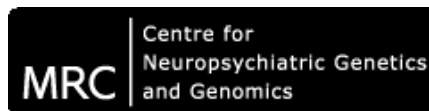


# **Longitudinal follow-up of 22q11.2 Deletion Syndrome: a study of individuals at high risk of schizophrenia**

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**PhD 2015**



**Supervisors:**

Professor Marianne van den Bree

Professor Sir Michael Owen

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## **Acknowledgements**

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## **Contributions**

When I started my PhD Cardiff University's ECHO study was already conducting its first wave of assessment of children with 22q11.2 Deletion Syndrome (22q11.2DS). I have been responsible for coordinating the second wave of assessments in this cohort. Although I have taken the lead, this has very much been a collaborative effort of many people. I have worked particularly closely with Hayley Moss who coordinated the first wave of assessments, Dr Maria Niarchou who analysed data from the first wave, and with Dr Joanne Doherty who is conducting an imaging study in this cohort. Dr Joanne Doherty and I worked together in gaining ethical approval to re-contact families whose child had taken part in the first wave of assessment. I have personally visited and conducted 57/70 assessments of children with 22q11.2DS. Children and their families were visited in their homes and this has involved substantial travel throughout Wales, England, Scotland and Northern Ireland. Research assessments were conducted with at least one other colleague.

I have also conducted 35/52 assessments of autism spectrum disorder (ASD) over the phone. I have double coded 17 ASD assessments by other colleagues. Dr Joanne Doherty has helped with double coding and consensus coding of ASD interviews.

Data from the first wave of assessments was already entered for analysis. For the second wave of assessments I have derived all psychiatric diagnoses which were double-checked by colleagues and psychiatrist Dr Jane Scourfield. I have managed the process of data entry with the assistance of undergraduate students who have worked on the project. I have done all the analysis and writing of this thesis.

My work has been under the guidance of my supervisors, Professor Marianne van den Bree and Professor Sir Michael Owen. Dr Joanne Doherty, Dr Jane Scourfield and Professor Anita Thapar have all provided support with clinical issues that have arisen in the project and have given advice on diagnosis and interpreting psychopathology measures.

## **Thesis summary**

22q11.2 Deletion Syndrome (22q11.2DS) is one of the strongest known risk factors for schizophrenia. The syndrome provides a rare opportunity to prospectively examine development that precedes schizophrenia. 22q11.2DS is also associated with a range of psychiatric disorders and cognitive deficits. The overall aim of this thesis is to examine the neuropsychiatric phenotype of 22q11.2DS through a developmental lens. This thesis uses data from Cardiff University's ECHO (Experiences of CHildren with cOpy number variants) study which includes a longitudinal cohort of children with 22q11.2DS. Development in 22q11.2DS is contrasted to that of the unaffected siblings of children with 22q11.2DS.

First psychopathology is examined longitudinally across early adolescence in 22q11.2DS. Children with 22q11.2DS have a significant burden of psychopathology across early adolescence, including attention-deficit/hyperactivity disorder (ADHD), anxiety disorders and autism spectrum disorder (ASD). There is a striking increase in the prevalence of psychotic experiences and a decrease in ADHD prevalence. The ASD phenotype is examined further using a diagnostic interview of developmental history. ASD and subthreshold phenomenology is found to be highly prevalent in the early development of children with 22q11.2DS.

Next cognitive development in 22q11.2DS is considered and contrasted to that in unaffected siblings. Cognitive deficits across a range of domains are present in 22q11.2DS. Cognitive development in 22q11.2DS is found to be similar to that reported in children who later develop idiopathic schizophrenia.

This is followed by an exploration of the relations between psychopathology and cognitive development in 22q11.2DS. Cognitive development is found to predict the emergence of psychotic experiences and the persistence of ADHD in 22q11.2DS.

This thesis extends what is known about the development of the neuropsychiatric phenotype in 22q11.2DS. Furthermore, findings give an insight into the developmental pathways associated with a high risk of developing schizophrenia.

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# **1. Introduction: 22q11.2 Deletion Syndrome**

## **1.1 22q11.2 Deletion Syndrome background**

### **1.1.1 Genetic characterization and prevalence**

22q11.2 Deletion Syndrome is a submicroscopic microdeletion at region q11.2 on one copy of human chromosome 22 (Drew, Crabtree et al. 2011) and occurs at a frequency of approximately 1 in 4000 live births (Scambler 2000). Population-based prevalence rates reported vary from 1 in 2000 to 1 in 7000 and are highly dependent on ascertainment method. It is likely many individuals remain undiagnosed and it has been estimated that the true population prevalence is around 1 in 1600 live births (Shprintzen 2008). There is a high selection pressure on this locus due to its negative effect on reproductive fitness, however it persists in the population due to a high 'de novo' mutation rate (Rees, Moskvina et al. 2011). The majority of cases occur 'de novo', only in 5-10% of cases is the deletion inherited from an affected parent (Williams 2011). Regions of low copy repeats flanking the q11.2 region increase the likelihood of non-allelic homologous recombination resulting in a deletion during meiosis (Edelmann, Pandita et al. 1999, Kurahashi, Shaikh et al. 2000, Bittel, Yu et al. 2009). 87% of deletions include a common 3 Megabase (Mb) region which includes at least 48 known genes, 8% span a smaller 1.5 Mb region (nested within the 3Mb region) which contains at least 28 genes (Shaikh, Kurahashi et al. 2000) and the remainder are atypical deletions (Urban, Korbel et al. 2006).

22q11.2 Deletion Syndrome is also known as DiGeorge syndrome or Velo-cardio-facial syndrome (VCFS). These other names refer to clinical presentations that were found in 1992 to have the same underlying genetic aetiology (Driscoll, Budarf et al. 1992, Driscoll, Spinner et al. 1992, Scambler, Kelly et al. 1992). For the purposes of this thesis I will use the term 22q11.2 Deletion Syndrome (22q11.2DS). 22q11.2DS is an example of a copy number variant (CNV). CNVs are structural genomic variations that are >1 kilobase in size and occur in the form of deletions and duplications (Lee and Scherer 2010, Malhotra and Sebat 2012).

### **1.1.2 Phenotype of 22q11.2DS**

The phenotype is highly variable and exhibits incomplete penetrance with some individuals not surviving the neonatal period and others who remain relatively unaffected (McDonald-McGinn and Zackai 2008, Shprintzen 2008). Multiple organ systems can be affected and common clinical features include heart and velopharyngeal defects, immunodeficiency, hypocalcaemia, short stature and

cognitive impairment (Shprintzen, Goldberg et al. 1978, Ryan, Goodship et al. 1997, Scambler 2000, Kobrynski and Sullivan 2007). It is also associated with a striking elevated risk for neuropsychiatric disorder (Schneider, Debbané et al. 2014). The phenotype shows marked variable expression, over 180 clinical features have been identified though no single feature occurs in all cases (Robin and Shprintzen 2005, Shprintzen 2008). Phenotypic variability could in theory be caused by deletion size, breakpoint heterogeneity, genomic variation outside the q11.2 region, environmental and stochastic factors (Drew, Crabtree et al. 2011). However, phenotypic severity has not been found to correlate with deletion size and it has been argued that the 1.5Mb region contains the causative genes (Carlson, Sirotkin et al. 1997).

### **1.1.3 Diagnosis of 22q11.2DS**

A range of techniques have traditionally been used to identify the deletion, ranging from fluorescence in situ hybridization (FISH) analysis, quantitative polymerase chain reaction (PCR), comparative genome hybridization (CGH) and genome-wide arrays of single nucleotide polymorphisms (SNPs) (Williams 2011). Individuals can be referred for medical genetic testing for a wide variety of reasons and at a range of ages, from embryo to adulthood. Pre-implantation genetic diagnosis of embryos is available for couples where one of the parents is known to be affected by 22q11.2DS (Iwarsson, Ahrlund-Richter et al. 1998). Prenatal testing can occur if there are pregnancy difficulties or physical abnormalities in the foetus (Driscoll 2001). However most individuals are diagnosed at a young age after birth (Swillen, Vogels et al. 2000), those identified as infants often present with congenital cardiac anomalies (Momma 2010), cleft palate, feeding difficulties with nasal reflux and neonatal hypocalcaemia (Vogels, Schevenels et al. 2014). Those identified after the age of two often present with speech-language impairment, developmental delay or learning difficulties and recurrent infections (Lima, Følling et al. 2010). In a minority of cases individuals are not identified until adulthood, particularly if they have no obvious physical features. Referral in these cases is mainly because of familial occurrence, cardiac defects and comorbid intellectual disability and psychiatric disorder (Vogels, Schevenels et al. 2014).

## **1.2 Neuropsychiatric phenotype of 22q11.2DS**

There is a strong consensus that 22q11.2DS greatly increases risk of neuropsychiatric disorder across the lifespan (Schneider, Debbané et al. 2014). Regardless of ascertainment method, at least 60% of individuals with 22q11.2DS meet diagnostic criteria for one or more psychiatric disorder (Green, Gothelf et al. 2009, Antshel, Shprintzen et al. 2010, Fung, McEvilly et al. 2010). There are many studies reporting prevalence of psychiatric disorder in 22q11.2DS, though one study I will refer back

to is an international, multi-site study of psychiatric morbidity by members of the International 22q11.2DS Brain and Behaviour Consortium (IBBC) that describes prevalence in 22q11.2DS stratified by age. 1402 individuals are included in this cross-sectional study which is the largest of its kind (Schneider, Debbané et al. 2014). I will refer back to this as the IBBC study.

### **1.2.1 Schizophrenia**

*Schizophrenia is characterised by delusions, hallucinations, negative symptoms (i.e. diminished emotional expression or avolition), and disorganized speech and behaviour. Level of functioning in work, interpersonal relations, or self-care is impaired relative to before onset (American Psychiatric Association 2013). Psychosis is not exclusive to schizophrenia and occurs in various diagnostic categories of psychotic disorder (see (van Os and Kapur 2009) for a review).*

22q11.2DS is one of the strongest known genetic risk factors for schizophrenia (Jonas, Montojo et al. 2014). This association was first established in 1992 when it was reported that some adults with the clinical VCFS presentation developed schizophrenia (Shprintzen, Goldberg et al. 1992), the same year that the VCFS clinical presentation was associated with 22q11.2 deletion (Driscoll, Spinner et al. 1992, Scambler, Kelly et al. 1992). There are several lines of evidence that support this initial finding.

#### **1. Bidirectional association between 22q11.2DS and schizophrenia**

There is a bidirectional association in that 22q11.2DS frequency is elevated in schizophrenia and schizophrenia prevalence is elevated in 22q11.2DS. Large cohorts of idiopathic schizophrenia patients and population controls have been screened for CNVs and it has been reported that 22q11.2DS is enriched in schizophrenia cases occurring in 0.2-0.3% of cases compared to 0.0% in controls (Stefansson, Rujescu et al. 2008, Levinson, Duan et al. 2011, Malhotra and Sebat 2012, Rees, Walters et al. 2014). Furthermore, clinical studies of 22q11.2DS consistently replicate high rates of schizophrenia (Pulver, Nestadt et al. 1994, Murphy, Jones et al. 1999, Bassett, Chow et al. 2005, Gothelf, Eliez et al. 2005, Ikeda, Williams et al. 2010, Monks, Niarchou et al. 2014, Schneider, Debbané et al. 2014).

#### **2. Schizophrenia in 22q11.2DS does not differ from idiopathic schizophrenia**

A valid concern is that schizophrenia is somewhat different in 22q11.2DS and that the clinical presentation could represent a genetic subtype or be attributed to other features of the syndrome. However clinical studies of 22q11.2DS do not report this. Individuals appear to have a typical form of schizophrenia as indicated by their level of functioning, need for psychiatric hospitalizations and antipsychotic treatment (Bassett, Hodgkinson et al. 1998). Furthermore,

22q11.2DS individuals do not differ from idiopathic schizophrenia patients in terms of manifest symptom clusters or symptom severity (Bassett, Chow et al. 2003, Monks, Niarchou et al. 2014).

### 3. 22q11.2DS increases risk of phenomena across the psychotic continuum

Psychotic phenomenology in clinical samples exists on a continuum, varying in terms of conviction, pre-occupation and implausibility (Strauss 1969, Van Os, Hanssen et al. 2000). Psychosis can be present at the level of disorder, schizophrenia and other defined psychotic disorders, but also at subclinical levels, referred to as psychotic experiences, psychosis proneness, schizotypy or at high risk states (Meehl 1962, Crow 1998, van Os, Linscott et al. 2009). Prevalence of all these phenomena is greatly elevated in 22q11.2DS. Approximately 20-30% of adults with 22q11.2DS develop schizophrenia, 30-40% when broadened to any psychotic disorder (Murphy, Jones et al. 1999, Monks, Niarchou et al. 2014, Schneider, Debbané et al. 2014), whereas lifetime prevalence in the general population is 0.30-0.66% and 2.3-3.5% respectively (Perälä, Suvisaari et al. 2007, McGrath, Saha et al. 2008, van Os and Kapur 2009). 22q11.2DS adults without schizophrenia have higher schizotypy scores than population controls (Monks, Niarchou et al. 2014). Psychotic symptomatology is greater in 22q11.2DS adults when compared to adults with general developmental disability (Gothelf, Eliez et al. 2005). Adolescents and young adults with 22q11.2DS are at elevated risk of developing a prodromal psychosis syndrome (Shapiro, Cubells et al. 2011) and half report psychotic-like experiences (Baker and Skuse 2005) whereas the population prevalence of such experiences is 5% (van Os, Linscott et al. 2009).

### 4. Biological plausibility

Within the 22q11.2 deletion there are many genes implicated in brain functioning. Of particular interest is COMT (catechol-O-methyltransferase) which encodes a postsynaptic enzyme that modulates prefrontal cortical dopamine clearance (Yavich, Forsberg et al. 2007). Common variation of this gene modulates activity of the enzyme and thus dopamine clearance. The COMT-val allele (codon 18) has been associated with higher COMT enzyme activity in dorsolateral prefrontal cortex (Chen, Lipska et al. 2004). In 22q11.2DS hemizyosity of this gene may lead to dopamine dysregulation which is well documented to contribute to the aetiology of schizophrenia (Howes and Kapur 2009). Hemizyosity may also mean genetic variation in COMT genotype on the intact chromosome has more of an effect on phenotypic expression (Jonas, Montojo et al. 2014).

PRODH (Proline dehydrogenase 1) encodes an enzyme that converts proline to glutamate, the dysfunction of which has been linked to schizophrenia development (Jacquet, Raux et al. 2002). Common variation of this gene has been associated with schizophrenia (Li, Ma et al. 2004, Sullivan, Lin et al. 2008) and brain structural differences (Kempf, Nicodemus et al. 2008), specifically, the schizophrenia-risk allele has been associated with decreased striatal volume and increased striatal-frontal functional connectivity.

PIK4CA (phosphatidylinositol-4-kinase-catalytic- $\alpha$ ) encodes a catalytic enzyme in the phosphatidylinositol pathway which is involved in synaptic transmission and signal transduction (Jungerius, Hoogendoorn et al. 2008) and has been identified as potential schizophrenia susceptibility gene (Saito, Stopkova et al. 2003).

Although these are plausible causal genes for schizophrenia risk in 22q11.2DS (Prasad, Howley et al. 2008), in reality findings are inconsistent regarding the role of COMT (Murphy, Jones et al. 1999, Gothelf, Eliez et al. 2005) and PIK4CA (Vorstman, Chow et al. 2009, Ikeda, Williams et al. 2010), and negative regarding the role of PRODH (Gothelf, Eliez et al. 2005) in 22q11.2DS psychosis development.

#### 5. 22q11.2DS is enriched in child-onset schizophrenia cohorts

Child-onset schizophrenia is defined as onset before the age of 12 and is associated with greater disease severity (Gordon, Frazier et al. 1994). It is rare, with an estimated prevalence of 1 in 30000 births (Jacobsen and Rapoport 1998). Early studies report cases of 22q11.2DS within child-onset schizophrenia cohorts (Yan, Jacobsen et al. 1998, Usiskin, Nicolson et al. 1999). More recently it was established that 22q11.2 deletion was the most frequent genetic variant in child-onset schizophrenia, occurring in 4.0% of cases, a rate that is much higher than the frequency of 22q11.2DS in adult onset schizophrenia (0.3-1%) (Ahn, Gotay et al. 2014), thus indicating that 22q11.2DS is associated with an earlier age of onset and greater severity of schizophrenia.

#### 6. Duplication of the 22q11.2 region is protective of schizophrenia

As well as deletions, duplication events can occur of the 22q11.2 region (Portnoi 2009). The phenotype of 22q11.2 Duplication Syndrome is variable and can include physical manifestations and neuropsychiatric disorder (Kaminsky, Kaul et al. 2011, Malhotra and Sebat 2012, Van Campenhout, Devriendt et al. 2012). There is recent evidence that 22q11.2 duplications are protective of schizophrenia as they occur less frequently in schizophrenia cases than in controls (0.014% vs 0.085%) (Rees, Kirov et al. 2014). This is the first protective variant to be described

for schizophrenia and further demonstrates the strong relationship that copy number variation of the 22q11.2 region has with schizophrenia risk.

Thus, the association between 22q11.2DS and schizophrenia is well established. It also appears to be the most specific neuropsychiatric phenotype associated with 22q11.2DS as it has been suggested that it is the only disorder that appears to be found at a much higher rate in comparison to other genetic and developmental disorders associated with intellectual disability (Gothelf, Feinstein et al. 2007, Karayiorgou, Simon et al. 2010). Nonetheless prevalence of other neuropsychiatric disorders in 22q11.2DS is high. Below I review other aspects of the neuropsychiatric phenotype of 22q11.2DS.

### **1.2.2 Intellectual disability, cognitive deficits and adaptive functioning**

*Intellectual disability (ID) is a condition with a developmental onset that includes both intellectual and adaptive functioning deficits in conceptual, social and practical domains (American Psychiatric Association 2013).*

Intellectual and adaptive functioning is highly variable in 22q11.2DS. I will review ID and broader cognitive deficits present in 22q11.2DS as well as adaptive functioning and psychoeducational deficits.

#### **1. ID prevalence in 22q11.2DS**

Reported prevalence of mild to moderate ID in 22q11.2DS varies from 30% to 55% (Swillen, Devriendt et al. 1997, Bassett, Hodgkinson et al. 1998, Moss, Batshaw et al. 1999, Niklasson, Rasmussen et al. 2001, Niklasson, Rasmussen et al. 2002, De Smedt, Devriendt et al. 2007, Niklasson, Rasmussen et al. 2009, Butcher, Chow et al. 2012, Niarchou, Zammit et al. 2014). Few individuals have moderate to severe ID (Swillen, Devriendt et al. 1997, Bassett, Hodgkinson et al. 1998, Niklasson, Rasmussen et al. 2009). It is important to note that the majority of studies diagnose ID on the basis of IQ score, 55-70 for mild, 40-54 for moderate, and <40 for severe ID. However, IQ score alone is not sufficient for DSM-5 criteria. Diagnosis of ID requires clinical assessment as well as standardised intelligence testing and adaptive functioning deficits in conceptual, social and practical domains must be present (American Psychiatric Association 2013). DSM-5 advocates defining severity of ID on the basis of adaptive functioning and not IQ score as IQ measures are less valid at the lower range.

#### **2. Frequency of ID in 22q11.2DS**

22q11.2DS has an elevated incidence in combined ID/developmental delay/congenital malformation cohorts compared to controls (0.61% vs 0.0%,  $p=8.4 \times 10^{-72}$ ), which is at a higher

incidence and significance level than for 22q11.2DS in schizophrenia (0.30% vs 0.0%,  $p=1.0\times 10^{-30}$ ) (Malhotra and Sebat 2012).

### 3. Neurocognitive deficits

Average IQ in 22q11.2DS is consistently reported to be approximately 70 (Swillen, Devriendt et al. 1997, Moss, Batshaw et al. 1999, Niklasson, Rasmussen et al. 2001, Niklasson, Rasmussen et al. 2002, Niklasson, Rasmussen et al. 2009, Butcher, Chow et al. 2012, Schneider, Debbané et al. 2014). There is great variability in IQ with one study reporting a range of 53 to 109 (Niarchou, Zammit et al. 2014). There is a suggestion that verbal IQ is higher than performance IQ (Moss, Wang et al. 1995, Swillen, Devriendt et al. 1997, Moss, Batshaw et al. 1999, Woodin, Wang et al. 2001), though no difference has also been reported (Niarchou, Zammit et al. 2014). Many studies report that children with 22q11.2DS decline in IQ with age (Gothelf, Eliez et al. 2005, Gothelf, Penniman et al. 2007, Antshel, Shprintzen et al. 2010, Duijff, Klaassen et al. 2012, Duijff, Klaassen et al. 2013, Gothelf, Schneider et al. 2013, Schneider, Schaer et al. 2014, Vorstman, Breetvelt et al. 2015), though not all studies (Schaer, Debbané et al. 2009, Hooper, Curtiss et al. 2013) and the magnitude of decline reported is highly variable (discussed in greater depth in Chapter 5).

22q11.2DS individuals are impaired across numerous neurocognitive domains including executive function, attention, working memory, verbal and nonverbal memory, visuospatial processing, visuomotor functioning, processing speed and social cognition (Woodin, Wang et al. 2001, Henry, Van Amelsvoort et al. 2002, Sobin, Kiley-Brabeck et al. 2004, Bish, Chiodo et al. 2007, Majerus, Van der Linden et al. 2007, Rockers, Ousley et al. 2009, Campbell, Azuma et al. 2010, Cabaral, Beaton et al. 2012, Gur, Yi et al. 2014, Niarchou, Zammit et al. 2014). There is evidence that impairments across neurocognitive domains are not strongly inter-correlated in 22q11.2DS and are relatively independent of intellectual ability (Niarchou, Zammit et al. 2014), a finding which is consistent to that reported in children with idiopathic neuropsychiatric disorder (Rommelse, Altink et al. 2008).

One study has compared ability in 22q11.2DS individuals across a wide range of domains in contrast to individuals with developmental delay and to typically developing controls. This comparison allowed deficits specific to 22q11.2DS to be distinguished from the nonspecific effects of developmental delay in 22q11.2DS. They found that deficits in face memory, social cognition and complex cognition (reasoning tasks) were specific to 22q11.2DS (Gur, Yi et al. 2014).



#### 4. Psychoeducational ability

Children with 22q11.2DS have deficits in academic achievement that persist into adolescence (Hooper, Curtiss et al. 2013). Their academic profile has been suggested to be consistent with the diagnosis of non-verbal learning disability as non-verbal deficits are greater than verbal deficits (Moss, Batshaw et al. 1999, Swillen, Vandeputte et al. 1999). In particular children exhibit difficulties in mathematics but relative strengths in reading and spelling (Moss, Batshaw et al. 1999, De Smedt, Swillen et al. 2009). Nonetheless there is great variability in academic achievement and some individuals go on to complete Bachelor's and Master's degrees (McDonald-McGinn and Zackai 2008).

#### 5. Adaptive functioning

The IBBC study finds that 22q11.2DS individuals are approximately two standard deviations below the general population on adaptive functioning measures (Schneider, Debbané et al. 2014). Intellectual functioning is a predictor of adaptive functioning in adulthood but not in childhood (Butcher, Chow et al. 2012), instead anxiety has been highlighted as important for functioning in childhood (Angkustsiri, Leckliter et al. 2012). However intellectual functioning only appears to explain a small proportion of the variance in adaptive functioning (Schneider, Debbané et al. 2014).

#### 6. Real-life deficits

22q11.2DS adults experience many real-life deficits. A low proportion of individuals are financially independent, develop long term romantic relationships or live away from family. These difficulties appear independent of diagnosis as they are present in 22q11.2DS individuals without ID and schizophrenia. Relative strengths are found in activities of daily living and employment, with 35% to 65% (McDonald-McGinn, Tonnesen et al. 2001, Butcher, Chow et al. 2012) of adults in employment. Types of jobs reported are diverse, however few individuals are financially independent suggesting work is low wage, part-time, or temporary. A proportion of adults show adaptive functioning higher than expected for their level of intellectual functioning suggesting that for some individuals effective management of their condition and appropriate social and vocational support may promote improved functioning (Butcher, Chow et al. 2012).

### **1.2.3 Autism spectrum disorder**

*Autism spectrum disorder (ASD) is characterised by persistent deficits in social communication and social interaction and by restricted, repetitive patterns of behaviour (American Psychiatric Association 2013).*

Children with 22q11.2DS exhibit many difficulties in social behaviour and language development (Golding-Kushner, Weller et al. 1984, Swillen, Devriendt et al. 1997, Heineman-de Boer, Van Haelst et al. 1998, Woodin, Wang et al. 2001, Niklasson, Rasmussen et al. 2002, Baker and Skuse 2005, Kiley-Brabeck and Sobin 2006, Shashi, Veerapandiyam et al. 2012), though there is uncertainty to what extent this is autism spectrum disorder (Eliez 2007).

### 1. ASD prevalence in 22q11.2DS

Reports of prevalence vary considerably from 10%-50% (Fine, Weissman et al. 2005, Vorstman, Morcus et al. 2006, Antshel, Aneja et al. 2007, De Smedt, Devriendt et al. 2007, Niklasson, Rasmussen et al. 2009, Niklasson and Gillberg 2010, Schneider, Debbané et al. 2014) though all greater than population prevalence of 1% (Baird, Simonoff et al. 2006, Kogan, Blumberg et al. 2009). Inconsistency in prevalence is likely due to the range of assessment tools and ascertainment methods employed by studies. A recent study found prevalence drops to 0% when both measures of clinical history and direct observation are utilised (Angkustsiri, Goodlin-Jones et al. 2014), though their sample may not be representative as prevalence on the basis of just clinical history was lower than other studies (Vorstman, Breetvelt et al. 2013, Niarchou, Zammit et al. 2014). The IBBC study of 22q11.2DS unexpectedly found ASD prevalence to peak in adolescence. This could reflect that autism measures often index severity of other neuropsychiatric disorders (Angkustsiri, Goodlin-Jones et al. 2014, Cooper, Martin et al. 2014, Schneider, Debbané et al. 2014).

### 2. Frequency of 22q11.2DS in ASD

It has been claimed that 22q11.2DS is not enriched in ASD cases (Karayiorgou, Simon et al. 2010, Hiroi, Takahashi et al. 2013), however this has been on the basis of older studies with small sample sizes. A meta-analysis of several studies reveals that the frequency of 22q11.2DS is significantly increased in ASD (0.07% cases vs 0% controls), albeit at a frequency and significance level much lower than for other genetic variants in ASD and for 22q11.2DS in schizophrenia (ASD vs schizophrenia; frequency 0.07% vs 0.30%, p-value 0.002 vs  $1.0 \times 10^{-30}$ ) (Malhotra and Sebat 2012).

### 3. Comparison of ASD in 22q11.2DS and idiopathic ASD

Only one study has compared ASD features present in children with 22q11.2DS and ASD to those present in idiopathic ASD. The two groups did not differ in severity of social interaction deficits and restricted, repetitive patterns of behaviour, but the idiopathic ASD group did have greater communication deficits. In terms of symptom profile they differed on 2 out of 12 domains with

the idiopathic ASD group more likely to have idiosyncratic speech and deficits in socioemotional reciprocity (Kates, Antshel et al. 2007).

#### 4. Lack of gender difference in ASD prevalence

The well documented male preponderance for ASD (Baron-Cohen 2002) is not observed in 22q11.2DS. This could be a consequence of the strong pathogenicity conferred by 22q11.2DS or that neuropsychiatric disorders which do not exhibit gender differences are misdiagnosed as ASD (Vorstman, Morcus et al. 2006, Schneider, Debbané et al. 2014).

#### 5. Features of 22q11.2DS may be misdiagnosed as autism.

It has been argued that other features of 22q11.2DS underlie deficits in social behaviour and language development.

- i. These deficits may be indicative of prepsychotic phenomena (Vorstman, Morcus et al. 2006, Eliez 2007) as many studies have found that individuals with idiopathic schizophrenia exhibit social and language deficits during childhood (Clegg, Hollis et al. 2005, Rutter, Kim-Cohen et al. 2006). Analogous concerns are present in the child-onset schizophrenia literature where early development is reminiscent of ASD but may be better conceptualised as part of the premorbid phase (Sporn, Addington et al. 2004). In contrast there are case studies of individuals with ASD being misdiagnosed with psychosis (Van Schalkwyk, Peluso et al. 2014). It is important to emphasise that social deficits are not synonymous with ASD and they differentially predict schizophrenia risk trajectories in 22q11.2DS. Deterioration in social functioning precedes psychosis onset in 22q11.2DS (Yuen, Chow et al. 2013) whereas 22q11.2DS individuals with ASD in childhood do not show increased risk for psychosis in adulthood (Vorstman, Breetvelt et al. 2013).
- ii. It has been argued that anxiety in 22q11.2DS contributes to a false elevation of ASD prevalence in the syndrome (Angkustsiri, Goodlin-Jones et al. 2014). Although anxiety is a common comorbidity in children with idiopathic ASD (Kim, Szatmari et al. 2000), this does not necessarily mean that ASD and anxiety diagnoses have to be mutually exclusive. Also, unlike anxiety disorders, ASD diagnosis requires symptoms to be present during the early developmental period (American Psychiatric Association 2013).

- iii. Misdiagnosis has been attributed to physical speech difficulties which are common in 22q11.2DS due to cleft palate and velopharyngeal dysfunction (Eliez 2007). However, communication deficits do not show diagnostic specificity in distinguishing 22q11.2DS children with and without autism, rather it is the ability for make-believe play that is crucial (Kates, Antshel et al. 2007).

Overall there is some evidence for a bidirectional association of 22q11.2DS and ASD, albeit not as strong as the association with schizophrenia. However, the clinical presentation of ASD is potentially less severe than that in idiopathic ASD. To some the question whether social and communication deficits present in 22q11.2DS constitutes ASD may seem arbitrary and an issue of classification. There are those who propose the complexities of the 22q11.2DS phenotype would be better conceptualised using dimensional measures rather than diagnostic categories (Baker and Vorstman 2012, Doherty and Owen 2014). However diagnostic categories are currently clinical psychiatry's means for informing treatment. Future work is needed to fully clarify the clinical presentation of ASD in 22q11.2DS to better inform treatment recommendations and care delivery (Angkustsiri, Goodlin-Jones et al. 2014).

#### **1.2.4 Attention-deficit/hyperactivity disorder**

*Attention-Deficit/Hyperactivity Disorder (ADHD) is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (American Psychiatric Association 2013).*

##### **1. ADHD prevalence in 22q11.2DS**

Reported prevalence in 22q11.2DS ranges from 12% to 68% (Arnold, Siegel-Bartelt et al. 2001, Feinstein, Eliez et al. 2002, Gothelf, Gruber et al. 2003, Antshel, AbdulSabur et al. 2005, Baker and Skuse 2005, Sobin, Kiley-Brabeck et al. 2005, Zagursky, Weller et al. 2006, De Smedt, Devriendt et al. 2007, Lewandowski, Shashi et al. 2007, Green, Gothelf et al. 2009, Jolin, Weller et al. 2009, Niklasson, Rasmussen et al. 2009, Sobin, Kiley-Brabeck et al. 2009, Antshel, Shprintzen et al. 2010, Stoddard, Niendam et al. 2010, Niarchou, Zammit et al. 2014) which is elevated in comparison to the general population prevalence of 5% (Polanczyk, de Lima et al. 2007). Lower estimates from this range are similar to ADHD prevalence reported in children with intellectual disability (Dekker and Koot 2003).

## 2. ADHD persistence across the lifespan

The IBBC study examined ADHD prevalence across the lifespan and found a rate of 37% in childhood, 24% in adolescence and 16% in adulthood (Schneider, Debbané et al. 2014). The 65% persistence rate from childhood to adolescence is consistent with longitudinal findings in 22q11.2DS (Antshel, Hendricks et al. 2013). This longitudinal course appears typical of that observed in idiopathic ADHD (70%) (Langley, Fowler et al. 2010) and persistence in both groups is predicted by the same factors (Antshel, Hendricks et al. 2013).

## 3. ADHD in 22q11.2DS in comparison to idiopathic ADHD

Children with 22q11.2DS and ADHD appear to have a different profile of ADHD symptoms and comorbidity in comparison to children with idiopathic ADHD (Antshel, Faraone et al. 2007). The inattentive subtype is more common in children with 22q11.2DS and they are less likely to display symptoms of hyperactivity and impulsivity (Schneider, Debbané et al. 2014). In particular symptoms relating to academic inattention are highly reported in 22q11.2DS. Academic struggles are a prominent feature of 22q11.2DS (Moss, Batshaw et al. 1999) and this could be partly caused by inattention, but alternatively in some cases ADHD diagnosis could simply index academic difficulties. Children with idiopathic ADHD have higher rates of comorbid major depression and disruptive behaviour disorders in comparison to children with ADHD and 22q11.2DS. There is also a suggestion that ADHD diagnosis captures features of 22q11.2DS that emerge during adolescence. A longitudinal study of 22q11.2DS found that 5 individuals gained the diagnosis of ADHD during adolescence, though all exhibited subthreshold symptoms at time 1 (Antshel, Hendricks et al. 2013).

## 4. Frequency of 22q11.2DS in ADHD

22q11.2DS is reported in ADHD cases, but at rates that are not significantly higher than in controls (Williams, Franke et al. 2012). However there could be ascertainment bias as the differing ADHD profile in 22q11.2DS may mean individuals are less likely to be included in genome-wide CNV studies.

## 5. Sex difference in ADHD prevalence

Unlike in ASD, ADHD in 22q11.2DS shows a male preponderance (Schneider, Debbané et al. 2014), as also observed in the general population (Merikangas, He et al. 2010).

Overall the symptom profile in 22q11.2DS differs from that in idiopathic ADHD but the level of persistence into adolescence is consistent with idiopathic ADHD.

### 1.2.5 Disruptive disorders

*Oppositional Defiance Disorder (ODD) is the persistent pattern of angry/irritable mood, defiant behaviour, or vindictiveness.*

*Conduct Disorder (CD) is the persistent pattern of behaviour in which the rights of others and societal norms or rules are violated (American Psychiatric Association 2013).*

#### 1. ODD

Reported ODD prevalence in 22q11.2DS varies from 5% to 43% (Papolos, Faedda et al. 1996, Arnold, Siegel-Bartelt et al. 2001, Feinstein, Eliez et al. 2002, Antshel, Fremont et al. 2006, Vorstman, Morcus et al. 2006, Green, Gothelf et al. 2009, Jolin, Weller et al. 2009, Sobin, Kiley-Brabeck et al. 2009, Antshel, Shprintzen et al. 2010, Romanos, Ehli et al. 2010, Stoddard, Niendam et al. 2010, Niarchou, Zammit et al. 2014). The IBBC study found childhood prevalence to be slightly higher than in the general population (14% (Schneider, Debbané et al. 2014) vs 8% (Kessler, Avenevoli et al. 2012)) but similar in comparison to children with intellectual disability (14% (Dekker and Koot 2003)). ODD in 22q11.2DS may not be similar to idiopathic ODD; it has been suggested that impairment is only present within the family context, whereas outside the family children are introverted (Schneider, Debbané et al. 2014). The frequency of 22q11.2DS in ODD and CD patients is unknown.

#### 2. No evidence for transition of ODD to CD

A large proportion of individuals with idiopathic ODD develop CD (Rowe, Costello et al. 2010, American Psychiatric Association 2013), yet CD is rarely diagnosed in 22q11.2DS. The IBBC study identified no child onset CD cases and a rate of 1.5% in adults (Schneider, Debbané et al. 2014). Smaller clinical samples report no cases (Arnold, Siegel-Bartelt et al. 2001, Baker and Skuse 2005, Antshel, Fremont et al. 2006, Green, Gothelf et al. 2009, Sobin, Kiley-Brabeck et al. 2009, Antshel, Shprintzen et al. 2010) except in one study where 4 out of 13 individuals met criteria for CD (Romanos, Ehli et al. 2010). These findings suggest the developmental course of ODD in 22q11.2DS differs from idiopathic ODD.

#### 3. Sex difference in disruptive disorders

There is a male preponderance for disruptive disorders in 22q11.2DS (Schneider, Debbané et al. 2014), consistent with findings in the general population (Maughan, Rowe et al. 2004).

### **1.2.6 Anxiety disorders**

*Anxiety disorders involve excessive fear and the anticipation of future threat and cause behavioural disturbance. Fear or anxiety has to be excessive or persisting beyond developmentally appropriate periods (American Psychiatric Association 2013).*

#### **1. Anxiety disorder prevalence in 22q11.2DS**

Reported prevalence varies from 5% to 60% (Arnold, Siegel-Bartelt et al. 2001, Baker and Skuse 2005, Lewandowski, Shashi et al. 2007, Green, Gothelf et al. 2009, Jolin, Weller et al. 2009, Sobin, Kiley-Brabeck et al. 2009, Antshel, Shprintzen et al. 2010, Stoddard, Niendam et al. 2010, Niarchou, Zammit et al. 2014). The IBBC study found anxiety disorders are particularly prevalent during childhood (36%) and adolescence (34%) and they persist into adulthood (25%) (Schneider, Debbané et al. 2014). The frequency of 22q11.2DS in anxiety disorder patients is unknown.

#### **2. Individual anxiety disorders**

Disorders reported include separation anxiety disorder, specific phobia, social phobia, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder and generalized anxiety disorder. Many individuals meet criteria for multiple anxiety disorders. Most frequent in childhood and adolescence are generalized anxiety disorder, specific phobia and social phobia. In adulthood generalized anxiety disorder and panic disorder are the most frequent. Only social phobia and generalized anxiety disorder are overrepresented in 22q11.2DS relative to individuals with intellectual disability (Schneider, Debbané et al. 2014). This along with the high prevalence of ASD indicates that social difficulties are a core deficit in 22q11.2DS that transcends diagnostic boundaries (Baker and Vorstman 2012).

#### **3. Impairment of Anxiety Disorders in 22q11.2DS**

In 22q11.2DS, anxiety disorders have the greatest negative effect on daily living skills when compared to mood disorders and schizophrenia spectrum disorders (Schneider, Debbané et al. 2014).

### **1.2.7 Mood disorders**

*The presence of sad, empty, or irritable mood which is accompanied by somatic and cognitive changes that significantly affects the individual's capacity to function (American Psychiatric Association 2013).*

## 1. Mood disorder prevalence in 22q11.2DS

The reported rate of mood disorder in 22q11.2DS varies from 3% to 64% (Arnold, Siegel-Bartelt et al. 2001, Niklasson, Rasmussen et al. 2002, Baker and Skuse 2005, Vorstman, Morcus et al. 2006, Lewandowski, Shashi et al. 2007, Green, Gothelf et al. 2009, Niklasson, Rasmussen et al. 2009, Sobin, Kiley-Brabeck et al. 2009, Antshel, Shprintzen et al. 2010, Stoddard, Niendam et al. 2010). The IBBC study finds mood disorders emerge during late adolescence and reach a prevalence of 20% in adulthood with major depressive disorder accounting for the majority of cases whereas bipolar disorder and dysthymia occur infrequently (Schneider, Debbané et al. 2014). In contrast early studies of 22q11.2DS report high rates of bipolar disorder (Papolos, Faedda et al. 1996, Gothelf, Frisch et al. 1999), albeit in small cohorts. This may reflect ascertainment or diagnosis issues of early studies. Alternatively it may reflect that individuals with 22q11.2DS experience periods of mood liability without meeting criteria for manic or hypomanic episodes (Schneider, Debbané et al. 2014). The extent to which 22q11.2DS directly contributes to mood disorders is uncertain as rates of mood disorders are known to be elevated in individuals with somatic disorders (Kroenke and Rosmalen 2006).

## 2. Frequency of 22q11.2DS in mood disorder

22q11.2DS has an elevated incidence in mood disorder patients compared to controls (0.05% vs 0.00%,  $p=8.0 \times 10^{-5}$ ), though at a lower incidence and significance level than for 22q11.2DS in schizophrenia (0.30% vs 0.00%,  $p=1.0 \times 10^{-30}$ ) (Malhotra and Sebat 2012).

### 1.2.8 Substance-related disorders

*A problematic pattern of alcohol or drug use leading to clinically significant impairment or distress* (American Psychiatric Association 2013).

Prevalence of substance related disorders is low, with the majority of studies reporting 0%-7% (Gothelf, Penniman et al. 2007, Antshel, Shprintzen et al. 2010, Stoddard, Niendam et al. 2010, Schneider, Debbané et al. 2014). An exception is an early small study that reported 3 out of 14 adults had alcohol abuse or dependence (Pulver, Nestadt et al. 1994). Of individuals who do report substance misuse the majority abused alcohol, whereas drug use disorders are rare.

### 1.2.9 Comorbidity

High rates of comorbidity are observed in individuals with 22q11.2DS. In children there is substantial comorbidity between ADHD, anxiety disorder, ASD and ODD (Niarchou, Zammit et al. 2014). In adults overlap is reported between anxiety, mood and psychotic disorders (Schneider, Debbané et



al. 2014). However there is evidence that not all features overlap as schizophrenia and ASD in 22q11.2DS appear to be distinct phenotypic manifestations (Vorstman, Breetvelt et al. 2013). Also 22q11.2DS has independent effects on intellectual impairment and psychopathology, in that IQ does not mediate risk for psychopathology (Niarchou, Zammit et al. 2014).

### **1.3 Summary**

22q11.2DS is associated with a wide range of physical abnormalities and neuropsychiatric problems. There is elevated prevalence of schizophrenia, ID, cognitive deficits, ASD, ADHD, ODD, anxiety and mood disorders. Some disorders such as CD and substance-related disorder, however, have a low prevalence in 22q11.2DS. There is evidence for a strong bidirectional association between 22q11.2DS and schizophrenia, ID and mood disorder but less so for other psychiatric features of 22q11.2DS. The nature of schizophrenia in 22q11.2DS is similar to clinical presentation in the general population, but there is uncertainty whether this is true for other features of the neuropsychiatric phenotype such as ASD, ADHD and ODD. The neuropsychiatric phenotype of 22q11.2DS is complex. However, there are apparent themes which transcend diagnostic categories and cognitive domains such as social impairments, attention difficulties and affective dysregulation. This chapter has described the features of 22q11.2DS in depth, next I will discuss the insights that researching neuropsychiatric development in 22q11.2DS can provide.

## **2. Introduction: Insights that can be gained from examining neuropsychiatric development in 22q11.2DS**

### **2.1 Understanding schizophrenia risk trajectories**

#### **2.1.1 22q11.2DS as a high risk condition for schizophrenia**

It has been discussed in Chapter 1 that 22q11.2DS is a high risk condition for schizophrenia. 30-40% of adults develop psychotic disorder and 20-30% of adults are diagnosed with schizophrenia (Murphy, Jones et al. 1999, Monks, Niarchou et al. 2014, Schneider, Debbané et al. 2014). Thus, following child patients over time provides a rare opportunity for prospective examination of the development of schizophrenia.

Studies based on retrospective accounts by patients with idiopathic schizophrenia often lack relevant standardized records. Population cohort studies on the other hand may have low power, because only a very small proportion of participants will transition to schizophrenia, while furthermore at risk individuals may also be more likely to drop out of the study. High risk studies represent an effective methodology, particularly if a high proportion of young people will develop psychotic disorder.

The transition rate to psychosis in 22q11.2DS is much higher than that observed in the Edinburgh High Risk Study (clinical risk of 12% (McIntosh, Owens et al. 2011)) and the New York High-Risk Project (familial risk of 23.8% (Erlenmeyer-Kimling, Adamo et al. 1997)). Only one genetic condition has been reported to confer even higher risk of psychosis of 60-100%, the maternal uniparental disomy (mUPD) genetic subtype of Prader-Willi syndrome (PWS), where individuals inherit two maternal copies of chromosome 15 (Larson, Whittington et al. 2014). 22q11.2DS individuals are generally diagnosed early in development and are not ascertained on the basis of psychotic phenomenology. 22q11.2DS offers a unique window into psychosis development without bias introduced by use of antipsychotic medication (as is the case in clinical high risk studies) and provides a means to explore the neurodevelopmental hypothesis of schizophrenia.

However, it should be highlighted that it is difficult to achieve large cohorts of 22q11.2DS individuals because of the rarity of the syndrome. Also, the range of difficulties experienced by children with 22q11.2DS can complicate longitudinal follow-up.

### 2.1.2 Neurodevelopmental hypothesis of schizophrenia

First formulated by Weinberger (Weinberger 1986), and Murray and Lewis (Murray and Lewis 1987) the 'neurodevelopmental hypothesis of schizophrenia', posits that, although schizophrenia generally manifests in adulthood, diagnosis is the endpoint of an extended period of perturbed developmental processes (Seidman 1990, Owen, O'Donovan et al. 2011, Rapoport, Giedd et al. 2012). Below I summarise the main sources of evidence for this hypothesis.

#### 1. Longitudinal epidemiology

Retrospective and population cohort studies find significant neurodevelopmental deviance pre-existing to the diagnosis of idiopathic schizophrenia. Individuals who develop schizophrenia exhibit childhood deficits in cognition, language, social skills and motor development (Clegg, Hollis et al. 2005, Rutter, Kim-Cohen et al. 2006, Woodberry, Giuliano et al. 2008, Dickson, Laurens et al. 2012). One study finds impairments are evident from as early as age one (Isohanni, Murray et al. 2004). The pattern of premorbid cognitive deficits is specific to schizophrenia rather than being non-specific to adult psychiatric disorder (Reichenberg, Caspi et al. 2010). Also subclinical psychotic experiences can be present in childhood and have a prevalence of 5% (van Os, Linscott et al. 2009) and are predictive of later psychotic disorder (Chapman, Chapman et al. 1994, Poulton, Caspi et al. 2000, Hanssen, Bak et al. 2005, Zammit, Kounali et al. 2013).

#### 2. Prenatal risk

Prenatal infection, famine and obstetric complications have been highlighted as risk factors for schizophrenia (Brown and Derkits 2010, Rapoport, Giedd et al. 2012). *Toxoplasma gondii* is a specific infection which has been consistently associated (Mortensen, Nørgaard-Pedersen et al. 2007, Pedersen, Stevens et al. 2011) and the immune system has been further implicated with a recent finding that many genes associated with schizophrenia are involved in immune pathways (O'Dushlaine, Rossin et al. 2015). Retrospective studies of the Dutch Hunger Winter and Chinese Cultural Revolution find in utero exposure to famine increases risk for later schizophrenia development (Susser and Lin 1992, St Clair, Xu et al. 2005, Xu, Sun et al. 2009). Although there is an association between obstetrical complications and schizophrenia (Rapoport, Addington et al. 2005), the link may not be causal, rather obstetrical events may be markers of abnormal foetal development (Rapoport, Giedd et al. 2012). Overall it is evident that processes related to schizophrenia risk manifest very early on in development.

### 3. Adverse postnatal early environment

Minority group position is associated with psychotic phenomena with effects being mediated by social adversity (Bourque, Van der Ven et al. 2011). Migration into a country where the individual becomes part of the minority particularly impacts on psychosis risk when the individual is between ages 0-4, again highlighting that early development is crucial in the aetiology of schizophrenia (Veling, Hoek et al. 2011). Childhood trauma has been linked to psychosis, however the small sample size of studies and methodological issues means the causal nature of this relationship remains uncertain (Morgan and Fisher 2007).

### 4. Structural brain differences

The developmental origin of structural brain abnormalities in schizophrenia patients has been inferred from the observation that post-mortem brain studies find an absence of evidence for neurodegeneration (Owen, O'Donovan et al. 2011). There is also direct evidence from imaging studies of individuals identified as clinically ultra-high-risk with reports that those who develop psychosis have reductions in white matter volume in the left fronto-occipital fasciculus (Walterfang, McGuire et al. 2008) and white matter abnormalities in the medial frontal cortex (Bloemen, De Koning et al. 2010).

#### **2.1.3 Evidence from 22q11.2DS**

The phenotype of 22q11.2DS supports 'the neurodevelopmental hypothesis of schizophrenia' as in addition to schizophrenia 22q11.2DS is associated with a wide range of early onset neurodevelopmental problems (as discussed in Chapter 1). The hypothesis can be explored further as studies of 22q11.2DS provide a rare opportunity to uncover the childhood antecedents of schizophrenia.

#### **2.1.4 Antecedents of psychotic disorder in 22q11.2DS**

There are few 22q11.2DS studies which are able to test for associations between early behaviour and later psychotic disorder. The majority of longitudinal studies following child cohorts over time are yet to reach the adulthood phase. However, studies have highlighted potential risk factors.

##### 1. Cognitive development

Decline in intelligence particularly in the verbal domain has been implicated. Emergence of psychotic disorder has been reported to be predicted by baseline IQ (Gothelf, Feinstein et al. 2007) as well as decline in Verbal IQ (VIQ) (Gothelf, Penniman et al. 2007, Gothelf, Schneider et al. 2013). A recent longitudinal study of 411 22q11.2DS individuals, the largest to date,

replicated these findings. They also reported that the VIQ trajectories of the group who subsequently developed psychotic disorder began to differ from age 11 (Vorstman, Breetvelt et al. 2015). It should be noted that such a large sample size was achieved from combining 22q11.2DS cohorts from different countries. Assessment protocols differed across sites and psychotic disorder was not necessarily assessed concurrently with cognition so the question whether decline precedes onset or is due to onset of psychotic disorder remains open.

## 2. Anxiety and Mood

Two longitudinal studies report that diagnosis of an anxiety disorder predicts later emergence of psychotic disorder (Gothelf, Feinstein et al. 2007, Gothelf, Schneider et al. 2013). Anxiety is also predictive when it is measured dimensionally (Gothelf, Feinstein et al. 2007, Schonherz, Davidov et al. 2014). Findings are inconsistent with regards to the predictive nature of mood (Gothelf, Feinstein et al. 2007, Gothelf, Schneider et al. 2013, Schonherz, Davidov et al. 2014).

## 3. Prepsychotic phenomena

Subthreshold psychotic symptoms in 22q11.2DS are found to be predictive of later psychotic disorder (Gothelf, Feinstein et al. 2007). A retrospective study of 22q11.2DS adults with and without schizophrenia examined premorbid adjustment and reported deterioration in social and academic skills from childhood to adolescence in those who later developed schizophrenia (Yuen, Chow et al. 2013).

## 4. No evidence for differences in brain morphology

Two studies report no brain morphology differences in those who subsequently developed psychotic disorder, however sample sizes were small (psychotic disorder n/total n; 7/19, 9/28) (Gothelf, Feinstein et al. 2007, Gothelf, Penniman et al. 2007).

### **2.1.5 Antecedents of psychotic symptoms in 22q11.2DS**

Studies have also assessed the factors preceding emergence of psychotic and prodromal symptoms, rather than frank psychotic disorder, in 22q11.2DS.

#### 1. Cognitive development

VIQ decline has been implicated in emergence of psychotic symptoms (Gothelf, Eliez et al. 2005, Kates, Antshel et al. 2011) but not by all studies (Antshel, Shprintzen et al. 2010, Hooper, Curtiss et al. 2013). Baseline IQ is also reported to be a risk factor (Hooper, Curtiss et al. 2013, Schneider, Schaer et al. 2014). Many other neurocognitive domains have been investigated and

there is strong evidence for a link with worse baseline cognitive performance across several domains (Antshel, Shprintzen et al. 2010, Hooper, Curtiss et al. 2013, Kates, Russo et al. 2014, Schneider, Schaer et al. 2014). Change in these non-IQ neurocognitive domains has not been implicated (Schneider, Schaer et al. 2014), however studies have not always examined change in relation to psychotic symptoms (Antshel, Shprintzen et al. 2010, Hooper, Curtiss et al. 2013).

## 2. Psychopathology

Anxiety is a predictor of prodromal symptoms (Antshel, Shprintzen et al. 2010). There is evidence that this relationship may be moderated by verbal learning ability, that is good verbal learning ability is protective of psychotic symptoms in 22q11.2DS individuals with high anxiety (Kates, Russo et al. 2014). Other childhood behaviours, such as externalizing, odd eccentric and problem social behaviours have also been implicated (Hooper, Curtiss et al. 2013).

## 3. Family Environment

Family dis-organization has been found to amplify the relationship between childhood mood dysregulation and later emergence of prodromal symptoms (Kates, Russo et al. 2014), however it remains unclear to what extent family background factors antecede occurrence of children's mental health problems.

## 4. Brain morphology

Differences in brain morphology have been associated with development of psychotic symptoms, but a consistent pattern is not yet emerging. The following differences have been reported; reduction in grey matter volume in the left dorsal prefrontal cortex (Gothelf, Hoefft et al. 2011), decreased temporal lobe grey matter volume (Kates, Antshel et al. 2011), change in cortical gyrification in the left occipital lobe (Kunwar, Ramanathan et al. 2012) and larger baseline hippocampal volume (Flahault, Schaer et al. 2012). One study has claimed to be able to predict risk for psychotic symptoms with >94% accuracy using multivariate pattern analysis (Gothelf, Hoefft et al. 2011), but sample size was small so this result could be an artefact of having too many predictor variables.

### 2.1.6 Discussion

Development in 22q11.2DS provides many clues to the neurodevelopmental processes that precede psychosis, particularly highlighting childhood cognitive development, anxiety, subclinical psychotic phenomena and brain morphology. However many findings are inconsistent and/or need replication. There is an overlap in the risk factors for psychotic disorder and symptoms but there are

differences, which is consistent with the idiopathic literature (van Os, Linscott et al. 2009, Zammit, Hamshere et al. 2014).

Examining development in 22q11.2DS could uncover risk factors for psychiatric disorders other than schizophrenia. Depression has been examined in one study but no cognitive risk factors were identified (Antshel, Shprintzen et al. 2010). There is potential for risk trajectories for ASD and ADHD to be investigated, but current 22q11.2DS studies do not capture ages at the extremities of the life span.

## **2.2 Understand genetic risk for psychiatric disorder**

### **2.2.1 CNVs confer risk for psychiatric disorder**

22q11.2DS offers the opportunity to explore how genetic risk contributes to psychiatric disorder. As mentioned briefly in Chapter 1 22q11.2DS is a CNV. CNVs represent an important source of genetic variation, and unlike 22q11.2DS, many can be benign and present in healthy individuals (Kirov, Rees et al. 2015). A number of pathogenic CNVs have been identified (Girirajan, Rosenfeld et al. 2012, Vissers and Stankiewicz 2012) and there is consensus that multiple CNVs confer risk for neuropsychiatric disorder (Cook and Scherer 2008), including 22q11.2DS. I will now discuss what has been learnt from psychiatric-risk CNVs in relation to findings with 22q11.2DS.

#### **1. CNVs are rare but penetrant**

Initial evidence for a genetic contribution to psychiatric illness came from twin studies, which consistently indicate that neuropsychiatric disorders are highly heritable (Bailey, Le Couteur et al. 1995, Kendler 2001, Faraone, Perlis et al. 2005). Molecular genetic studies suggest that the genetic architecture of psychiatric disorder is complex with combined effects of many common variants of small effect, as well as rare variants of large effect (Gratten, Wray et al. 2014). In schizophrenia research, odd ratios (ORs) ranging from 2 to <50 have been reported for CNVs (Kirov, Rees et al. 2015). Large variants such as CNVs may provide a starting point for investigation into the biological mechanisms of neuropsychiatric dysfunction (Stefansson, Meyer-Lindenberg et al. 2014). As mentioned in Chapter 1, 22q11.2DS is both rare (1 in 4000 live births) and penetrant for schizophrenia (20-30% prevalence).

#### **2. The same CNVs confer risk for multiple neuropsychiatric disorders**

CNVs are not specific risk factors for particular psychiatric disorders. Like 22q11.2DS, many CNVs that confer risk for schizophrenia also increase risk for early developmental disorders such as

ASD, ADHD and ID. These findings suggest that there may be a general overlap in genetic risk amongst early developmental disorder and schizophrenia, a proposition that challenges nosological views in psychiatry (Owen, O'Donovan et al. 2011, Kirov, Rees et al. 2015).

### 3. CNVs contribute to severe cases of neuropsychiatric disorder

There is evidence to suggest CNVs are more enriched in extreme populations and have a more severe phenotype in contrast to idiopathic psychiatric cases. CNVs are more frequent in child-onset schizophrenia (Walsh, McClellan et al. 2008, Lee, Mattai et al. 2012), indeed 22q11.2DS occurs at a rate of 4.0% in child-onset cases vs 0.3-1.0% of adult cases (Ahn, Gotay et al. 2014). Psychosis in the mUPD subtype of Prader-Willi syndrome is severe, showing a cycloid PWS specific pattern (Soni, Whittington et al. 2007, Soni, Whittington et al. 2008). In an ADHD cohort it was reported that the rate of comorbid ID was elevated in children with CNVs (Langley, Martin et al. 2011), although the nature and severity of ADHD in CNV carriers did not differ from idiopathic ADHD.

### 4. The phenotype of CNVs provides insight into potential models of psychiatric disorder

Crespi and Badcock propose that autism and psychosis are reciprocal disorders of the social brain. They have highlighted physiological, neurological, and psychological evidence as well as studies from psychiatric risk CNVs as supporting this hypothesis. They comment that deletions and duplications at the same loci confer opposing risk for autism and psychosis (Crespi and Badcock 2008, Crespi, Summers et al. 2009). The recent finding described in Chapter 1 (1.2.2) that 22q11.2 duplications are protective of schizophrenia in contrast to the deletion supports this view (Rees, Kirov et al. 2014). However both ASD and schizophrenia are elevated in 22q11.2DS which would appear to go against the hypothesis, though Crespi has cited the argument discussed in Chapter 1 (1.2.3) that ASD is misdiagnosed in 22q11.2DS and is in fact prepsychotic phenomena (Crespi and Crofts 2012). This ongoing debate highlights the importance of critically examining the phenotype of CNVs and the implications this has for wider aetiological understanding of psychiatric disorder.

### 5. CNVs can help identify endophenotypes

Endophenotypes are intermediary phenotypes which fall on the causal pathway between genes and disease (Gottesman and Gould 2003, Walters and Owen 2007). They are useful for studying the functional consequences of genetic risk variants and will hopefully provide a window onto the biological mechanisms underlying neuropsychiatric disorder. Neuropsychiatric risk CNVs are variants of large effect and thus provide an opportunity to uncover endophenotypes.



A study conducted using the Icelandic DeCODE genetic population cohort (n=101,655) demonstrates the utility of this approach (Stefansson, Meyer-Lindenberg et al. 2014). They identified neuropsychiatric risk CNV carriers from their cohort and examined their cognition and brain structure. They found that carriers who had not been diagnosed with ASD, ID or schizophrenia still exhibited intermediary endophenotypes in cognition and brain structure that are consistent with that observed in first-episode psychosis, thus affirming the role of genetic risk variants, as well as cognition and brain development in the pathogenesis of schizophrenia. However this study could not give much insight into 22q11.2DS as only 18 individuals had 22q11.2DS of which just 3 agreed to take part in the cognitive assessment and structural brain scanning. This illustrates that although large population cohorts can identify 22q11.2DS individuals who have not necessarily been identified by medical genetic services and therefore reflect the wider range of manifestations associated with the 22q11.2DS phenotype, they are unlikely to provide sample sizes as large as current clinically ascertained cohorts.

## **2.2.2 Endophenotypes in 22q11.2DS**

Here I discuss some of the endophenotypes identified in 22q11.2DS. Mouse models of 22q11.2DS have been particularly useful in identifying endophenotypes. The human 22q11.2 region is syntenic with a region of chromosome 16 in mice, therefore allowing recapitulation of human 22q11.2DS (Drew, Crabtree et al. 2011).

### **1. Cognition**

A study of 22q11.2DS children reported decline in IQ between the ages of 5.5 and 9.5, demonstrating that decline is occurring very early on and before the period of schizophrenia risk (Duijff, Klaassen et al. 2012). However there was no comparison group to control for methodological artefacts (more detail in Chapter 5).

Sensorimotor gating deficits, as indexed by prepulse inhibition (PPI), is consistently identified as an endophenotype of ASD and schizophrenia (Baker, Adler et al. 1987). PPI is reduced both in children with 22q11.2DS (Sobin, Kiley-Brabeck et al. 2005) and in mouse models (Paylor, Glaser et al. 2006).

### **2. Brain Structure**

Human studies report whole brain volumetric reduction in 22q11.2DS (Jonas, Montojo et al. 2014) which is consistent with findings in schizophrenia patients (Ward, Friedman et al. 1996). Reduction occurs in the parietal lobes and there is thinning of midline brain regions. Studies in

mice suggest this is due to abnormal cortical neurogenesis (Stark, Xu et al. 2008, Meechan, Tucker et al. 2009).

### 3. Brain Physiology

Cortical dysconnectivity as measured by resting state functional magnetic resonance imaging is consistently implicated in idiopathic neuropsychiatric disorder (Broyd, Demanuele et al. 2009). Reduced synchronicity in long distance connectivity is observed in 22q11.2DS adolescents and may act as an intermediary endophenotype for schizophrenia risk (Debbané, Lazouret et al. 2012). Findings from a mouse model of 22q11.2DS suggest the neuronal basis for this lies in reduced hippocampal-prefrontal functional connectivity (Jonas, Montojo et al. 2014). With the advent of induced pluripotent stem cell (iPSC) technology it will be possible for 22q11.2DS patient derived neurons to be grown and physiologically interrogated for possible endophenotypes (Drew, Crabtree et al. 2011).

### **2.2.3 Reconceptualising the neuropsychiatric phenotype in 22q11.2DS**

22q11.2DS offers a genetic starting point for exploring development of psychiatric disorder. It is clear the phenotype transcends multiple diagnostic boundaries and cognitive domains and it is questioned whether current nosology adequately captures the phenotype of 22q11.2DS. I will discuss potential models and approaches for reconceptualising the neuropsychiatric phenotype.

#### 1. Symptom-cognitive domains

Baker and Vorstman propose that a core neuropsychiatric phenotype underlies disruptions across multiple symptom domains in 22q11.2DS and would have the potential to predict later psychiatric morbidity (Baker and Vorstman 2012). This core phenotype can be characterized by four symptom-cognitive domains which cross-cut traditional classifications; attention-executive deficits, social-cognitive deficits, anxiety-affective dysregulation and psychosis. However this hypothesis currently lacks empirical evidence.

#### 2. Developmental Brain Dysfunction

It has been proposed that developmental brain dysfunction underlies the variable phenotype of psychiatric risk in CNV carriers and that if brain dysfunction is measured quantitatively there is 100% penetrance in carriers (Moreno-De-Luca, Myers et al. 2013). Quantitative measurement of different aspects of brain dysfunction in 22q11.2DS could help delineate a neurodevelopmental profile of strengths and weaknesses in 22q11.2DS. IQ is normally distributed in 22q11.2DS, but is two standard deviations below the general population (Moss, Batshaw et al. 1999, Niarchou,

Zammit et al. 2014), but other aspects of the 22q11.2DS profile such as behavioural, emotional and social deficits are yet to be explored quantitatively.

### 3. Research Domain Criteria

There is a growing consensus that psychiatry needs to move away from using traditional diagnostic measures to quantitative dimensional measures (Craddock and Owen 2010, Owen 2012, Moreno-De-Luca, Myers et al. 2013). The National Institute of Mental Health (NIMH) have developed one such dimensional system, research domain criteria (RDoC) (Cuthbert and Insel 2013). This approach could be applied to 22q11.2DS to better understand how it confers risk for neuropsychiatric disorder and how it impacts cognitive and neural systems (Doherty and Owen 2014).

## 2.3 Understanding the factors that modulate psychiatric risk

It has been discussed that there is great variability in the neuropsychiatric phenotype of 22q11.2DS. Here I discuss some of the factors that may underlie this variation.

### 2.3.1 Genetic factors

#### 1. Deletion size

As previously mentioned deletion size is variable, 87% of deletions are 3 Mb region and the rest are smaller nested regions (Shaikh, Kurahashi et al. 2000). This could contribute to phenotypic variability. One study reports schizophrenia and ASD not being present in smaller deletion cases, the though authors emphasise that this may reflect the small sample size of their study (Michaelovsky, Frisch et al. 2012). Smaller deletions have been reported in cohorts of schizophrenia and ASD patients but also in control samples (Hiroi, Takahashi et al. 2013), so it remains unclear to what extent deletion size is associated with neuropsychiatric outcomes.

#### 2. Two-hit hypothesis

Other genetic variants may contribute to variability. Risk for neuropsychiatric features could be conferred by the combination of 22q11.2DS and a second variant, a two-hit hypothesis.

##### i. Modifier genes

The 22q11.2 deletion could be unmasking a deleterious allele within the remaining 22q11.2 region. The combination of a CNV occurring in combination with an inherited

gene variant has been reported in autism (Vorstman, van Daalen et al. 2011). COMT has received a lot of attention as an initial report suggested common variation of this gene predicts longitudinal change in cognition, prefrontal cortical volume and psychotic symptoms in 22q11.2DS (Gothelf, Eliez et al. 2005). Two other studies report that variation in COMT genotype predicts psychotic phenomena (Gothelf, Feinstein et al. 2007, Boot, Booij et al. 2011) but there are many studies which have found no association with psychotic phenomena, depression or anxiety (Murphy, Jones et al. 1999, Bassett, Caluseriu et al. 2007, van Amelsvoort, Zinkstok et al. 2008, Antshel, Shprintzen et al. 2010, de Koning, Boot et al. 2012, Gothelf, Schneider et al. 2013). However, there is evidence that COMT genotype influences frontal lobe volume and functioning in 22q11.2DS (Bassett, Caluseriu et al. 2007, van Amelsvoort, Zinkstok et al. 2008, de Koning, Boot et al. 2012). Another gene in the 22q11.2 region, PIK4CA, has been investigated but genotype did not predict psychosis (Ikeda, Williams et al. 2010). For background information on COMT and PIK4CA see section 1.2.1.

ii. Second hit CNVs

It could be that a second CNV outside the 22q11.2DS region explains phenotypic variability. One study suggests second-hit CNVs may be enriched in 22q11.2DS individuals with psychosis, however the sample size is small and findings need replicating (Williams, Monks et al. 2013).

3. Polygenic risk

Variability may be explained by the summation of risk from multiple genes outside the 22q11.2 region. Risk alleles have been identified for many psychiatric disorders (Collins and Sullivan 2013). There is evidence that CNV carriers with psychiatric disorder have a lower polygenic risk than non-carriers with psychiatric disorder, suggesting CNVs lower the threshold for polygenic risk (Ripke, Neale et al. 2014, Martin, O'Donovan et al. 2015). The role of polygenic risk in the 22q11.2DS phenotype has not been investigated.

### **2.3.2 Family factors**

Neuropsychiatric traits in children with 'de novo' 22q11.2DS may be predicted by the presence of similar traits in their parents. The intellectual functioning of parents has been found to be predictive of childhood intelligence in 22q11.2DS (Klaassen, Duijff et al. 2014, Olszewski, Radoeva et al. 2014). Also familial ADHD is predictive of persistence of ADHD into adolescence in 22q11.2DS (Antshel,

Hendricks et al. 2013). The mechanisms are uncertain but it could reflect a combination of inherited polygenic risk from the parent but also shared family environment. It is also possible that gene-environment covariation is occurring, in that exposure to an environment is influenced by genotype (Mackintosh 2011).

### **2.3.3 Environmental factors**

This is an understudied area in 22q11.2DS research. It has been suggested that 22q11.2DS confers susceptibility to stress, thus providing a sensitised background for exploring environmental risk factors for psychiatric disorder (Beaton and Simon 2011, Jonas, Montojo et al. 2014). As mentioned previously, family environment has been found to amplify the relationship between childhood mood dysregulation and later emergence of prodromal symptoms (Kates, Russo et al. 2014). Identification of protective environmental factors will be useful for informing interventions.

## **2.4 Potential impact**

Research into the neuropsychiatric phenotype is needed to help 22q11.2DS individuals and their families. 22q11.2DS is one of the strongest risk factors for schizophrenia, yet no effective intervention is available. Parents report anxiety in response to behavioural difficulties in their child and they worry about the development of psychosis (Briegel, Schneider et al. 2007, Hercher and Bruenner 2008). Understanding the pathways to psychiatric disorder in 22q11.2DS will hopefully inform potential treatments and interventions. Preliminary trials of cognitive remediation and social cognitive training interventions have been conducted and show some positive benefits but their long term efficacy on psychosis risk remains unknown (Harrell, Eack et al. 2013, Shashi, Harrell et al. 2015).

Investigation into neuropsychiatric development in 22q11.2DS will give insights which can be expected to be applicable to general psychiatry. Understanding development and prevention of neuropsychiatric disorder in high risk conditions, such as 22q11.2DS, is arguably an important step before understanding how complex multifactorial risk for psychiatric disorder manifests.

## **2.5 Summary**

22q11.2DS provides a rare opportunity to examine the developmental pathways of neuropsychiatric disorders. Potential causal pathways to psychotic phenomena have been identified involving prodromal features, anxiety, cognition, brain morphological changes and family environment. However there are many inconsistencies in findings, difficulties in interpreting causality and a need for replication. 22q11.2DS represents a genetic starting point to explore how risk for

neuropsychiatric disorder manifests and allows investigation into endophenotypes. Heightened psychiatric risk in 22q11.2DS allows the genetic and environmental factors that modulate psychiatric risk to be explored.

The following chapters summarise the work I have undertaken on neuropsychiatric development in 22q11.2DS. I report findings from a longitudinal cohort of children with 22q11.2DS. My aims are to:

1. Characterise development of psychopathology in 22q11.2DS
2. Examine cognitive development in 22q11.2DS
3. Explore the relationship between psychopathology and cognitive development in 22q11.2DS

### **3. The ECHO study 22q11.2DS cohort**

The Cardiff University ECHO study (Experiences of CHildren with cOpy number variants) started in 2010, led by principal investigators Professor Marianne van den Bree and Professor Sir Michael Owen. The study assesses children with CNVs associated with increased risk of intellectual disability and psychiatric problems, including 22q11.2DS. In 2013 a second wave of assessment was initiated.

#### **3.1 Recruitment**

##### **3.1.1 Wave 1 assessment**

Currently 121 children with 22q11.2DS have been assessed. Children are recruited from NHS medical genetics clinics, UK support groups Max Appeal!, 22crew and Unique, and the ECHO study website. Children have been assessed from Wales, England, Scotland and Northern Ireland. The closest unaffected sibling in age to the child with 22q11.2DS is recruited as a control. 22q11.2DS is confirmed by medical genetics clinics, medical reports from the primary carer and also by the Institute of Psychological Medicine and Clinical Neurosciences laboratory.

##### **3.1.2 Wave 2 assessment**

The target time gap between assessments was 2.5 years. At the time of writing of the 121 children who were initially assessed 102 were eligible to be re-contacted, in that 2.5 years had passed since initial assessment. Of these, 70 children have been assessed for a second time. This represents a participation rate of 69%, which is consistent with other longitudinal 22q11.2DS studies (Antshel, Shprintzen et al. 2010, Gothelf, Schneider et al. 2013). 29 controls (unaffected siblings) have also been assessed longitudinally.

##### **3.1.3 Ethics**

Informed written consent was obtained at both waves of assessment from the primary carer of the participant and directly from the participant if aged 16 and above. Protocols were approved by National Health Service (NHS) South East Wales Research Ethics and Research and Development committees of individual NHS Trusts.

## 3.2 Measures

### 3.2.1 Psychiatric

#### 1. Psychopathology: CAPA

Psychopathology, during the last 3 months and including psychotic experiences, was assessed at both waves using the Child and Adolescent Psychiatric Assessment (CAPA) (Angold, Prendergast et al. 1995) by means of semi-structured interview (parent CAPA) with the primary carer. Criteria were applied to establish DSM-IV-TR (Diagnostic Statistical Manual of mental disorders, Fourth edition, Text Revision) (American Psychiatric Association 2000) diagnosis. Rules regarding mutually exclusive diagnoses were not applied. Presence of the following psychiatric disorders were established (numbers referring to DSM-IV-TR code):

##### i. Psychotic Disorder

Schizophrenia 295.10/295.20/295.30/295.90

Schizophreniform Disorder 295.40

Schizoaffective Disorder 295.70

Delusional Disorder 297.10

Brief Psychotic Disorder 298.8

##### ii. Mood Disorder

Bipolar I Disorder – Single Manic Episode 296.0

Major Depressive Disorder – Single Episode 296.2

Major Depressive Disorder – Recurrent 296.3

Bipolar II Disorder – Recurrent Major Depressive Episodes with Hypomanic Episodes 296.89

Dysthymic Disorder 300.4

##### iii. Anxiety Disorder

Generalised Anxiety Disorder 300.02

Panic Disorder without Agoraphobia 300.1

Panic Disorder with Agoraphobia 300.21

Agoraphobia without history of Panic Disorder 300.22

Social Phobia 300.23

Specific Phobia 300.29

Obsessive Compulsive Disorder 300.3

Separation Anxiety 309.21

Selective Mutism 313.23



- iv. Tic Disorders – Chronic Motor or Vocal Tic Disorder 307.2
- v. Trichotillomania 312.39
- vi. Conduct Disorder 312.81/312.82/312.89
- vii. Oppositional Defiant Disorder 313.81
- viii. Attention Deficit Hyperactivity Disorder 314.00/314.01

In addition, psychotic experiences were assessed through child-report using the psychosis section of the child CAPA at both waves. In this section, initial screening questions probed for any evidence of perceptual disorders or hallucinations, delusions or psychotic abnormalities of thought processes. If participants scored on the screening questions, the interviewer continued with more detailed probing about the nature of possible experiences. Questions were asked about the content and location of auditory, olfactory and tactile hallucinations, thought insertion and broadcast, thought echo and withdrawal and delusional thinking. Phenomena not coded as psychotic experiences included hypnagogic/pompic hallucinations, eidetic imagery, elaborated fantasies, imaginary companions, illusions, hallucinations occurring as part of a seizure or clouded sensorium, spots/stripes before the eyes and sensory changes associated with headaches. Psychotic experiences were counted as present if reported by either the primary carer or child.

All interviews were conducted by trained researchers, who were supervised by a consultant child and adolescent psychiatrist. Interviews were audio-taped for monitoring purposes.

## 2. ASD traits: SCQ

ASD traits were assessed using the Social Communication Questionnaire (SCQ) (Rutter, Bailey et al. 2003), which was completed by the primary carer at both waves of assessment. Total scores can range from 0 to 39. Questions cover three domains; reciprocal social interaction, language and communication, repetitive and stereotyped patterns of behaviour. Behaviour both current and during the ages 4 to 5 are assessed. A score of 15 or higher is suggestive of ASD and a score of 22 or higher is suggestive of autism (Berument, Rutter et al. 1999).

## 3. ASD diagnosis: ADI-R

The SCQ does not provide a formal research diagnosis. At wave 1 of the ECHO study, 26.0% of participants with 22q11.2DS had SCQ scores which were suggestive of ASD in comparison to 5.3% of control siblings (Niarchou, Zammit et al. 2014). In light of this it was decided at wave 2 to administer the Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur et al. 2003), a semi-structured interview with the primary carer, to assess autism. The ADI-R was conducted over the telephone due to time restraints during the home visit. This method of administration has been validated for the

ADI-R (Ward-King, Cohen et al. 2010) and used by another 22q11.2DS study (Kates, Antshel et al. 2007). All interviews were conducted by trained researchers. Interviews were audio-taped for consensus coding and monitoring purposes.

The ADI-R assesses autism symptomatology across three domains and whether abnormality in development is evident before age 3. The interview focuses on current behaviour and developmental history, particularly between ages 4 to 5. It should be noted that the SCQ was developed from the ADI-R so the domains of each measure are analogous. Algorithms are applied for ASD diagnosis. Below is a list of the domains and subdomains for the ADI-R with the cut-offs used for diagnosis.

#### A: Qualitative Abnormalities in Reciprocal Social Interaction

Diagnostic cut-off = 10

- A1: Failure to use nonverbal behaviours to regulate social interaction
- A2: Failure to develop peer relationships
- A3: Lack of shared enjoyment
- A4: Lack of socioemotional reciprocity

#### B: Qualitative Abnormalities in Communication

Diagnostic cut-off = 8 (7 if non-verbal)

- B1: Lack of, or delay in, spoken language and failure to compensate through gesture
- B2: Relative failure to initiate or sustain conversational interchange
- B3: Stereotyped, repetitive, or idiosyncratic speech
- B4: Lack of varied spontaneous make-believe or social imitative play

#### C: Restricted, Repetitive, and Stereotyped Patterns of Behaviour

Diagnostic cut-off = 3

- C1: Encompassing preoccupation or circumscribed pattern of interest
- C2: Apparently compulsive adherence to non-functional routines or rituals
- C3: Stereotyped and repetitive motor mannerisms
- C4: Preoccupation with parts of objects or non-functional elements of material

#### D: Abnormality of Development Evident at or Before 36 Months

Diagnostic cut-off = 1

### 3.2.2 Cognitive Assessment

#### 1. Global cognitive ability

General intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler 1999) at both waves of assessment. It is comprised of four subtests; two verbal tasks, vocabulary and similarities, and two non-verbal tasks, block design and matrix reasoning from which Verbal IQ (VIQ), Performance IQ (PIQ) and Full Scale IQ (FSIQ) can be derived. Rater drift was avoided by double-rating and anonymising transcripts so raters were blind to deletion status and wave. There was a high correlation between ratings (22q11.2DS  $r=0.989$ , Control  $r=0.970$ ). Below is a fuller description of each subtest adapted from the manual (Wechsler 1999).

#### Verbal IQ subtests

VIQ is a measure of verbal ability but can also be conceptualised as acquired, crystallized intelligence.

#### *Vocabulary*

It has 42 items, items 1-4 require the participant to name pictures and items 5-42 involves orally and visually presented words that the participant orally defines.

The subtest is a measure of expressive vocabulary and verbal knowledge. As well as being considered a good measure of crystallized intelligence it also taps other abilities such as memory, learning ability, and concept and language development.

#### *Similarities*

It has 26 items, items 1-4 are picture items and 5-26 are verbal items. For each picture item the participant is shown a picture of three common objects on the top row and four response options on the bottom row. The participant has to pick the response option that best matches the pictures on the top row. For the verbal items, a pair of words is presented orally and the participant has to explain the similarity between the objects or concepts that the words represent.

The subtest is a measure of verbal concept formation and abstract verbal reasoning.

#### Performance IQ

PIQ is a measure of nonverbal ability and perceptual organisation and can be conceptualised as fluid intelligence.

### *Block design*

It has 13 items where the participant has to replicate a geometric pattern within a time limit using two-colour cubes.

The subtest taps spatial visualisation, visual-motor coordination, abstract conceptualisation and perceptual organisation.

### *Matrix reasoning*

It has 35 items of incomplete gridded patterns which the participant completes by choosing a response from five possible choices.

It is a measure of nonverbal fluid reasoning.

## 2. Specific neurocognitive functions

Neurocognitive domains were assessed using the Wisconsin Card Sorting Test (WCST) (Heaton, Chelune et al. 1993) which measures set-shifting ability and the CANTAB (Cambridge Neuropsychological Test Automated Battery) (CANTAB 2006) computerised touch screen platform where the following tests were administered: spatial working memory, stockings of Cambridge, five choice reaction time, match to sample and rapid visual information processing. Below is a description of the neurocognitive domains they assess and their administration based upon details in the test manuals (Heaton, Chelune et al. 1993, CANTAB 2006).

### Wisconsin Card Sorting Test

The WCST consists of four stimulus cards and sixty-four response cards that depict figures of varying form, colour, and numbers of figures. The participant has to match each response card to a stimulus card. They are told whether the response was right or wrong but are never explicitly told the correct matching principle. Once the participant makes ten consecutive correct matches the matching principle is changed without warning.

When a participant persists in responding to a stimulus characteristic that is incorrect this is scored as a perseverative error. The total number of perseverative errors is used as the outcome measure in this thesis.

Performance on the WCST measures set-shifting aspect of executive function and requires, strategic planning, organised searching, utilising feedback to shift cognitive sets, goal directing behaviour, and modulation of impulsive responding.

## Cambridge Neuropsychological Test Automated Battery (CANTAB)

### Spatial working memory (SWM)

The SWM task measures the spatial working memory aspect of executive function.

The SWM task begins with a number of coloured boxes being shown on the screen. The aim is for the participant to find which box the blue token is hidden in. Once it has been found behind one box it will not appear in that that location on the next round.

The outcome measure is “SWM between errors” which is defined as the number of times the subject revisits a box in which a token has previously been found. A lower score is better.

### Stockings of Cambridge (SOC)

The SOC task measures spatial planning, which is an aspect of executive function.

The participant is shown two displays containing three coloured balls which are stacked in stockings suspended from a beam and they must use the balls in the lower display to copy the pattern of the upper display. The balls can only be moved one at a time and balls at the bottom of a stack cannot be moved until ones higher up in the stack have been moved.

The outcome measure used was “SOC Problems solved in minimum moves” which is the number of occasions the participant completed the test problem in the minimum possible number of moves. A higher score is better.

### Five Choice Reaction Time (RTI)

RTI is a measure of processing speed

The participant holds down a press pad button. When a yellow spot appears on the screen in one of five possible locations the participant has to respond and tap it as quickly as possible. Child mode was administered.

The outcome measure is the time it takes to release the press pad button in response to the yellow spot. Quicker is better.

### Match to Sample Visual Search (MTS)

MTS is a measure of visual attention.

The participant is presented an abstract patterned stimulus in the middle of the screen. Then a number of similar patterns are shown in a circle of boxes around the edge of the screen. The participant must tap the pattern which matches.

The outcome measure is the number of correct responses out of a possible 48 trials. A higher score is better.

### Rapid Visual Processing (RVP)

RVP is a measure of visual sustained attention.

Digits from 2 to 9 are presented in a pseudo-random order on the screen. Participants have to tap the press pad button when 3, 5, 7 appear in a row. Child mode was administered.

The outcome measure is RVP A prime which is the signal detection measure of sensitivity to the target sequence (3,5,7) and ranges from 0 to 1 (bad to good).

### **3.2.3 Consistency across assessments**

Effort was made to keep the testing environment and testing procedures as consistent as possible. Cognitive measures were always administered in the following order: IQ, WCST, SWM, SOC, RTI, MTS and RVP. The majority of participants were assessed at the same time of day, in the afternoon and were assessed at home, though it should be noted that 10% were tested at the Institute of Psychological Medicine and Clinical Neurosciences in Cardiff when they were visiting to take part in the ECHO study's brain imaging project.

## **3.3 Sample characteristics**

### **3.3.1 Age and gender**

**Table 1** gives the age characteristics of the longitudinal sample. Age distribution did not differ between 22q11.2DS children and controls. Gender distribution did not differ between groups (22q11.2DS: 41M 29F, controls: 16M 13F,  $\chi^2$  p=0.825).

**Table 1:** Assessment ages

	<b>N</b>	<b>Age at wave 1 years (SD)</b>	<b>Age at wave 2 years (SD)</b>	<b>Time gap years (SD)</b>
<b>22q11.2DS</b>	70	10.0(2.3)	12.5(2.2)	2.5(0.4)
<b>Controls</b>	29	10.7(2.0)	13.4(2.1)	2.7(0.4)
<b>T-test p-value</b>	-	0.166	0.090	0.137

### 3.3.2 Representativeness of longitudinal cohort

**Table 2** displays the wave 1 characteristics of 22q11.2DS individuals in the longitudinal cohort and compares this to 22q11.2DS individuals who were eligible to take part in terms of 2.5 years passing since wave 1 but have not taken part in wave 2 assessments. The longitudinal cohort is representative in terms of age, gender, deletion origin, psychiatric disorder, ASD traits (SCQ), ethnicity, maternal education and family income. However the longitudinal cohort underrepresents those who reported psychotic experiences at wave 1 ( $p=0.011$ ) and on average individuals have a lower wave 1 FSIQ than those who did not take part again (-5.8 FSIQ points,  $p=0.035$ ). This may suggest that the longitudinal cohort has greater cognitive deficits but lower proneness to psychotic phenomena. These issues will be considered when interpreting findings in later chapters.

**Table 2:** Characteristics of longitudinal cohort compared to those not revisited

N	Longitudinal Not revisited		p-value <sup>#</sup>
	70	32	
<b>Mean age in years (SD)</b>	10.0 (2.3)	10.0(2.2)	0.949
<b>Gender (% male)</b>	58.6%	43.8%	0.201
<b>Inherited 22q11.2DS</b>	10.0 %	3.0%	0.430
<b>Mean FSIQ (SD) n(62,29)</b>	74.4 (11.1)	80.2 (14.3)	0.035
<b>Any DSM IV Psychiatric disorder prevalence</b>	55.7 %	56.3 %	0.999
<b>Psychotic experience prevalence</b>	2.9 %	18.8 %	0.011
<b>Mean SCQ score (SD)</b>	12.8 (7.1)	11.7 (7.0)	0.488
<b>Family ethnic background</b>			0.167
European	92.9 %	88.8 %	
Non-European	1.4 %	3.1 %	
Mixed	5.7 %	3.1 %	
Unknown	0.0 %	6.3 %	
<b>Highest maternal educational qualification</b>			0.480
Low: O-levels or GCSEs	21.4 %	21.9 %	
Middle: A-levels/highers or vocational training	42.9 %	28.1 %	
High: university degree and/or other higher postgraduate qualification	22.9 %	34.4%	
Unknown	12.9 %	15.6 %	
<b>Family income, £</b>			0.142
≤19,999	24.3 %	9.4 %	
20,000-39,999	27.1 %	25.0%	
40,000-59,999	20.0 %	12.5%	
≥60,000	18.6 %	34.4 %	
Unknown	10.0 %	18.8 %	

# ( $\chi^2$  for categorical, t-test for continuous data)

### 3.3.3 Representativeness of the ECHO study cohort

This section will briefly discuss to what extent the ECHO study 22q11.2DS cohort represents all 22q11.2DS children. There is likely to be ascertainment bias for several reasons. Not all individuals with 22q11.2DS will receive a diagnosis in childhood and it is likely there are many individuals who go throughout life without a diagnosis particularly if they have a mild phenotype. There is evidence that those diagnosed later in life differ in symptom profile so child cohorts may not be fully representative of the full age range (Vogels, Schevenels et al. 2014). The ECHO study recruits from the UK so findings may not be internationally representative, though previous cross-sectional findings from the ECHO study (Niarchou, Zammit et al. 2014) are consistent with a recent international study (Schneider, Debbané et al. 2014). However, it should be noted that the ECHO



study was a major contributor to this study. Research participation is voluntary so families who take part in research may differ from those who do not.

An advantage of recruiting via medical genetics clinics and support groups is that individuals are not directly ascertained on the basis of neuropsychiatric disorder. However it is likely the presence of ID increases chance of referral to medical genetic clinics and perhaps there is perhaps a bias in families who join support groups and volunteer for research.

## **4. Longitudinal psychopathology in 22q11.2DS**

This chapter will examine how psychopathology develops in 22q11.2DS. I will introduce the insights that can be gained from such work and highlight longitudinal trends previously reported in 22q11.2DS. There will also be a focus on the nature of autism spectrum disorder in 22q11.2DS. I will present findings on psychopathology from the longitudinal 22q11.2DS ECHO cohort.

### **4.1 Potential insights from longitudinal studies of 22q11.2DS**

#### **4.1.1 Characterise psychiatric morbidity developmentally**

CNVs are not specific risk factors for particular psychiatric disorders (see 2.2.1) and 22q11.2DS is no exception, conferring risk for multiple conditions (see 1.2). There are different possible underlying explanations for non-specific risk. One explanation could be cross-sectional comorbidity where a proportion of individuals meet criteria for multiple psychiatric disorders. Another possibility is that heterogeneity may be present such that different psychiatric disorders may affect different individuals. There could also be sequential comorbidity in that psychiatric disorder at one point in the life course is associated with psychiatric disorder later in the life. This latter issue can only be clarified using a longitudinal design. There has been a concerted research effort to examine whether early psychopathology in 22q11.2DS predicts development of psychotic phenomenology (see 2.1.4, 2.1.5). Longitudinal studies can also examine the stability and persistence of psychiatric disorder over time. Characterising cross-sectional and sequential comorbidity will help understand the extent to which psychiatric disorders across the life course have shared aetiology.

#### **4.1.2 Examine early psychopathology associated with schizophrenia risk**

22q11.2DS provides a rare opportunity to explore childhood development associated with schizophrenia (see 2.1.2, 2.1.3). Longitudinal studies of idiopathic cohorts have identified several factors.

##### **1. ADHD and ASD symptomatology**

Symptoms of ADHD and attentional deficits have been reported in those who later develop schizophrenia (Cornblatt, Obuchowski et al. 1999, Pine and Fox 2015). Attentional impairment has been suggested as an endophenotype for uncovering risk genes for schizophrenia (Cornblatt and Malhotra 2001). Also there is evidence that polygenic risk for ADHD overlaps with that for schizophrenia (Hamshere, Stergiakouli et al. 2013).

Historically autism was described as childhood onset schizophrenia (American Psychiatric Association 1975). It was not until the third edition that DSM considered autism/pervasive developmental disorder to be a separate category (American Psychiatric Association 1987). In modern clinical practice the disorders are rarely diagnosed in the same individual (Rapoport, Chavez et al. 2009), partly because some clinicians consider them mutually exclusive and classification in DSM-5 has specific extra requirements for diagnosing schizophrenia in those with a history of ASD (American Psychiatric Association 2013). There are a few studies that report children with ASD are at increased risk of developing schizophrenia in adulthood (Stahlberg, Soderstrom et al. 2004, Mouridsen, Rich et al. 2007, Sprong, Becker et al. 2008). This relationship is stronger when ASD is considered more broadly in terms of impairments in ASD related domains such as language and social ability. Impairment in receptive language has been identified as a precursor for schizophrenia (Rutter, Kim-Cohen et al. 2006) and adults with a childhood diagnosis of developmental language disorder show increased schizotypal traits and prevalence of schizophrenia (Clegg, Hollis et al. 2005). Social deficits are a well-documented feature of the premorbid phase of psychosis (Häfner, Nowotny et al. 1995), though it should be noted that social deficits are not synonymous with ASD.

## 2. Affective symptomatology

Children who later develop schizophrenia are more likely than typically developing children to exhibit social, emotional and behavioural problems (Rutter and Garmezy 1983). Childhood anxiety and stressful life events are also associated with the development of schizophrenia (McReynolds 1960, Walker and Diforio 1997, Rapoport, Giedd et al. 2012).

## 3. Subclinical psychotic experiences

Psychotic experiences are predictive of later psychotic disorder (Chapman, Chapman et al. 1994, Poulton, Caspi et al. 2000, Hanssen, Bak et al. 2005, Zammit, Kounali et al. 2013), varying from 5.5% to 25% increased risk depending on criteria of establishing such experiences. Findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) suggest psychotic experiences and schizophrenia have shared aetiology as they share some of the same risk factors, including childhood cognitive deficits, adverse pre-natal exposures, childhood infection, and stress and cannabis use (Niarchou, Zammit et al. 2015). There is however no strong evidence from the ALSPAC cohort for shared genetic aetiology for psychotic experiences and schizophrenia (Zammit, Hamshere et al. 2014).

## **4.2 Childhood psychopathology in 22q11.2DS**

There is a high burden of childhood psychopathology in 22q11.2DS including a high prevalence of ADHD, ASD, anxiety, mood disorder and ODD (see 1.2). There is evidence that childhood psychopathology associated with 22q11.2DS cannot be fully attributed to cognitive impairment (Niarchou, Zammit et al. 2014).

### **4.2.1 Nature of psychotic experiences in 22q11.2DS**

The prevalence of subthreshold psychotic symptoms varies from 10% to 83% depending on the measure used, study age range and relative representation of children versus adults (Feinstein, Eliez et al. 2002, Baker and Skuse 2005, Niarchou, Zammit et al. 2014, Schneider, Schaer et al. 2014, Tang, Yi et al. 2014). As seen in idiopathic schizophrenia, subthreshold symptoms are predictive of later disorder (Gothelf, Feinstein et al. 2007). Prevalence in one study that used the CAPA, as was used in the ECHO cohort that this thesis is based on, was 48% (mean age = 16.4 , age range = 13 - 25) (Baker and Skuse 2005). Phenomena reported were diverse and included delusional thinking, auditory and visual hallucinations, depersonalisation and thought broadcast, but they were generally of short duration and were not perceived to be highly distressing or intrusive. It should be mentioned that the findings from these cohorts are not necessarily fully comparable to what may be found in the ECHO sample as they had an older age range.

### **4.2.2 Longitudinal trends reported in 22q11.2DS**

Longitudinal findings in 22q11.2DS have been discussed in the introductory chapters, albeit in separate sections. Here I briefly summarise and bring together different aspects.

1. ADHD prevalence declines with age at a similar rate to idiopathic ADHD (see 1.2.4).
2. Mood disorder prevalence increases with age (Antshel, Shprintzen et al. 2010) (also see 1.2.7)
3. Differential prevalence change for different anxiety disorders

Prevalence for presence of any anxiety disorder remains relatively stable from childhood to adolescence (Schneider, Debbané et al. 2014). However, there is evidence that phobia prevalence decreases whereas generalised anxiety disorder prevalence increases from childhood to adolescence (Antshel, Shprintzen et al. 2010).

4. Prevalence of psychotic phenomena increases with age

The prevalence of psychotic disorder and subthreshold symptoms increases with age (Gothelf, Feinstein et al. 2007, Gothelf, Schneider et al. 2013, Hooper, Curtiss et al. 2013, Schneider, Debbané et al. 2014, Schneider, Schaer et al. 2014).

5. Anxiety and mood disorder/symptomatology predict later psychotic phenomena (see 2.1.4 and 2.1.5)

6. Childhood ASD does not predict later psychotic phenomena (see 1.2.3)

### **4.2.3 Limitations of 22q11.2DS longitudinal psychopathology studies**

1. Subthreshold psychotic symptoms not always examined at every time points

Some studies have only assessed subthreshold psychotic symptoms at the final time point (Antshel, Shprintzen et al. 2010, Kates, Russo et al. 2014). This makes it difficult to distinguish whether psychotic phenomenology is preceded by other psychopathology or whether psychotic phenomenology covaries with other psychopathology.

2. Few studies have considered stability and individual change in diagnosis

Although studies report prevalence and statistically test for change, few have examined stability. At a group level prevalence may not change but this could mask significant change at the level of the individual. Change in prevalence provides no indication of whether the same individuals are affected at both time points and whether individuals vary in developmental course. One study that considered this when examining the longitudinal course of ADHD found 15% of 22q11.2DS children without ADHD at time 1 had ADHD by time 2 (Antshel, Hendricks et al. 2013), though overall ADHD prevalence decreased between time points. This could represent measurement error. Alternatively, it could suggest that in some 22q11.2DS individuals ADHD traits may be present early but do not impact enough to reach diagnostic threshold until they are older. Important insights and variability in development may be missed by not examining individual change in diagnosis.

### **4.3 The nature of autism spectrum disorder in 22q11.2DS**

There is great uncertainty in the 22q11.2DS literature whether difficulties in social behaviour and language development can be considered ASD (see 1.2.3). This issue is important to clarify in terms of informing treatment and care provision for individuals with 22q11.2DS and in terms of understanding whether 22q11.2DS, as a genetic risk variant for schizophrenia, also confers risk for ASD. This has implications for Crespi and Badcock's hypothesis that ASD and psychosis are reciprocal disorders of the social brain (see section 2.2.1.4). Before exploring this issue empirically using the ECHO cohort, this section will discuss ASD diagnosis, ASD assessment instruments and current issues in the 22q11.2DS ASD literature.

#### **4.3.1 ASD criteria**

Diagnostic classification has changed between DSM-IV and DSM-5. DSM-IV had a section on disorders usually first diagnosed in infancy, childhood, or adolescence which included a subsection on Pervasive Developmental Disorders which included Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder and Asperger's Disorder (American Psychiatric Association 2000). A diagnosis of Autistic Disorder was on the basis of impairments in three domains which included deficits in communication, deficits in social interaction and finally the presence of restricted, repetitive patterns of behaviour, interests or activities. The classification Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) was applied to individuals who only showed impairment in some domains. Symptoms from these domains have to be present in the early developmental period and cause clinical impairment. Diagnostic classification was restructured in DSM-5 and the different Pervasive Developmental Disorders were replaced by one disorder, Autism Spectrum Disorder (ASD) which is placed within the category of Neurodevelopmental Disorders (American Psychiatric Association 2013). DSM-5 criteria of ASD is different to DSM-IV Autistic Disorder with only two domains, the domains of communication and social interaction were combined.

22q11.2DS research studies are yet to transition to DSM-5 criteria, including the ECHO study. The term autism in 22q11.2DS studies generally refers to the DSM-IV criteria of impairments in all three domains. However when the term ASD is used in studies it has not referred to DSM-5 ASD criteria, rather it has referred to the presence of impairments in only some domains. This can be seen to be analogous to DSM-IV PDD-NOS criteria. There is also a habit in studies that use trait measures of ASD, to use the term autism to indicate greater severity than ASD. In this chapter I have followed suit of previous 22q11.2DS studies and so have not used DSM-5 criteria. Below I specify exactly how the terms ASD and autism have been applied to measures used.

### 4.3.2 ASD assessment instruments

Ideally, clinical diagnosis of ASD requires both parent-report of the child's developmental history as well as the observation of the child's behaviour (Charman and Baird 2002, Johnson and Myers 2007). A range of parent-report, self-report and observational measures of ASD have been developed for clinical and research purposes (Volkmar 2013). The ECHO study uses the Social Communication Questionnaire (SCQ) and the Autism Diagnostic Interview-Revised (ADI-R), which have already been described in the Chapter 3. Here I will discuss their psychometric properties as well as findings from previous research studies. I will also discuss the Autism Diagnostic Observation Schedule (ADOS) as this has been used in other studies of 22q11.2DS.

#### 1. ADI-R

The ADI-R is a standardised, semi-structured, investigator led interview administered to parents or caregivers to assess the presence of ASD in an individual (Lord, Rutter et al. 1994, Rutter, Le Couteur et al. 2003). It provides a useful structure for obtaining the developmental history and caregiver's perspective of their child's ASD symptomatology, with a particular focus on ages 4 to 5. It requires substantial training and practice to administer reliably and takes approximately two to three hours to complete.

The ADI-R assesses three domains of functioning: communication, reciprocal social interaction, and restricted, repetitive, and stereotyped patterns of behaviour. There is also a fourth domain, abnormality of development evident at or before 36 months, which indicates whether symptomatology is present early in development. For an ADI-R classification of autism an individual must meet or exceed cut-offs in all three domains plus meet the criteria of the fourth domain. Algorithms for the broader classification of ASD can also be applied to ADI-R items (Dawson, Webb et al. 2004, Lainhart, Bigler et al. 2006).

One of the strengths of the ADI-R is its ability to distinguish ASD from ID, which is pertinent to the assessment of children with 22q11.2DS, given the syndrome's association with ID. The ADI-R algorithm for autism shows high sensitivity and specificity (both over 0.90) when differentiating children with autism from those with ID (Lord, Rutter et al. 1994). Also the majority of ADI-R items demonstrate good discriminative ability between children with autism and children with ID.

Researchers have used individual domain scores and the overall total of the three functional domains to estimate autistic symptom severity (Volkmar 2013). However, the validity of this approach has not been directly investigated.

An important caveat to recognise is that diagnostic classification based on ADI-R algorithms and true clinical diagnosis is not the same thing. Clinical diagnosis is based on multiple sources of information (Le Couteur, Haden et al. 2008).

## 2. SCQ

The SCQ when first developed was originally called the Autism Screening Questionnaire (ASQ) (Berument, Rutter et al. 1999). It consists of 40 questions derived from the ADI-R which have been modified into a form understandable by parents and can be completed as a written questionnaire rather than a semi-structured interview. Questions were selected to focus on behaviours that can be identified by non-professionals.

Questions assess both current behaviour and developmental history. A cut-off of 15 suggests ASD and a cut-off of 22 is used to distinguish autism from other disorders on the spectrum (Berument, Rutter et al. 1999). The ASD cut-off has a high sensitivity and specificity when comparing those with autism to typically developing children, 0.96 and 0.80 respectively. The ASD cut-off is not as effective in discriminating ASD from ID, specificity is lower (0.67). The higher cut-off of 22 discriminates children with autism from other spectrum disorders with a sensitivity of 0.75 and specificity of 0.60.

## 3. Comparing the SCQ and ADI-R

As the SCQ is administered as a written questionnaire rather than a semi-structured interview it takes much less time to complete and is therefore often chosen over the ADI-R for inclusion in research protocols (Charman and Baird 2002). SCQ score correlates highly with ADI-R total score (0.71). The SCQ is as effective as the ADI-R in discriminating children with autism from typically developing children, but the ADI-R is better at discriminating autism from ID (Berument, Rutter et al. 1999). Therefore the ADI-R, although lengthy, may be a better measure for assessing ASD in 22q11.2DS given that ID is associated with the syndrome. Also in general the researchers who developed both the SCQ and ADI-R consider the SCQ as a good screening instrument but inappropriate for making a diagnosis at the level of the individual, for which the ADI-R is better suited (Berument, Rutter et al. 1999).

## 4. ADOS

The ADOS is one of the most widely used observational measures of autism (Lord, Rutter et al. 2008). It is a semi-structured assessment of social interaction, play and imagination administered directly with the individual. It is one of the few diagnostic measures that involves



direct observation of the individual's interactions and that takes account of age and developmental level. Similar to the ADI-R it requires substantial training to administer reliably, though administration is much shorter than the ADI-R at 30 to 45 minutes.

ADOS classifications are based on specific coded behaviours from which communication, reciprocal social interaction and total scores can be derived. Thresholds for autism and ASD can be applied to overall scores. Findings from the ADOS validity sample report high sensitivity and specificity (both over 0.80) (Lord, Rutter et al. 2008) and that it is very effective in discriminating individuals with ASD from those with non-spectrum disorders. However a more recent study suggests that the ADOS has difficulty discriminating children with ASD from children with other developmental and behavioural disorders (Molloy, Murray et al. 2011). This suggests that the ADOS may not be appropriate for assessing children with 22q11.2DS given the range of developmental and behavioural disorders associated with the syndrome. In general it is recommended that the ADOS outcome is used alongside other sources of information.

#### 5. ADI-R and ADOS

Combined, the ADI-R and ADOS are considered the gold standard in assessing autism. The ADI-R provides developmental history ascertained through semi-structured interview and the ADOS provides an observational measure. Combined usage provides better diagnostic accuracy than the use of either alone (Zander, Sturm et al. 2014).

Although the combined ADI-R and ADOS diagnostic procedure is comprehensive, it does have drawbacks. It is very time consuming, and in clinical samples of 'diagnostically challenging' children there is not strong agreement between the ADI-R and ADOS (Bishop and Norbury 2002). Another criticism is that in development of the ADI-R and ADOS the selection of items was based on clinical judgment rather than a statistical approach such as discriminant function analysis. The latter could improve diagnostic accuracy and potentially remove non-discriminatory items.

#### **4.3.3 The extent to which autism measures index other psychopathology**

There is increasing evidence that psychiatric disorders, including ASD, overlap in symptomatology and share aetiology (Owen 2014). A study that assessed psychiatric comorbidity in children with ASD found 70% had at least one comorbid disorder, with the most common diagnoses being anxiety disorder (42%), ADHD (28%) and ODD (28%) (Simonoff, Pickles et al. 2008). This study assessed psychiatric comorbidity using the CAPA, as is used in the ECHO study, presenting optimal opportunities for comparison with findings in this chapter.

ASD may be associated with high levels of psychopathology but there is also the possibility that measures of ASD misdiagnose ASD when other psychopathology is present. This is an important issue to consider given the high level of psychopathology and comorbidity in 22q11.2DS. Here I discuss what other psychopathology is indexed by ASD measures and present evidence of clinical presentations where ASD measures have a tendency to misdiagnosis.

The ADI-R and ADOS diagnostic systems have been highlighted to being prone to identifying individuals with ID as having autism (Fombonne 1992). Though as mentioned before, the ADI-R can discriminate ASD from ID better than the SCQ can. In children with ADHD the SCQ has been reported to index ADHD clinical severity and cognitive impairment (Cooper, Martin et al. 2014). One study reports that the ADI-R and ADOS misdiagnose ASD in children with childhood-onset schizophrenia (Reaven, Hepburn et al. 2008). However this may not necessarily represent an issue with the ADI-R and ADOS specifically, as there is a debate whether child-onset schizophrenia and ASD symptomatology overlap (Sporn, Addington et al. 2004). It has been found that whilst ASD domains of communication and reciprocal social interaction discriminate ASD rather well from ADHD and anxiety disorder, the repetitive and stereotyped behaviour domain did not (Hartley and Sikora 2009).

#### **4.3.4 Studies that have assessed ASD in 22q11.2DS**

First I will recap what was discussed about ASD and 22q11.2DS in Chapter 1 (1.2.3),

- Reported prevalence of ASD in 22q11.2DS varies considerably (10%-50%)
- One study that used both an observational measure (ADOS) and a measure of clinical history (SCQ) found no individuals met cut-offs for both (Angkustsiri, Goodlin-Jones et al. 2014)
- One study (which used the ADI-R) reported that the clinical presentation of ASD in 22q11.2DS is less severe than in children with idiopathic ASD (Kates, Antshel et al. 2007)
- The well documented male preponderance for ASD is not observed in 22q11.2DS
- It is argued that prepsychotic phenomena and anxiety are misdiagnosed as ASD in 22q11.2DS

There are several noteworthy issues regarding the investigation of ASD in the 22q11.2DS literature.

1. Not all studies of psychopathology assess ASD

Compared to other psychopathology, ASD has been investigated less so in the 22q11.2DS literature. In the IBBC study fifteen sites contributed psychopathology data, of which only seven assessed ASD. ASD was one of the least investigated disorders in children and adolescents in the IBBC study (Schneider, Debbané et al. 2014).

2. Inconsistency in ASD measures used

Within the IBBC study, sites administered different measures; the ADI-R and/or ADOS and the Mini Psychiatric Assessment Schedules for Adults with Developmental Disabilities (Mini PAS-ADD) (Schneider, Debbané et al. 2014). One site used the Mini PAS-ADD and reported an unusually high prevalence of 80%. Only three sites used the gold-standard combination of ADI-R and ADOS.

Studies based on single cohorts have assessed ASD using the ADI-R (Vorstman, Morcus et al. 2006, Antshel, Aneja et al. 2007) and the SCQ (Vorstman, Breetvelt et al. 2013, Angkustsiri, Goodlin-Jones et al. 2014, Niarchou, Zammit et al. 2014), with one study using the SCQ in combination with the ADOS (Angkustsiri, Goodlin-Jones et al. 2014). One study has used the SCQ as a screening measure and then the ADI-R for those who screen positively (Fine, Weissman et al. 2005).

3. Ascertainment bias

Reported prevalence varies even amongst studies that have administered the same measure suggesting that ascertainment bias plays a part. See **Table 3** for reported using the ADI-R.

**Table 3:** ASD and autism prevalence using the ADI-R from previous 22q11.2DS studies

Study	ASD	Autism
Fine, Weissman et al. 2005	14.3%	11.2%
Vorstman, Morcus et al. 2006	50.0%	33.3%
Antshel, Aneja et al. 2007	41.5%	19.5%

Note Fine, Weissman et al. 2005 used the SCQ as a screener to identify individuals for ADI-R assessment.

Reported prevalence<sup>3</sup> is variable for the SCQ. The percentage of 22q11.2DS individuals who meet the ASD cut-off of 15 has been reported to be 7% (Angkustsiri, Goodlin-Jones et al. 2014), 17% (Vorstman, Breetvelt et al. 2013) and 26% (Niarchou, Zammit et al. 2014). As the SCQ is a

questionnaire filled in by the parent, differences cannot be attributable to differences in interviewer style. The study with the lower prevalence mainly recruits participants by self-referral via their website whereas the other two recruit mainly via medical genetics clinics.

#### 4. Issues in interpreting findings

Studies that have reported very low or very high prevalence have not always been critical in their interpretation. The previously mentioned study (Angkustsiri, Goodlin-Jones et al. 2014) that reports that no individuals meet criteria for ASD when using both the SCQ and the ADOS makes a strong conclusion that ASD is not as common as once thought in 22q11.2DS. However, as mentioned in 7.2.3, prevalence of those who meet criteria on the SCQ is lower than in other studies suggesting ascertainment bias.

Another study reported a high ASD prevalence of 50%, however they used relatively relaxed criteria for interpreting ADI-R scores by including individuals who met cut-offs on any two functional domains (Vorstman, Morcus et al. 2006). The ADI-R has an official algorithm for autism that is based on meeting specific cut-offs across all three functional domains (Lord, Rutter et al. 1994). There is no official ADI-R algorithm for ASD, however studies which have developed ASD criteria have applied stricter criteria compared to Vorstman, Morcus et al, 2006 (Dawson, Webb et al. 2004, Kaufmann, Cortell et al. 2004, Lainhart, Bigler et al. 2006).

#### 5. Previous studies have not examined gender difference in ASD rigorously

Although studies do not report a gender difference in ASD in 22q11.2DS (1.2.3), detailed summary statistics are not always provided. Often the p-value is reported but not the male-to-female ratios (Vorstman, Morcus et al. 2006, Schneider, Debbané et al. 2014), so it is not possible to identify if gender has a large effect size, albeit non-significant. There are studies that have not formally tested for a gender difference in ASD but inspection of their sample demographics indicates male preponderance for ASD (Fine, Weissman et al. 2005, Antshel, Aneja et al. 2007).

No study has examined whether there is a gender difference in ASD symptomatology in 22q11.2DS. A previous 22q11.2DS study that investigated gender differences in psychopathology, which did not focus on ASD, found marked differences on dimensional measures which were not reflected by differences in categorical diagnoses (Sobin, Kiley-Brabeck et al. 2009).

## 6. Not all studies have investigated comorbidity of ASD with psychopathology

It has been strongly argued that ASD in 22q11.2DS represents a misdiagnosis of anxiety or prepsychotic phenomena, even when measures such as the ADI-R which examine developmental history have been used (Eliez 2007). There is a danger that no matter what ASD instrument is used such arguments will continue to be made. A different perspective that may give insight into the debate is to investigate to what extent such psychopathology overlaps and whether variation in ASD severity is associated with presence of other psychopathology. One study found that ASD symptomatology (as measured by the SCQ) and psychotic symptomatology were distinct phenotypic manifestations in 22q11.2DS (Vorstman, Breetvelt et al. 2013).

An alternative perspective is that ASD rather than being misidentified may be a core feature of the neuropsychiatric phenotype in 22q11.2DS. Indeed one study reports that 94% of children with 22q11.2DS and ASD had a co-occurring psychiatric disorder, which is higher than the overall prevalence of psychiatric disorder in their sample (60%) (Antshel, Aneja et al. 2007).

The largest study of psychopathology in 22q11.2DS to date, based on the IBBC data, did not examine comorbidity of ASD with other psychopathology (Schneider, Debbané et al. 2014). This has been previously examined in the cross-sectional ECHO cohort using the SCQ, and ASD showed comorbidity with ADHD (41.2%), anxiety (52.4%) and ODD (30.0%) (Niarchou, Zammit et al. 2014). However the SCQ is known to index other psychopathology (see section 7.1.3) so it is important to confirm these findings using the ADI-R in the ECHO cohort.

## 7. ASD prevalence not examined longitudinally

No longitudinal study of psychopathology in 22q11.2DS has examined ASD symptomatology (Gothelf, Eliez et al. 2005, Antshel, Shprintzen et al. 2010, Gothelf, Schneider et al. 2013, Hooper, Curtiss et al. 2013). This may be because many semi-structured interviews of psychopathology often do not include ASD and therefore ASD assessment requires additional time-consuming measures. Also as ASD is a neurodevelopmental disorder it is diagnosed on the basis of developmental history, so in a sense once a diagnosis has been made, it is present for life. However it is of interest to what extent symptoms continue to present and impact throughout the life course. The IBBC study reports ASD prevalence to peak in adolescence perhaps suggesting ASD measures are indexing other psychiatric features (Schneider, Debbané et al. 2014). However, this needs to be explored in longitudinal cohorts.

## 4.4 Aims

The aims of this chapter are:

1. Examine the prevalence of psychopathology longitudinally in 22q11.2DS and controls
2. Describe diagnostic stability and consider diagnostic change at the level of the individual
3. Examine the prevalence of psychotic experiences longitudinally in 22q11.2DS and controls and describe their nature and content
4. Examine whether psychopathology is associated with psychotic experiences at wave 2
5. Explore the nature of ASD in 22q11.2DS in depth using the ADI-R
  - a) Establish the prevalence of ASD in the ECHO cohort using the ADI-R
  - b) Examine inter-method reliability between the SCQ and ADI-R in 22q11.2DS
  - c) Examine whether there is a gender difference in the ASD phenotype of 22q11.2DS
  - d) Investigate whether ASD indexes comorbidity in 22q11.2DS

## 4.5 Methodology

Sample description and assessment details have been presented in Chapter 3. Psychiatric data was available at both time points for 70 children with 22q11.2DS and 29 controls. SCQ data was available for 64 children with 22q11.2DS and 26 controls (missing cases due to missing questionnaire data).

### 4.5.1 Aim 1: Examine the prevalence of psychopathology longitudinally in 22q11.2DS and controls including ASD

DSM-IV-TR criteria were applied to symptoms elicited from the CAPA. A score of 15 or more on the SCQ was used to screen for probable ASD. The category 'any DSM-IV-TR psychiatric disorder' did not include probable ASD. To investigate whether prevalence of psychiatric disorder changes between waves of assessment McNemar's test (analogous to chi-square but for paired data) was conducted separately for 22q11.2DS children and controls. To investigate whether level of comorbidity differs across wave of assessment a related-samples Wilcoxon signed rank test was conducted.

To further explore longitudinal development of autism domains, change in SCQ total score and domain scores were examined. Also items were split into those that assess behaviours at age 4 to 5 and current behaviour and longitudinal change were examined for these. Correlations were calculated for each type of score separately for children with 22q11.2DS and controls. For each type of score related samples Wilcoxon signed rank test was conducted to investigate if there was significant change over time. Mann Whitney U test was conducted to investigate whether the distribution of change scores differs between children with 22q11.2DS and controls. This analysis was conducted for all individuals with an SCQ score at both wave 1 and wave 2.

It was investigated whether those who met criteria for 'any DSM-IV-TR psychiatric disorder' at wave 1 differed in the following demographics: age using an independent t-test; gender, 22q11.2DS inheritance and ethnicity using Fisher's exact test; household income and maternal education using Mann-Whitney U tests. The same analysis was conducted for those who met ASD criteria at wave 1 on the SCQ, except for gender which will be explored in depth in Aim 5.

#### **4.5.2 Aim 2: Describe diagnostic stability and consider diagnostic change at the level of the individual**

For each diagnosis 22q11.2DS individuals were categorised into the following groups:

Diagnosis gain - individuals with no diagnosis at wave 1 but a diagnosis at wave 2

Diagnosis loss - individuals with a diagnosis at wave 1 but not at wave 2

Diagnosis at both waves - individuals with a diagnosis at wave 1 and wave 2

No diagnosis at both waves - individuals with no diagnosis at wave 1 and wave 2

For each diagnosis the following statistics were calculated for children with 22q11.2DS. These statistics have been used in idiopathic psychiatric cohorts to examine diagnostic stability (Schwartz, Fennig et al. 2000, Baca-Garcia, Perez-Rodriguez et al. 2007). No 22q11.2DS study has studied diagnostic stability using this approach.

##### **1. Kappa coefficient**

One way of assessing diagnostic stability is by examining agreement between first wave and second wave diagnostic status as calculated by the kappa coefficient. This statistic measures agreement whilst correcting for the effect of chance. A kappa coefficient  $\leq 0$  indicates no agreement and a score of 1 indicates perfect agreement. The magnitude of kappa coefficients

can be classified, albeit somewhat arbitrarily, with 0.75 as being excellent, 0.40 to 0.75 as fair to good, and below 0.40 as poor (Fleiss 1981).

## 2. Prospective consistency

This is the proportion of individuals with a diagnosis at first assessment who had the same diagnosis at the second assessment.

## 3. Retrospective consistency

This is the proportion of individuals with a diagnosis at the second assessment who had the same diagnosis at the first assessment.

Prospective and retrospective consistency values can provide insight into the longitudinal course of psychiatric disorders. The combination of a high prospective and retrospective consistency indicates high stability and low values low stability. A low prospective consistency indicates low persistence of the disorder. A low retrospective consistency indicates emergence of the disorder between waves. There are no formal cut-offs for what is low prospective consistency and retrospective consistency, however values are relatively intuitive to interpret. A prospective consistency of 50% translates as a 50% persistence rate and a retrospective consistency of 50% indicates that individuals without emerging disorder between assessments account for 50% of those with a diagnosis at second assessment.

### **4.5.3 Aim 3: Examine the prevalence of psychotic experiences longitudinally in**

#### **22q11.2DS and controls and describe their nature and content**

Vignettes were written for each individual who reported psychotic experiences. McNemar's test was conducted to investigate whether the prevalence of psychotic experience changes across the two waves. It was investigated whether those who with psychotic experiences differed in the following demographics: age using an independent t-test; gender, 22q11.2DS inheritance and ethnicity using Fisher's exact test; household income and maternal education using Mann-Whitney U tests.

### **4.5.4 Aim 4: Examine whether psychopathology is associated with psychotic experiences**

#### **at wave 2**

To investigate whether psychotic experiences were associated with psychopathology at wave 2 Fisher's exact test was conducted for each psychiatric disorder. To investigate whether psychopathology at wave 1 was associated with the emergence of psychotic experiences at wave 2



Fisher's exact test was conducted and excluded two 22q11.2DS individuals who reported psychotic experiences at both waves.

In addition to the above analyses, the association of psychotic experiences with comorbidity was examined using an independent sample Mann-Whitney U test.

Spearman correlation coefficients were calculated to quantify the magnitude of associations.

#### **4.5.5 Aim 5: Explore the nature of ASD in 22q11.2DS in depth using the ADI-R**

The ADI-R was completed for 74.3% (52/70) of children with 22q11.2DS and for 69.0% (20/29) of controls. Non-participation was due to difficulties scheduling a phone call after the home visit. However the participation rate of 74.3% is higher than a previous 22q11.2DS study that also telephone administered the ADI-R (45%, 41/87) (Antshel, Aneja et al. 2007). The sub-sample of children with 22q11.2DS for which ADI-R data was available is representative of the longitudinal cohort in terms of autism symptomatology as the sub-sample did not differ in SCQ score (ADI-R present mean SCQ=12.1, ADI-R absent mean SCQ=11.8, independent samples Mann-Whitney U test  $p=0.610$ ). 45.8% (33/72) of ADI-R interviews were double coded. Inter-rater reliability for ADI-R subdomain scores was very good (intra-class correlation=0.917). A full description of the autism symptomatology assessed by the SCQ and the ADI-R can be found in section 3.2.1.

#### **4.5.6 Aim 5a: Establish the prevalence of ASD in the ECHO cohort using the ADI-R**

Criteria for autism and ASD were applied to ADI-R scores. The ADI-R manual provides an algorithm for autism (described in section 3.2.1); the individual has to meet the cut-off on all three functional domains and there has to be evidence of abnormality of development at or before 36 months (Rutter, Le Couteur et al. 2003). Official ASD criteria for the ADI-R are not available in the manual, but there are recommendations from the literature. The following criteria from a study of ASD in children with Fragile X syndrome were used (Kaufmann, Cortell et al. 2004); the individual has to meet the cut-off on the reciprocal social interaction domain and at least one other domain, while there also has to be evidence of abnormality of development at or before 36 months. ASD and autism classifications were not mutually exclusive, in that an individual who met criteria for autism also met criteria for ASD. For each individual the frequency of functional domain cut-offs met was calculated. Prevalence of autism, ASD and the proportion who met cut-offs for each domain was calculated for children with 22q11.2DS and controls. Fisher's exact test was conducted to investigate whether prevalence differed between children with 22q11.2DS and controls.

It was investigated whether those who met criteria for ASD on the ADI-R differed in the following demographics: age using an independent t-test; 22q11.2DS inheritance and ethnicity using Fisher's exact test; household income and maternal education using Mann-Whitney U tests.

#### **4.5.7 Aim 5b: Examine inter-method reliability between the SCQ and ADI-R in 22q11.2DS**

Autism and ASD criteria were applied to the SCQ and ADI-R. Prevalence rates were compared using Fisher's exact test.

Fisher's exact test was also conducted to investigate whether meeting criteria on the SCQ was associated with meeting criteria on the ADI-R. Spearman's rank correlation was conducted to measure the magnitude of association. Sensitivity and specificity values were calculated. Sensitivity is the proportion of those who meet criteria on the ADI-R that are correctly identified by the SCQ. Specificity is the proportion of those who do not meet criteria on the ADI-R that are correctly identified as such by the SCQ.

Spearman's rank correlation was conducted between SCQ and ADI-R total scores and domain scores. The variance shared between measures was estimated by squaring the rho coefficient.

SCQ scores from wave 2 were used as the ADI-R was conducted at wave 2.

#### **4.5.8 Aim 5c: Examine whether there is a gender difference in the ASD phenotype of 22q11.2DS**

It was investigated whether a gender difference exists in children with 22q11.2DS who met autism and ASD criteria on the SCQ and ADI-R. Fisher's exact test was conducted to test whether meeting criteria is associated with gender. Spearman's rank correlation was conducted to measure the magnitude of association. Male-to-female ratios were calculated.

Gender difference in SCQ and ADI-R total scores was investigated by conducting a Mann Whitney U test.

SCQ scores from wave 2 were used as the ADI-R was conducted at wave 2. Also, so results could be compared for the SCQ and ADI-R, analysis was conducted in a subsample which completed both the ADI-R and SCQ at wave 2.

#### **4.5.9 Aim 5d: Investigate whether ASD indexes comorbidity in 22q11.2DS**

Fisher's exact test was conducted to investigate whether other psychopathology in 22q11.2DS might be associated with presence of ASD as measured by SCQ and ADI-R. Spearman's rank correlation was

conducted to measure the magnitude of association. For each type of psychopathology, prevalence in those with and without ASD was calculated.

The level of comorbidity, in terms of number of DSM diagnoses was compared between children with 22q11.2DS with and without ASD using a Mann Whitney U test. Also it was investigated whether level of comorbidity was correlated with SCQ and ADI-R total score.

Psychopathology at wave 2 was used in analysis as the ADI-R was conducted at wave 2. Also, so results could be compared for the SCQ and ADI-R, analysis was conducted in a subsample which completed both the ADI-R and SCQ at wave 2.

## 4.6 Results

### 4.6.1 Aim 1: Examine the prevalence of psychopathology longitudinally in 22q11.2DS and controls including ASD

At both waves of assessment at least half of children with 22q11.2DS met criteria for one or more DSM-IV psychiatric disorders compared to 10% of sibling controls ( $p < 0.001$ ) (**Table 4**). In relation to controls, children with 22q11.2DS exhibited higher rates of ADHD and anxiety disorder, and more individuals met the cut-off for probable ASD diagnosis at both waves of assessment. ADHD prevalence in children with 22q11.2DS decreased from 38.6% to 21.4% (McNemar's  $p = 0.004$ ). Within anxiety disorders, prevalence of specific (22q11.2DS=18.6%, controls=0.0%, Fisher's  $p = 0.009$ ) and social phobias (22q11.2DS=21.4%, controls=0.0%, Fisher's  $p = 0.005$ ) were only significantly elevated in 22q11.2DS children compared to controls at wave 1 and generalised anxiety disorder (22q11.2DS=15.7%, controls=0.0%, Fisher's  $p = 0.031$ ) only at wave 2. Although to some extent this indicates change, significant changes in prevalence were not found for specific and social phobia, and generalised anxiety disorder. Significant prevalence change was not found for other psychiatric disorders.

There were three individuals at wave 2 who were receiving psychiatric medication. One individual was prescribed diazepam for anxiety and met criteria for specific phobia and GAD at wave 1 and wave 2 and social phobia only at wave 1. It is unclear whether medication contributed to this change. One individual was prescribed fluoxetine for anxiety and the medication had ameliorated their social phobia to the extent they did not meet criteria at wave 2. The parent reported a distinct change once the individual was on medication. One individual was on antipsychotic medication to control aggressive outbursts. This individual met criteria for ADHD and ODD at both waves of

assessment. Medication was not prescribed because of psychotic phenomenology and the individual did not report psychotic experiences at either wave of assessment.

**Table 4:** DSM-IV-TR psychiatric disorder prevalence in 22q11.2DS and controls

	22q11.2DS			Controls			Prevalence difference 22q11.2DS vs Controls	
	Wave 1 %(n)	Wave 2 %(n)	McNemar's p-value	Wave 1 %(n)	Wave 2 %(n)	McNemar's p-value	Wave 1 Fisher's p-value	Wave 2 Fisher's p-value
<b>Any DSM-IV-TR Psychiatric Disorder</b>	<b>55.7%(39)</b>	<b>50.0%(35)</b>	<b>0.454</b>	<b>10.3%(3)</b>	<b>10.3%(3)</b>	<b>0.999</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
<b>Any Anxiety Disorder</b>	<b>35.7%(25)</b>	<b>27.1%(19)</b>	<b>0.238</b>	<b>0.0%(0)</b>	<b>6.9%(2)</b>	<b>0.500</b>	<b>&lt;0.001</b>	<b>0.030</b>
Agoraphobia	8.6%(6)	10.0%(7)	0.999	0.0%(0)	0.0%(0)	-	0.176	0.102
Generalised Anxiety Disorder	8.6%(6)	15.7%(11)	0.125	0.0%(0)	0.0%(0)	-	0.176	0.031
OCD	2.9%(2)	0.0%(0)	0.500	0.0%(0)	0.0%(0)	-	0.999	-
Panic Disorder	2.9%(2)	2.9%(2)	0.999	0.0%(0)	0.0%(0)	-	0.999	0.999
Separation Anxiety Disorder	5.7%(4)	7.1%(5)	0.999	0.0%(0)	0.0%(0)	-	0.318	0.318
Specific Phobia	18.6%(13)	10.0%(7)	0.070	0.0%(0)	3.4%(1)	0.999	0.009	0.431
Social Phobia	21.4%(15)	17.1%(12)	0.607	0.0%(0)	3.4%(1)	0.999	0.005	0.101
<b>Any Mood Disorder</b>	<b>2.9%(2)</b>	<b>5.7%(4)</b>	<b>0.625</b>	<b>0.0%(0)</b>	<b>3.4%(1)</b>	<b>0.999</b>	<b>0.999</b>	<b>0.999</b>
Bipolar Disorder	0.0%(0)	0.0%(0)	-	0.0%(0)	0.0%(0)	-	-	-
Dysthymic Disorder	2.9%(2)	4.3%(3)	0.999	0.0%(0)	3.4%(1)	0.999	0.999	0.999
Major Depressive Disorder	0.0%(0)	1.4%(1)	0.804	0.0%(0)	0.0%(0)	0.999	-	0.999
<b>ADHD</b>	<b>38.6%(27)</b>	<b>21.4%(15)</b>	<b>0.004</b>	<b>3.4%(1)</b>	<b>3.4%(1)</b>	<b>0.999</b>	<b>&lt;0.001</b>	<b>0.034</b>
Conduct disorder	0.0%(0)	1.4%(1)	0.999	0.0%(0)	0.0%(0)	-	-	0.999
Oppositional Defiance Disorder	17.1%(12)	14.3%(10)	0.754	3.4%(1)	3.4%(1)	0.999	0.101	0.167
Any Psychotic disorder	0.0%(0)	0.0%(0)	-	0.0%(0)	0.0%(0)	-	-	-
Selective Mutism	4.3%(3)	4.3%(3)	0.999	3.4%(1)	0.0%(0)	0.999	0.999	0.553
Tic Disorder	5.7%(4)	2.9%(2)	0.625	0.0%(0)	0.0%(0)	0.999	0.318	0.999
Trichillomania	0.0%(0)	0.0%(0)	-	0.0%(0)	0.0%(0)	-	-	-
<b>ASD screening (SCQ)</b>	<b>29.7%(19)</b>	<b>39.1%(25)</b>	<b>0.070</b>	<b>0.0%(0)</b>	<b>0.0%(0)</b>	<b>-</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>

There was a high level of comorbidity (Table 5) and this did not differ across wave of assessment (related-samples Wilcoxon signed rank test p=0.065).

**Table 5:** Comorbidity in 22q11.2DS and controls

Number of DSM-IV-TR Diagnoses	22q11.2DS		Controls	
	Wave 1	Wave 2	Wave 1	Wave 2
0	44.3%(31)	50.0%(35)	89.7%(26)	89.7%(26)
1	20.0%(14)	18.6%(13)	10.3%(3)	3.4%(1)
2	17.1%(12)	14.3%(10)	0.0%(0)	6.9%(2)
3	4.3%(3)	8.6%(6)	0.0%(0)	0.0%(0)
4	7.1%(5)	4.3%(3)	0.0%(0)	0.0%(0)
≥5	7.1%(5)	4.3%(3)	0.0%(0)	0.0%(0)

The longitudinal development of autism domains was examined using the SCQ. There were strong correlations between wave 1 and wave 2 SCQ scores, including individual domain scores (**Table 6**). Children with 22q11.2DS declined in score on Communication (change score=-0.7,  $p=0.004$ ), Restricted, Repetitive and Stereotyped Patterns of Behaviour (change score=-0.4,  $p=0.018$ ) domains and also on items that assess current behaviour. However there was not a significant change in total score (change score=-0.8,  $p=0.311$ ). Controls declined in score on the Repetitive and Stereotyped Patterns of Behaviour (change score=-0.4,  $p=0.025$ ) domain. There was not a significant change in 22q11.2DS scores relative to controls (see last column **Table 6**).

The finding of a stable total score is in contrast to findings in **Table 4** where ASD prevalence (using the SCQ) shows a slight increase. Scores for these individuals were examined and increases in Reciprocal Social Interaction ( $p=0.001$ ) and Communication ( $p=0.003$ ) domain scores were observed. Also there were score increases for items that assessed current behaviour ( $p=0.041$ ) and behaviour at age 4 to 5 ( $p<0.001$ ).

**Table 6:** Longitudinal SCQ scores for 22q11.2DS and controls

	22q11.2DS				Controls				22q11.2DS vs Controls	
	Wave 1 Mean(SD)	Wave 2 Mean(SD)	Correlation Rho(p-value)	Change p-value	Wave 1 Mean(SD)	Wave 2 Mean(SD)	Correlation Rho(p-value)	Change p-value	Change p-value	Change p-value
<b>Total score</b>	12.8(7.2)	12.0(7.2)	0.817(<0.001)	0.311	2.9(2.7)	2.4(2.8)	0.575(0.002)	0.158		0.813
<b>Reciprocal Social Interaction</b>	6.8(4.5)	7.1(4.8)	0.762(<0.001)	0.502	1.8(2.4)	1.7(2.1)	0.596(0.001)	0.793		0.819
<b>Communication</b>	3.6(2.2)	2.9(2.0)	0.666(<0.001)	0.004	0.8(0.9)	0.7(1.1)	0.345(0.085)	0.428		0.173
<b>Restricted, Repetitive and Stereotyped Patterns of Behaviour</b>	2.4(2.1)	2.0(2.0)	0.759(<0.001)	0.018	0.3(0.7)	0.1(0.4)	0.486(0.012)	0.025		0.414
<b>Age 4 to 5 items</b>	6.8(4.6)	7.0(5.0)	0.749(<0.001)	0.515	2.0(2.6)	1.8(2.5)	0.549(0.004)	0.487		0.412
<b>Current behaviour items</b>	6.0(3.9)	5.0(3.6)	0.785(<0.001)	0.002	0.8(1.0)	0.6(0.8)	0.421(0.032)	0.196		0.105

Individuals who met criteria for 'any DSM-IV-TR psychiatric disorder' did not differ in terms of age, gender, 22q11.2DS inheritance, ethnicity and maternal education but did on average come from families with a lower household income.

Children who met ASD criteria (SCQ) did not differ in terms of age, 22q11.2DS inheritance, ethnicity, household income and maternal education.

No significant gender differences were found for individual psychiatric disorders at either wave of assessment.

#### **4.6.2 Aim 2: Describe diagnostic stability and consider diagnostic change at the level of the individual**

The stability of psychiatric diagnosis in 22q11.2DS differs amongst disorders (**Table 7**). ASD (SCQ) had good stability ( $\kappa = 0.726$ ) whereas social phobia ( $\kappa = 0.314$ ) mood disorder ( $\kappa = 0.307$ ) and tic disorder ( $\kappa = 0.307$ ) had poor stability.

The presence of any psychiatric disorder had a high prospective consistency, 74.4% of children with 22q11.2DS with a diagnosis at wave 1 met criteria for a disorder at wave 2. There was also a high retrospective consistency, 82.9% of those with a psychiatric disorder at wave 2 met criteria for a disorder at wave 1. Overall this indicates high stability.

Prospective and retrospective consistency values differed across individual disorders. Generalised anxiety disorder, selective mutism and ASD had a high prospective consistency indicating high persistence across waves. Agoraphobia, panic disorder, separation anxiety disorder, specific and social phobias, ADHD, mood disorder, ODD and tic disorder had a prospective consistency of 50% or less which indicates relatively low persistence.

Agoraphobia, generalised anxiety disorder, panic disorder, separation anxiety disorder, social phobia, mood disorder and tic disorder had a retrospective consistency of 50% or less indicating that emergence of these disorders across waves was contributing to wave 2 prevalence. In contrast specific phobia, ADHD, ODD, selective mutism and ASD had a high retrospective consistency indicating that the majority of cases at wave 2 met criteria at wave 1 and thus wave 2 rates were not mainly due to individuals developing the disorder between waves.

It is interesting to note the disparity between prospective and retrospective consistency values for the presence of any anxiety disorder and the values for individual anxiety disorders.

Although the prevalence of any psychiatric disorder remains consistent over time at the level of the group in 22q11.2DS (**Table 4**) there was variation at the level of the individual. 10% of 22q11.2DS children did not meet criteria at wave 1 but did at wave 2 and 14.3% did meet criteria at wave 1 but did not at wave 2 (**Table 7**). It is interesting to note that for ADHD and ASD there were individuals who gained a diagnosis between waves despite these being neurodevelopmental disorders. These individuals did however have high levels of subthreshold symptoms at wave 1, suggesting they just failed to meet criteria when they were younger. Two individuals gained an ADHD diagnosis and they were both one symptom below the DSM-IV-TR threshold at wave 1. The seven individuals who met the ASD cut-off at wave 2 but not wave 1 all had a score between 10 and 14. Of the psychopathology assessed, ASD had the highest number of individuals who exhibited a gain between waves of assessment.

**Table 7:** Diagnostic stability and variability across waves of assessment in 22q11.2DS

	Diagnostic stability				Category of diagnosis change			
	Kappa value	Kappa p-value	Prospective consistency	Retrospective consistency	Diagnosis at both waves % (n)	Diagnosis gain % (n)	Diagnosis loss % (n)	No diagnosis at both waves % (n)
<b>Any DSM-IV-TR Psychiatric Disorder</b>	<b>0.543</b>	<b>&lt;0.001</b>	<b>74.4%</b>	<b>82.9%</b>	<b>41.4%(29)</b>	<b>8.6%(6)</b>	<b>14.3%(10)</b>	<b>35.7%(25)</b>
<b>Any Anxiety Disorder</b>	<b>0.408</b>	<b>&lt;0.001</b>	<b>52.0%</b>	<b>68.4%</b>	<b>18.6%(13)</b>	<b>8.6%(6)</b>	<b>17.1%(12)</b>	<b>55.7%(39)</b>
Agoraphobia	0.407	0.001	50.0%	42.9%	4.3%(3)	5.7%(4)	4.3%(3)	85.7%(60)
Generalised Anxiety Disorder	0.537	<0.001	83.3%	45.5%	7.1%(5)	8.6%(6)	1.4%(1)	82.9%(58)
OCD	-	-	-	-	0.0%(0)	0.0%(0)	2.9%(2)	97.1%(68)
Panic Disorder	0.485	<0.001	50.0%	50.0%	1.4%(1)	1.4%(1)	1.4%(1)	95.7%(67)
Separation Anxiety Disorder	0.407	0.001	50.0%	40.0%	2.9%(2)	4.3%(3)	2.9%(2)	90.0%(63)
Specific Phobia	0.540	<0.001	46.2%	85.7%	8.6%(6)	1.4%(1)	10.0%(7)	80.0%(56)
Social Phobia	0.314	0.008	40.0%	50.0%	8.6%(6)	8.6%(6)	12.9%(9)	70.0%(49)
<b>Any Mood Disorder</b>	<b>0.307</b>	<b>0.006</b>	<b>50.0%</b>	<b>25.0%</b>	<b>1.4%(1)</b>	<b>4.3%(3)</b>	<b>1.4%(1)</b>	<b>92.9%(65)</b>
Bipolar Disorder	-	-	-	-	0.0%(0)	0.0%(0)	0.0%(0)	100.0%(0)
Dysthymic Disorder	0.379	0.001	50.0%	33.3%	1.4%(1)	2.9%(2)	1.4%(1)	94.3%(66)
Major Depressive Disorder	-	-	-	-	0.0%(0)	1.4%(1)	0.0%(0)	98.6%(69)
<b>ADHD</b>	<b>0.474</b>	<b>&lt;0.001</b>	<b>48.1%</b>	<b>81.3%</b>	<b>18.6%(13)</b>	<b>2.9%(2)</b>	<b>20%(14)</b>	<b>58.6%(41)</b>
<b>Conduct disorder</b>	-	-	-	-	<b>0.0%(0)</b>	<b>1.4%(1)</b>	<b>0.0%(0)</b>	<b>98.6%(69)</b>
<b>Oppositional Defiance Disorder</b>	<b>0.462</b>	<b>&lt;0.001</b>	<b>50.0%</b>	<b>60.0%</b>	<b>8.6%(6)</b>	<b>5.7%(4)</b>	<b>8.6%(6)</b>	<b>77.1%(54)</b>
<b>Any Psychotic disorder</b>	-	-	-	-	<b>0.0%(0)</b>	<b>0.0%(0)</b>	<b>0.0%(0)</b>	<b>100.0%(0)</b>
<b>Selective Mutism</b>	<b>0.652</b>	<b>&lt;0.001</b>	<b>66.7%</b>	<b>66.7%</b>	<b>2.9%(2)</b>	<b>1.4%(1)</b>	<b>1.4%(1)</b>	<b>94.3%(66)</b>
<b>Tic Disorder</b>	<b>0.307</b>	<b>0.006</b>	<b>25.0%</b>	<b>50.0%</b>	<b>1.4%(1)</b>	<b>1.4%(1)</b>	<b>4.3%(3)</b>	<b>92.9%(65)</b>
<b>Trichillomania</b>	-	-	-	-	<b>0.0%(0)</b>	<b>0.0%(0)</b>	<b>0.0%(0)</b>	<b>100.0%(0)</b>
<b>ASD screening (SCQ)</b>	<b>0.726</b>	<b>&lt;0.001</b>	<b>94.7%</b>	<b>72%</b>	<b>28.1%(18)</b>	<b>10.9%(7)</b>	<b>1.6%(1)</b>	<b>59.4%(38)</b>



### 4.6.3 Aim 3: Examine the prevalence of psychotic experiences longitudinally in

#### 22q11.2DS and controls and describe their nature and content

The prevalence of psychotic experiences increased in 22q11.2DS from 2.9% (n=2) to 21.4% (n=15) (McNemar's  $p < 0.001$ ). Psychotic experiences were present in one control at wave 1 (3.4%) but these did not persist at wave 2. Prevalence in 22q11.2DS is elevated compared to controls at wave 2 ( $\chi^2 p = 0.005$ ) but not at wave 1 ( $\chi^2 p = 0.999$ ). There were two 22q11.2DS individuals with psychotic experiences at wave 1 which persisted at wave 2, and thirteen individuals where psychotic experiences emerged between waves.

At wave 1 all cases of psychotic experiences were identified by child report. At wave 2, one case was identified by parent report, thirteen cases by child report, with only one case where there was both child and parent report. Psychotic experiences in 22q11.2DS were reported from age 10 upwards.

**Table 8** describes psychotic experiences identified in children with 22q11.2DS and controls. **Table 9** shows for 22q11.2DS individuals with psychotic experiences the percentage of individuals who reported each type of psychotic phenomena. The majority of experiences were hallucinatory, particularly auditory and tactile experiences. Other phenomena identified included perceptual changes, delusions and abnormalities in thought.

Children with psychotic experiences did not differ in terms of age, gender, 22q11.2DS inheritance, ethnicity, household income and maternal education.

**Table 8:** Psychotic experiences in 22q11.2DS and controls

	Wave 1				Wave 2		
	Gender	Age	Wave 1 parent report	Wave 1 child report	Age	Wave 2 parent report	Wave 2 child report
22q11.2DS 1	M	7	-	-	10	-	Auditory hallucinations
22q11.2DS 2	F	7	-	-	10	-	Auditory pseudo-hallucinations, tactile hallucinations
22q11.2DS 3	F	11	-	Auditory hallucinations	13	-	Changed perception of time, auditory and tactile hallucinations, partial delusion of assistance
22q11.2DS 4	F	10	-	-	13	Non-specific verbal hallucinations	Auditory hallucinations
22q11.2DS 5	F	14	-	-	16	Delusions & delusional interpretation	-
22q11.2DS 6	M	8	-	-	11	-	Jamais vu
22q11.2DS 7	F	12	-	-	14	-	Auditory and tactile hallucinations
22q11.2DS 8	M	12	-	-	15	-	Auditory, olfactory, tactile and visual hallucinations
22q11.2DS 9	M	13	-	-	16	-	Abnormalities in thought processes
22q11.2DS 10	M	11	-	-	14	-	Auditory hallucinations
22q11.2DS 11	M	12	-	Depersonalisation	15	-	Derealisation, depersonalisation, tactile hallucinations
22q11.2DS 12	M	9	-	-	12	-	Partial delusion of grandiose ability
22q11.2DS 13	F	11	-	-	13	-	Tactile hallucinations
22q11.2DS 14	M	12	-	-	14	-	Auditory pseudo-hallucinations, tactile hallucinations
22q11.2DS 15	F	9	-	-	12	-	Visual hallucinations
Control	F	11	-	Visual pseudo-hallucinations	13	-	-

**Table 9:** Nature of psychotic experiences in 22q11.2DS

Phenomena	%(n)
<b>Hallucinations</b>	<b>73.3%(11)</b>
Auditory	53.3%(8)
Olfactory	6.7%(1)
Tactile	40.0%(6)
Visual	33.3%(5)
<b>Perceptual changes</b>	<b>20.0%(3)</b>
Jamais vu	6.7%(1)
Derealisation	6.7%(1)
Depersonalisation	6.7%(1)
Changed perception of time	6.7%(1)
<b>Delusions</b>	<b>13.3%(2)</b>
<b>Abnormalities in thought processes</b>	<b>6.7%(1)</b>

#### **4.6.4 Aim 4: Examine whether psychopathology is associated with psychotic experiences at wave 2**

Psychiatric disorder at wave 1 or wave 2 was not strongly associated with psychotic experiences at wave 2 (**Table 10**). Anxiety disorder has been previously highlighted in the 22q11.2DS literature to be a risk factor for the emergence of psychotic experiences; it is therefore worth noting that out of the associations examined the presence of anxiety disorder at wave 1 had a relatively higher correlation ( $\rho=0.250$ ). However, in absolute terms, the magnitude of correlation was low and indicated anxiety disorder at wave 1 only predicts 6.25% of variability in psychotic experiences. Level of comorbidity at either wave 1 or wave 2 was not associated with the presence of psychotic experiences (independent samples Mann-Whitney U test, wave 1  $p=0.205$ , wave 2  $p=0.435$ ).

**Table 10:** Association between psychiatric disorder and psychotic experiences in 22q11.2DS

	Wave 1 diagnosis		Wave 2 diagnosis	
	Rho	Fisher's p-value	Rho	Fisher's p-value
<b>Any DSM IV Psychiatric Disorder</b>	<b>0.192</b>	<b>0.133</b>	<b>0.174</b>	<b>0.244</b>
<b>Any Anxiety Disorder</b>	<b>0.250</b>	<b>0.056</b>	<b>-0.006</b>	<b>0.999</b>
Agoraphobia	-0.019	0.999	-0.058	0.999
Generalised Anxiety Disorder	-0.019	0.999	0.061	0.691
OCD	0.137	0.348	-	-
Panic Disorder	-0.085	0.999	-0.090	0.999
Separation Anxiety Disorder	0.037	0.999	0.126	0.290
Specific Phobia	0.144	0.254	-0.058	0.999
Social Phobia	0.192	0.142	-0.053	0.999
<b>Any Mood Disorder</b>	<b>-0.085</b>	<b>0.999</b>	<b>0.171</b>	<b>0.199</b>
Bipolar Disorder	-	-	-	-
Dysthymic Disorder	-0.085	0.999	0.061	0.521
Major Depressive Disorder	-	-	0.231	0.214
<b>ADHD</b>	<b>0.141</b>	<b>0.346</b>	<b>-0.018</b>	<b>0.999</b>
<b>Conduct disorder</b>	<b>-</b>	<b>-</b>	<b>-0.063</b>	<b>0.999</b>
<b>Oppositional Defiance Disorder</b>	<b>-0.029</b>	<b>0.999</b>	<b>0.185</b>	<b>0.205</b>
<b>Any Psychotic disorder</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>
<b>Selective Mutism</b>	<b>0.260</b>	<b>0.091</b>	<b>0.061</b>	<b>0.521</b>
<b>Tic Disorder</b>	<b>0.037</b>	<b>0.999</b>	<b>-0.090</b>	<b>0.999</b>
<b>Trichotillomania</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>
<b>ASD screening</b>	<b>-0.038</b>	<b>0.999</b>	<b>-0.065</b>	<b>0.765</b>

#### 4.6.5 Aim 5a: Establish the prevalence of ASD in the ECHO cohort using the ADI-R

In 22q11.2DS 44.2% met ASD criteria and 15.4% met autism criteria, as measured by the ADI-R (Table 11). No controls met criteria for autism, ASD, or clinical cut-offs on functional domains. ASD prevalence was found to be significantly elevated in 22q11.2DS compared to controls ( $p < 0.001$ ) but prevalence of autism was not ( $p = 0.096$ ). In 22q11.2DS more individuals met the clinical cut-offs in the domains of Reciprocal Social Interaction (51.9%) and Communication (50.0%) compared to the Restricted, Repetitive and Stereotyped Patterns of Behaviour domain (23.1%). 92.3% of children with 22q11.2DS exhibited abnormality in development before the age of 36 months compared to 20% of controls ( $p < 0.001$ ).

**Table 11:** Prevalence of ASD phenomenology in 22q11.2DS and controls as measured by the ADI-R

n (22q11.2DS=52, Controls =20)	22q11.2DS %(n)	Controls %(n)	Fishers p-value
<b>Diagnosis</b>			
Autism criteria	15.4%(8)	0.0%(0)	0.096
ASD criteria	44.2%(23)	0.0%(0)	<0.001
<b>Proportion who meet domain cut-offs</b>			
Reciprocal Social Interaction	51.9%(27)	0.0%(0)	<0.001
Communication	50.0%(26)	0.0%(0)	<0.001
Restricted, Repetitive and Stereotyped Patterns of Behaviour	23.1%(12)	0.0%(0)	0.029
Abnormality of Development Evident at or Before 36 months	92.3%(48)	20.0%(0)	<0.001

63.5% of children with 22q11.2DS met the clinical cut-off for impairment in at least one functional domain compared to 0.0% of controls (Table 12).

**Table 12:** Number of ADI-R functional domains in 22q11.2DS and controls

Functional Domains	22q11.2DS %(n)	Controls %(n)
0	36.5%(19)	100.0%(20)
1	17.3%(9)	0.0%(0)
2	30.8%(16)	0.0%(0)
3	15.3%(8)	0.0%(0)

Individuals who met ADI-R ASD criteria did not differ in age, 22q11.2DS inheritance, ethnicity, household income and maternal education

#### 4.6.6 Aim 5b: Examine inter-method reliability between the SCQ and ADI-R in 22q11.2DS

SCQ and ADI-R data were available for 51 children with 22q11.2DS. Prevalence of ASD using the SCQ (41.2%, n=21) and ADI-R (43.1%, n=22) was found to be similar ( $p=0.999$ ) and so the same was found for autism (SCQ, 5.9%, n=3; ADI-R, 13.7%, n=7;  $p=0.318$ ).

However, a discrepancy was found between the SCQ and ADI-R in identifying individuals as meeting criteria for ASD and autism (**Table 13**).

The SCQ ASD cut-off misidentified 6/22 individuals who met ADI-R ASD criteria (**Table 13a**) and 2/7 individuals who met ADI-R autism criteria (**Table 13c**). The SCQ ASD cut-off has 72.7% sensitivity and 82.8% specificity in identifying those who met ADI-R ASD criteria. Sensitivity is similar (71.4%) but specificity is lower (63.6%) for the SCQ ASD cut-off in identifying those who met ADI-R autism criteria. Meeting SCQ ASD cut-off was found to be associated with meeting ADI-R SCQ criteria ( $\rho=0.558$ ,  $p<0.001$ ).

The SCQ autism cut-off did not identify any individuals who met ADI-R autism criteria (**Table 13b**), sensitivity 0.0% and specificity 95.3%. Meeting SCQ autism cut-off was not associated with meeting ADI-R autism criteria ( $\rho=-0.100$ ,  $p<0.999$ ).

**Table 13:** Discrepancy between SCQ and ADI-R

		SCQ				SCQ				SCQ	
		ASD-	ASD+			Autism-	Autism+			ASD-	ASD+
ADI-R	ASD-	47.1% (24)	9.8% (5)	ADI-R	Autism-	80.4% (41)	5.9% (3)	ADI-R	Autism-	54.9% (28)	31.4% (16)
	ASD+	11.8% (6)	31.4% (16)		Autism+	13.7% (7)	0.0% (0)		Autism+	3.9% (2)	9.8% (5)

a) SCQ ASD vs ADI-R ASD

b) SCQ autism vs ADI-R autism

c) SCQ ASD vs ADI-R autism

SCQ total score correlated with ADI-R total score ( $\rho=0.695$ ,  $p<0.001$ ) and was found to be similar to the correlation magnitude reported in the idiopathic literature (0.71). Shared variance between SCQ and ADI-R total score was 48.3%. Scores for individual domains correlated (**Table 14**).

**Table 14:** Correlation between SCQ and ADI-R scores in 22q11.2DS

	Correlation Rho	p-value	Shared variance
<b>Total Score</b>	0.695	<0.001	48.3%
<b>Domain score</b>			
Reciprocal Social Interaction	0.581	<0.001	33.8%
Communication	0.614	<0.001	37.7%
Restricted, Repetitive and Stereotyped Patterns of Behaviour	0.443	0.001	19.6%

#### 4.6.7 Aim 5c: Examine whether there is a gender difference in the ASD phenotype of 22q11.2DS

Prevalence of those who met the SCQ ASD cut-off was greater for males (male-to-female ratio=2.63,  $p=0.021$ ). For SCQ autism, ADI-R autism and ADI-R ASD, although there was a trend for male preponderance there was no significant gender difference (Table 15). Analysis included 51 22q11.2DS individuals with both SCQ and ADI-R scores.

**Table 15:** ASD and autism prevalence by gender in 22q11.2DS

	Male	Female	Male-to- female ratio	Correlation Rho	Fishers p-value
n	28	23			
<b>ADI-R</b> ASD %(n)	53.6%(15)	30.4%(7)	1.76	0.232	0.115
Autism %(n)	21.4%(6)	4.3%(1)	4.92	0.247	0.112
<b>SCQ</b> ASD %(n)	57.1%(16)	21.7%(5)	2.63	0.358	0.021
Autism %(n)	10.7%(3)	3.7%(0)	-	0.227	0.227

On average males had a higher total score on both the SCQ ( $p=0.017$ ) and the ADI-R ( $p=0.012$ ) (Table 16).

**Table 16:** SCQ and ADI-R total score by gender in 22q11.2DS

	Male		Female		Mann-Whitney p-value
	Mean	SD	Mean	SD	
<b>ADI-R total score</b>	24.5	13.8	15.5	10.4	0.012
<b>SCQ total score</b>	14.1	6.5	9.7	5.9	0.017

#### **4.6.8 Aim 5d: Investigate whether ASD indexes comorbidity in 22q11.2DS**

59.1% of individuals who met ADI-R ASD criteria had a comorbid psychiatric disorder but this did not significantly differ from those without ASD (44.8%,  $p=0.400$ ). The prevalence of comorbid psychiatric disorder (59.1%), anxiety disorder (36.4%), ADHD (27.3%) and ODD (18.2%) in children with 22q11.2DS and ASD (ADI-R) was high and similar to that reported for idiopathic ASD (Simonoff, Pickles et al. 2008). However prevalence of psychiatric disorder was also high in those without ASD (**Table 17**).

Meeting SCQ ASD criteria was found to be associated with the presence of anxiety disorder ( $\rho=0.422$ ,  $p=0.004$ ) whereas meeting ADI-R ASD criteria was not ( $\rho=0.133$ ,  $p=0.371$ ). No other psychopathology measure was associated with SCQ and ADI-R criteria. This analysis included 51 22q11.2DS individuals who had both SCQ and ADI-R scores. The association between meeting SCQ ASD criteria and anxiety disorder was also present at a similar magnitude in the larger sample of 64 individuals who completed the SCQ ( $\rho=0.425$ ,  $p=0.001$ ).



**Table 17:** Association between ASD and other psychopathology in 22q11.2DS

ASD+ = ASD present, ASD- = ASD not present

	ASD SCQ				ASD ADI-R			
	Prevalence of psychopathology in		Association		Prevalence of psychopathology in		Association	
	ASD+ (%)	ASD- (%)	Rho	Fisher's p-value	ASD+ (%)	ASD- (%)	Rho	Fisher's p-value
<b>Any DSM IV Psychiatric Disorder</b>	<b>66.7</b>	<b>40.0</b>	<b>0.263</b>	<b>0.089</b>	<b>59.1</b>	<b>44.8</b>	<b>0.141</b>	<b>0.400</b>
<b>Any Anxiety Disorder</b>	<b>52.4</b>	<b>13.3</b>	<b>0.422</b>	<b>0.004</b>	<b>36.4</b>	<b>24.1</b>	<b>0.133</b>	<b>0.371</b>
Agoraphobia	14.3	0.0	0.299	0.064	9.1	3.4	0.119	0.571
Generalised Anxiety Disorder	33.3	10.0	0.289	0.070	27.3	13.8	0.168	0.295
OCD	-	-	-	-	-	-	-	-
Panic Disorder	9.5	0.0	0.241	0.165	8.3	0.0	0.232	0.181
Separation Anxiety Disorder	14.3	3.3	0.200	0.293	9.1	6.9	0.040	0.999
Specific Phobia	19.0	3.3	0.260	0.146	18.2	3.4	0.245	0.152
Social Phobia	28.6	10.0	0.240	0.136	22.7	13.8	0.116	0.474
<b>Any Mood Disorder</b>	<b>0.0</b>	<b>10.0</b>	<b>-0.209</b>	<b>0.259</b>	<b>9.1</b>	<b>3.4</b>	<b>0.119</b>	<b>0.571</b>
Bipolar Disorder	-	-	-	-	-	-	-	-
Dysthymic Disorder	0.0	10.0	-0.209	0.259	9.1	3.4	0.119	0.571
Major Depressive Disorder	-	-	-	-	-	-	-	-
<b>ADHD</b>	<b>33.3</b>	<b>16.7</b>	<b>0.193</b>	<b>0.196</b>	<b>27.3</b>	<b>20.7</b>	<b>0.077</b>	<b>0.741</b>
<b>Conduct disorder</b>	<b>0.0</b>	<b>3.3</b>	<b>-0.118</b>	<b>0.999</b>	<b>0.0</b>	<b>3.4</b>	<b>-0.123</b>	<b>0.999</b>
<b>Oppositional Defiance Disorder</b>	<b>14.3</b>	<b>13.3</b>	<b>0.014</b>	<b>0.999</b>	<b>18.2</b>	<b>10.3</b>	<b>0.113</b>	<b>0.447</b>
<b>Any Psychotic disorder</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>
<b>Selective Mutism</b>	<b>0.0</b>	<b>6.7</b>	<b>-0.169</b>	<b>0.506</b>	<b>0.0</b>	<b>6.9</b>	<b>-0.176</b>	<b>0.500</b>
<b>Tic Disorder</b>	<b>4.8</b>	<b>0.0</b>	<b>0.169</b>	<b>0.412</b>	<b>4.5</b>	<b>0.0</b>	<b>0.162</b>	<b>0.431</b>
<b>Trichotillomania</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>
<b>Psychotic Experiences</b>	<b>19.0</b>	<b>33.3</b>	<b>-0.158</b>	<b>0.346</b>	<b>18.2</b>	<b>34.5</b>	<b>-0.181</b>	<b>0.225</b>

Those who met SCQ ASD criteria had on average more DSM diagnoses ( $p=0.034$ ), however this was not the case for those who met ADI-R ASD criteria ( $p=0.186$ ) (**Table 18**).

**Table 18:** Number of DSM diagnoses by ASD status

ASD+ = ASD present, ASD- = ASD not present

	Number of DSM diagnoses				Mann-Whitney p-value
	ASD+		ASD-		
	Mean	SD	Mean	SD	
ADI-R	1.6	1.8	0.9	1.2	0.186
SCQ	2.0	1.9	0.8	1.1	0.034

Level of comorbidity was correlated with both ADI-R ( $p=0.020$ ) and SCQ ( $p<0.001$ ) total score (**Table 19**). SCQ total score indexed a greater proportion of variance in level of comorbidity compared to ADI-R total score (SCQ=22.2%, ADI-R=10.6%).

**Table 19:** Correlation between number of DSM diagnoses and total score of SCQ and ADI-R

	Correlation Rho	p-value	Shared variance
ADI-R total score	0.325	0.020	10.6%
SCQ total score	0.471	<0.001	22.2%

## 4.7 Vignettes

REMOVED TO RESPECT PARTICIPANT'S PRIVACY

## 4.8 Discussion

This is one of the few longitudinal 22q11.2DS studies to examine a wide range of psychopathology including subthreshold psychotic symptoms and ASD symptomatology at both waves of assessments. Analysis has focused on characterising diagnostic stability and also change at the level of the individual.

### 4.8.1 Findings

#### 1. High burden of psychopathology in 22q11.2DS

Across waves of assessment (mean age, wave 1=10 years, wave 2=12.5 years) there was a high burden of psychopathology in children with 22q11.2DS, with at least 50% meeting criteria for a DSM-IV-TR psychiatric disorder, in contrast to 10% of controls. Prevalence in controls is consistent to prevalence of psychiatric disorder in large population study of children that used the CAPA (13%) (Costello, Mustillo et al. 2003). This replicates previous cross-sectional and

longitudinal studies that report high psychiatric morbidity in 22q11.2DS (Green, Gothelf et al. 2009, Antshel, Shprintzen et al. 2010, Fung, McEvilly et al. 2010). Prevalence of ADHD, anxiety disorders and ASD (using the SCQ) was robustly elevated in 22q11.2DS in relation to controls. Overall psychopathology had high stability across age and level of comorbidity did not change with age. 74.4% of those who met criteria for any diagnosis at wave 1 met criteria again at wave 2. 82.9% of those with any diagnosis at wave 2 had a diagnosis at wave 1. This highlights the utility and potential for early, targeted intervention in children with 22q11.2DS and psychopathology.

## 2. The longitudinal course of individual disorders differs

### i. ADHD prevalence declined in 22q11.2DS

ADHD prevalence declined across adolescence from 38.6% at wave 1 to 21.4% at wave 2 in 22q11.2DS whereas prevalence was 3.4% at both waves of assessment in controls. ADHD persisted in 13/27 which is a rate of 48.1% which is lower than that previously reported for 22q11.2DS (65% from age 11 to 15) (Antshel, Hendricks et al. 2013) and for idiopathic ADHD (70% from age 9.4 to 14.5) (Langley, Fowler et al. 2010). This decline was not due to medication as only one child with ADHD was on medication, which was prescribed for aggression and did not ameliorate ADHD symptomatology. The longitudinal course of ADHD in 22q11.2DS fitted that expected of a neurodevelopmental disorder as there was strong retrospective consistency in that the majority of those with diagnosis at wave 2 had ADHD at wave 1. Though there were two individuals with subthreshold symptomatology at wave 1 who met ADHD diagnostic criteria at wave 2. Although perhaps unexpected, this has been documented in 22q11.2DS (Antshel, Hendricks et al. 2013) and may indicate that ADHD measures index features of the 22q11.2DS that increase during adolescence. Alternatively this may reflect measurement error or stochastic fluctuation.

### ii. Longitudinal course differed amongst anxiety disorders

In children with 22q11.2DS there was an elevated prevalence of anxiety disorder (wave 1=35.7%, wave 2=27.1%) in comparison to controls (wave 1=0.0%, wave 2=6.9%). There are dynamic changes in anxiety disorders across early adolescence. 48% of those with an anxiety disorder at wave 1 did not meet criteria at wave 2. Although there was low persistence, there was strong retrospective consistency in

that of those with an anxiety disorder at wave 2 68.4% previously met criteria at wave 1.

Amongst individual anxiety disorders longitudinal course differed. At wave 1, only specific phobia and social phobia were elevated in prevalence in relation to controls and at wave 2 only generalised anxiety disorder prevalence was elevated. Though, it should be noted that these are not large changes in prevalence. These findings suggest that the type of anxiety that emerges in the early adolescence of 22q11.2DS is more generalised whereas anxiety at younger ages is more specific in nature. This replicates a previous study that found phobia prevalence decreases whereas generalised anxiety disorder prevalence increases with age (Antshel, Shprintzen et al. 2010). There were two individuals on anxiety medication who no longer met social phobia criteria at wave 2, so although medication is contributory to change, it is by no means fully responsible.

Generalised anxiety disorder had a large prospective consistency but a low retrospective consistency suggesting that it is both an emerging as well as a persistent disorder in early adolescence.

Specific phobia had the opposite pattern with a low prospective consistency and a high retrospective consistency suggesting low persistence, but that the majority of those with specific phobia at wave 2 met criteria at wave 1.

Social phobia had low diagnostic stability across with low prospective and retrospective consistency values and low diagnostic agreement ( $\kappa=0.314$ ).

Anxiety has been associated with the emergence of psychotic phenomenology in 22q11.2DS (see sections 2.1.4 and 2.1.5). Given that anxiety disorders differ in longitudinal course, future studies should consider the nature of the anxiety that is predictive of psychotic phenomenology.

- iii. In some 22q11.2DS individuals ASD symptomatology emerged in adolescence

ASD prevalence (using the SCQ) is elevated in 22q11.2DS in comparison to controls (wave 1=29.7%, wave 2=39.1%). Overall ASD (SCQ) had the highest stability out of the psychopathology assessed ( $\kappa=0.726$ ). SCQ total score correlated highly between assessment waves ( $\rho=0.817$ ,  $p<0.311$ ). Although some SCQ domain scores declined slightly between assessment waves, there was not decline relative to controls. It also had the highest prospective consistency, 94.7% of individuals who met the screening cut-off at wave 1 also did so at wave 2.

However in several individuals ASD symptomatology emerged between waves to the extent they met the cut-off at wave 2, which is unexpected for a neurodevelopmental disorder. These findings are consistent with the IBBC study, which found ASD prevalence peaks in adolescence (Schneider, Debbané et al. 2014). This was driven by an increase in score on domains of Reciprocal Social Interaction ( $p=0.001$ ) and Communication ( $p=0.003$ ). Also there was evidence that severity of current behaviour may influence parents' reporting of past behaviour as increased scores were found both on items that asked about current and past behaviours. Overall emergence of ASD symptoms in these individuals cannot be attributed to age-related change in a specific domain and emergence may reflect measurement error.

iv. Prevalence of mood disorder remained low in early adolescence

Prevalence of mood disorder in 22q11.2DS was low (wave 1=2.9%, wave 2=5.7%) and was not elevated in relation to controls (wave 1=0.0%, wave 2=3.4%). This is in contrast to a previous longitudinal study that reported mood disorder prevalence of 21 % at wave 1 and 64% at wave 2, though their waves of assessment occurred at an older age (wave 1=11.8 years, wave 2=15.0 years) and they used a different measure of psychiatric disorder (Antshel, Shprintzen et al. 2010).

v. ODD not elevated in longitudinal cohort

ODD prevalence was not greatly elevated in 22q11.2DS (wave 1=17.1%, wave 2=14.3%) in relation to controls (wave 1=3.4%, wave 2=3.4%)( $p$ -value, wave

1=0.101, wave 2=0.167). This could be due to a lack of power as ODD prevalence was found to be significantly elevated (22q11.2DS=18.8%) compared to controls in a study that reported findings from the larger cross-sectional ECHO cohort sample (Niarchou, Zammit et al. 2014), despite the reported prevalence being similar (17.1%) to that reported in this chapter.

vi. Conduct disorder prevalence was low

Consistent with the IBBC consortium study, there was a low prevalence of conduct disorder (Schneider, Debbané et al. 2014). There was only one 22q11.2DS individual who met criteria.

3. Psychotic phenomenology emerges during early adolescence

This longitudinal study captures the emergence of the first signs of psychotic phenomena in 22q11.2DS. Prevalence of psychotic experiences increased across waves from 2.9% to 21.4%. Only one control reported psychotic experiences. In 22q11.2DS experiences were reported from age 10 and were most commonly reported by the child in the absence of parental awareness. This highlights the importance of child report, which is lacking in some studies of 22q11.2DS (Hooper, Curtiss et al. 2013). Experiences were varied in content with the most commonly reported experience being auditory hallucinations. No individuals met criteria for psychotic disorder as experiences were transient and generally did not impact on the individual's level of functioning. This cohort can be seen to capture the premorbid phase of psychosis when symptoms are emerging but not yet florid nor greatly impacting. Psychotic experience prevalence is lower than in a previous study that used the CAPA interview in an older sample (Baker and Skuse 2005).

The development of subthreshold psychotic phenomenology in 22q11.2DS appears independent of other psychopathology as the presence of psychotic experiences at wave 2 was not associated with psychopathology at wave 1 or wave 2. The lack of association between ASD and psychotic experiences suggests that ASD in 22q11.2DS is not explained by misdiagnosed prepsychotic phenomena as argued by some authors (Vorstman, Morcus et al. 2006, Eliez 2007). Findings do not replicate previous studies that find anxiety precedes emergence of psychotic phenomena in 22q11.2DS (Antshel, Shprintzen et al. 2010). These results are not necessarily contradictory as these studies have measured prodromal symptoms, which are potentially greater in severity than psychotic experiences assessed in the ECHO sample. It may be that early psychopathology

plays more of a role in the emergence of more severe psychotic phenomena. In the general population there is not always overlap in risk factors for differing severity of psychotic phenomena (Zammit, Hamshere et al. 2014).

#### 4. Prevalence of ASD and autism using the ADI-R

Using the ADI-R, a gold-standard measure, ASD prevalence was found to be high with 44.2% of children with 22q11.2DS meeting criteria for ASD compared to 0.0% of controls. Approximately a third of individuals who met ASD criteria also met autism criteria (15.4%). ASD prevalence was found to be in the upper end of the range of previous studies that used the ADI-R and autism prevalence at the lower end of the range (see **Table 3**). There were high rates of subthreshold ASD symptomatology with 65.3% of children with 22q11.2DS meeting clinical cut-off for at least one autism domain compared to 0.0% of controls. Fewer children with 22q11.2DS met the clinical cut-off for Restricted, Repetitive and Stereotyped Patterns of Behaviour domain (23.1%) than Reciprocal Social Interaction (51.9%) and Communication (50.0%) domains.

#### 5. The SCQ and ADI-R measure overlapping but different constructs

##### i. Inter method reliability differs for ASD and autism

Prevalence of autism and ASD was similar using the SCQ however the SCQ did not identify the same individuals as the ADI-R.

The SCQ is advocated as a screening measure for ASD to help identify those who should undergo an in depth assessment such as the ADI-R. An effective screening tool should have a high sensitivity and specificity but arguably if screening is followed by a more in depth assessment then the main concern is sensitivity - avoiding false negatives. Findings suggest the SCQ is not an effective screener in 22q11.2DS. The SCQ ASD cut-off had a sensitivity of 72.7% for identifying those who met ADI-R ASD criteria, which is lower than sensitivity of the SCQ in identifying ASD in the general population (96%). The SCQ ASD cut-off misidentified those who met ADI-R autism criteria as well as those who met ADI-R ASD criteria. This indicates that the SCQ was not just misidentifying individuals whose score was on the borderline of the ADI-R ASD cut-off.

The SCQ and ADI-R were found to capture overlapping but different aspects of the ASD phenotype. On one hand their total scores correlated highly ( $\rho=0.695$ ,  $p<0.001$ ), however this only means 48.3% shared variance between measures leaving over half

unexplained. There was no overlap in the SCQ and the ADI-R when higher cut-offs for autism were applied, no individual who met the autism cut-off on the SCQ met autism criteria on the ADI-R.

ii. The SCQ indexes other psychopathology more than the ADI-R

In idiopathic ASD the presence of comorbid psychiatric disorder is common (Simonoff, Pickles et al. 2008) so it would not be unexpected for ASD to be associated with other psychopathology, however scoring on the SCQ seems to be more influenced by the presence of comorbid psychiatric disorder than is the case for the ADI-R. Meeting SCQ ASD criteria was found to be associated with the presence of anxiety disorder ( $\rho=0.422$ ,  $p=0.004$ ) whereas meeting ADI-R ASD criteria was not ( $\rho=0.133$ ,  $p=0.371$ ). 22q11.2DS individuals who met SCQ ASD criteria had a greater level of comorbidity than those who did not (ASD+=2.0 DSM diagnoses, ASD-=0.8 DSM diagnoses,  $p=0.034$ ), whereas such relationship was not found using the ADI-R (ASD+=1.6 DSM diagnoses, ASD-=0.9 DSM diagnoses,  $p=0.186$ ). When the SCQ and ADI-R were considered dimensionally, the total scores of both measures correlated with level of comorbidity (SCQ,  $\rho=0.471$ ,  $p<0.001$ ; ADI-R,  $\rho=0.325$ ,  $p=0.020$ ). However, the shared variance between level of comorbidity and SCQ total score (22.2%) was found to be greater than that for ADI-R total score (10.6%).

Overall this suggests that in a population with high level of psychopathology and comorbidity, such as 22q11.2DS, the ADI-R maybe a better measure as scoring on the ADI-R is relatively more independent of psychiatric disorder compared to the SCQ. The fact the SCQ indexes more comorbid psychiatric disorder than the ADI-R may explain why there is a discrepancy between the SCQ and ADI-R measures.

Meeting ASD criteria on the ADI-R was found to be independent of the presence of all psychiatric disorders and psychotic experiences. Previous authors have argued that autism measures in 22q11.2DS are misdiagnosing prepsychotic phenomena and anxiety (Eliez 2007, Angkustsiri, Goodlin-Jones et al. 2014). However this chapter has demonstrated that this depends on the instrument used with present findings indicating that the ADI-R is independent of such psychopathology.



## 6. Gender difference at the symptom level of the autism phenotype

When ASD is considered in terms of symptomatology a gender difference is observed. At the level of categorical diagnosis a gender difference in ASD was observed using the SCQ (male-to-female ratio 2.63:1) but not the ADI-R, but there was a trend for male preponderance using the ADI-R (ASD=1.76:1, autism=4.92:1). This discrepancy could be due to the SCQ indexing other psychopathology which may contribute to gender differences, however Chapter 4 did not find gender differences in psychiatric disorder in 22q11.2DS.

Overall findings suggest that a gender difference in ASD in 22q11.2DS is present, albeit less pronounced than in idiopathic ASD. ASD male-to-female ratio was 1.76:1 using the ADI-R and 2.63:1 using the SCQ. These values are less than the male-to-female ratio for ASD in the general population (4.3:1) but similar to that in those with ID (2:1) (Newschaffer, Croen et al. 2007). The presence of a trend for a male preponderance at the level of categorical diagnosis using the ADI-R and a difference at the symptom level indicates this study may be underpowered to detect gender differences at the level of categorical diagnosis.

## 7. Psychiatric comorbidity is prevalent but not specific to ASD in 22q11.2DS

In children with 22q11.2DS and ASD (ADI-R) there was a high prevalence of comorbid psychiatric disorder (59.1%), anxiety disorder (36.4%), ADHD (27.3%) and ODD (18.2%). These values are consistent with those reported in a study that assessed comorbid psychiatric disorder in idiopathic ASD using the same psychiatric measure as the ECHO study cohort (CAPA) (Simonoff, Pickles et al. 2008). However prevalence of psychiatric disorder did not differ greatly from those with 22q11.2DS without ASD. This suggests that although ASD and 22q11.2DS is associated with high levels of psychiatric disorder, the combination of both is not associated with higher prevalence. The similarity in the profile of psychiatric disorder between 22q11.2DS and idiopathic ASD suggests neurodevelopmental deviance regardless of aetiology confers risk for psychiatric disorder. This is in contrast to the finding that ADI-R total score is correlated with level of comorbidity. This is not necessarily contradictory as relationships found at symptom level are not always reflected at the level of diagnosis in 22q11.2DS (Sobin, Kiley-Brabeck et al. 2009).

## 4.8.2 Limitations

### 1. No comparison with idiopathic groups

The lack of an idiopathic psychopathology group meant it was not possible to examine whether the 22q11.2DS psychopathology phenotype differs from idiopathic psychopathology. A previous 22q11.2DS study has found the ASD phenotype in individuals with 22q11.2DS and ASD is less severe than in idiopathic ASD (Kates, Antshel et al. 2007).

### 2. Factors that may bias prevalence of psychotic experiences

Not all children with 22q11.2DS may be able to report internal phenomena such as psychotic experiences and this may lead to an underestimation in prevalence. Also there may be bias in the experiences children with 22q11.2DS are able to report. From my experience children seem to understand the questions regarding hallucinations more so than those on delusions. In one case the parent reported that the child experienced delusional thinking but the child did not have insight. Also as mentioned in Chapter 3, the longitudinal cohort is underrepresented in terms of those who reported psychotic experiences at wave 1 so prevalence at wave 2 is likely to be an underestimate.

### 3. No external criterion of ASD

In analysis it has been assumed that the ADI-R is a better measure of ASD than the SCQ. To some extent this is a safe assumption to make. The ADI-R is semi-structured interview that is investigator driven whereas the SCQ is a parent report questionnaire. The creators of the SCQ and ADI-R state that the SCQ is not appropriate for individual diagnoses, whereas the ADI-R is (Berument, Rutter et al. 1999). However it cannot necessarily be assumed that this is the case for 22q11.2DS. There could be ADI-R items which are biased in the context of 22q11.2DS. It would be ideal if the SCQ and ADI-R could be compared to expert clinician diagnosis. From my experience many children with 22q11.2DS do not receive a formal diagnosis of ASD from clinicians. However much cannot be interpreted from this as many parents anecdotally report reluctance of clinicians to diagnose neurodevelopmental disorders in the context of 22q11.2DS.

### 4. No observational measure of ASD

The gold standard of ASD assessment is to use the ADI-R to assess developmental history and to use the ADOS which is an observational measure (Charman and Baird 2002, Johnson and Myers 2007). The use of the ADOS in combination with the ADI-R in the ECHO study sample may

identify fewer individuals as meeting criteria for ASD and autism compared to the ADI-R alone. Therefore prevalence rates reported in this chapter are likely to be an overestimate.

#### 5. ADI-R was completed at wave 2

The ADI-R was introduced into the ECHO study assessment protocol at wave 2. However ideally it would have been more reliable if administered at wave 1 as it would not require the parent to remember as far back.

#### 6. Power

The sample size, although large for 22q11.2DS studies, may be underpowered to detect more subtle trends. Indeed for specific phobia, social phobia and generalised anxiety disorder prevalence is differentially elevated at waves, which would indicate change in prevalence. However when change was directly tested for with McNemar's test, p-values were above the 0.05 threshold.

#### 7. Issues of multiple comparisons

Analysis should be considered exploratory as analysis was not adjusted for multiple comparisons. This increases the risk of type 1 errors occurring, whereby the null hypothesis is incorrectly rejected. For instance when investigating change in psychopathology prevalence, there was not a correction for the number of psychopathology categories investigated. Whilst this is an important issue it should also be considered in the context of 22q11.2DS as a rare disorder which limits sample size and thus power.

#### 8. Ascertainment bias

Children with 22q11.2DS referred for medical genetic testing will probably be more likely to have neurodevelopmental disorder or developmental delay than children with 22q11.2DS who remain untested. This means prevalence rates reported in this chapter are likely to be an overestimate.

#### 9. Categorical diagnosis

The use of categorical diagnosis reduces variation in psychopathology to a binary variable. This reduction in variation reduces the power to detect change in psychopathology. On the other hand categorical diagnoses provide a way to distinguish whether a change in an individual's psychopathology has reached clinically impacting levels.

### 4.8.3 Future work

#### 1. Approaches based on symptom counts and dimensional measures

This chapter has examined psychopathology at the level of psychiatric disorder and has not focused on symptoms in depth. Future work could examine the longitudinal course of the 22q11.2DS symptom profile to understand what underlies changes in diagnosis.

In the future dimensional measures which cross traditional diagnostic boundaries could be used to examine longitudinal psychopathology continuously rather than categorically.

#### 2. Further waves of assessment

A third wave of assessment would allow the next stage of development to be examined in the ECHO 22q11.2DS cohort and this is now underway. Also the use of a prodromal measure to capture phenomenology between the severity of psychotic experiences and psychotic disorder will be crucial as the cohort enters the risk period of psychosis development and this has been incorporated into the ECHO study wave 3 assessments.

#### 3. Contrast neuropsychiatric phenotype of 22q11.2DS to that of other psychiatric-risk CNVs

The neuropsychiatric phenotype of 22q11.2DS could be contrasted to the phenotype of other psychiatric risk CNVs. At 22q11.2 there is a mirror phenotype for schizophrenia risk, with 22q11.2 deletion conferring risk and 22q11.2 duplication being protective of schizophrenia (Rees, Kirov et al. 2014). Both 22q11.2 deletion and duplication have elevated prevalence in developmental disorder cohorts (Malhotra and Sebat 2012), but it would be interesting to investigate whether the nature of the neuropsychiatric phenotype differs in duplication carriers.

### 4.8.4 Conclusions

Schizophrenia has been associated with early psychopathology in the general population but a lot remains unknown. 22q11.2DS provides a rare opportunity to examine the early psychopathology that precedes psychosis development. Previous longitudinal studies of children with 22q11.2DS report high psychiatric morbidity. This chapter aimed to examine psychiatric disorder, psychotic phenomenology and ASD symptomatology concurrently and longitudinally. Particular consideration was given to diagnostic stability and change at the level of the individual.

22q11.2DS is one of the strongest genetic risk factors for schizophrenia and findings from this chapter confirm that genetic risk for schizophrenia is also associated with significant psychiatric morbidity before adulthood. This overlap in risk brings into question the utility of current diagnostic criteria and suggests that at least some of the genetic risk for schizophrenia may be non-specific at the level of diagnosis. ADHD, ASD and anxiety disorders were found to be particularly elevated in 22q11.2DS.

There does not appear to be a core neuropsychiatric deficit in 22q11.2DS, as different disorders were found to have their own distinct longitudinal course, with differing stability and persistence. Across early adolescence psychotic phenomena emerged whereas ADHD declined and within anxiety disorders there was considerable variation. There were individuals who unexpectedly gained diagnoses of neurodevelopmental disorders, suggesting diagnoses may be indexing psychopathology that is not neurodevelopmental. The emergence of psychotic experiences in 22q11.2DS was striking and was found to be independent of other psychopathology.

Previous 22q11.2DS study investigators have argued that autism measures are simply indexing other features of 22q11.2DS and this is leading to misdiagnosis. Findings in this chapter suggest the ADI-R is comparatively more independent of other psychopathology compared to the SCQ. This highlights that 22q11.2DS confers risk for ASD as well as schizophrenia and provides evidence against Crespi and Badcock's proposal that autism and psychosis are reciprocal disorders (Crespi and Badcock 2008, Crespi, Summers et al. 2009). However the finding that in children with 22q11.2DS ASD was not associated with psychotic experiences indicates that within 22q11.2DS these are distinct phenotypic manifestations. The presence of ASD in 22q11.2DS has been greatly debated in 22q11.2DS and there should be caution when assessing ASD in 22q11.2DS, given its complex clinical presentation. However, given the findings in this chapter, ASD should be considered by clinicians who support individuals with 22q11.2DS.

The neuropsychiatric phenotype in 22q11.2DS is complex. The next chapter will examine development further by considering cognition.

## **5. Cognitive development in 22q11.2DS**

This chapter aims to examine cognitive development in 22q11.2DS. Characterising cognitive trajectories associated with 22q11.2DS provides an opportunity to uncover endophenotypes associated with psychiatric risk. First I will introduce general issues relating to the consideration of cognitive change. Then I will review cognitive development associated with psychiatric disorder and I will critically assess findings from the 22q11.2DS literature. Finally I will investigate cognitive development within the longitudinal 22q11.2DS ECHO cohort.

### **5.1 Capturing cognitive development**

Behaviour is not a static construct; rather it is dynamic and can be highly variable between and within individuals. First I describe cognitive development in the typical population. Then I discuss the factors that influence variation within individuals when they undergo serial cognitive assessment and the issues that should be considered in longitudinal studies of cognition. I hope to highlight the unique consideration that has to be given to variables derived from test-retest situations.

#### **5.1.1 Cognitive development is relatively stable in the general population**

An individual's performance may fluctuate depending on their sharpness of mind and concentration that day, but generally measures of intelligence have long-term stability (Mackintosh 2011). The correlation between childhood IQ and IQ at age 40 is over 0.70 (McCall 1977) and the correlation of childhood IQ with IQ at age 77 is 0.73 (Deary, Whalley et al. 2000). Measures of executive function, attention and processing speed also show stability across childhood and adolescence, albeit modest in magnitude (Kail and Miller 2006, Polderman, Posthuma et al. 2007, Harms, Zayas et al. 2014).

Stability does not necessarily mean cognitive performance remains constant. IQ is standardised by ranking an individual's ability in relation to others the same age in the typical population. The distinction between absolute ability and age-adjusted ability is important. Absolute ability refers to the raw score on a test, i.e. the number of actual marks received. Age-adjusted ability takes account of the individual's performance relative to their age group and allows comparability of ability across ages.

Absolute intellectual ability changes across the life course with an increase in childhood and decline in old age, which is driven by changes in processing speed and executive function (Mackintosh 2011). It is proposed that increased processing speed triggers a developmental cascade whereby working memory capacity is enhanced which in turn leads to greater intelligence (Fry and Hale 1996). In old age, prevalence of white matter lesions in the brain is correlated with decline in processing speed,

though this is not necessarily causal of decline in intelligence (Rabbitt, Scott et al. 2007). Growth in executive function is associated with brain maturation during childhood and adolescence, particularly in the prefrontal cortex (Gogtay, Giedd et al. 2004) and in old age decline is accompanied by a reduction in prefrontal cortex volume (West 1996, Raz 2000).

Overall, absolute cognitive ability changes across the lifespan and is driven by many dynamic processes but an individual's age-adjusted ranking remains relatively stable.

### **5.1.2 Factors affecting test-retest cognitive performance**

Given the general stability of cognition one would expect the cognitive performance of a typical individual to be the same at initial testing and at retest. However, in reality there are numerous factors affecting an individual's test-retest performance.

#### **1. Variable of interest**

Within research and clinical settings there are many variables that potentially cause cognitive change such as surgery, medical intervention and disease progression (Lineweaver and Chelune 2003). In this chapter the variable of interest is disease progression in 22q11.2DS. Ability to attribute meaningful change to 22q11.2DS will depend on being able to separate out effects associated with 22q11.2DS from other factors.

#### **2. Statistical Errors**

Test-retest scores have unique statistical properties that have to be considered when interpreting findings.

##### **i. Measurement Error**

Cognitive measures are imperfect and test scores will represent both the underlying cognitive construct as well as measurement error. If a measure is less reliable, retest scores are more likely to deviate from the true value. This is an important consideration when interpreting change scores as they are influenced by the measurement error present at both test and retest assessments (Lineweaver and Chelune 2003).

##### **ii. Regression to the Mean**

This concept, referred to by Galton as “reversion to mediocrity” (Galton 1886) is a bias whereby direction of change is related to baseline ability. That is, an individual scoring highly at baseline is more likely to perform worse at retest and conversely an individual with a low score at baseline is more likely to improve at retest. This relationship is not causal, rather it occurs by chance. In a hypothetical situation where an individual’s performance is based purely on chance the probability of a baseline score above the population mean is 0.5 and below the mean is 0.5. Baseline scores would be normally distributed around the mean. If an individual’s baseline score deviates from the group mean then at retest the probability of a score higher or lower than baseline score will not be 0.5. Clinically this could lead to false conclusions, for example a patient undergoing rehabilitation could appear to improve simply due to the effects of regression to the mean. Regression to the mean should be considered when interpreting observed change in research studies (Barnett, van der Pols et al. 2005).

The magnitude of the effect of regression to the mean is dependent on two factors. One factor is the reliability (test-retest correlation) of the cognitive measure, whereby highly reliable measures are less susceptible to the effects of regression to the mean. The other factor is the magnitude of deviation at baseline ability from the population mean. The greater the deviation the greater the chance that retest performance regresses to the mean (Lineweaver and Chelune 2003).

To control for the effects of regression to the mean many studies control for baseline ability, however this introduces bias due to mathematical coupling. This occurs when variables which are mathematically related are included in the same regression model. This violates one of the assumptions of the null hypothesis that variables are not correlated (Tu and Gilthorpe 2012).

### 3. Natural individual differences in test-retest change scores

Cognitive ability is relatively stable and within a group of individuals one would expect the average test-retest change to be minimal. However, strong correlations over time disguise considerable individual differences. For instance a correlation coefficient of 0.7, indicating high stability, still leaves over 50% of variation unexplained. Considerable variation in cognitive development has been reported in adolescents from the typical population with changes ranging from -18 to +21 IQ points over a 3.5 year time gap. The same study found IQ change score



correlates with structural brain changes occurring during adolescence, suggesting IQ change has construct validity and does not simply represent only measurement error (Ramsden, Richardson et al. 2011).

#### 4. Practice effects

A common form of bias is a positive practice effect whereby performance is enhanced because of previous exposure to the testing materials or situation. For some tasks practice effects are expected, for instance the average test-retest change for the Wechsler Memory Scale-III (WMS-III) General Memory Index is 12.15 points (Wechsler 1997). This effect has been attributed to explicit memory for test content, procedural learning of task completion and development of effective strategies (Benedict and Zgaljardic 1998). Other factors may also play a role such as familiarity with the testing procedure, environment and examiner. Conversely an unpleasant experience at initial testing may heighten anxiety at retest and dampen a potential practice effect (Lineweaver and Chelune 2003).

A common misconception is that practice effects can be diminished by using an alternative measure of the same construct. Whilst some carefully designed alternative forms dampen content-specific practice effects (Benedict and Zgaljardic 1998), they do not control for procedural learning or familiarity with testing environment and significant practice effects are still reported (Goldstein, Materson et al. 1990, Benton, Hamsher et al. 1994, Franzen, Paul et al. 1996, Ruff, Light et al. 1996). Alternative forms also introduce other issues such as lower reliability as the test-retest correlation of a single measure will be higher than the correlation between two different measures. This makes the interpretation of test-retest change scores more difficult (Lineweaver and Chelune 2003).

#### 5. Test-retest time gap

The longer the time gap the less test-retest change is expected due to practice effects. Practice effects diminish after 1 year for verbal tasks and 1-2 years for spatial tasks (Rapport, Brines et al. 1997, Canivez and Watkins 1998, McCaffrey, Duff et al. 2000, Canivez and Watkins 2001, Wechsler and Hsiao-pin 2011).

#### 6. Flynn effect

The Flynn effect is a well-documented cohort effect whereby performance on IQ tests by modern cohorts is higher than cohorts from previous generations (Flynn 1984, Flynn 1987, Flynn 2007). IQ performance in a modern cohort will be greater for an old test than a current one. A

recent meta-analysis examined IQ performance across over 100 years from 271 studies and reported an annual increase of 0.28 Full Scale IQ points (Pietschnig and Voracek 2015). This differs across domains with greater effects for fluid and spatial intelligence than crystallized intelligence (0.41, 0.30, 0.21 IQ points annually, respectively). It is important to emphasise that this is a cohort effect which is not the same as IQ increasing with age within individuals. Suspected causes of generational gains in IQ are manifold and include current generations being more accustomed to testing, demographic changes, improvement in nutrition and health and changes in education. It has been pointed out that this does not necessarily mean older generations were less intelligent, but rather the nature of intelligence differed from that captured by IQ tests (Mackintosh 2011).

The Flynn effect has consequences for longitudinal studies that use the same measures over time. It is not that the IQ test has become inappropriate, but rather that the normative sample has. Normative samples are used to standardise raw performance into an age-adjusted IQ score and although they include a wide range of ages the sample is cross-sectional rather than longitudinal. The norms calculated are generation specific, therefore at retest the normative sample will be outdated and IQ performance will be an overestimate (Hiscock 2007).

Revised versions of IQ tests are released partly to overcome the Flynn effect. It is debatable whether longitudinal studies should use new standardised measures as they become available. Administering the same test across time points could lead to overestimation at later time points. Also the Flynn effect differentially affects IQ domains, making it difficult to interpret longitudinal change within domains (Hiscock 2007). However, as discussed before for practice effects, changing measures decreases reliability. One possible solution is to have a control group to see if change is specific to the group of interest, though the nature of the Flynn effect may differ between groups. The Flynn effect is a gradual effect so will particularly impact those studies with larger time gaps.

## 7. Demographic factors

Demographic factors impact on test-retest change. Age has an effect, even though cognitive tests adjust for age. This does not necessarily control for the effect of age on the benefit from practice. In children a positive maturational effect is reported and in the elderly there is a negative effect for test-retest change. Education level, gender and ethnicity also systematically influence test-retest scores (Lineweaver and Chelune 2003). Baseline performance has an effect with those with higher overall ability benefitting more from practice (Rapport, Axelrod et al. 1997, Rapport, Brines et al. 1997).

## 8. Extraneous variables

Differences in test administration and testing environment at time points may have an effect. For instance time of day affects performance in executive function and processing speed with college students having optimal performance in the afternoon and evening (Allen, Grabbe et al. 2008). Group rather than individual assessment has a negative effect (Moser, Schatz et al. 2011). It is important that studies control for these factors.

## 9. Random effects

There will naturally be stochastic error and random, uncontrolled events that influence test-retest performance.

There are many factors that influence test-retest performance. Change scores have unique properties which warrant specific statistical considerations. This highlights the need for specific longitudinal methodology that critically and reliably distinguishes true change attributable to the variable of interest from other potential sources.

### **5.1.3 Longitudinal methodology considerations**

Here I summarise issues of study design, statistical analysis and interpretation that should be considered when examining cognitive change.

#### 1. Having a control group

Many of the factors discussed above, such as practice effects and extraneous variables, can be controlled for by having an appropriate control group. This allows change due to the variable of interest to be distinguished from change due to the study methodology (provided this is kept the same for the two groups). However it should be noted that factors such as a practice effect may differ between the group of interest and the control group.

#### 2. Minimising potential extraneous variables

Controlling extraneous variables across time points minimises the impact on change scores. It is important that there is consistency of the testing environment and protocol across time points.

#### 3. The reliability of the cognitive measure

The reliability of a change score is dependent on the magnitude of the test-retest correlation of the cognitive measure. Change scores from cognitive measures with a high coefficient are considered more reliable as the proportion of variance that represents the underlying cognitive

construct is high and noise is reduced (Lineweaver and Chelune 2003). Test-retest correlation coefficients for cognitive measures are often available in the test manual. On the other hand, a very high correlation across time indicates rank stability, reduced individual differences and so in fact change scores could still be unreliable (Rogosa, Brandt et al. 1982).

#### 4. Utilising the same measures across time points

The use of different versions of a cognitive test across time points decreases the reliability of the cognitive construct being measured. Though if the same measure is used, one should be wary of practice effects and the Flynn effect.

#### 5. Change scores alone are not sufficient for examining true change

Change scores although simple to calculate, are related to many systematic biases. They do not necessarily represent true change and researchers are recommended to use other procedures to critically examine change (Cronbach and Furby 1970, Rogosa, Brandt et al. 1982, Lineweaver and Chelune 2003). Later in this chapter I will discuss approaches which help to capture true change and take account of statistical error.

#### 6. Ecological validity

It is important to emphasise that if cognitive change is shown to have statistical validity this does not necessarily correspond to ecological validity. Change identified as being reliable may or may not correspond to functional or clinical outcomes (Lineweaver and Chelune 2003).

## **5.2 Cognitive trajectories associated with psychiatric disorder**

As previously mentioned 22q11.2DS offers an opportunity to investigate cognitive development associated with psychiatric risk. In this section I discuss what is currently known about cognitive development in idiopathic psychiatric disorder. Within 22q11.2DS research there has been a particular focus on the cognitive pathways to schizophrenia, so first I will cover cognitive development associated with schizophrenia and then briefly cover other psychiatric disorders. Finally I explore to what extent genetic risk for psychiatric disorder is associated with cognitive deficits.

### 5.2.1 Cognitive development in idiopathic schizophrenia

#### 1. Cognitive impairment is a core feature of schizophrenia

Neuropsychological deficits are observed in the majority of schizophrenia patients (Goldberg, Ragland et al. 1990, Palmer, Heaton et al. 1997, Kremen, Seidman et al. 2000, Keefe, Eesley et al. 2005). Cognitive impairment is considered a core feature which impacts functional outcome and is not simply an artefact of medication or a secondary consequence of illness progression (Elvevag and Goldberg 2000, Kremen, Seidman et al. 2000). Cognitive impairment is persistent and enduring as it is present when psychotic phenomenology remits and is not ameliorated by current antipsychotic medications (Reichenberg and Harvey 2007). It has been suggested that cognitive impairment rather than psychotic phenomenology underlies variability in functional outcome and schizophrenia recovery (Elvevag and Goldberg 2000).

Impairment is observed across a range of domains with patients exhibiting approximately a one standard deviation deficit in attention, processing speed, working and episodic memory, executive function and social cognition (Fioravanti, Carlone et al. 2005). Deficits in language and perceptual processes are present but are comparatively smaller in magnitude (Reichenberg and Harvey 2007).

#### 2. Cognitive impairments are premorbid

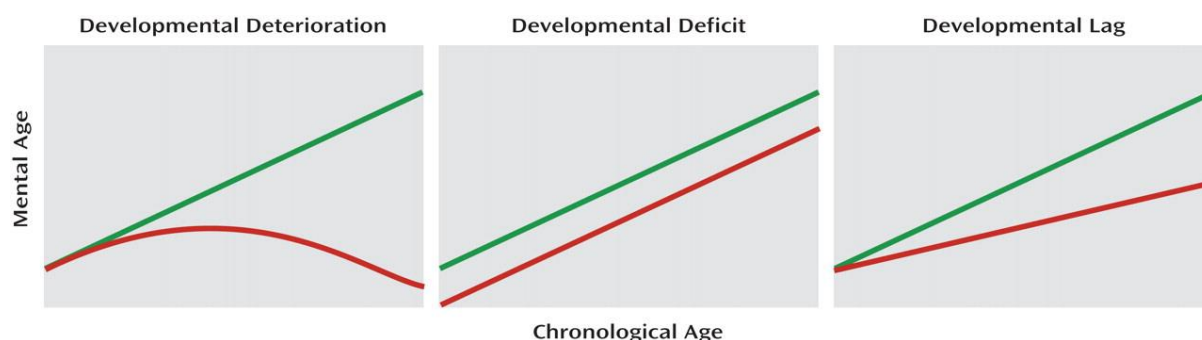
Cognitive impairment in adult schizophrenia is the result of cognitive decline associated with schizophrenia onset, but pre-existing deficits also contribute (Woodberry, Giuliano et al. 2008). When examining cognitive performance over time, the differentiation between a static deficit versus decline in age-adjusted cognitive ability is important. The former refers to no change from the individual's base level and the latter to a relative decline. Currently it is uncertain whether premorbid deficits are static or decline with age. Several studies find no evidence for cognitive decline relative to comparison samples (Lane and Albee 1968, Watt and Lubensky 1976, Jones, Murray et al. 1994, Ott, Spinelli et al. 1998, Cannon, Bearden et al. 2000, Cannon, Caspi et al. 2002), but not all (Reichenberg, Caspi et al. 2010).

Hypotheses for the developmental course of premorbid deficits have been suggested and are illustrated in **Figure 1**. Static deficits characterise the developmental deficit hypothesis (Weinberger 1987), whereby impaired cognition manifests early in development but remains stable with age. Decline in age-adjusted scores could be underpinned by either the developmental deterioration hypothesis or the developmental lag hypothesis and can only be

distinguished by examining raw scores of cognitive ability (see section 5.5.3). The developmental deterioration hypothesis (Jones and Done 1997, Fuller, Nopoulos et al. 2002, Reichenberg, Weiser et al. 2005, Bilder, Reiter et al. 2006) predicts decline in raw cognitive ability whereas the developmental lag hypothesis (Fish, Marcus et al. 1992, Bedwell, Keller et al. 1999, Wood, De Luca et al. 2004) predicts growth in raw cognitive ability, but growth that lags behind the rate of the general population resulting in a decline in age-adjusted score. Conceptualising the developmental nature of cognitive deficits in this way may give insight into the aetiology of schizophrenia. For example if cognitive development follows the developmental deficit hypothesis this could indicate early atypical brain development whereas the developmental deterioration hypothesis may indicate neurodegeneration.

**Figure 1:** Schematic representation of three hypotheses of the developmental course of premorbid deficits in schizophrenia from (Reichenberg, Caspi et al. 2010)

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The green line represents healthy comparison subjects and the red line represents children who later develop schizophrenia.

### 3. Developmental nature may differ by domain

Few studies have examined a range of domains and instead most have focused on global cognitive measures such as IQ. Findings from the Dunedin longitudinal birth cohort study suggest developmental trajectory varies across cognitive domains (Reichenberg, Caspi et al. 2010). These authors report developmental deficits for verbal tasks and developmental lags in nonverbal cognitive domains (processing speed, attention, visual-spatial problem solving ability and working memory) in children who would later develop schizophrenia. There was no evidence of cognitive deterioration. They conclude that both an early static neuropathology and a later developmental lag contribute to the development of schizophrenia.

Cross-sectional studies report greater nonverbal deficits than verbal deficits in childhood, though this difference seems to be driven by a discrepancy in the comparison group rather than

a true discrepancy in children who later develop schizophrenia (Ott, Spinelli et al. 1998, Amminger, Schlogelhofer et al. 2000, Sørensen, Mortensen et al. 2006). A meta-analysis reports no overall difference in the magnitude of verbal and nonverbal deficits (Woodberry, Giuliano et al. 2008). It is important to note that these findings are cross-sectional so do not necessarily conflict with the longitudinal findings of the Dunedin study.

#### 4. Development in different domains is related

The development of cognitive domains does not appear to be entirely independent. The Dunedin study found that children who exhibit verbal developmental deficits are more likely to have non-verbal developmental lags (Reichenberg, Caspi et al. 2010).

#### 5. Specificity of deficits to schizophrenia

An important question is whether premorbid cognitive impairments are specific to schizophrenia or are common to other psychiatric disorders. Deficits in global cognition (IQ) appear nonspecific as they have been linked to increased risk of many psychiatric disorders, particularly depression (van Os, Jones et al. 1997, Zammit, Allebeck et al. 2004, Gale, Deary et al. 2008, Koenen, Moffitt et al. 2009). However, the pattern of deficits across cognitive domains reported in the Dunedin study is specific to schizophrenia and is not observed in children who later develop depression (Reichenberg, Caspi et al. 2010).

#### 6. The importance of having a suitable comparison group

A comparison group is important for critically examining cognitive change, especially for distinguishing the nature of cognitive development in terms of the hypotheses described earlier. There are longitudinal studies in the schizophrenia literature where interpretation has been altered by the comparison group. Two studies report cognitive decline in individuals who later develop schizophrenia but the rate of decline was similar to that in controls (Watt and Lubensky 1976, Jones, Murray et al. 1994).

The nature of the comparison group is an important consideration. A study by Lane and Albee of the educational records of schizophrenia inpatients initially found cognitive decline in the schizophrenia group but not in other children within the same school system (Lane and Albee 1963). 5 years later the authors re-examined the data due to concerns that the groups were not socioeconomically matched. They reported cognitive decline was non-specific to the schizophrenia group as it was present in siblings of the schizophrenia group and in controls matched for school and IQ (Lane and Albee 1968). Additionally, when cognitive measures were

standardised in a larger group of controls cognitive decline was not present in the schizophrenia group or in any of the control groups.

## **5.2.2 Cognitive development in other psychiatric disorders**

### **1. Mood disorder**

Low premorbid IQ is a risk factor for depression (Zammit, Allebeck et al. 2004) and longitudinal findings from the Dunedin cohort suggest developmental deficits across several domains and a slight developmental lag in arithmetic in those who later develop depression (Reichenberg, Caspi et al. 2010), albeit a smaller effect size in comparison to those who develop schizophrenia. Aetiology may differ amongst mood disorders as premorbid deficits in IQ are associated with development of depression but not bipolar disorder (Zammit, Allebeck et al. 2004). For bipolar disorder there is indication that those with excellent academic achievement are at greater risk of developing the disorder (MacCabe, Lambe et al. 2010). Furthermore, individuals with bipolar disorder are overrepresented in creative professions whereas those with depression do not differ from controls (Kyaga, Lichtenstein et al. 2011).

### **2. Anxiety Disorders**

There have been relatively fewer high-risk studies of anxiety. One study found however, that children who are at high risk of anxiety due to having an affected sibling are reported to have deficits in paired associative learning but also higher verbal IQ compared to controls (Merikangas, Avenevoli et al. 1999).

### **3. Early developmental disorders**

There are few prospective studies of ASD and ADHD due to the early developmental onset in these disorders. A longitudinal study of infants with a family history of ASD reported that attentional deficits are precursors for later social and communication difficulties (Bedford, Elsabbagh et al. 2012). For ADHD, it has been suggested that deficits in metacognition and subclinical attention deficits may be precursors to the disorder (Perricone, Morales et al. 2013).

## **5.2.3 Cognitive development in individuals at genetic risk for psychiatric disorder**

There is increasing evidence that risk variants for psychiatric disorder overlap with those for cognitive deficits.



## 1. Psychiatric-risk CNVs

CNVs which confer risk for psychiatric disorder also confer risk for intellectual disability (Owen, O'Donovan et al. 2011, Kirov, Rees et al. 2015). The Icelandic DeCODE genetic population cohort found that psychiatric-risk CNV carriers who had not been diagnosed with psychiatric disorder still exhibited cognitive deficits (Stefansson, Meyer-Lindenberg et al. 2014). This highlights that cognitive deficits in CNV carriers are not necessarily secondary consequences of psychiatric disorder.

## 2. Polygenic risk

There is overlap in the genes that contribute to psychiatric disorder and cognitive ability. From genome wide association studies of psychiatric disorder, each single nucleotide polymorphism (SNP) can be attributed a risk for the psychiatric disorder being investigated. Then in non-clinical cohorts individuals can be genotyped and their polygenic risk calculated by summing risk across SNPs. This polygenic risk score can then be associated with cognitive measures administered in the non-clinical cohort. Conversely, genome-wide association studies of cognition in non-clinical cohorts can be used to generate polygenic scores of cognitive ability in psychiatric and control cohorts.

One study reports both that polygenic risk score for schizophrenia is associated with lower cognitive ability in a non-clinical cohort and that polygenic score for cognitive ability is lower in schizophrenia cohorts compared to controls (Lencz, Knowles et al. 2014).

Interestingly, findings from the non-clinical Lothian Birth Cohort suggest that schizophrenia polygenic risk score does not predict childhood cognitive ability, but rather cognitive decline (McIntosh, Gow et al. 2013). IQ scores from age 11 and 70 were analysed so it is uncertain whether this association is driven by development across a specific life stage or the whole life span.

Polygenic risk for ADHD differentially predicts cognitive domains with reports of negative associations for IQ and working memory but not inhibitory control or emotion recognition (Martin, O'Donovan et al. 2015).

It should be noted that the amount of trait variance explained by polygenic risk score is currently low but this could reflect that current studies are underpowered.

## 5.3 Cognition in 22q11.2DS

It is important to make a distinction between the examination of cognitive development associated with 22q11.2DS and cognitive development associated with psychopathology in 22q11.2DS. This chapter will address the former and the next chapter the latter.

### 5.3.1 Cognitive development in 22q11.2DS

In section 1.2.2 I discussed how cognitive deficits in 22q11.2DS are prevalent across many domains and most but not all longitudinal studies report cognitive decline. It is clear from cross-sectional studies of children with 22q11.2DS that deficits are premorbid (Swillen, Devriendt et al. 1997, Woodin, Wang et al. 2001, De Smedt, Devriendt et al. 2007, Gur, Yi et al. 2014, Niarchou, Zammit et al. 2014), with one study reporting cognitive deficits in children aged 13–63 months (Gerdes, Solot et al. 2001). However it remains uncertain whether there is premorbid longitudinal decline in 22q11.2DS.

Deficits in different cognitive domains appear to be independent of each other in 22q11.2DS (Niarchou, Zammit et al. 2014). Longitudinal evidence from one study suggests that development across domains is related, however, as decline in two or more IQ subdomains predicts decline in the remaining IQ subdomains (Duijff, Klaassen et al. 2012). Though it is currently unclear to what extent this is true for cognitive measures other than IQ.

### 5.3.2 Limitations of 22q11.2DS studies

**Table 20** describes 22q11.2DS studies that have examined longitudinal change in cognition. Below I discuss the limitations of these studies.

#### 1. Lack of comparison group

Only five studies have included a comparison group, which is needed to control for extraneous variables and methodological artefacts. As mentioned in section 5.2.1, there are cases in the schizophrenia literature where availability of a comparison group has influenced interpretation.

Out of the five studies with a comparison group, one study recruited children with idiopathic developmental delay who were IQ matched as controls (Gothelf, Eliez et al. 2005), three studies recruited typically developing community controls (Gothelf, Penniman et al. 2007, Schaefer, Debbané et al. 2009, Hooper, Curtiss et al. 2013) and one study assessed both community controls and unaffected siblings (Antshel, Shprintzen et al. 2010).

Each type of control group has its benefits and limitations. IQ matched developmental delay controls allow cognitive development specific to 22q11.2DS to be distinguished from development related to low IQ. Contrasting development in 22q11.2DS to that in typically developing community controls allows the magnitude of the impact of 22q11.2DS to be characterised. It is worth noting here, however, that the Lane and Albee schizophrenia study mentioned in section 5.2.1 found utilising community controls led to misleading conclusions because they were not necessarily matched for socioeconomic background (Lane and Albee 1968). Comparison to unaffected siblings allows for family specific genetic and environmental factors to be controlled for. However unaffected siblings may not be truly representative of the general population as they have developed in a family with a child with a genetic syndrome. One study that included both community and unaffected sibling controls found increased mood disorder with age in the unaffected siblings but not the community controls (Antshel, Shprintzen et al. 2010). To some extent the suitability of a control group depends on the hypothesis under examination and the variables the investigator wishes to control for.

## 2. Different IQ test versions

No longitudinal 22q11.2DS study to date has reported administering the same IQ test across the whole sample and across time points. Sometimes this is the case because the sample includes data collected from various sites (Gothelf, Schneider et al. 2013, Vorstman, Breetvelt et al. 2015). On the one hand performance on different IQ measures does highly correlate, but the use of different measures across time points does decrease reliability (Lineweaver and Chelune 2003).

In many studies Wechsler scales are used for the whole sample but different versions for children and adults. Comparative studies of Wechsler scales report that performance on the adult test version is inflated relative to the child version, with an effect of between two to five IQ points (Strauss, Sherman et al. 2006), and this disparity is greater in individuals with intellectual disabilities (Spitz 1988, Gordon, Duff et al. 2010). One 22q11.2DS study adjusted for this by deducting five IQ points from their adult scores (Antshel, Shprintzen et al. 2010). Another study argues that this means the decline reported in their sample is actually an underestimate (Vorstman, Breetvelt et al. 2015). However, it is not necessarily justified to extrapolate that the magnitude and direction of disparity between measures is the same in 22q11.2DS as the general population. Indeed one study reports decline rather than an increase in the group that changed from child to adult IQ test version and the magnitude of decline was greater in this group than in the rest of the sample (Gothelf, Schneider et al. 2013).

The use of different IQ test versions within a study means raw scores cannot be examined across the whole sample. This along with the lack of comparison groups has meant 22q11.2DS studies have not been able to characterise cognitive development using hypotheses described in the schizophrenia literature (section 5.2.1). Only one 22q11.2DS study has examined raw scores (Duijff, Klaassen et al. 2012) in a subsample where 29 out of 69 participants were assessed using the same measure (Duijff, Klaassen et al. 2012).

### 3. Focus exclusively on IQ

Seven of the ten studies have focused exclusively on IQ. As different neural processes underlie performance on different neuropsychological tests, it is important that other cognitive processes such as executive function and attention are examined. In children who later develop schizophrenia there is differential development in cognitive domains (Reichenberg, Caspi et al. 2010) and in other psychiatric disorders development of IQ can be typical while deficits are present in other cognitive domains (see section 5.2.2.). Therefore focusing exclusively on IQ in 22q11.2DS will not give a full picture of the developmental processes occurring. Though it is worth noting that some studies which have exclusively used IQ have explored the differential development of IQ domains such as verbal and performance IQ and subdomains such as processing speed, arithmetic and comprehension (Duijff, Klaassen et al. 2012, Duijff, Klaassen et al. 2013, Gothelf, Schneider et al. 2013, Vorstman, Breetvelt et al. 2015).

### 4. Inability to distinguish whether change is premorbid or due to psychosis onset

There is only one study where it is clear that cognitive development is premorbid as cognition and psychotic disorder were assessed concurrently and no individuals met criteria for a psychotic disorder at either time point (Antshel, Shprintzen et al. 2010).

One study created an IQ growth chart from 829 individuals and although assessment of cognition and psychotic disorder was not concurrent in this study the growth chart shows decline occurs at a greater rate early in development, suggesting decline is premorbid and not necessarily due to disorder onset (Vorstman, Breetvelt et al. 2015).

Two studies did not assess psychosis so it is unclear whether cognitive development reflects premorbid development. However one of these studies did examine early childhood (ages 5.5, 7.5 and 9.5) so is likely to reflect premorbid development.

In six of the studies individuals had already developed psychotic disorder so it is unclear whether cognitive development reflects changes in the premorbid period or disorder onset (Gothelf, Eliez

et al. 2005, Gothelf, Penniman et al. 2007, Schaer, Debbané et al. 2009, Gothelf, Schneider et al. 2013, Hooper, Curtiss et al. 2013, Schneider, Schaer et al. 2014). This is partly due to the wide age ranges in these studies or because they examined later developmental periods. In one sense the presence of psychotic disorder in 22q11.2DS adolescents is to be expected and therefore makes it difficult to capture longitudinal development before disorder onset. There could also be differential interpretation and application of psychotic disorder diagnosis amongst 22q11.2DS studies as the Antshel, Shprintzen et al. 2010 study did include individuals in late adolescence, yet no individuals met criteria for psychotic disorder. Overall there is a need for 22q11.2DS studies to delineate the developmental processes associated with the different stages of psychosis development.

5. Variability in cognitive development is not always considered

22q11.2DS studies have related variability in cognitive development to psychopathology (this will be discussed in greater depth in Chapter 6) but only two studies have attempted to characterise variability in cognitive development. One study reports that a third of 22q11.2DS children exhibit deterioration in raw score (Duijff, Klaassen et al. 2012). Another study has created an IQ growth chart with percentile bands (Vorstman, Breetvelt et al. 2015). However with neither study including a comparison group it is uncertain to what extent this differs from the general population.

**Table 20:** Characteristics of longitudinal 22q11.2DS studies assessing cognition

Study	N (cases)	Baseline age	Follow-up age	Comparison group	Same IQ test across whole sample and time	Cognitive measure other than IQ?	Finding	IQ change per year
(Gothelf, Eliez et al. 2005)	24	13.3±3.7	18.1±3.4	Yes	No	No	<b>IQ decline</b>	
(Gothelf, Penniman et al. 2007)	19	13.1±4.0	17.9±3.8	Yes	No	No	<b>IQ decline</b>	22q11.2DS = 0.96 Controls = +0.73
(Schaer, Debbané et al. 2009)	32	11.4±3.5	14.5±3.6	Yes	Version not reported	No	<b>No IQ change</b>	22q11.2DS = +0.29 Controls = -1.38
(Antshel, Shprintzen et al. 2010)	70	11.9±2.2	15.0±1.9	Yes	No	Yes	<b>Decline:</b> IQ, processing speed, distractibility, verbal learning and mathematics ability <b>Increase:</b> reading ability and executive function	
(Duijff, Klaassen et al. 2012)	69	5.5±0.2	T2 = 7.5±0.2 T3 = 9.5±0.1	No	No	No	<b>IQ decline</b>	-2.43
(Duijff, Klaassen et al. 2013)	53	9.5±0.4	15.3±0.6	No	No	No	<b>IQ decline</b>	-1.02
(Gothelf, Schneider et al. 2013)	Children = 49 Adolescents = 46 Adults = 30	Children = 8.4±1.8 Adolescents = 14.0±1.9 Adults = 27.6±7.2	Children = 12.4±2.5 Adolescents = 18.3±2.9 Adults = 32.3±7.4	No	No	No	<b>IQ decline</b>	Children = -1.27 Adolescents = -0.98 Adults = -0.43
(Hooper, Curtiss et al. 2013)	42	10.05±2.49	13.59±2.47	Yes	No	Yes	<b>No IQ change</b> <b>Slower gains in attention</b>	-0.3
(Schneider, Schaefer et al. 2014)	56	16.6±6.73	20.5±6.84	No	No	Yes	<b>IQ and memory decline</b>	
(Vorstman, Breetvelt et al. 2015)	Created growth charts from 829 individuals aged 8 - 24 of which 440 assessed on ≥2 occasions			No	No	No	<b>IQ decline</b>	-0.31

## 5.4 Aims

In this chapter I present cognitive findings from the ECHO study 22q11.2DS cohort. This cohort has several features that address limitations of previous studies of 22q11.2DS:

- i. A comparison group of unaffected siblings were assessed, allowing cognitive development in 22q11.2DS to be contrasted to controls.
- ii. The same cognitive measures were administered to all participants at both waves of assessment.
- iii. Cognitive measures other than IQ were administered.
- iv. No individual has developed psychotic disorder (see chapter 4), thus findings will reflect premorbid development.

The specific aims of analysis in this chapter are:

1. Examine the magnitude and stability of deficits in 22q11.2DS.
2. Characterise premorbid cognitive development in terms of the developmental deficit, developmental deterioration and developmental lag hypotheses.
3. Examine variability in change by:
  - a) Comparing the distribution of cognitive change in 22q11.2DS children with that in controls.
  - b) Reliably categorising individuals into improving, stable and declining groups based on their age-adjusted cognitive performance.
  - c) Categorising individuals based on their raw scores to examine the prevalence of cognitive deterioration.
4. Investigate whether cognitive development in different domains is related.

## 5.5 Methodology

Sample description and assessment details have been presented in Chapter 3. Cognitive test-retest data was available for 64 children with 22q11.2DS and 27 controls. Missing data occurred because in some cases psychiatric assessment was conducted by video call with the primary carer for geographical reasons so the cognitive measures could not be administered (22q11.2DS n=5, controls

n=2) and one 22q11.2DS individual could not complete any of the cognitive tests. Missingness was variable across cognitive measures (reported in **Table 22**).

### **5.5.1 Transformation of raw scores to age-adjusted standardised scores.**

Raw scores reflect absolute performance on the cognitive measure. Standardised scores allow comparison of ability across ages and reflect the extent an individual's ability deviates from the general population. Cognitive measures often have their own standardisation procedures, with one of the steps often including an adjustment for age. Here I document the transformations that occur when generating standardised scores for the WASI, WCST and CANTAB.

#### **1. WASI**

Each individual receives a raw score for each of the four IQ subtests completed. These raw scores are converted to age-adjusted t-scores according to the WASI manual normative sample tables (Wechsler 1999). The transformation is such that the resulting distribution has a mean of 50 and a standard deviation of 10.

The final FSIQ score is the result of transforming the additive total of the age-adjusted t-scores from the four subtests according to the WASI manual. VIQ is the result of transforming the additive total of the Vocabulary and Similarities subtests. PIQ is the result of transforming the additive total of the Block Design and Matrix Reasoning subtests. The transformation is such that the resulting FSIQ, VIQ and PIQ score distributions have a mean of 100 and a standard deviation of 15. For all of the above, a higher score reflects greater performance.

#### **2. WCST**

The number of perseverative errors is calculated from the WCST transcripts according to the WCST manual (Heaton, Chelune et al. 1993). A higher raw score reflects poorer performance. The raw score is transformed to an age-adjusted standardised score according to the WCST normative sample tables. The transformation is such that the resulting distribution has a mean of 100 and a standard deviation of 15. A higher score reflects greater performance.

#### **3. CANTAB**

For MTS, RVP, and SOC a higher raw score reflects better performance, whilst for SWM and RTI a higher raw score indicates poorer performance. The raw scores for RTI, RVP, SOC and SWM are transformed to an age-adjusted standardised score according to the CANTAB normative sample tables. CANTAB standardised scores are calculated as a z-score, i.e. a mean of 0 and a standard deviation of 1. A higher score reflects greater performance.



In my analyses I will use both standardised scores and raw scores depending on the question being addressed. Analysis of MTS performance will be based on just raw scores as standardisation was not possible as there is no normative data for this measure.

### **5.5.2 Aim 1: Examine the stability and magnitude of deficits in 22q11.2DS**

To examine stability, test-retest correlations for standardised cognitive performance were calculated separately for 22q11.2DS and controls. To examine the average deficit across waves, repeated measures ANOVA was conducted and the mean difference in performance between 22q11.2DS children and controls was estimated. The mean deficit was then standardised to a z-score representing 22q11.2DS cognitive performance relative to controls.

### **5.5.3 Aim 2: Characterise premorbid cognitive development in terms of the developmental deficit, developmental deterioration and developmental lag hypotheses.**

The ECHO longitudinal sample can be conceptualised as an accelerated longitudinal study. Individuals have been assessed at two waves, but the age of assessment is variable at each wave. Linear mixed modelling was used to investigate the effect of age rather than wave on cognitive performance. This approach allowed trajectories to be fitted across the age range of the whole sample (age range 6 -17 years), beyond the mean age at each wave. It is possible to estimate the average change in cognitive score per year for children with 22q11.2DS and controls.

A trajectory of cognitive performance by age was fitted for 22q11.2DS and controls whilst taking account of collinearity as well as familial clustering. The model included age, deletion status and the interaction between age and deletion status as fixed effects, familial clustering was controlled for by including family number as a random effect and repeated effects were included. This was conducted for both raw scores and standardised scores. Results from these analyses were used to answer the following questions.

#### **1. Does absolute cognitive ability change with age?**

In typically developing children, absolute cognitive performance increases with age. However it is important to test whether this true for both children with 22q11.2DS and controls, indeed deterioration in raw score may occur in children with 22q11.2DS. Linear mixed modelling was conducted on raw cognitive scores to investigate the effect age has on raw cognitive score. Each cognitive measure was classified as either showing an increase or decrease with age.

2. Does standardised cognitive ability change with age?

In typically developing children one would expect cognitive ability standardised for age to not have a relationship with age. Linear mixed modelling was conducted on standardised scores for children with 22q11.2DS and controls to reveal whether there was deviation in cognitive development. Significant trajectories were classified as showing improvement if positive and as decline if negative. This approach did not control for potential methodological factors.

Investigating the interaction between deletion status and age on standardised cognitive score reveals whether cognitive development in 22q11.2DS deviates from controls. Interaction slope parameter terms from linear mixed modelling provide a measure of the extent to which cognitive development in 22q11.2DS diverged from controls. An interaction with a positive sign indicates maturation and a negative sign a worsening deficit. This approach helped control for potential methodological factors that may of been causing deviation in both groups.

3. Which model best describes cognitive development in 22q11.2DS?

Development was classified using the following criteria. See section 5.2.1 for an introduction to the following models of cognitive development.

*Developmental deficit.* Indicated by the absence of an interaction between deletion status and age, and increased raw score with age in both children with 22q11.2DS and controls.

*Developmental lag.* Indicated by a worsening deficit in 22q11.2DS relative to controls (negative interaction) and increased raw score with age in both children with 22q11.2DS and controls.

*Developmental deterioration.* Indicated by a worsening deficit in 22q11.2DS relative to controls (negative interaction) and decreased raw score with age in children with 22q11.2DS but not controls.

*No strong evidence.* If there was no relationship of raw score with age in controls, this suggested there was no evidence of a developmental relationship in controls or alternatively there was not the power to detect a relationship. To be cautious it was decided it would not be appropriate to contrast 22q11.2DS cognitive development to controls in this situation.

Raw scores were not available for composite scores (VIQ, PIQ and FSIQ) and it would of not been correct to total the raw scores of the subtests that comprise each composite score as each is scaled differently. However direction of change of absolute ability was able to be inferred if the raw score of all comprising subtests changed in the same direction.

#### **5.5.4 Aim 3a: Comparing the variance of cognitive change in 22q11.2DS children with that in controls.**

Levene's test for equality of variance was conducted on standardised scores to compare the variance of cognitive change in 22q11.2DS children to the variance of change in controls. For MTS, raw scores were analysed.

#### **5.5.5 Aim 3b: Reliably categorising individuals into improving, stable and declining groups based on their age-adjusted cognitive performance**

Within children with 22q11.2DS and controls change was categorised (wave 2 - wave 1) for all standardised cognitive measures. To distinguish true change from noise, cut-offs were specified, based on reliable change indices (RCI) (Lineweaver and Chelune 2003). This approach took account of the measurement error at each wave of assessment and regression to the mean.

The following formula was used:

$$RCI = \pm 1.96 SE_p$$

where

$$SE_p = SD_2 * (1 - r_{12}^2)^{1/2}$$

and

$SE_p$  = standard error of prediction

$SD_2$  = standard deviation of observed retest

$r_{12}^2$  = the test-retest reliability coefficient

$SE_p$  describes the spread of the distribution of change scores that would be expected to occur in the absence of true underlying change. 95% of change scores would be expected to fall between  $\pm 1.96 SE_p$  from the expected mean difference, therefore any change scores that lie outside this range represent reliable change and would be classified as improving or declining depending on direction of effect.

$r_{12}^2$  values were provided by the WASI manual (Wechsler 1999), WCST manual (Heaton, Chelune et al. 1993) and current literature for the CANTAB (Harrison, Iddon et al. 2006). However it should be noted that CANTAB do not provide values specific to children and adolescents.  $SD_2$  was provided by

the WASI manual but was not available for WCST and CANTAB so the population standard deviation was used instead for these measures. See **Table 21** for  $r^2_{12}$ ,  $SD_2$  and RCI values.

**Table 21:** Reliable Change Indices for cognitive assessments

Cognitive Measure		$r^2_{12}$	$SD_2$	95% RCI
<b>WASI</b>	FSIQ	0.93	14.17	±10.2
	VIQ	0.92	13.58	±10.4
	PIQ	0.88	14.92	±13.9
<b>WASI subtest</b>	Vocabulary	0.85	9.57	±9.9
	Similarities	0.86	8.55	±8.6
	Block design	0.81	10.46	±12.0
	Matrix Reasoning	0.77	9.6	±12.0
<b>CANTAB</b>	RTI	0.57	1	±1.6
	RVP	0.64	1	±1.5
	SWM	0.70	1	±1.4
	SOC	0.64	1	±1.5
<b>WCST</b>	perseverative errors	0.52	15	±25.1

Subsequently the sample was subdivided into those who were improving, stable or declining. To focus on cognitive decline in 22q11.2DS, the declining group was compared to the combined group of those who were either stable or improving. Fisher's exact test was conducted to test whether deletion status was associated with cognitive decline.

### **5.5.6 Aim 3c: Categorising individuals based on their raw scores to examine the prevalence of cognitive deterioration.**

To examine cognitive deterioration wave 1 raw scores were subtracted from wave 2 raw scores for all the cognitive measures. For RTI, SWM and WCST the sign of the change scores was reversed as a lower raw score reflects better performance for these tasks. Fisher's exact test was conducted to investigate whether deterioration compared to one's earlier performance is associated with deletion status.

### **5.5.7 Aim 4: Investigate whether cognitive development in different domains is related.**

When establishing change over time, it is important to take into account mean level at each wave of assessment. Principal Components Analysis was conducted on 22q11.2DS test-retest standardised

cognitive scores. For MTS, raw scores were analysed. This identified two factors  $s_{\text{average}}$  and  $s_{\text{change}}$  where  $s_{\text{average}}$  represents the average cognitive performance across both waves and  $s_{\text{change}}$  cognitive change (Niarchou, Zammit et al. 2013). To investigate whether the development in different cognitive domains was related, separate correlation matrices were produced for the  $s_{\text{average}}$  and  $s_{\text{change}}$  components for cognitive measures.

## 5.6 Results

### 5.6.1 Aim 1: Examine the magnitude and stability of deficits in 22q11.2DS.

**Table 22** displays cognitive test-retest correlations for both 22q11.2DS and controls. Metrics derived from the WASI had a higher reliability than other cognitive measures. This is consistent with values reported in the test manuals (see **Table 21**). Overall there was a trend for higher correlations in 22q11.2DS individuals than controls.

Children with 22q11.2DS had significant deficits across all cognitive measures compared to controls. There was approximately a 2 SD deficit in all the IQ metrics ( $p < 0.001$ ), attention (RVP,  $p < 0.001$ ) and set shifting ability (WCST,  $p < 0.001$ ) in contrast to approximately a 1 SD deficit in processing speed (RTI,  $p = 0.011$ ), spatial planning (SOC,  $p < 0.001$ ) and spatial working memory (SWM,  $p < 0.001$ ) (see **Table 23** and **Figure 2**).

**Table 22:** Test-retest correlations of cognitive measures in 22q11.2DS children and controls

		22q11.2DS			Control		
Cognitive measure		n	r	p	n	r	p
<b>WASI</b>	FSIQ	62	0.832	<0.001	27	0.751	<0.001
	VIQ	62	0.728	<0.001	27	0.628	<0.001
	PIQ	63	0.904	<0.001	27	0.829	<0.001
<b>WASI subtest</b>	Vocabulary	62	0.726	<0.001	27	0.749	<0.001
	Similarities	62	0.593	<0.001	27	0.252	0.205
	Block design	63	0.855	<0.001	27	0.783	<0.001
	Matrix reasoning	63	0.713	<0.001	27	0.724	<0.001
<b>CANTAB</b>	MTS	60	0.548	<0.001	27	0.235	0.238
	RTI	60	0.411	0.001	26	0.182	0.373
	RVP	54	0.544	<0.001	26	0.183	0.371
	SOC	58	0.323	0.013	26	0.231	0.257
	SWM	63	0.520	<0.001	27	0.521	0.005
<b>WCST</b>	Perseverative errors	61	0.350	0.004	27	0.238	0.232

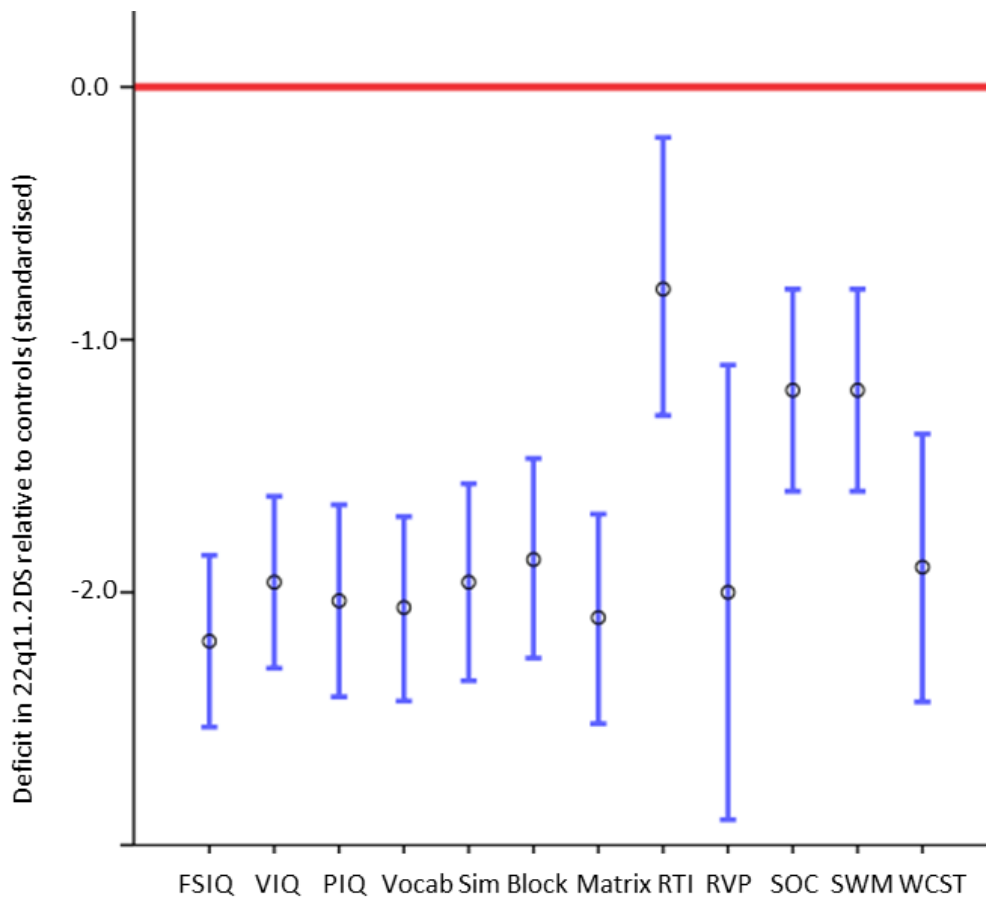
**Table 23:** Mean cognitive performance for 22q11.2DS and controls by wave and mean deficit in 22q11.2DS

Mean deficit is the mean cognitive performance of children with 22q11.2DS subtracted from the mean performance of controls. Standardised mean deficit is the number of SD 22q11.2DS children are below controls. These standardised values are plotted in **Figure 2**.

Cognitive measure	22q11.2DS Mean (SD)				Controls Mean (SD)				Contrast: Controls - 22q11.2DS			
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	95% CI lower bound	95% CI upper bound	Standardised mean deficit	p
<b>WASI</b>												
FSIQ	74.4 (11.1)	72.0 (12.9)	107.2 (12.7)	105.6 (10.8)					-38.4	-28.0	-2.2	<0.001
VIQ	75.7 (12.3)	73.0 (12.9)	106.7 (13.7)	101.7 (9.8)					-35.1	-24.6	-2.0	<0.001
PIQ	78.0 (11.2)	75.5 (13.7)	106.2 (13.9)	108.5 (12.8)					-36.3	-25.0	-2.0	<0.001
<b>WASI subtest</b>												
Vocabulary	30.2 (8.4)	28.8 (8.7)	51.4 (9.5)	48.8 (7.6)					-24.2	-16.9	-2.1	<0.001
Similarities	35.8 (10.3)	34.1 (10.7)	56.1 (7.8)	53.3 (7.0)					-23.7	-15.8	-2.0	<0.001
Block design	36.8 (8.0)	35.1 (9.2)	53.6 (10.4)	55.3 (9.6)					-22.6	-14.7	-1.9	<0.001
Matrix reasoning	34.0 (9.2)	32.5 (11.4)	53.9 (8.8)	54.7 (7.7)					-25.2	-16.9	-2.1	<0.001
<b>CANTAB</b>												
MTS	39.8 (7.0)	42.3 (6.5)	44.6 (3.1)	46.2 (1.8)					-6.7	-2.0	-	<0.001
RTI	-0.3 (2.1)	-0.1 (1.3)	0.5 (0.8)	0.6 (0.7)					-1.3	-0.2	-0.8	0.011
RVP	-2.4 (2.3)	-1.7 (2.7)	-0.4 (1.0)	0.3 (0.8)					-2.9	-1.1	-2.0	<0.001
SOC	-1.1 (0.9)	-1.3 (1.1)	-0.1 (0.8)	0.1 (1.1)					-1.6	-0.8	-1.2	<0.001
SWM	-1.1 (0.9)	-1.3 (1.2)	-0.1 (1.0)	0.0 (1.1)					-1.6	-0.8	-1.2	<0.001
<b>WCST</b>												
Perseverative errors	89.7 (22.6)	95.9 (19.9)	116.4 (21.3)	126.3 (20.3)					-36.5	-20.6	-1.9	<0.001

**Figure 2:** Visualisation of Table 23, cognitive deficits in 22q11.2DS relative to controls

Error bars represent 95% CI



**5.6.2 Aim 2: Characterise premorbid cognitive development in terms of the developmental deficit, developmental deterioration and developmental lag hypotheses.**

**Table 24** displays the findings from the linear mixed modelling. Change in raw score is displayed followed by standardised change for children with 22q11.2DS and controls, then change in 22q11.2DS relative to controls and the final column describes the model that best describes cognitive development.

Children with 22q11.2DS showed a decline in FSIQ of -0.98 IQ points per year ( $p=0.002$ , 95% CI - 1.61,-0.36). Though there was no evidence of a developmental deterioration as raw scores for all the subtests increased with age. As expected, there was no relationship between IQ and age in controls ( $p=0.305$ ). However when cognitive development was directly compared there was not strong evidence that the rate of decline in 22q11.2DS differed from controls ( $p=0.231$ ) and therefore development of IQ in 22q11.2DS fitted a developmental deficit model (see **Figure 3** for visualisation).



Clearer patterns of development were observed when VIQ and PIQ components of IQ were considered separately (see **Figure 4** and **Figure 5**).

Development in VIQ fitted a developmental deficit model because although there was a decline of -1.06 VIQ points per year in 22q11.2DS ( $p=0.005$ ) a similar decline was also present in controls ( $p=0.002$ ) and there was no strong evidence that the trajectories differed in slope ( $p=0.337$ ).

Development of PIQ fitted a developmental lag model. 22q11.2DS children had a worsening deficit of -1.90 points per year relative to controls ( $p<0.001$ ). Examination of the subtests that comprise PIQ indicated this was driven by both block design ( $p=0.001$ ) and matrix reasoning performance ( $p=0.035$ ). The raw scores of both subtests increased with age (block design  $p<0.001$ , matrix reasoning  $p<0.001$ ), confirming that a developmental lag rather than developmental deterioration underlies the worsening deficit in PIQ.

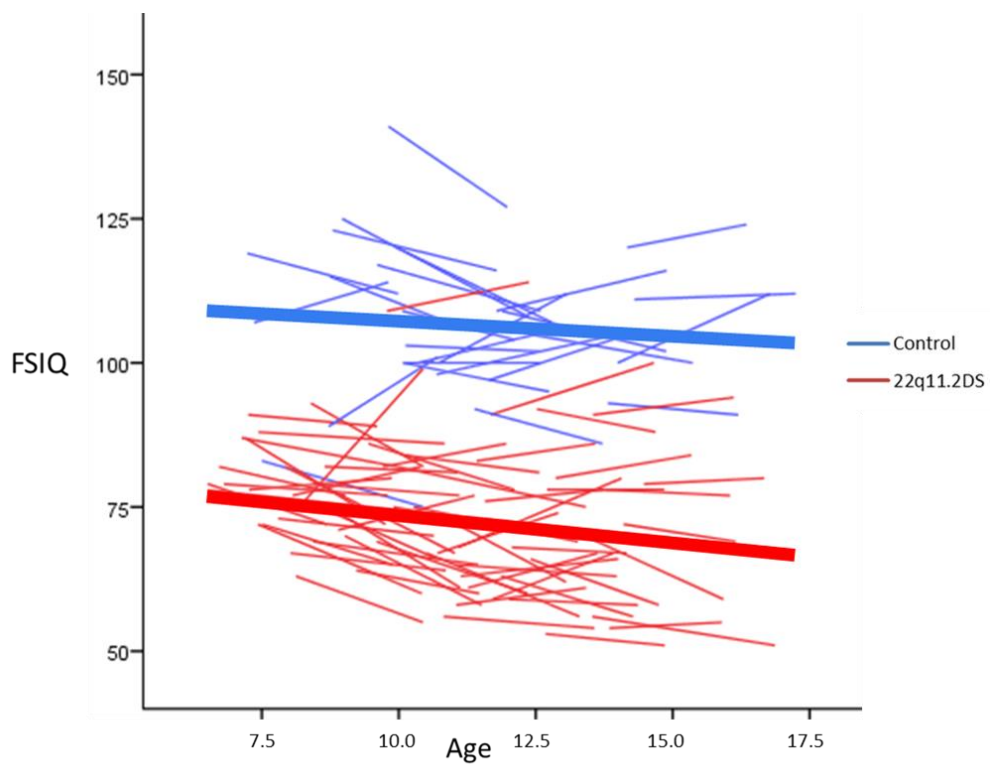
Development of spatial planning (SOC), spatial working memory (SWM) and sustained attention (RVP) fitted a developmental deficit model. For processing speed (RTI) and set shifting ability (WCST) developmental models were not applied to the data as there was not strong evidence that raw score had a relationship with age in controls. Children with 22q11.2DS improved in processing speed (RTI,  $p=0.011$ ), and sustained attention (RVP,  $p=0.001$ ). Development of executive function differed across subdomain. Set shifting ability improved (WCST, 0.006), spatial working memory declined (SWM,  $p=0.033$ ) and there was no relationship with age for spatial planning (SOC,  $p=0.656$ ).

**Table 24:** Cognitive development in 22q11.2DS relative to controls: linear mixed modelling

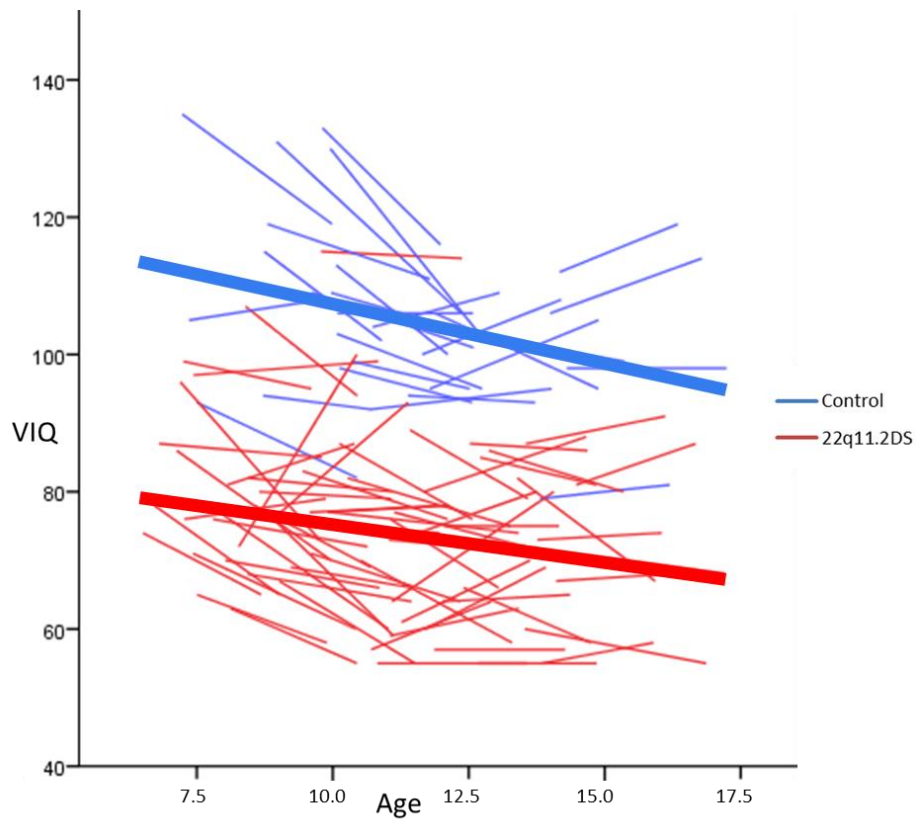
# inferred from subtest raw score change

Cognitive measure	Change in raw cognitive		22q11.2DS standardised cognitive change		Controls standardised cognitive change		22q11.2DS relative to controls		Model of change			
	22q11.2DS (p-value)	Controls (p-value)	cognitive score / year (95% CI)	p-value	Change	cognitive score / year (95% CI)	p-value	Change		cognitive score divergence / year (95% CI)	p-value	Change in 22q11.2DS relative to controls
FSIQ	Increase # (<0.001)	Increase #	-0.98 (-1.61,-0.36) IQ points	0.002	Decline	-0.47 (-1.38,0.44) IQ points	0.305	No strong evidence	-0.51 (-1.61,0.60) IQ points	0.231	No strong evidence	Developmental Deficit
VIQ	Increase # (<0.001)	Increase #	-1.06 (-1.80,-0.32) VIQ points	0.005	Decline	-1.70 (-2.79,-0.61) VIQ points	0.002	Decline	0.64 (-0.68,1.96) VIQ points	0.337	No strong evidence	Developmental Deficit
PIQ	Increase # (<0.001)	Increase #	-1.02 (-1.60,-0.44) PIQ points	0.001	Decline	0.88 (0.04,1.72) PIQ points	0.041	Improvement	-1.90 (-2.92,-0.87) PIQ points	<0.001	Worsening deficit	Developmental Lag
Vocabulary	Increase (<0.001)	Increase (<0.001)	-0.51 (-1.02,0.00)	0.050	Decline	-0.75 (-1.51,0.00)	0.050	Decline	0.24 (-0.67,1.15)	0.601	No strong evidence	Developmental Deficit
Similarities	Increase (<0.001)	Increase (<0.001)	-0.89 (-1.54,-0.25)	0.007	Decline	-1.13 (-2.10,-0.16)	0.023	Decline	0.23 (-0.94,1.40)	0.698	No strong evidence	Developmental Deficit
Block design	Increase (<0.001)	Increase (<0.001)	-0.64 (-1.11,-0.18)	0.007	Decline	0.78 (0.09,1.47)	0.026	Improvement	-1.42 (-2.25,-0.59)	0.001	Worsening deficit	Developmental Lag
Matrix Reasoning	Increase (<0.001)	Increase (<0.001)	-0.77 (-1.35,-0.19)	0.010	Decline	0.34 (-0.51, 1.18)	0.431	No strong evidence	-1.10 (-2.13,-0.08)	0.035	Worsening deficit	Developmental Lag
RTI	Increase (<0.001)	Increase (0.165)	0.14 (0.03,0.24)	0.011	Improvement	0.01 (-0.15,0.17)	0.854	No strong evidence	0.12 (-0.07,0.32)	0.210	No strong evidence	No strong evidence
RVP	Increase (<0.001)	Increase (0.020)	0.27 (0.12,0.43)	0.001	Improvement	0.21 (-0.01,0.44)	0.065	No strong evidence	0.06 (-0.21,0.34)	0.663	No strong evidence	Developmental Deficit
SOC	Increase (<0.001)	Increase (<0.001)	-0.02 (-0.09,0.06)	0.656	No strong evidence	0.07 (-0.04,0.19)	0.196	No strong evidence	-0.09 (-0.22,0.04)	0.185	No strong evidence	Developmental Deficit
SWM	Increase (<0.001)	Increase (<0.001)	-0.08 (-0.15,-0.01)	0.033	Decline	0.05 (-0.06,0.16)	0.392	No strong evidence	-0.13 (-0.26,0.01)	0.058	No strong evidence	Developmental Deficit
Perseverative errors	Increase (<0.001)	Increase (0.153)	2.15 (0.61,3.68)	0.006	Improvement	1.86 (-0.46,4.19)	0.115	No strong evidence	0.29 (-2.50,3.07)	0.840	No strong evidence	No strong evidence

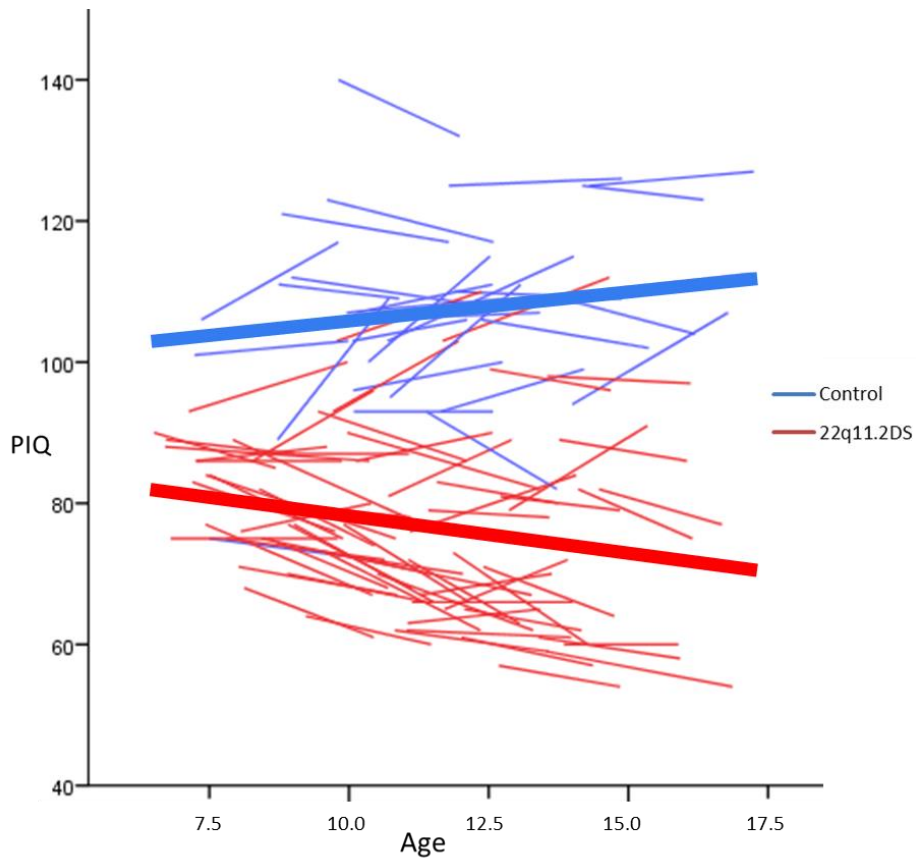
**Figure 3:** FSIQ development in 22q11.2DS and controls



**Figure 4: VIQ development in 22q11.2DS and controls**



**Figure 5: PIQ development in 22q11.2DS and controls**



**5.6.3 Aim 3a: Comparing the variance of cognitive change in 22q11.2DS children with that in controls in standardised scores.**

**Table 25** displays separately for 22q11.2DS children and controls the range of change scores and the standard deviation of change for each cognitive measure. Change scores for 22q11.2DS children were more variable for tasks of attention (MTS  $p=0.009$ , RVP  $p=0.034$ ) when compared to controls. For all other measures there was no strong evidence for a difference in change score variability.

**Table 25:** Minimum, maximum and standard deviation of change scores for 22q11.2DS and controls

Cognitive Measure	22q11.2DS change scores			Controls change scores			Comparison
	Minimum	Maximum	SD	Minimum	Maximum	SD	Levene's test for equality of variance
FSIQ	-15	23	6.91	-17	12	8.18	0.113
VIQ	-23	28	8.78	-28	10	8.78	0.351
PIQ	-13	12	5.98	-11	20	7.78	0.149
Vocabulary	-15	17	6.17	-19	7	6.32	0.899
Similarities	-24	31	8.92	-19	19	8.58	0.681
Block Design	-10	10	4.76	-9	15	6.66	0.084
Matrix Reasoning	-16	22	8.07	-10	12	6.25	0.278
MTS	-20.00	19.00	6.42	-6.00	10.00	3.25	0.009
RTI	-3.75	7.52	1.93	-2.00	2.02	0.98	0.089
RVP	-8.69	6.34	2.37	-1.55	3.26	1.14	0.034
SWM	-2.28	2.64	1.06	-1.61	1.69	1.01	0.706
SOC	-3.01	2.41	1.16	-2.02	2.12	1.20	0.553
Perseverative errors	-54.00	75.00	24.15	-36.00	59.00	25.71	0.380

**5.6.4 Aim 3b: Reliably categorising individuals into improving, stable and declining groups based on their standardised score**

Reliable change indices (RCIs) were utilised to establish the percentage of participants who showed reliable cognitive decline (**Table 26**). For all cognitive measures, there was not strong evidence that children with 22q11.2DS differed from controls in terms of the percentage who exhibited reliable cognitive decline.

**Table 26:** Reliable change in 22q11.2DS and controls

Cognitive measure	22q11.2DS			Controls			Association of deletion status with declining
	Declining %	Stable %	Improving %	Declining %	Stable %	Improving %	Fishers exact p-value
FSIQ	12.9	83.9	3.2	11.1	77.8	11.1	0.999
VIQ	17.7	77.4	4.8	29.6	70.4	0	0.262
PIQ	0.0	100.0	0.0	0	88.9	11.1	-
Vocabulary	9.7	83.9	6.5	11.1	88.9	0	0.999
Similarities	21.0	71.0	8.1	29.6	59.3	11.1	0.421
Block design	0.0	100.0	0.0	0	88.9	11.1	-
Matrix reasoning	6.3	85.7	7.9	0	96.3	3.7	0.312
RTI	11.7	73.3	15.0	3.8	84.6	11.5	0.426
RVP	13.0	53.7	33.3	3.8	80.7	15.4	0.264
SOC	10.3	79.3	10.3	11.5	76.9	11.5	0.999
SWM	9.5	82.5	7.9	11.1	74.1	14.8	0.999
Perseverative errors	3.7	68.9	21.3	3.7	66.7	29.6	0.431

### 5.6.5 Aim 3c: Categorising individuals based on their raw scores to examine the prevalence of cognitive deterioration.

For all cognitive measures, the proportion of children with 22q11.2DS who exhibited deterioration in raw score did not differ from controls (**Table 27**).

**Table 27:** Cognitive deterioration in 22q11.2DS and controls

Cognitive measure	22q11.2DS Cognitive Deterioration %	Controls Cognitive Deterioration %	Fishers exact p-value
Vocabulary	22.6	11.1	0.253
Similarities	14.5	11.1	0.999
Block design	12.7	3.7	0.269
Matrix reasoning	20.6	11.1	0.374
MTS	29.3	22.2	0.609
RTI	31.7	23.1	0.604
RVP	33.3	23.1	0.439
SOC	25.9	23.1	0.999
SWM	36.5	29.6	0.632
Perseverative errors	41.0	40.7	0.459

#### 5.6.6 Aim 4: Investigate whether cognitive development in different domains is related.

**Table 28** displays the correlation matrices for the  $s_{\text{average}}$  principal component of cognitive performance and the  $s_{\text{change}}$  principal component of cognitive change for children with 22q11.2DS.

$s_{\text{average}}$  reflects performance on each of the cognitive tasks averaged over the two waves. FSIQ correlated with visual attention (MTS,  $p=0.010$ ) and executive function (SOC,  $p=0.005$ ; SWM,  $p<0.001$ ; WCST,  $p=0.001$ ) but not processing speed (RTI,  $p=0.112$ ) nor sustained attention (RVP,  $p=0.068$ ). This pattern of association of FSIQ with other cognitive domains remained when IQ was unpacked into VIQ and PIQ. There were correlations between different cognitive domains but also within executive function (SOC, SWM, and WCST) and attention (MTS, RVP) domains.

$s_{\text{change}}$  reflects change in performance between waves 1 and 2 on each cognitive task. Change in FSIQ was not associated with change in other cognitive domains. Though within FSIQ, VIQ and PIQ were strongly correlated ( $p<0.001$ ). Also change in sustained attention was correlated with change in set-shifting ability (RVP, WCST,  $p=0.003$ ).

**Table 28:** Correlation matrix for  $s_{\text{average}}$  and  $s_{\text{change}}$  components in 22q11.2DS

$s_{\text{average}}$  correlations are in the top right triangle and  $s_{\text{change}}$  correlations are in the bottom left triangle

$s_{\text{average}}$ $s_{\text{change}}$	FSIQ	PIQ	VIQ	MTS	RTI	RVP	SOC	SWM	WCST
FSIQ	-	-	-	0.334 (0.010)	0.210 (0.111)	0.250 (0.068)	0.369 (0.005)	0.494 (<0.001)	0.420 (0.001)
PIQ	-	-	0.624 (<0.001)	0.331 (0.010)	0.222 (0.088)	0.247 (0.072)	0.423 (0.001)	0.494 (<0.001)	0.281 (0.028)
VIQ	-	0.483 (<0.001)	-	0.259 (0.047)	0.167 (0.205)	0.217 (0.115)	0.203 (0.134)	0.384 (0.002)	0.423 (0.001)
MTS	0.116 (0.383)	0.107 (0.415)	0.105 (0.426)	-	0.352 (0.007)	0.655 (<0.001)	0.308 (0.022)	0.222 (0.092)	0.201 (0.130)
RTI	-0.078 (0.555)	-0.187 (0.152)	-0.022 (0.870)	-0.057 (0.669)	-	0.164 (0.242)	0.295 (0.029)	0.060 (0.654)	0.227 (0.086)
RVP	-0.164 (0.235)	-0.111 (0.425)	-0.223 (0.106)	0.233 (0.091)	0.224 (0.108)	-	0.186 (0.195)	0.371 (0.006)	0.220 (0.117)
SOC	-0.018 (0.898)	0.048 (0.723)	0.060 (0.663)	0.179 (0.190)	-0.051 (0.712)	0.144 (0.318)	-	0.408 (0.002)	0.303 (0.023)
SWM	0.085 (0.516)	0.096 (0.457)	0.125 (0.336)	0.030 (0.823)	0.055 (0.667)	0.040 (0.775)	0.017 (0.898)	-	0.263 (0.042)
WCST	-0.025 (0.852)	0.028 (0.833)	-0.096 (0.468)	0.238 (0.072)	0.062 (0.643)	0.398 (0.003)	0.044 (0.749)	-0.006 (0.964)	-



## 5.7 Discussion

This is the first longitudinal 22q11.2DS study that has administered the same cognitive measures across all participants and waves of assessment and is one of the few studies that has assessed a range of cognitive domains and that has included a comparison group. Cognitive development examined in this chapter represents the premorbid period as no 22q11.2DS individual met criteria for psychotic disorder at either wave of assessment (see Chapter 4). By utilising raw scores, this is the first study to investigate whether worsening deficits in 22q11.2DS represent a developmental lag or developmental deterioration model of cognitive development.

### 5.7.1 Findings

#### 1. Measurement of cognition in 22q11.2DS had high reliability

Despite a high burden of psychopathology in children with 22q11.2DS, test-retest correlations for all cognitive measures were high. Correlation magnitudes varied by cognitive measure with high values for IQ and its subcomponents and lower values for other neurocognitive domains. This pattern reflects test-retest correlations in the general population (compare **Table 21** and **Table 22**).

#### 2. The magnitude of premorbid deficits in 22q11.2DS differs by cognitive domain

Children with 22q11.2DS had a premorbid deficit of -33.2 IQ points (95%CI=-38.4,-28.0). Premorbid deficits in IQ, attention and set shifting ability were approximately twice the magnitude of deficits in processing speed, spatial planning and spatial working memory. This is consistent with a cross sectional 22q11.2DS study that reported greater deficits in complex cognition and relative strengths in working memory and spatial processing (Gur, Yi et al. 2014). Deficits in processing speed, spatial planning and spatial working memory in 22q11.2DS are similar in magnitude to the deficits present in patients with schizophrenia (Fioravanti, Carlone et al. 2005), whereas attention deficits are greater in 22q11.2DS. VIQ and PIQ deficits were found to be similar in magnitude whereas previous studies have indicated greater deficits for PIQ (Moss, Wang et al. 1995, Swillen, Devriendt et al. 1997, Moss, Batshaw et al. 1999, Woodin, Wang et al. 2001).

#### 3. Premorbid deficits were not independent of each other

Different cognitive measures were positively correlated in 22q11.2DS, both between measures capturing the same domain and between measures of different domains. IQ was correlated with

visual attention, executive function but not processing speed. This differs from cross-sectional findings from wave 1 of the ECHO study where IQ was found to be independent of other domains (Niarchou, Zammit et al. 2014). This disparity could be because, in comparison to cross sectional data, test-retest data provides extra power to detect associations. Also Principal Components Analysis helped distinguish core ability,  $s_{\text{average}}$ , from measurement error.

#### 4. Intelligence declined in 22q11.2DS but not relative to controls

IQ declined in 22q11.2DS by approximately -1 FSIQ point/year. This magnitude of decline falls within the middle of the range of previously reported IQ change (see **Table 20**). However, there was not strong evidence that developmental change in IQ differed from controls. This could be due to power as on average children with 22q11.2DS did diverge from controls -0.51 IQ points/year, but the 95% confidence interval was wide (-1.61 to 0.60 IQ points). Also, only 12.9% of children with 22q11.2DS had a FSIQ change greater than the reliable change index. Overall, there was some suggestion that IQ declines in 22q11.2DS but there was no evidence of a large IQ decline relative to controls and there did not appear to be a large subgroup of children with 22q11.2DS that exhibited IQ decline.

#### 5. The longitudinal course of premorbid deficits differs by domain

This study highlights the importance of considering the subcomponent IQ scores as differing developmental patterns were observed. Children with 22q11.2DS exhibited a developmental lag in PIQ and a developmental deficit in VIQ relative to controls. PIQ captures spatial ability, perceptual organization, nonverbal concept formation, spatial reasoning and fluid intelligence, whereas VIQ captures verbal concept formation, verbal reasoning and crystallized intelligence (Wechsler 1999). The magnitude of the developmental lag was approximately 2 PIQ points/year. This decline was not driven by a subgroup of 22q11.2DS children exhibiting extreme decline, as none of the participants had a PIQ decline greater than the reliable change index. Rather this would suggest a gradual decline in the majority of 22q11.2DS children.

This pattern of verbal developmental deficits and nonverbal developmental lags is consistent with premorbid cognitive development observed in idiopathic schizophrenia (Reichenberg, Caspi et al. 2010). Some, (Duijff, Klaassen et al. 2012, Vorstman, Breetvelt et al. 2015) but not all (Gothelf, Schneider et al. 2013), previous 22q11.2DS studies have found greater decline for VIQ than PIQ, but it should be noted that these studies lacked a comparison group. Although VIQ deficit in this cohort was static, there was decline within both 22q11.2DS and control groups. It could be that the control group is not representative of the general population; however decline

has been described in comparison groups from idiopathic schizophrenia studies (Lane and Albee 1968, Watt and Lubensky 1976, Jones, Murray et al. 1994). These findings question whether previously reported VIQ decline in 22q11.2DS is a true effect or attributable to study artefacts.

Children with 22q11.2DS also exhibited developmental deficits in spatial planning, spatial working memory and sustained attention. This is in contrast to the Dunedin study and suggests spatial tasks as measured by the IQ test (WASI) differ in development from spatial tasks as measured by the CANTAB. However CANTAB tasks do have lower test-retest reliability, so measurement error is likely to have a greater effect making it difficult to detect a developmental lag. Indeed there was a trend for spatial planning and spatial working memory to decline with age relative to controls but these findings were not robust.

Developmental change differs across aspects of executive function in 22q11.2DS, though this could reflect differing methodological artefacts such as differing practice effects.

None of the cognitive domains exhibited development that fitted the model of developmental deterioration.

6. Development of attention is more variable in 22q11.2DS but the same is not true for other domains, including IQ

Development of attention in children with 22q11.2DS was more variable than in controls. The standard deviations of change scores for attention measures were twice the magnitude of controls. Attentional deficits are reported both in patients with schizophrenia (Cornblatt and Malhotra 2001) and as premorbid deficits in those who later develop schizophrenia (Reichenberg, Caspi et al. 2010). Variability in the development of IQ, executive function and processing speed were not specific to 22q11.2DS as controls were just as variable.

There was a subgroup of children with 22q11.2DS who exhibited large reliable changes in cognition (as defined by RCIs). 12.9% of children with 22q11.2DS declined in IQ -10.2 IQ points (RCI for IQ) or more between assessments. However, this was not specific to 22q11.2DS as a similar size subgroup of declining children was present in controls. Both children with 22q11.2DS as well as intrafamilial controls displayed large individual FSIQ changes, ranging from -15 to +23 FSIQ points (**Table 25**), which is similar to adolescents from the general population (Ramsden, Richardson et al. 2011).

One previous study of 22q11.2DS has examined IQ subtest raw scores and identified a subgroup with cognitive deterioration (Duijff, Klaassen et al. 2012). This finding was replicated across

measures in the ECHO cohort, but it was also found that prevalence of cognitive deterioration did not differ from controls. Findings indicate that cognitive deterioration is not specific to children with 22q11.2DS.

7. Premorbid decline in IQ is independent of change in other cognitive domains

Intelligence did not co-vary with other neurocognitive domains over time which is in contrast to the earlier finding that ability in different domains was related (see 5.7.1.3). This could reflect that the brain processes underlying different cognitive domains are related but over time these processes develop differentially in 22q11.2DS.

8. Different aspects of impulsivity change together in 22q11.2DS

Set-shifting ability positively co-varies over time with sustained attention. This could reflect that both tap into impulsivity. Although set-shifting ability is conceptualised as an aspect of executive function, it is dependent on modulating impulsive responding (Heaton, Chelune et al. 1993).

## 5.7.2 Limitations

1. Sample size of controls

The sample size of the control group was smaller than the 22q11.2DS group thus reducing power to contrast development. However, strong relationships within the dataset were still able to be identified.

2. Reliability of neurocognitive measures

Test-retest reliability was lower for the cognitive measures other than IQ. Although this is consistent with normative data this may have affected power to detect patterns of cognitive development.

3. Issues of multiple comparisons

Analysis should be considered exploratory as analysis was not adjusted for multiple comparisons. This increases the risk of type 1 errors occurring, whereby the null hypothesis is incorrectly rejected. For instance in the linear mixed model analysis, there was not a correction for the number of cognitive measures investigated. Analysis could have been confined to fewer domains, however as investigation into the longitudinal change of multiple neurocognitive domains is not common in the 22q11.2 literature it was decided to not restrict analysis. This

exploratory analysis has highlighted sustained attention, a cognitive domain not previously focused on much in the 22q11.2DS literature.

#### 4. Ascertainment bias

It is likely many children with 22q11.2DS were referred for medical genetic testing because of developmental delay and individuals with higher cognitive ability are perhaps less likely to be referred for testing. Together this could mean the magnitude of cognitive deficits calculated may be an overestimate. Conversely, families with severely affected children may be less likely to volunteer as part of a research project so findings could be an underestimate. Also it should be considered that Chapter 3 found there was a bias for children with lower IQ (by -5.8 IQ points) to take part again at wave 2.

#### 5. Representativeness of controls

Controls in this study were unaffected siblings and may not be fully representative of the general population. Their FSIQ was higher than 100 at both waves of assessment (wave 1=106.6, wave 2=105.6). Also a previous study found increased mood disorder in unaffected siblings (Antshel, Shprintzen et al. 2010). However findings in Chapter 4 indicate that the prevalence of psychiatric disorder in unaffected siblings (controls) within the ECHO cohort was representative of that in the general population.

#### 6. Potential cohort effects

The accelerated longitudinal design allowed examination of cognitive development from 6-17 years (age range of current data set), however a potential issue is that there may be cohort effects that change with age.

#### 7. Linear cognitive development was assumed

In the linear mixed models analysis linear trajectories were fitted for 22q11.2DS children and controls. However development may be non-linear. If so, this could account for why 22q11.2DS studies report differing magnitudes of change as each study has examined a different snapshot of development.

#### 8. Other factors could be affecting test-retest performance

Practice effects, the Flynn effect and extraneous factors could be contributing to the change examined, however their effect is likely to be minimal. The time gap of 2.5 years means practice effects are likely to be diminished (see section 5.1.2). The Flynn effect has been estimated to be

an increase of 0.28 IQ points per year (Pietschnig and Voracek 2015) and it could affect children with 22q11.2DS and controls differently. However, if it was inflating control performance relative to children with 22q11.2DS its effect would still be smaller than the magnitude of the changes observed. As explained in Chapter 3 the testing environment, time of assessment, and order of test administration was kept as consistent as possible. However participants may be more familiar to cognitive assessment at the second wave of assessment and arguably this effect could be different for children with 22q11.2DS and controls.

### 5.7.3 Future work

#### 1. Further wave of assessment

Change between two waves of assessment could be due to methodological factors affecting one of the waves of assessment. A third wave of assessment would clarify this.

*“Two waves of data are better than one, but maybe not much better”* (Rogosa, Brandt et al. 1982)

Also a third wave would give insight into how cognition in 22q11.2DS develops as individuals enter the risk period of schizophrenia development.

The nature of early cognitive development in 22q11.2DS should also be considered. Deficits have been reported from age 13 months but it is uncertain whether deficits are present at birth and no study has examined longitudinal development across this period.

#### 2. Large collaborative studies

Moving forward, studies of 22q11.2DS need to be more consistent in the cognitive measures they use. International collaboration of different research groups is occurring (Vorstman, Breetvelt et al. 2015) but research sites are yet to align their cognitive assessments.

#### 3. Investigate other psychiatric-risk CNVs

Longitudinal development of cognition in other psychiatric-risk CNVs should be investigated. It is uncertain whether different schizophrenia-risk CNVs converge on the same cognitive trajectories or are specific in the cognitive domains and trajectories they affect. Cross-sectional evidence suggests that different CNVs affect different cognitive domains (Stefansson, Meyer-Lindenberg et al. 2014). Cognitive decline appears to be more severe in Kleefstra syndrome (9q34.3 deletion) as there are reports of individuals showing regression in adolescence and adulthood (Willemsen, Vulto-van Silfhout et al. 2011).

#### 5.7.4 Conclusions

Schizophrenia has been associated with cognitive deficits, however, their developmental course remains uncertain. Because approximately 25% of children with 22q11.2DS develop schizophrenia (Murphy, Jones et al. 1999), carefully conducted studies of their cognitive development can provide important insights into the development of this severe and debilitating psychiatric disorder, with implications beyond this genetic syndrome, for the wider population of at risk individuals.

This chapter has aimed to critically examine cognitive development in 22q11.2DS. The analysis of cognitive change is complex and has its own unique considerations. Previous longitudinal studies of cognition in 22q11.2DS have suffered various limitations. Study design and statistical methodology has allowed cognitive change to be examined critically, reducing risk of interpreting measurement error as meaningful bias over time.

Findings confirmed that there is premorbid decline in intelligence in 22q11.2DS, though there was not a strong effect. Some authors have recommended regular cognitive testing for children with 22q11.2DS (Swillen and McDonald-McGinn 2015). However findings in this chapter question the usefulness of this as no individuals reached cut-offs for reliable decline in nonverbal intelligence even though there was decline at the level of the group.

The nature and development of intelligence in 22q11.2DS differed by IQ domain. There were developmental deficits in verbal and crystallized intelligence suggesting that there is early atypical brain development in 22q11.2DS that affects the acquirement of language and knowledge across childhood and adolescence. Developmental lags in nonverbal and fluid intelligence highlight that 22q11.2DS children fall further behind their peers on visual-spatial and abstract tasks as they get older but not to the extent of losing ability in these areas. These patterns are observed in those who later develop idiopathic schizophrenia (Reichenberg, Caspi et al. 2010) and therefore 22q11.2DS represents a useful model for exploring the cognitive antecedents of schizophrenia. Developmental deficits were also present for spatial planning, spatial working memory and sustained attention. The mixture of developmental deficits and lags suggests that both processes early in development and later in childhood and adolescence may be associated with genetic risk of schizophrenia.

The cognitive phenotype of 22q11.2DS is highly variable, though for many domains development of cognition was not more variable than for typically developing children.

This chapter has characterised childhood cognitive development of 22q11.2DS, a high-risk condition for schizophrenia development. The next chapter will explore to what extent cognitive development in 22q11.2DS is associated with psychopathology, including the emergence of psychotic experiences.

## **6. Relations between cognition and psychopathology in 22q11.2DS**

This chapter aims to relate findings from Chapter 4 on psychopathology to those from Chapter 5 on cognition. Findings in Chapter 4 indicate a high burden of psychopathology in children with 22q11.2DS. This chapter will explore how this high level of psychopathology relates to cognitive development. I will also address whether cognitive development characterised in Chapter 5 relates to the emergence of psychotic experiences. In Chapter 4 ADHD persistence rate was 48.1%, in this chapter it will be investigated whether cognitive development predicts ADHD persistence.

First I will discuss what is currently known about the relations between cognitive development and psychopathology from the idiopathic and 22q11.2DS literature before investigating these questions in the ECHO longitudinal 22q11.2DS cohort.

### **6.1 Psychotic phenomena and cognition**

Section 5.2.1 has already given an introduction to cognitive development associated with the development of schizophrenia. Here I will discuss cognitive development that has been associated with psychotic experiences in idiopathic populations and subsequently in 22q11.2DS.

#### **6.1.1 Psychotic experiences and cognitive development in idiopathic populations**

Relatively little research has been conducted on the relationship between cognition and psychotic experiences in comparison to schizophrenia (Niarchou, Zammit et al. 2013). Studies have associated deficits in a number of cognitive functions with increased risk of psychotic experiences. Lower childhood IQ, decline in IQ and impairment in a range of neurocognitive domains have been associated with psychotic experiences (Cosway, Byrne et al. 2000, Cannon, Caspi et al. 2002, Horwood, Salvi et al. 2008, Niarchou, Zammit et al. 2015). One study has highlighted defective processing speed as a particularly strong predictor of psychotic experiences (Niarchou, Zammit et al. 2013). Psychoeducational deficits are also reported to be associated with psychotic experiences (Hameed, Lewis et al. 2013). Some (Polanczyk, Moffitt et al. 2010, Thompson, Sullivan et al. 2011, Sullivan, Bentall et al. 2013), but not all (Thompson, Sullivan et al. 2011), measures of impaired social cognition are related to risk of psychotic experiences.

#### **6.1.2 Psychotic experiences and cognitive development in 22q11.2DS**

This was reviewed in section 2.1.5. Below are the cognitive risk factors that have been associated with subclinical psychotic phenomena.

- VIQ decline



- Baseline IQ
- Baseline neurocognitive ability

### 6.1.3 Limitations of current 22q11.2DS studies

Section 5.3.2 discussed some of the limitations of current longitudinal studies of cognition in 22q11.2DS and some of these apply here as well, such as the use of different IQ test versions at different waves of assessment and an exclusive focus on IQ only. There are also limitations specific to the examination of the link between cognition and psychotic phenomena, including:

#### 1. Change is not always examined in relation to psychotic phenomena

Studies have related baseline neurocognitive ability to psychotic phenomena for non-IQ domains (Antshel, Shprintzen et al. 2010, Hooper, Curtiss et al. 2013, Kates, Russo et al. 2014, Schneider, Schaer et al. 2014). However, the relationship between change in cognition and psychotic phenomena has received considerably less attention (e.g., (Antshel, Shprintzen et al. 2010, Hooper, Curtiss et al. 2013)), despite a number of studies conducting longitudinal assessments of non-IQ neurocognitive domains.

#### 2. Longitudinal assessment of cognition and psychotic phenomena is not always concurrent

Of the 10 studies that have examined cognition longitudinally in 22q11.2DS (see 5.3.2) only two have concurrently examined subclinical psychotic phenomena (Hooper, Curtiss et al. 2013, Schneider, Schaer et al. 2014). Some studies have assessed psychotic disorder concurrently but not subclinical symptoms (Gothelf, Penniman et al. 2007, Schaer, Debbané et al. 2009). In other studies a subclinical symptom based measure of psychotic phenomena is available but only at one assessment wave (Gothelf, Eliez et al. 2005, Antshel, Shprintzen et al. 2010, Gothelf, Schneider et al. 2013).

#### 3. Issues of mathematical coupling

Some 22q11.2DS studies have included both baseline cognitive ability and change within the same regression analysis (Gothelf, Schneider et al. 2013, Vorstman, Breetvelt et al. 2015). This introduces bias due to mathematical coupling (see section 5.1.2).

## 6.2 Psychopathology and cognitive development

In section 5.2.3 I have discussed the cognitive patterns that precede emergence of other psychiatric disorders. The current section considers to what extent the presence of psychopathology is related to cognitive development.

### 6.2.1 Psychopathology and cognitive development in idiopathic populations

#### 1. ASD

In children with ASD, development in many cognitive domains shows stability. There is evidence that development of domains often co-vary together and that cognitive development predicts later adult psychosocial outcomes. IQ from childhood to adulthood remains relatively stable (Lockyer and Rutter 1970, Venter, Lord et al. 1992, Ballaban-Gil, Rapin et al. 1996, Howlin, Goode et al. 2004). There is a positive relationship between intellectual functioning and academic attainment (Venter, Lord et al. 1992). Childhood IQ broadly predicts adult psychosocial outcome, with those with a childhood IQ below 70 having poor outcomes (Howlin, Goode et al. 2004, Taylor and Seltzer 2010, Smith, Maenner et al. 2012, Ben-Itzhak, Watson et al. 2014), whereas variability of IQ within the normal range does not predict outcome (Howlin, Goode et al. 2004). There is evidence from other cognitive domains that early childhood cognitive performance predicts later development. Strong executive function skills between the ages 4 to 7 predicts theory of mind ability assessed three years later (Pellicano 2013). Language ability in adolescence is predicted by joint attention in childhood (Sigman and McGovern 2005).

There is a disparity between development in verbal and nonverbal cognition. PIQ is generally higher than VIQ, though VIQ increases over time whereas, depending on study, PIQ remains stable (Gotham, Pickles et al. 2012) or declines (Mawhood, Howlin et al. 2000, Howlin, Goode et al. 2004, Gotham, Pickles et al. 2012). Language and comprehension improves with age, though in a majority of individuals deficits persist, with only a third achieving typical level of ability (Ballaban-Gil, Rapin et al. 1996).

#### 2. Anxiety

The relationship between intelligence and anxiety has been heavily explored, but findings are mixed. Some studies report a negative correlation between intelligence and anxiety (Spielberger 1958, Phillips, Hindsman et al. 1960). It is thought anxiety arises because individuals with a lower IQ are less likely to give a successful response in situations that are cognitively demanding. Others have argued that “the higher the IQ is, the greater the psychological fragility” but this

notion is based on case studies of gifted children with psychological disturbance and may not be generalisable to the broader category of high IQ individuals (Catheline-Antipoff and Poinso 1994). The relationship between intelligence and anxiety appears to differ between clinical and non-clinical populations with one study reporting a positive relationship between intelligence and anxiety in individuals with generalised anxiety disorder but an inverse relationship in healthy volunteers (Coplan, Hodulik et al. 2011).

A clear relationship in the literature is that the presence of anxiety disorders in adolescence increases the risk of educational underachievement and premature withdrawal from school (Woodward and Fergusson 2001, Van Ameringen, Mancini et al. 2003). This appears to be driven by adolescents feeling anxious in class rather than by cognitive impairment.

### 3. ADHD

Studies support a maturational lag hypothesis of ADHD, in that children with ADHD have cognitive deficits which lessen as they grow older (Øie, Sundet et al. 2010). Delayed development is seen for control of attention (Øie, Sundet et al. 2010) and is supported by neuroanatomical evidence of delayed cortical maturation in ADHD (Shaw, Eckstrand et al. 2007).

In contrast, development of IQ, executive function, perceptual recognition and perceptual learning in ADHD appears to follow a developmental deficit model (Biederman, Petty et al. 2009, Coghill, Hayward et al. 2014). That is children with ADHD show deficits in these cognitive domains but their cognitive performance still improves over time at a similar rate as controls.

It is clear that childhood psychopathology is related to later cognitive development and functioning, with particularly strong evidence for ASD and ADHD.

#### **6.2.2 Psychopathology and cognitive development in 22q11.2DS**

Longitudinal studies of cognition and psychopathology in 22q11.2DS have focused on predicting the emergence of psychosis (see section 2.1.4 and 2.1.5) and mood problems (Antshel, Shprintzen et al. 2010). No longitudinal studies of cognition in 22q11.2DS have considered whether the presence of childhood psychopathology in 22q11.2DS predicts cognitive development. Given the high prevalence of psychopathology in 22q11.2DS and the fact that psychopathology influences cognitive development in idiopathic samples, it is important to investigate to what extent the developmental patterns identified in Chapter 5 are influenced by early psychopathology.

## **6.3 Cognition and the persistence of ADHD**

### **6.3.1 Persistence of idiopathic ADHD**

There is evidence that cognition can modulate the longitudinal course of ADHD. Perceptual learning has been found to predict clinical improvements (Biederman, Petty et al. 2009) but higher functions such as executive function and IQ do not (Biederman, Petty et al. 2009, Coghill, Hayward et al. 2014). Studies have also found that IQ does not predict persistence of ADHD into adolescence (Antshel, Faraone et al. 2008, Langley, Fowler et al. 2010), though IQ does predict comorbidity of conduct disorder in ADHD (Langley, Fowler et al. 2010).

### **6.3.2 Persistence of ADHD in 22q11.2DS**

One study has examined cognitive predictors of the persistence of ADHD in 22q11.2DS and identified deficits in verbal learning (Antshel, Hendricks et al. 2013). Similar to idiopathic ADHD (Antshel, Faraone et al. 2008, Langley, Fowler et al. 2010), IQ does not predict ADHD persistence in 22q11.2DS (Antshel, Hendricks et al. 2013).

## **6.4 Aims**

The aims of analysis in this chapter are to investigate the following questions:

1. Psychotic experiences and cognitive development in 22q11.2DS
  - a) Are psychotic experiences associated with cognitive differences?
  - b) Are cognitive differences pre-existing to the emergence of psychotic experiences?
  - c) Is the emergence of psychotic experiences associated with cognitive change?
2. Does psychopathology influence cognitive development in 22q11.2DS?
3. Does cognition predict persistence of ADHD in 22q11.2DS?

## **6.5 Methods**

Sample description and assessment have been presented in Chapter 3. See Chapter 4 for detailed information on psychopathology including frequency of each disorder and vignettes of psychotic experiences. See Chapter 5 for description on how standardised cognitive scores are derived from

raw cognitive performance. Analysis in this chapter explores variation in 22q11.2DS individuals therefore there was no need to use data from controls.

### **6.5.1 Aim 1: Psychotic experiences and cognitive development in 22q11.2DS**

*Are psychotic experiences associated with cognitive differences?*

Cognitive difference attributable to psychotic experiences was calculated by subtracting wave 2 cognitive performance of individuals with psychotic experiences (PE+) from the wave 2 cognitive performance of individuals without psychotic experiences (PE-). Independent t-tests were conducted to determine whether cognitive difference was significant.

*Are cognitive differences pre-existing to the emergence of psychotic experiences?*

To examine whether cognitive differences pre-exist the emergence of psychotic experiences, analysis excluded two individuals with psychotic experiences at both waves of assessment. Cognitive difference was calculated by subtracting the wave 1 cognitive performance of PE+ individuals from the wave 1 cognitive performance of PE- individuals. Independent t-tests were conducted to determine whether cognitive difference was significant.

*Is the emergence of psychotic experiences associated with cognitive change?*

Logistic regression analysis was used to test for associations between  $s_{\text{average}}$ ,  $s_{\text{change}}$  (from the previously described Principal Components Analysis in section 5.5.7) and psychotic experiences. The measurement of change is affected by mean performance at individual time points and this procedure allowed the link between change in cognition and psychotic experiences to be established without being biased by mean cognitive level. Also as the components extracted are not correlated, these analyses, unlike previous studies on this topic in 22q11.2DS (Gothelf, Schneider et al. 2013, Vorstman, Breetvelt et al. 2015) are not biased by mathematical coupling.

Fisher's exact test was conducted to investigate whether having a negative trajectory, as defined by reliable change indices (RCIs), or cognitive deterioration, as defined by a decrease in raw scores, was associated with wave 2 psychotic experiences. As a reminder, reliable change indices are cut-offs applied to change scores to determine whether the magnitude of change is large enough to be a reliable change. Individuals were classified as exhibiting cognitive deterioration if they decreased in raw score.

Again, analysis excluded two individuals with psychotic experiences at both waves of assessment to focus on the emergence of psychotic experiences.

### **6.5.2 Aim 2: Does psychopathology influence cognitive development in 22q11.2DS?**

The psychopathology variables used in this analysis were those that were found to be significantly elevated in children with 22q11.2DS compared to controls in Chapter 4; any DSM-IV-TR psychiatric disorder, any anxiety disorder, generalised anxiety disorder, specific phobia, social phobia, ADHD, ASD screening (using SCQ) and ASD diagnosis (using ADI-R).

The cognitive variables used in this analysis were those from Chapter 5 which could be characterised reliably by models of cognitive development; FSIQ, VIQ, PIQ, Vocabulary, Similarities, Block Design, Matrix Reasoning, RVP, SOC and SWM.

Cognitive differences were calculated by subtracting the cognitive performance of individuals who met psychopathology criteria from the cognitive performance of individuals who had not met psychopathology criteria. Independent t-tests were performed to investigate whether  $s_{average}$  and  $s_{change}$  components of cognition differed in children with 22q11.2DS with and without psychopathology.

### **6.5.3 Aim 3: Does cognition predict persistence of ADHD in 22q11.2DS?**

Analysis was conducted within children with 22q11.2DS and wave 1 ADHD diagnosis. Cognitive differences were calculated by subtracting the cognitive performance of individuals with persistent ADHD from the cognitive performance of individuals with ADHD that did not persist. Logistic regression analysis was used to test for associations between  $s_{average}$ ,  $s_{change}$  (from the previously described Principal Components Analysis in section 5.5.7) and ADHD diagnosis at wave 2.

## **6.6 Results**

### **6.6.1 Aim 1: Psychotic experiences and cognitive development in 22q11.2DS**

*Are psychotic experiences associated with cognitive differences?*

Children with 22q11.2DS and psychotic experiences had a -0.70 SD deficit ( $p=0.036$ ) in spatial working memory (SWM) compared to other 22q11.2DS children (**Table 29**). No differences were observed for the other cognitive measures. It is important to note that in Chapter 4 it was found that children with psychotic experiences did not differ in terms of age, gender, 22q11.2DS inheritance, ethnicity, household income and maternal education.

**Table 29:** Cognitive differences in children with 22q11.2DS and psychotic experiences

Cognitive differences were calculated by subtracting the cognitive performance of individuals with psychotic experiences (PE+) from individuals without psychotic experiences (PE-). Wave 1 analysis did not include two individuals who had psychotic experiences at wave 1 and wave 2. Wave 2 analysis included all individuals.

Cognitive measure	Cognitive difference PE(-) - PE (+)	
	Pre-existing at wave 1# Mean (p-value)	Wave 2 Mean (p-value)
FSIQ	2.02 IQ points (0.601)	1.09 IQ points (0.768)
VIQ	2.24 VIQ points (0.602)	2.25 VIQ points (0.548)
PIQ	2.30 PIQ points (0.561)	0.03 PIQ points (0.994)
Vocabulary	1.50 (0.609)	1.85 (0.458)
Similarities	2.20 (0.542)	1.10 (0.726)
Block Design	0.46 (0.871)	-1.13 (0.671)
Matrix Reasoning	2.63 (0.415)	0.99 (0.760)
MTS	-0.13 (0.960)	1.80 (0.361)
RTI	1.00 SD (0.176)	0.35 SD (0.349)
RVP	0.26 SD (0.749)	-1.25 SD (0.135)
SOC	-0.01 SD (0.982)	-0.07 SD (0.850)
SWM	<b><u>-0.68 SD (0.032)</u></b>	<b><u>-0.70 SD (0.036)</u></b>
Perseverative errors	0.96 (0.904)	-2.16 (0.711)

**Bold and underlined** indicates  $p < 0.05$

# This represents the cognition at wave 1 of individuals who later develop psychotic experiences (PE) at wave 2

*Are cognitive differences pre-existing to the emergence of psychotic experiences?*

At wave 1 a pre-existing deficit in spatial working memory (SWM) of -0.68 SD ( $p=0.032$ ) was found in those who later developed psychotic experiences (**Table 29**). No pre-existing differences were observed for other cognitive measures.

*Is the emergence of psychotic experiences associated with cognitive change?*

A large decline in sustained attention (RVP), as defined by RCI, was associated with the emergence of psychotic experiences ( $r=0.379$ ,  $p=0.020$ ). The development of psychotic experiences seems particularly related to a large decline in sustained attention as a negative RCI is more strongly associated than cognitive deterioration ( $r=0.284$ ,  $p=0.062$ ) with wave 2 psychotic experiences. Across all cognitive measures  $s_{\text{change}}$ , a continuous measure of cognitive change, was not associated with psychotic experiences (**Table 30**). There is further evidence of a relationship between spatial working memory deficits and psychotic experiences as spatial working memory (SWM)  $s_{\text{average}}$  was negatively associated ( $OR=0.39$ ,  $p=0.020$ ) with the emergence of psychotic experiences.

**Table 30:** Association between cognition and the emergence of psychotic experiences in 22q11.2DS

Analysis did not include two individuals who had psychotic experiences at wave 1 and wave 2.

Cognitive measure	$S_{\text{average}}$	$S_{\text{change}}$	Negative RCI	Cognitive deterioration
	OR (p-value)	OR (p-value)	r ( $\chi^2$ p-value)	r ( $\chi^2$ p-value)
FSIQ	1.25 (0.508)	1.17 (0.656)	-0.175 (0.330)	-
VIQ	1.30 (0.436)	1.24 (0.519)	-0.212 (0.183)	-
PIQ	1.20 (0.599)	0.85 (0.665)	-	-
Vocabulary	1.31 (0.422)	1.23 (0.526)	0.000 (0.999)	-0.141 (0.427)
Similarities	1.28 (0.467)	1.04 (0.922)	-0.122 (0.436)	-0.063 (0.999)
Block Design	1.09 (0.797)	1.12 (0.749)	-	-0.020 (0.999)
Matrix Reasoning	1.25 (0.532)	0.78 (0.521)	-0.117 (0.999)	0.094 (0.432)
MTS	1.05 (0.901)	1.12 (0.747)	-	0.025 (0.999)
RTI	1.82 (0.234)	0.80 (0.403)	-0.029 (0.999)	-0.010 (0.999)
RVP	0.84 (0.635)	0.484 (0.080)	<b>0.379 (0.020)</b>	0.284 (0.062)
SOC	0.94 (0.844)	1.01 (0.981)	-0.026 (0.999)	-0.198 (0.255)
SWM	<b>0.39 (0.020)</b>	0.96 (0.918)	-0.012 (0.999)	-0.086 (0.731)
Perseverative errors	1.05 (0.901)	0.94 (0.854)	-0.152 (0.577)	-0.068 (0.729)

**Bold and underlined** indicates  $p < 0.05$

### 6.6.2 Aim 2: Does psychopathology influence cognitive development in 22q11.2DS?

Cognitive deficits were not observed in individuals with any DSM-IV-TR psychiatric disorder at wave 1 (**Table 31**). However individuals with any psychiatric disorder at wave 1 did differ in terms of change over time in FSIQ ( $p=0.017$ ) and on average exhibited cognitive decline (-3.91 FSIQ points) relative to those without any psychiatric disorder. This was driven by the VIQ similarities ( $p=0.049$ ) and the PIQ matrix reasoning ( $p=0.022$ ) subtests. Although there was decline in FSIQ in those with psychiatric disorder, mean FSIQ was in fact slightly elevated at both waves of assessment. It is important to note that in Chapter 4 it was found that children with psychiatric disorder did not differ in terms of age, gender, 22q11.2DS inheritance, ethnicity and maternal education but did on average come from families with a lower household income.



**Table 31:** Cognitive differences of those with any psychiatric disorder at wave 1

Cognitive differences were calculated by subtracting cognitive performance of individuals who meet criteria for psychiatric disorder from individuals who did not meet criteria.

Cognitive measure	Cognitive difference		$S_{\text{average}}$	$S_{\text{change}}$
	Wave 1	Wave 2	t-test p-value	t-test p-value
FSIQ	5.71 IQ points	1.80 IQ points	0.161	<b><u>0.017</u></b>
VIQ	5.75 VIQ points	2.15 VIQ points	0.205	0.073
PIQ	3.54 PIQ points	0.45 PIQ points	0.408	0.052
Vocabulary	2.67	1.61	0.284	0.536
Similarities	5.75	2.16	0.143	<b><u>0.049</u></b>
Block Design	1.32	1.04	0.428	0.661
Matrix Reasoning	4.00	-0.30	0.370	<b><u>0.022</u></b>
RVP	-0.94 SD	-1.41 SD	0.106	0.775
SOC	0.12 SD	0.23 SD	0.307	0.249
SWM	-0.26 SD	0.00 SD	0.574	0.238

**Bold and underlined** indicates  $p < 0.05$

The longitudinal profile of cognition differed between psychiatric disorders (**Table 32**). Those with any anxiety disorder at wave 1 differed in PIQ change ( $p=0.017$ ), exhibiting a relative decline of -3.77 PIQ points. This was driven by decline in the PIQ subtest matrix reasoning ( $p=0.040$ ). The longitudinal profile of cognition differed amongst anxiety disorders, though all affected non-verbal cognition. Those with generalised anxiety disorder at wave 1 had a relatively increased ability in spatial planning (SOC  $p=0.008$ ). Those with social phobia differed in FSIQ change ( $p=0.045$ ), exhibiting a relative decline of -4.82 FSIQ points. This was driven by decline in performance on the matrix reasoning subtest ( $p=0.041$ ). Those with specific phobia at wave 1 had a deficit in spatial working memory (SWM  $p=0.008$ ) and differed in PIQ change ( $p=0.034$ ), exhibiting a relative decline of -4.12 PIQ points which was driven by a decline in performance on the matrix reasoning subtest ( $p=0.035$ )

Those with ADHD at wave 1 had a deficit in sustained attention (RVP  $p=0.046$ ) but increased ability on the similarities IQ subtest.

Meeting ADI-R ASD criteria was found not to be associated with reduced IQ or reduced performance in other cognitive domains ( $s_{\text{average}}$  **Table 33**). It was however associated with changes between assessment waves ( $s_{\text{change}}$  **Table 33**); that is, a decline in performance on the similarities subtest and an increase on block design subtest performance. This is a different profile to that reported for SCQ ASD; those who met SCQ ASD criteria differed in spatial planning change (SOC,  $p=0.004$ ) exhibiting a relative decline of -0.99 SD. It should be noted that Chapter 4 found that children who met ASD

criteria did not differ in terms of age, 22q11.2DS inheritance, ethnicity, household income and maternal education but there was a male preponderance for ASD.

**Table 32:** Cognitive differences of those with psychopathology at wave 1

Cognitive differences were calculated by subtracting the cognitive performance of individuals who meet criteria from individuals who did not meet criteria.

Cognitive measure	Any anxiety disorder				ADHD			
	Cognitive difference		S <sub>average</sub>	S <sub>change</sub>	Cognitive difference		S <sub>average</sub>	S <sub>change</sub>
	Wave 1	Wave 2	t-test p-value	t-test p-value	Wave 1	Wave 2	t-test p-value	t-test p-value
FSIQ	-0.48 IQ points	-4.25 IQ points	0.487	0.065	6.04 IQ points	4.00 IQ points	0.089	0.087
VIQ	-2.48 VIQ points	-4.01 VIQ points	0.294	0.508	7.50 VIQ points	4.42 VIQ points	0.060	0.086
PIQ	0.51 PIQ points	-3.68 PIQ points	0.729	<b>0.017</b>	2.81 PIQ points	2.05 PIQ points	0.420	0.420
Vocabulary	-2.84	-3.20	0.147	0.816	4.29	2.94	0.081	0.345
Similarities	-0.31	-2.54	0.513	0.258	6.71	3.98	<b>0.042</b>	0.111
Block Design	-0.38	-2.11	0.690	0.444	0.54	2.16	0.477	0.111
Matrix Reasoning	1.61	-2.81	0.901	<b>0.040</b>	3.53	0.50	0.406	0.062
RVP	-0.14 SD	-1.59 SD	0.370	0.461	-1.18 SD	-0.90 SD	<b>0.046</b>	0.718
SOC	0.21 SD	-0.05 SD	0.424	0.994	0.19 SD	0.16 SD	0.271	0.552
SWM	-0.47 SD	-0.37 SD	0.071	0.556	-0.12 SD	0.34 SD	0.649	0.072

Cognitive measure	Individual Anxiety Disorders							
	Generalised anxiety disorder				Social phobia			
	Cognitive difference		S <sub>average</sub>	S <sub>change</sub>	Cognitive difference		S <sub>average</sub>	S <sub>change</sub>
Wave 1	Wave 2	t-test p-value	t-test p-value	Wave 1	Wave 2	t-test p-value	t-test p-value	
FSIQ	5.33 IQ points	2.06 IQ points	0.469	0.132	1.66 IQ points	-3.16 IQ points	0.952	<b>0.045</b>
VIQ	-0.90 VIQ points	-3.21 VIQ points	0.620	0.392	-1.66 VIQ points	-4.79 VIQ points	0.376	0.261
PIQ	9.97 PIQ points	7.72 PIQ points	0.084	0.082	3.97 PIQ points	-0.39 PIQ points	0.484	0.078
Vocabulary	-1.38	-3.73	0.426	0.308	-2.90	-4.52	0.124	0.401
Similarities	0.18	-2.27	0.702	0.362	0.49	-2.98	0.635	0.167
Block Design	5.57	6.76	0.079	0.819	2.38	1.07	0.371	0.673
Matrix Reasoning	8.34	3.33	0.139	0.054	3.37	-1.81	0.644	<b>0.041</b>
RVP	0.67 SD	0.54 SD	0.373	0.610	0.12 SD	-1.66 SD	0.804	0.632
SOC	0.76 SD	1.03 SD	<b>0.008</b>	0.506	0.06 SD	0.36 SD	0.407	0.290
SWM	0.15 SD	0.85 SD	0.225	0.165	0.02 SD	-0.04 SD	0.975	0.851

**Bold and underlined** indicates p<0.05

**Table 33:** Cognitive differences of those with autism spectrum disorder

Cognitive difference was calculated by subtracting cognitive performance of individuals who meet criteria from individuals who did not meet criteria.

Cognitive measure	ASD: SCQ				ASD: ADI-R			
	Cognitive difference		S <sub>average</sub>	S <sub>change</sub>	Cognitive difference		S <sub>average</sub>	S <sub>change</sub>
	Wave 1	Wave 2	t-test p-value	t-test p-value	Wave 1	Wave 2	t-test p-value	t-test p-value
FSIQ	-0.27 IQ points	-0.13 IQ points	0.934	0.984	-1.24 IQ points	-1.28 IQ points	0.595	0.611
VIQ	-2.55 VIQ points	-3.41 VIQ points	0.380	0.800	-2.17 VIQ points	-5.28 VIQ points	0.304	0.267
PIQ	2.28 PIQ points	3.38 PIQ points	0.449	0.937	0.54 PIQ points	2.22 PIQ points	0.896	0.895
Vocabulary	-1.36	-0.93	0.681	0.604	-2.30	-0.54	0.593	0.327
Similarities	-1.57	4.59	0.232	0.203	0.12	-6.29	0.284	<b>0.018</b>
Block Design	1.38	3.65	0.288	0.126	-1.30	2.63	0.977	<b>0.035</b>
Matrix Reasoning	2.24	1.09	0.592	0.334	2.68	0.36	0.743	0.081
RVP	0.03 SD	-0.60 SD	0.893	0.981	-0.89 SD	0.20 SD	0.360	0.231
SOC	0.24 SD	-0.72 SD	0.905	<b>0.007</b>	0.18 SD	-0.40 SD	0.823	0.053
SWM	-0.44 SD	-0.12 SD	0.223	0.239	-0.32 SD	-0.08 SD	0.440	0.317

**Bold and underlined** indicates p<0.05

### 6.6.3 Does cognition predict persistence of ADHD in 22q11.2DS?

Of the 27 individuals with ADHD at wave 1, 13 continued to meet criteria at wave 2. A deficit in sustained attention (RVP) predicted ADHD persistence (p=0.034) (Table 34). Those with persistent ADHD had a deficit greater than 2 SD in sustained attention.

**Table 34:** Cognitive differences of those with persistent ADHD

Within children with 22q11.2DS and ADHD at wave 1, cognitive differences were calculated by subtracting the cognitive performance of individuals with ADHD at wave 2 from the cognitive performance of individuals with ADHD at wave 1 but not wave 2.

Cognitive measure	Cognitive Difference		S <sub>average</sub>	S <sub>change</sub>
	Wave 1	Wave 2	OR (p-value)	OR (p-value)
FSIQ	1.53 IQ points	-0.89 IQ points	1.02 (0.962)	0.52 (0.202)
VIQ	1.03 VIQ points	-2.61 VIQ points	0.89 (0.752)	0.54 (0.178)
PIQ	2.59 PIQ points	2.50 PIQ points	1.31 (0.539)	0.82 (0.634)
Vocabulary	-0.22	-1.76	0.84 (0.648)	0.77 (0.440)
Similarities	1.78	-1.89	1.01 (0.986)	0.53 (0.187)
Block Design	-0.89	3.23	0.97 (0.940)	2.74 (0.063)
Matrix Reasoning	4.64	0.34	1.43 (0.428)	0.43 (0.108)
RVP	-2.27 SD	-2.65 SD	<b>0.15 (0.034)</b>	2.00 (0.274)
SOC	-0.19 SD	-0.69 SD	0.68 (0.481)	0.93 (0.873)
SWM	0.09 SD	-0.31 SD	0.83 (0.631)	0.53 (0.255)

**Bold and underlined** indicates p<0.05

## 6.7 Discussion

This is the first longitudinal 22q11.2DS study to consider how childhood psychopathology impacts cognitive development and one of few to assess cognition and psychotic phenomena concurrently.

### 6.7.1 Findings

1. IQ deficit was not associated with the emergence of psychotic experiences but other cognitive domains were.

Children with 22q11.2DS and psychotic experiences did not exhibit deficits in IQ compared to children with 22q11.2DS without psychotic experiences and the emergence of psychotic experiences was not accompanied by a decline in IQ. However deficits in spatial working memory were present in those with psychotic experiences and this deficit was present before the emergence of psychotic experiences. The emergence of psychotic experiences was associated with a large decline in sustained attention, as defined by RCIs. This highlights the importance of assessing specific cognitive domains as well as IQ.

2. Method of classifying cognitive change is important

Cognitive change was analysed dichotomously by using RCIs to identify large reliable cognitive changes and also continuously by using principal components analysis to extract a component that represents change ( $s_{\text{change}}$ ). When change in the cognitive domain sustained attention was analysed dichotomously it was found to be associated with the emergence of psychotic experiences but not when analysed continuously. This suggests that the relationship between change in sustained attention and psychotic experiences may be non-linear and that there may be a cut-off where change becomes predictive of psychotic experiences. It is important that future studies consider the possibility of non-linear relationships.

3. In 22q11.2DS psychopathology modulates cognitive development

Children with 22q11.2DS and a psychiatric disorder exhibited decline in IQ relative to children with 22q11.2DS and no psychiatric disorder. This has not been investigated before in 22q11.2DS. Children with 22q11.2DS and psychiatric disorder did not exhibit cognitive deficits relative to those without psychiatric disorder (**Table 31**). This suggests that the -33.2 IQ deficit reported in Chapter 5 cannot be explained by the high burden of psychopathology reported in Chapter 4. This is consistent with cross-sectional findings from the ECHO cohort which report that

psychopathology and deficits in cognition are independent sequelae of 22q11.2DS (Niarchou, Zammit et al. 2014).

#### 4. Longitudinal cognitive profile differs amongst disorders

When psychopathology is considered in terms of individual disorders, each disorder was associated with a distinct longitudinal profile but there was also overlap.

##### i. Anxiety and ASD impact spatial cognition

Anxiety and ASD were associated with decline in spatial cognition over time with anxiety and ADI-R ASD impacting PIQ and SCQ ASD affecting spatial planning. They impact different aspects of the same cognitive domain and this is analogous to symptomatology as it has been argued that measures of anxiety and ASD in 22q11.2DS are capturing the same underlying affective endophenotype (Angkustsiri, Goodlin-Jones et al. 2014). It is also interesting to note that different measures of ASD are differentially related to cognitive development. This provides further evidence that the SCQ and ADI-R index different constructs.

##### ii. Longitudinal course differed amongst anxiety disorders

Individual anxiety disorders differed in longitudinal cognitive profile. In Chapter 4 it was reported that anxiety disorders differ in terms of longitudinal persistence and emergence. Given that anxiety has been associated with the emergence of psychotic phenomenology (see sections 2.1.4 and 2.1.5), these findings add to my previous argument (see 4.7.1) that it is important for future 22q11.2DS studies to consider the nature of anxiety.

Individuals with generalised anxiety disorder have increased spatial planning ability. This is consistent with findings in clinical cohorts that generalised anxiety disorder symptomatology is associated with increased cognitive performance (Coplan, Hodulik et al. 2011).

- iii. ADHD and ADHD persistence were associated with deficits in sustained attention.

At wave 1 children with 22q11.2DS and ADHD had approximately a 1 SD deficit in sustained attention. The deficit is greater by 2 SD in individuals whose ADHD persists to wave 2. In some respects this finding is expected but it highlights that cognitive and symptomatology measures of attention are related in 22q11.2DS as they are in the idiopathic ADHD literature (Barkley 1997). IQ was found not to predict persistence and this is consistent with previous idiopathic studies that found IQ did not predict ADHD persistence (Antshel, Faraone et al. 2008, Langley, Fowler et al. 2010).

5. Spatial cognition was related to both anxiety and the emergence of psychotic experiences

Childhood anxiety and decline in VIQ have been previously identified as risk factors for the emergence of psychotic phenomena in 22q11.2DS (see sections 2.1.4 and 2.1.5). Findings from this chapter found non-verbal cognition was related to anxiety and the emergence of psychotic experiences, in particular spatial tasks. The presence of anxiety disorder at wave 1 was associated with decline in PIQ. Amongst anxiety disorders, phobias impacted negatively on spatial cognition whereas ability was actually increased in generalised anxiety. Social and specific phobias were both associated with decline in spatial reasoning (PIQ subtest matrix reasoning) and specific phobia was related to deficits in spatial working memory. Deficits in spatial working memory were also found in those individuals who developed psychotic experiences. However in Chapter 4 specific phobia was not found to be associated with the emergence of psychotic experiences. A clear causal pathway between anxiety, spatial cognition and psychotic experiences cannot be defined from the analyses conducted. However results suggest that future studies should investigate spatial cognition as a possible mediator between anxiety and the development of psychotic phenomena.

Previous studies have implicated verbal cognition rather than spatial cognition in predicting psychotic phenomena in 22q11.2DS (Gothelf, Eliez et al. 2005, Gothelf 2014, Vorstman, Breetvelt et al. 2015). These findings are not necessarily contradictory as studies have measured cognitive change across the onset of psychosis. It could be that spatial cognition plays a role in the emergence of psychotic phenomena and that verbal cognition declines with onset of florid psychosis. It is important that future 22q11.2DS studies are developmentally specific and tease apart the cognitive changes associated with each stage of psychosis development.

## 6. Sustained attention was related to both ADHD and psychotic experiences

In 22q11.2DS those with ADHD have deficits in sustained attention and decline in sustained attention was related to the emergence of psychotic experiences. However, Chapter 4 found ADHD was not associated with the emergence of psychotic experiences. It is important to emphasise that ADHD was found to be associated with a static deficit in sustained attention whereas change was associated with the emergence of psychotic experiences. These findings warrant further investigation and attention should be investigated as a mediating endophenotype of psychosis risk in 22q11.2DS. Attention is considered an endophenotype for schizophrenia in the idiopathic literature (Cornblatt and Malhotra 2001).

### 6.7.2 Limitations

#### 1. Not able to infer chronology of development of cognition and psychopathology

Psychopathology and cognition were assessed concurrently which means cognitive change cannot be said to have occurred before or after the presence of psychopathology. So although decline in sustained attention is associated with the emergence of psychotic experiences it is uncertain whether this is due to the onset of psychotic experiences or preceded onset. Also the direction of effect is uncertain regarding the findings that psychopathology at wave 1 is associated with cognitive change.

#### 2. Issue of multiple comparisons

The findings reported in this chapter should be considered exploratory and treated cautiously as findings would not survive correction for multiple comparisons. This increases the risk of type 1 errors occurring, whereby the null hypothesis is incorrectly rejected. However it is noteworthy that several findings converge on spatial cognition.

### 6.7.3 Conclusions

Chapter 4 demonstrated that there is a high burden of psychopathology in 22q11.2DS and that psychotic experiences start to be reported from age 10. Chapter 5 found the pattern of cognitive development in 22q11.2DS is similar to that observed in childhood preceding idiopathic schizophrenia. This chapter has aimed to relate psychopathology and cognitive development.

Pre-existing deficits in spatial working memory were associated with the emergence of psychotic experiences but deficits in IQ were not. The presence of psychopathology had a modulatory effect on cognitive development but by no means accounted fully for the cognitive deficits present in



22q11.2DS. The presence of anxiety and ASD was associated with decline in spatial cognition. Deficit in sustained attention was associated with ADHD and also predicted the longitudinal persistence of ADHD. Overall cognitive development and psychopathology were related to some extent in 22q11.2DS, but by no means fully overlapped.

Across chapters there is converging evidence that non-verbal cognition and in particular spatial cognition may play a role in the development of psychotic phenomena in 22q11.2DS. Chapter 4 found premorbid decline in PIQ (nonverbal ability) and this chapter found that a deficit in spatial working memory was associated with the emergence of psychotic experiences. It may be that PIQ and spatial working memory measures capture different aspects of an underlying non-verbal cognitive construct that predicts the emergence of psychotic experiences. This chapter suggests that the presence of anxiety and ASD in childhood may impact on the development of this non-verbal cognitive construct.

This cohort now needs to be followed up again to gain insight into the development of psychotic disorder and whether the associated pattern of cognitive development differs from that identified for the emergence of psychotic experiences in this chapter.

## 7. Discussion

### 7.1 Overview

This thesis set out to examine the neuropsychiatric phenotype of 22q11.2DS through a developmental lens. The neuropsychiatric phenotype in 22q11.2DS is complex and spans diagnostic categories and cognitive domains. This thesis analysed data from the deeply phenotyped longitudinal ECHO cohort of children with 22q11.2DS and their unaffected siblings. Findings from a range of measures were utilised to characterise development.

- Psychopathology - the CAPA provided longitudinal information on the presence of DSM-IV-TR psychiatric disorder as well as subthreshold psychotic phenomena
- ASD - examined using the SCQ longitudinally, a brief light touch assessment, and at wave 2 the ADI-R provided a more in depth assessment of ASD and developmental history
- IQ – the longitudinal development of global cognition including verbal and non-verbal domains of intelligence were examined using performance on the WASI
- Specific neurocognitive domains - the longitudinal development of executive function, attention and processing speed were examined using performance on the WCST and the CANTAB

This thesis has examined change across various developmental stages in 22q11.2DS.

- Early development - in Chapter 4 findings from the ADI-R were analysed, which assesses developmental history with a particular focus between ages 4 to 5
- Early adolescence - in Chapter 4 longitudinal stability and changes in psychopathology were examined across a 2.5 year period (average ages 10 to 12.5), capturing the crucial period of early adolescence
- Development spanning childhood and adolescence - in Chapter 5 an accelerated longitudinal design was applied to cognitive data, allowing cognitive development to be examined from ages 6 to 17

In Chapter 4 a high prevalence of psychiatric disorder was found across early adolescence in 22q11.2DS, particularly ADHD, ASD and anxiety disorders. This confirms that 22q11.2DS as a risk factor for developing schizophrenia is also associated with significant psychiatric morbidity before

adulthood. Using the ADI-R, an in depth diagnostic interview that also assesses early development, prevalence of ASD and subthreshold symptomatology was found to be high in 22q11.2DS. This demonstrates that neurodevelopmental deviance is present in the early years of children with 22q11.2DS. Particularly striking was the emergence of psychotic experiences in early adolescence, which was found to be independent of other psychopathology. Over the same period ADHD prevalence decreased. The neuropsychiatric phenotype was found to be complex and did not seem to be underpinned by a core deficit as different aspects had their own distinct longitudinal course.

In Chapter 5, significant deficits spanning numerous cognitive domains were found in 22q11.2DS relative to controls. The longitudinal course of cognitive development differed by cognitive domain. In particular there were developmental deficits in verbal cognition and developmental lags in non-verbal cognition. The pattern of cognitive development in 22q11.2DS was found to be similar to that observed in children who later develop idiopathic schizophrenia (Reichenberg, Caspi et al. 2010). The mixture of developmental deficits and lags found in 22q11.2DS indicates that genetic risk for schizophrenia is associated with both processes in early development and later in adolescence. This highlights the utility of 22q11.2DS as a model for exploring premorbid development associated with schizophrenia.

Chapter 6 aimed to bring together psychopathology examined in Chapter 4 and cognition examined in Chapter 5. Each psychiatric disorder had a differing profile of cognitive development. However, psychopathology alone did not account for cognitive deficits; rather the presence of psychopathology had a modulatory effect on cognition. Chapter 6 also examined whether cognition predicted emergence of psychotic experiences and the persistence of ADHD. Pre-existing deficits in spatial working memory and a large drop in sustained attention were found to be associated with the emergence of psychotic experiences and deficits in sustained attention were associated with the persistence of ADHD.

## **7.2 Themes**

### **7.2.1 22q11.2DS is associated with significant neuropsychiatric burden**

Across chapters it is clear that 22q11.2DS is associated with a significant neuropsychiatric burden. The prevalence of psychiatric disorder was found to be greater than 50% at both waves of assessment with children meeting criteria across many diagnostic categories. Subthreshold symptomatology was found to be prevalent in children with 22q11.2DS, 63.5% had deficits in at least one ASD domain and, at wave 2, 21.4% had psychotic experiences. Significant cognitive deficits were

found in global cognition (IQ) and across neurocognitive domains of executive function, attention and processing speed.

### **7.2.2 Longitudinal trends and stability is present in 22q11.2DS**

Aspects of the neuropsychiatric phenotype in 22q11.2DS show longitudinal stability. ASD, as measured by the SCQ, showed stability both in terms of categorical ASD classification and symptom count. Global cognition in terms of IQ showed greater stability than the development of specific neurocognitive domains. This indicates that in 22q11.2DS if ASD traits and reduced IQ are present these are likely to persist through childhood and adolescence.

There are threads that run through development in 22q11.2DS. Children with spatial working memory deficits were found to be at greater risk of developing psychotic experiences. Also children who exhibited a large drop in sustained attention were found to be more likely to have psychotic experiences. In children with 22q11.2DS and ADHD, deficits in sustained attention predicted ADHD persistence.

### **7.2.3 The neuropsychiatric phenotype of 22q11.2DS is highly variable**

This thesis has found that the neuropsychiatric phenotype of 22q11.2DS is variable at many levels, including the range of psychiatric and cognitive manifestations present in 22q11.2DS.

Different aspects of psychopathology and cognitive development were found to vary in terms of longitudinal course and stability over time. Individual psychiatric disorders were found to vary in terms of prevalence and persistence, and deficit magnitude differed amongst cognitive domains.

Within 22q11.2DS it has been shown that the group mean of a trait masks considerable individual variation. For instance in Chapter 4 it was found that although there was no net change in prevalence of anxiety disorders, there were many individuals whose diagnostic status changed between assessment waves. In Chapter 5, children with 22q11.2DS were found to decline in IQ 1 point per year, but individual change between assessment waves (2.5 years) ranged from -15 to 23 IQ points.

### **7.2.4 The extent to which neuropsychiatric measures are capturing valid constructs**

Although a general issue in research, it has been a particular pertinent concern in this thesis whether measures used are actually capturing intended constructs. Unique consideration has had to be given to how to assess longitudinal change. Chapter 5 considered in depth how to reliably capture

cognitive change and how best to distinguish this from error. Analytical methods such as reliable change indices and principal components analysis were used to critically examine change.

The complexity of the neuropsychiatric phenotype in 22q11.2DS has meant the validity of psychopathology measures has been put under scrutiny. In 22q11.2DS measures of psychopathology should be interpreted critically and not necessarily taken at face value. In Chapter 4 it was found there were individuals who gained a diagnosis of neurodevelopmental disorder with age and that the SCQ measure of ASD indexes comorbid psychiatric disorder more so than the ADI-R.

## **7.2.5 The extent to which aspects of the neuropsychiatric phenotype are specific to 22q11.2DS**

Given the high risk 22q11.2DS confers for schizophrenia development, many studies have aimed to identify neuropsychiatric features associated with this genetic risk for schizophrenia. However it has not always been considered whether associated features are unique to 22q11.2DS.

Many 22q11.2DS studies have reported high levels of psychiatric morbidity in 22q11.2DS (see Chapter 1). In Chapter 4 it was highlighted that the pattern of psychiatric morbidity in 22q11.2DS is similar to that in idiopathic ASD and may not be specific to the syndrome.

It has been reported that development of IQ is highly variable in 22q11.2DS with many exhibiting decline (Duijff, Klaassen et al. 2012). However in Chapter 5 although it was found that longitudinal change in IQ is highly variable in 22q11.2DS, it was not more variable than in controls.

## **7.3 Implications of this thesis**

### **7.3.1 22q11.2DS warrants clinical attention**

The neuropsychiatric burden present in 22q11.2DS warrants clinical attention, support and treatment. In Chapter 4 it was found that 82.9% of those with psychiatric disorder at wave 2 had a diagnosis at wave 1. This highlights the potential for early, targeted intervention in children with 22q11.2DS.

However currently psychopathology in 22q11.2DS is not adequately treated and followed (Young, Shashi et al. 2011). One study found that half of those at risk of psychosis were not receiving any mental health care (Tang, Yi et al. 2014).

### **7.3.2 Genetic risk of schizophrenia is associated with neurodevelopmental deviance**

Findings in this thesis support the neurodevelopmental hypothesis of schizophrenia. 22q11.2DS as a genetic risk factor for schizophrenia was found to be associated with a range of problems that manifest early in development.

Chapter 5 reported developmental deficits across a range of cognitive domains. Although development through 6-17 was assessed, the static nature of these deficits, if extrapolated back, would suggest that cognitive deficits originate very early in development in 22q11.2DS.

This thesis has confirmed previous reports that there is a high prevalence of neurodevelopmental disorder in 22q11.2DS. In particular, Chapter 4 found through a retrospective interview that ASD symptomatology was highly prevalent in the early development of children with 22q11.2DS.

### **7.3.3 22q11.2DS has pleiotropic effects throughout development**

The neuropsychiatric phenotype of 22q11.2DS does not appear to be characterised by a core deficit that spans development. Findings in this thesis suggest 22q11.2DS has cross-sectional and temporal pleiotropic effects.

22q11.2DS is associated with both ASD and psychotic experiences, however Chapter 4 found they were independent of each other. Interestingly none of those who met strict autism criteria on the ADI-R met the highest cut-off on the SCQ autism measure and vice versa. On one level this highlights the discrepancy between the two ASD measures but it also indicates that differing aspects of ASD phenomenology may not show overlap in 22q11.2DS.

22q11.2DS is associated with both psychopathology and cognitive deficits. Chapter 6 found that although psychopathology was related to cognitive development, the effect is subtle and they by no means fully overlap.

22q11.2DS has pleiotropic effects on cognition across childhood and adolescence. Chapter 5 found that cognitive development in 22q11.2DS was a mixture of both developmental deficits and lags which suggests that both processes early in development and later in childhood and adolescence may be associated with the syndrome.

### **7.3.4 22q11.2DS is a useful model for investigating schizophrenia development**

This work confirms the utility of 22q11.2DS as an opportunity to prospectively investigate the development of schizophrenia. Chapter 5 found the pattern of cognitive development in 22q11.2DS to be similar to that in children who later develop idiopathic schizophrenia. Chapter 4 demonstrated

that longitudinal studies of 22q11.2DS are able to successfully capture the prospective emergence of psychotic phenomena. Chapter 6 was able to identify spatial working memory deficits and decline in sustained attention to be associated with the emergence of psychotic experiences in 22q11.2DS.

### **7.3.5 Implications of this thesis for future research**

#### **1. Implications for the 22q11.2DS research community**

This thesis has identified trends to be explored further in larger 22q11.2DS cohorts. The International 22q11.2DS Brain and Behaviour Consortium (IBBC) provides such an opportunity. 22q11.2DS research investigators have highlighted the decline of VIQ in the syndrome (Vorstman, Breetvelt et al. 2015). However Chapter 5 found a declining developmental lag in PIQ but a static developmental deficit in VIQ, this finding needs replication, but it highlights that longitudinal change PIQ should receive research attention as well as VIQ.

Previous longitudinal studies of cognition in 22q11.2DS have often focused exclusively on IQ measures. However findings in this thesis highlight that other neurocognitive domains warrant attention. Chapter 6 found that spatial working memory and sustained attention were related to the emergence of psychotic experiences.

This thesis also indicates that previously identified trends in the 22q11.2DS literature may be more complex in nature. Childhood anxiety has been previously been identified as a risk factor for the emergence of psychotic phenomena (see sections 2.1.4 and 2.1.5). Chapter 4 found different anxiety disorders had differing trajectories and Chapter 6 found this was matched by predicting different cognitive trajectories. This highlights that future studies should examine the nature of anxiety that predicts psychotic phenomena. Chapter 6 also found that anxiety and psychotic experiences were associated with differing aspects of spatial cognition. Although a clear causal pathway cannot be defined from the analysis conducted it does suggest that spatial cognition maybe a mediator between anxiety and the development of psychotic phenomena. This relationship could be explored in future studies.

#### **2. Methodological implications**

This thesis has focused on using methodology that critically examines longitudinal change. It has also considered what measures of cognition and psychopathology are really capturing. Here I summarise some of the main messages from this thesis regarding methodology which are applicable not just to 22q11.2DS research but wider developmental psychopathology research.

First, is the importance of having a control group to explore which neurodevelopmental features are specific to the group of interest, in this case 22q11.2DS, and which features are common to all children and adolescents. For example, a previous 22q11.2DS study identified a subgroup of children who exhibit cognitive deterioration on IQ domains and it was concluded that this is a feature of the syndrome (Duijff, Klaassen et al. 2012). However this study had no control group. This thesis has found that variability in IQ development and the proportion of those who exhibit cognitive deterioration does not differ from intrafamilial controls, suggesting that cognitive deterioration in IQ is not specific to 22q11.2DS. In contrast, development in attention was found to be more variable in 22q11.2DS compared to intrafamilial controls and thus specific to the syndrome.

Second is to highlight that data from longitudinal studies have unique statistical properties and these should be taken into account accordingly in analysis. As mentioned through this thesis, it is apparent that previous 22q11.2DS studies have not always considered such issues. The methodology sections have discussed analytical techniques that help overcome such problems.

Third is to be critical of what psychopathology assessments are actually measuring. This thesis found that the SCQ and ADI-R measured overlapping but different constructs and there was evidence that they were associated with different cognitive trajectories. The SCQ was found to index psychopathology other than ASD more so than the ADI-R. This highlights that in 'diagnostically challenging' children, in depth semi-structured interviews such as the ADI-R are necessary. However it should be considered whether it would be feasible for the ADI-R to be administered as part of a protocol of a large consortium. Large phenotyping studies have to find a balance between the use of in-depth measures and keeping the assessment protocol feasible. One compromise would be to utilise a two tier level of phenotyping, whereby there would be a light-touch phenotyping approach in many individuals and then a more in-depth rigorous phenotyping in a subgroup to validate the light-touch assessments used.

### **7.3.6 Limitations of this thesis**

This thesis has several limitations. Firstly there are issues of power, the sample size of the cohort reduces the power to detect relationships in the dataset and therefore it is likely that subtle developmental trends have been missed. This thesis has attempted to comprehensively examine the neuropsychiatric phenotype of 22q11.2DS, and in doing so many psychopathology and cognitive variables have been considered in analysis. A consequence of this is the issue of multiple comparisons. Analysis was not adjusted for multiple comparisons due to the power issues. This has been highlighted in the relevant sections of this thesis.



Another limitation is the use of psychopathology measures which are based on traditional diagnostic categories. It has been mentioned several times during this thesis that the use of current diagnostic classification systems is difficult in 22q11.2DS given the high level of comorbid psychiatric disorder and the presence of intellectual disability. Also Chapter 4 identified individuals who did not meet ASD criteria but who had subthreshold symptomatology. Moving forward it is important for studies to consider other approaches for characterising the neuropsychiatric phenotype in 22q11.2DS. Section 2.2.3 described some alternative approaches; symptom-cognitive domains, developmental brain dysfunction and research domain criteria.

Finally, ascertainment bias is likely to operate at many levels in this longitudinal study of children with 22q11.2DS. There is likely to be bias in those children who are identified by medical genetics clinics as having 22q11.2DS. Chapter 3 found there was a slight bias in those families with a child with 22q11.2DS lost to follow-up. Overall this means this thesis may not be necessarily capturing the true longitudinal phenotype of 22q11.2DS. It is likely that those identified by medical genetics clinics are likely to have more health problems than those who do not. Potentially the ECHO cohort is missing 22q11.2DS individuals with typical development.

## **7.4 Future Directions**

### **7.4.1 Large, deeply phenotyped 22q11.2DS cohorts**

Large cohorts of 22q11.2DS individuals are needed to provide greater power for analysis. In practice, given the rarity of 22q11.2DS, individuals with the syndrome are difficult to recruit. The IBBC study is a step forward, bringing together 1402 22q11.2DS individuals from fifteen sites around the world. However measures are not consistent between sites, which as discussed in Chapter 5 can cause difficulties when examining longitudinal change in cognition. In this thesis I have discussed that 22q11.2DS studies do not always assess psychopathology and cognition concurrently or do not always assess ASD. Moving forward it would be ideal if sites could synchronise and develop assessment protocols that capture the full neuropsychiatric phenotype of 22q11.2DS.

### **7.4.2 22q11.2DS studies that examine development across the life course**

This thesis has examined development of psychopathology across early adolescence, and for cognitive development from ages 6 to 17. However it is important that other stages of development are considered. Section 7.3.2 summarises that this thesis points to disruption in early development in 22q11.2DS. Future studies should directly examine early development, including prenatal development, to investigate the origins of psychopathology and cognitive deficits in 22q11.2DS. It is

unknown at what point cognitive deficits emerge and are apparent in 22q11.2DS. There is one study that reports cognitive deficits in children aged 13 months with 22q11.2DS (Gerdes, Solot et al. 2001) but their origin and longitudinal course is currently unknown. 22q11.2DS could offer a rare opportunity to prospectively examine the early development of those at high risk of developing schizophrenia. However, currently, 22q11.2DS is not routinely tested for during pregnancy or at birth so there is likely to be ascertainment bias in those identified early.

As discussed in Chapter 5, future assessment waves in the ECHO study 22q11.2DS cohort would give insight into development across the risk period for the emergence of psychosis. A third wave of assessment is currently being undertaken in the ECHO study cohort.

### **7.4.3 Longitudinal investigation of other psychiatric-risk CNVs**

In comparison to 22q11.2DS, many other psychiatric-risk CNVs have only been identified relatively recently (Levy, Xu et al. 2012) so longitudinal studies are relatively scarce. Although psychiatric-risk CNVs converge on the same disorders it is uncertain whether the pathway to psychiatric disorder differs amongst psychiatric-risk CNVs. Cross-sectional evidence suggests that different CNVs affect different cognitive domains (Stefansson, Meyer-Lindenberg et al. 2014). Contrasting development amongst psychiatric-risk CNVs could reveal developmental trajectories specific to genomic regions and could help pinpoint genes involved in specific pathways to psychiatric disorder. Alternatively such studies may reveal that different genomic regions impact on the same developmental risk pathway for psychiatric disorder.

### **7.4.4 Large population studies to reduce ascertainment bias**

One way to overcome ascertainment bias would be through studies which genotype a large population, identify individuals with 22q11.2DS and examine their phenotype. However given the rarity of 22q11.2DS this would require a very large cohort. The Icelandic DeCODE genetic population cohort (n=101,655) (discussed in section 2.2.1.5) was not large enough to give insight into 22q11.2DS, although it was sufficient for less rare psychiatric-risk CNVs (e.g. 15q11.2 deletion and duplication) (Stefansson, Meyer-Lindenberg et al. 2014). Only 18 individuals with 22q11.2DS were identified, of which just 3 took part in assessments.

## **7.5 Conclusion**

This thesis adds to the emerging literature on the neuropsychiatric phenotype of 22q11.2DS and more widely contributes to research on the development of schizophrenia. This is one of the few longitudinal 22q11.2DS studies that has used the same measures at both waves of assessment and

has examined both cognition and psychopathology. In the early adolescent period of 22q11.2DS psychotic experiences were found to emerge and this was associated with deficits in spatial working memory and attention, but emergence was independent of the high levels of other psychopathology associated with the syndrome. Retrospectively, ASD phenomenology was found to be highly prevalent in the early development of children with 22q11.2DS. Cognitive development in 22q11.2DS was found to follow similar patterns to that observed in children who develop idiopathic schizophrenia. Psychopathology and cognitive development were found to be largely independent, but some specific relationships were identified. Together these findings demonstrate that 22q11.2DS as a genetic risk factor for schizophrenia has a range of pleiotropic effects on development and has highlighted the utility of longitudinal studies of 22q11.2DS in that they can prospectively examine the emergence of psychotic phenomena.

22q11.2DS can pose challenges in research, given its rarity, complex neuropsychiatric phenotype and the likely presence of ascertainment bias. Hopefully large collaborative studies of clinical and population cohorts may help overcome some of these difficulties. 22q11.2DS is one of the strongest risk factors for schizophrenia and yet we still do not fully understand why. Solving this question has the potential to help those individuals with 22q11.2DS, and individuals with schizophrenia in the wider population, as well as understanding the aetiology of psychiatric disorder.

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