and general verbal expression.

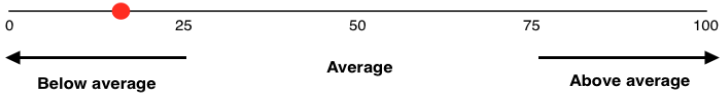
*Non-verbal ability*

The **non-verbal** tasks assess how well children understand categories and patterns, and how they process and organise visual information.

How did my child perform?

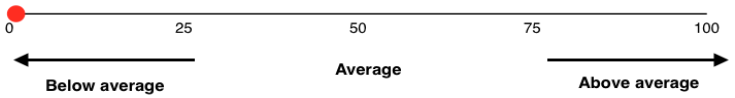
**Verbal ability**

NAME scored in the **16th** percentile.



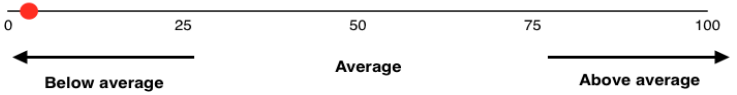

**Non-verbal ability**

NAME scored in the **1st** percentile.




**Overall Score**

Overall, NAME scored in the **3rd** percentile.




### (2) Language

What is this?

These tasks assess different aspects of language, and are from the Clinical Evaluation of Language Fundamentals test. Two key areas of language were tested:

- Receptive language
  - How well does a child understand language? How well do they understand words or sentences?
- Expressive language
  - How well does a child communicate verbally? How easy or hard do they find it to make themselves understood using language?

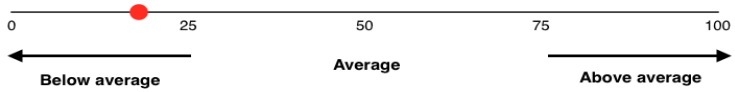
Overall language

- Receptive language and expressive language are combined to give an overall score for language ability.

How did my child perform?

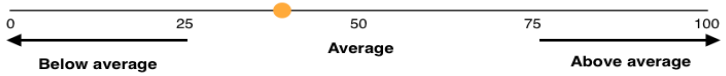
**Receptive language**

NAME scored in the **18th** percentile for receptive language.



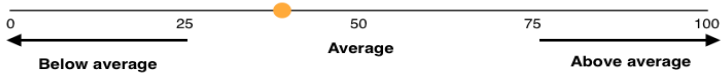

**Expressive language**

NAME scored in the **39th** percentile for expressive language.




**Overall language**

NAME scored in the **39th** percentile.




## (3) Working memory

What is this?

Working memory helps us to remember information over short periods of time (a few seconds). It is a bit like a mental notepad, and is very important for learning. There are two types of working memory.

- **Simple Working memory** is the ability to hold on to information. This information could be verbal (e.g., trying to remember a phone number you just been told), or visuospatial (e.g., sketching a drawing from memory that you've just seen but no longer have in front of you).

- **Complex working memory** includes both holding onto information *and* manipulation of the information. This can also involve verbal or visuospatial information. An example of complex working memory is being asked to do some 'mental maths', such as adding three numbers together (i.e. your answer has required you to manipulate the numbers you were holding in mind).

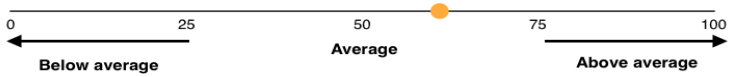
We assessed your child's working memory using tasks from the Working Memory Test Battery for Children.

How did my child perform?

**Simple working memory**

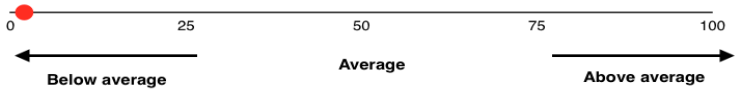
*Verbal*

NAME scored in the **61st** percentile.



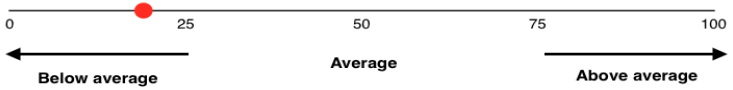

*Visuospatial*

NAME scored in the **2nd** percentile




**Complex working memory**

NAME scored in the **19th** percentile.



### (4) Cognitive Flexibility

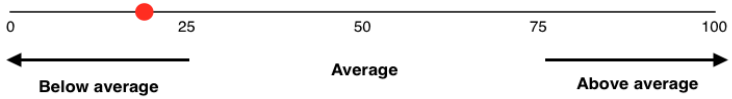
What is this?

Being able to think flexibly is an important skill in everyday activities. It includes being able to switch back and forth between different tasks, to switch our focus of attention, and to control our responses to changes in the environment so that we act only when it is appropriate to do so.

This was assessed using the Wisconsin Card Sorting task, which involves sorting a deck of cards using different categories (e.g., colour, shape), and being able to switch between different categories.

How did my child perform?

Overall, NAME scored in the **19th** percentile




## Motor skills

Motor skills help us with moving our body, and using our hands to complete tasks.

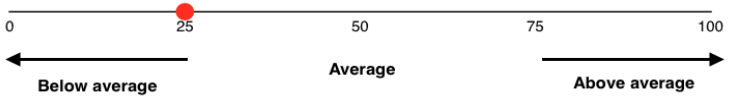
### (1) Fine motor skills

What is this?

Fine motor skills are those which require precision and accuracy. For example, skills that help us to hold a pen and write, fasten buttons, and use a knife and fork. The Movement ABC was used to assess fine motor skills through a series of tasks that required the manipulation of small objects such as placing pegs in a board and threading a lace.

How did my child perform?

NAME scored in the **25th** percentile.



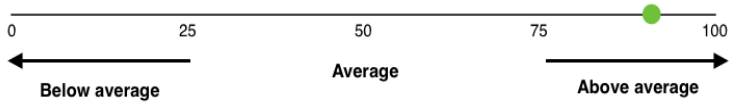

### (2) Gross motor skills

What is this?

Gross Motor Skills are movement behaviours involving larger muscle groups. For example, skills that help us to jump, walk, and balance, or to sit on a chair. We used the Movement ABC to assess these skills. This required children to balance on one leg, to hop, and to walk heel to toe along a narrow line.

How did my child perform?

NAME scored in the **91st** percentile.




## Part 2: Behaviour Questionnaires

### Scoring

Most of the questionnaires use 'cut-off' scores. A cut-off is a score that indicates when a child may have behaviours that are indicative of a particular disorder, such as autism or attention deficit/hyperactivity disorder. For example, a questionnaire may have a cut-off score of 10, which means that any score above 10 may suggest behaviours indicative of that disorder.

Different questionnaires use different cut-off scores. Also, some have a cut-off where a score BELOW the cut-off is indicative of possible issues, and some have a cut-off where a score ABOVE the cut-off is indicative of possible issues. Exact details about the cut-off scores will be explained for each separate questionnaire.

Some questionnaires use category ratings. These are explained in the relevant sections for those questionnaires.

**It is important to note that these are not clinical assessments for particular disorders, and only indicate where there may be behaviours consistent with certain disorders. These scores would need to be followed up in consultation with the child's geneticist, clinical psychologist, educational psychologist, and/or GP.**

## Behaviour

### (1) Strengths and difficulties questionnaire

What is this?

This questionnaire assesses psychological wellbeing in 5 different areas:

- Emotional difficulties
  - *Such as: worrying, feeling down, nervous or being scared*
- Behavioural difficulties
  - *Such as: temper tantrums, not listening to others, fighting*
- Hyperactivity/concentration difficulties
  - *Such as: overactive, restless, easily distracted*
- Peer problems
  - *Such as: finds it hard to get along with other children, prefers to be alone, has few friends*
- Kind and helpful behaviour
  - *Such as: considers other people's feelings, shares with others, helpful*

The first four scales are scored using four different categories:

1. **Average:** the responses do not indicate any problems
2. **Slightly raised**: the responses indicate there may be a few problematic behaviours
3. **High**: responses indicate that there are likely to be some problematic behaviours
4. **Very High**: responses indicate that there are highly likely to be problematic behaviours

The final scale (Kind and helpful behaviour) is scored as Average, Slightly Lowered, Low, and Very Low, where Very Low indicates the most problems.

What are the results?

| | |
|---|---|
| Emotional difficulties | Very High |
| Behavioural difficulties | Very High |
| Hyperactivity/concentration difficulties | Very High |
| Peer problems | Very High |
| | |
| Kind and helpful behaviour | Very low |

### (2) Social Communication Questionnaire

What is it?

This questionnaire is used to assess behaviours that may be indicative of Autistic Spectrum Disorder, for example, poor social communication, poor social interaction, and repetitive behaviours. Scores of **15 or higher** indicate traits more typical of Autism Spectrum Disorder.

What are the results?

NAME scored **4**, which is lower than the cut-off score and therefore does not suggest behaviours indicative of Autism Spectrum Disorder.

### (3) Vanderbilt ADHD Diagnostic Assessment Rating Scale

What is it?

This questionnaire assessed symptoms of inattention and hyperactivity. This can include behaviours such as:

- Finding it difficult to focus, organise information, and pay attention.
- Finding difficulty staying still, being patient, or waiting your turn.
- Finding it hard to follow instructions or tasks.

Based on the responses from the questionnaire children are categorised as:

- **No signs**

*Responses indicate that the child is not displaying behaviours consistent with inattention and hyperactivity.*

- **Inattentive (ADD)**

*Finds it hard to pay attention to work or activities, usually distracted when being spoken to, doesn't follow through on instructions, finds it hard to organise tasks, or can forget things easily*

- **Hyperactive/impulsive**

*Finds it hard to sit still, sometimes talks a lot, or finds it hard to wait their turn*

- **Combined inattention/hyperactivity (ADHD)**

*Displays behaviours consistent with both inattention and hyperactivity.*

How did my child perform?

Scoring indicated a profile of **combined inattention and hyperactivity.**

**(4) Developmental Coordination Disorder Questionnaire**

What is it?

Developmental Coordination Disorder is when children suffer from motor problems that can impact their everyday movement. Three main behaviours were assessed, and these provide an overall score for motor functioning.

1. Control during movement

   *Catching a ball, jumping or running*

2. Fine motor and handwriting

   *Handwriting or using scissors*

3. General coordination

   *Learning new skills or engaging in movement behaviours*

Scores **below 58** indicate behaviours more common in children with Developmental Coordination Disorder.

What are the results?

NAME scored **53**. This is below the cut off and therefore may indicate difficulties with motor skills.

# Appendix D: Project Feedback Questionnaire

School of Psychology
University of Leeds
Leeds
LS2 9JT

UNIVERSITY OF LEEDS

DATE

Dear

Thank you for taking part in the following research project: *An investigation into the relationship between genotype and cognitive phenotype* (NHS IRAS: 217545)

Your participation has allowed us to explore the impact of copy number variants on child development.

Enclosed is an anonymous evaluation form which asks a few questions about your experiences of taking part in the project. We ask for this feedback, so it can improve our research in the future.

Please return this in the prepaid envelope provided.

Yours sincerely,

Joyti Panesar *(Primary Researcher)*

Dr Amanda Waterman *(Project Lead)*

**PROJECT EVALUATION FORM**

Following your child's participation in the project you will have received a performance feedback booklet which details their performance on cognitive and motor assessments and behavioural questionnaires.
**Please indicate your response to the following with a ✓**

**Do you feel the project has:**

**1)** helped you understand more about your child's **overall** development?

| Strongly Disagree | | Disagree | | Neutral | | Agree | | Strongly Agree | |
|---|---|---|---|---|---|---|---|---|---|

**2)** helped you understand more about your child's **cognitive skills?**
(Intellectual Functioning, Working Memory, Language and Cognitive Flexibility)

| Strongly Disagree | | Disagree | | Neutral | | Agree | | Strongly Agree | |
|---|---|---|---|---|---|---|---|---|---|

**3)** helped you understand more about your child's **motor skills?**
(Fine and Gross Motor skills)

| Strongly Disagree | | Disagree | | Neutral | | Agree | | Strongly Agree | |
|---|---|---|---|---|---|---|---|---|---|

**4)** helped you understand more about your child's **behavioural symptoms?**
(Psychological Wellbeing, Social Communication, Attentional skills and Coordination)

| Strongly Disagree | | Disagree | | Neutral | | Agree | | Strongly Agree | |
|---|---|---|---|---|---|---|---|---|---|

**5)** Have you used the feedback in any way to support your child?

| No | | Yes | | **If yes, please provide more detail:** |
|---|---|---|---|---|

……
……

**6)** Please do you have any more comments, feedback or suggestions?
……
……

***Thank you for your time and support***